Partners in the polder

A vision for the life sciences in the Netherlands
and the role of public-private partnerships

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Summary of the main recommendations

The world has entered the age of the life sciences. More and more, the life sciences help us address social challenges in healthcare, food supply, energy security and environmental sustainability and enable our knowledge economy. The Netherlands has a unique position. Our scientific research in the life sciences is in the global top three, and our country is home to strong food, health, agricultural and chemicals & energy sectors that can deliver on the promise of the life sciences.

Nevertheless, translating our excellent knowledge into novel products, processes and services and delivering these to society is difficult. To overcome this challenge, academia, industry and the government have joined forces in recent years in precompetitive research collaboration on an unprecedented scale. It is now time to follow through and make that investment pay off.

Many representatives from the life sciences field have come together to write *Partners in the Polder.* The book articulates the promise of the life sciences and discusses how the Netherlands can deliver on that promise, paying particular attention to the role of public-private partnerships (PPPs). *Partners in the Polder* looks at how academia and industry are coming together to translate basic knowledge into practical applications: the origins of the PPP, its purpose and outlook, strengths and weaknesses, successes and failures.

Partners in the Polder makes three main recommendations that are broadly supported by the field and draw on the experience and expertise of scientists, researchers, business leaders and policymakers from all corners of the life sciences and on studies and publications from industry associations, the OECD, the Innovation Platform and others. The authors hope that this summary of the main recommendations piques your interest in the book itself. It contains many more observations, lessons and recommendations.

I. Provide continuity in innovation policy for 15 years or more (p. 62-66)

The Netherlands has the ambition to become an internationally leading knowledge economy and play a prominent role in addressing social challenges like climate change. For that, innovation is crucial. Innovation in the life sciences can take 15 years or more: from the initial idea to the uptake of a new product, process or service in society. Much time, energy and money needs to be invested in uncertain outcomes. The Dutch government stimulates innovation with many sound policy instruments. Innovation policy itself, however, changes at least every four years – in priorities, criteria, instruments, procedures and points of contact. If the rules keep changing during the innovation game, returns on previous investments will be low, new efforts will be few and we will not realize our ambitions.

To change this, the field must first articulate where it wants to go and what it needs to get there. That is what *Partners in the Polder* aims to do. With this, the government can formulate long-term objectives (> 15 years) to guide its innovation policy. Such objectives make it possible to keep the rules largely constant, in line with (inter)national best practices and tailored to the life sciences. The right (mix of) instruments can then be deployed in each stage of innovation and progress and results monitored throughout. This way, public money will be invested effectively and legitimately.

II. Build on the strengths that have been developed (p. 67-75)

All life sciences stakeholders need to build on the strengths developed. The first priority must be to reap the fruits of earlier investments by creating the best conditions for use and delivery of innovations. These include easy access to knowledge and patents, ample availability of (venture) capital, the absence of unnecessary regulatory constraints, well-informed and critical citizens, and a well-functioning market. The field and government together need to create such conditions, and *Partners in the Polder* contains many tips and ideas for doing so: from valorization mechanisms to certification systems to acting as launching customers.

We should take our rich (national) landscape of PPPs to the next level of scale and scope. It is recommended that the field consolidate the more than 40 Dutch PPPs in which life sciences play a role into ten or fewer clusters that are part of international networks, and that the government continue to invest in such partnerships. The government should also increase investment in the basic research in academia that is needed to preserve our world-leading knowledge position (especially in harsh economic times). Academia in turn has the responsibility to valorize its research results: to make it easy for entrepreneurs to acquire and build on its knowledge and patents. Another priority is education. Life sciences innovation needs educated scientists, entrepreneurs and venture capitalists, as well as informed citizens who can decide to use an innovation (or not).

III. Position the Netherlands as one bioregion (p.75-78)

In the Dutch life sciences, distances between world-leading academic groups and strong industry sectors (food, health, agriculture, and chemicals & energy) are small. By positioning itself as a single bioregion with local hotspots and capitalizing on the Dutch traditions of cooperation and trade, the Dutch life sciences could become incredibly competitive and attractive to international partners.

Successful collaboration will increasingly be a source of competitive advantage. The life sciences field will continue the cooperation that began with writing this book, share experiences and set up (informal) coordination wherever useful. Today's PPPs will help future ones take advantage of the lessons learned and existing back offices. In short: the Dutch life sciences stakeholders will be ever more *Partners in the Polder.*

Colophon

EDITORS
Colja Laane *(Netherlands Genomics Initiative)*
Koen Besteman *(Roland Berger Strategy Consultants)*

AUTHORS

Part I
Colja Laane *(Netherlands Genomics Initiative)*
Koen Besteman *(Roland Berger Strategy Consultants)*
Benno van Dongen *(Roland Berger Strategy Consultants)*
Jeroen Vugts *(W-rite!)*

Food
Jan Sikkema *(TI Food and Nutrition)*
Wim Verhoog *(MGMC)*

Health
Roland Lageveen *(High Profile Group)*
Peter Luijten *(Center for Translational Molecular Medicine)*
Daan Crommelin *(Top Institute Pharma)*
Emiel Staring *(BioMedical Materials Program)*
Edvard Beem *(ZonMw)*
Jorg Janssen *(Life Sciences & Health)*

Chemicals & energy
Luuk van der Wielen *(Delft University of Technology)*
Isabel Arends *(Delft University of Technology)*
Sef Heijnen *(Delft University of Technology)*
Johan Sanders *(Wageningen University and Research Center)*
Elinor Scott *(Wageningen University and Research Center)*
Andre Faaij *(Utrecht University)*
Bert Weckhuysen *(Utrecht University)*
Dick Janssen *(University of Groningen)*
Bert Poolman *(University of Groningen)*
Sascha Kersten *(University of Twente)*
Marcel Wubbolts *(DSM White Biotechnology)*
Jos Keurentjes *(AkzoNobel Industrial Chemicals)*
Jan van Breugel *(Purac International)*
Dirk den Ouden *(Avantium)*

Agriculture
Huub Löffler *(Wageningen University and Research Center)*
Arno Vermeulen *(Immuno Valley)*

Technology
Eduard Klasen *(Leiden University Medical Center)*
Ruben Kok *(Netherlands Bioinformatics Centre)*
Luc Rietveld *(Netherlands Genomics Initiative)*

Education & training
Leen van den Oever *(Netherlands Institute of Biology)*

Valorization
Koen Wiedhaup
Chrétien Herben *(Netherlands Genomics Initiative)*
Ingeborg Meijer *(Technopolis)*

Social aspects
Wiebe Bijker *(Maastricht University)*
Frans Brom *(Rathenau institute)*
Rob Hoppe *(University of Twente)*
Atie Schipaanboord *(Federation of Patients and Consumer Organisations)*
Erica Terpstra *(NOC*NSF)*
Annemiek Nelis *(Centre for Society and Genomics)*

ON BEHALF OF
Task Force Life Sciences
Rudy Rabbinge, Chairman
Luc Rietveld, Secretary
Edvard Beem *(ZonMw)*
Frans Martens *(Earth and Life Sciences – NWO-ALW)*
Louis Vertegaal *(Chemical Sciences – NWO-CW)*
Eppo Bruins *(Technology Foundation STW)*
Colja Laane *(Netherlands Genomics Initiative)*

CONTAINS CONTRIBUTIONS OF
Antoon van den Berg, Peter van Bladeren, Kerst Boersma, Piet Borst, Hans Bos, Douwe Breimer, Eppo Bruins, Maarten le Clercq, Tini Colijn, Hans Dons, Michel Dutrée, Anne Flierman, Thijs Hendrix, Janneke Hoekstra, Ab Klink, Martin Kropff, Emmo Meijer, Pauline Meurs, Gert-Jan van Ommen, Anton Pijpers, Ronald Plasterk, Rudy Rabbinge, Martin Scholten, Feike Sijbesma, Robert-Jan Smits, Onno van de Stolpe, Henri Termeer, Erica Terpstra, Gerda Verburg, Marco Waas, Edward van Wezel, Peter Wierenga, Rein Willems, Jan Wisse, Diederik Zijderveld

POSTFACE
Herman Wijffels

PROOFREADER
Megan Garr

DESIGN
i am - Grafische Vormgeving

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Preface

There is a Japanese proverb: "Beginning is easy, continuing hard". The central theme of this book may be that continuing is nevertheless both necessary and rewarding. *Partners in the Polder* is about the future of the life sciences in the Netherlands and the of role public-private partnerships (PPPs). Both are off to a good start. The life sciences are already impacting the food, health, chemicals & energy and agricultural sectors. Life sciences PPPs have been set up and are starting to produce results. Their resources, however, are temporal and will end in the short to medium term. Continuing efforts into a future where the life sciences deliver on their promise will be long and hard work – but it will be worth it.

Likewise, conceiving this book was relatively easy – writing it was not. The life sciences are not a single, coherent field. Rather, the life sciences are a knowledge base that impacts industry sectors which differ in dynamics, size and their application of that base. It is quite something that so many representatives from such diverse parts of the life sciences have come together to produce a joint vision of the future that also does justice to their individual perspectives. I am grateful for their hard work and valuable contributions and proud of the result. It gives me great pleasure to present and introduce the finished product of this unique collaboration.

There are a few things you should keep in mind when reading this book. For one, the life sciences often are and need to be combined with other fields, like ICT, nanotechnology, medical technology and chemistry, to find application and deliver results. Considering each of these in their entirety would take not one but several books. We limit our focus to the life sciences themselves. Also, life sciences innovation is not synonymous with public-private partnership. PPPs are but one means of organizing innovation and can only play a valuable role if they are part of a larger innovation system. They do not obviate the need for basic research in academia. On the contrary, they underline its continued importance. Nor can PPPs take the place of industrial R&D in developing new products, processes and services. The choice to focus on PPPs here was made because they are one way to address the difficult task of translating our world-class knowledge base into practical applications, and because they are emblematic of the emerging open innovation paradigm. This book tries to provide the broader context but cannot go into the same detail everywhere.

Partners in the Polder is a book in two parts. Part I is called Unity, and presents the field's joint vision of the future of the life sciences in the Netherlands, and the past, present and future role of public-private partnerships. Part II, Diversity, looks at (the future of) the life sciences and PPPs from the perspectives of the sectors involved (food, health, chemicals & energy and agriculture) and the disciplines linking them (technology, education, valorization and social aspects).The two parts can be read separately, but together illustrate a field united in diversity. Each chapter in Part II can be read on its own.

We hope that you enjoy reading *Partners in the Polder* as much as we enjoyed writing it. The book is written for policymakers, the life sciences field and the general public. We hope this book will help you to enable, drive and benefit from life sciences innovation. We invite you to reflect on these pages, and to join the discussion and continue the work that has begun.

On behalf of the Task Force Life Sciences and the authors,

Colja Laane
Director of the Netherlands Genomics Initiative

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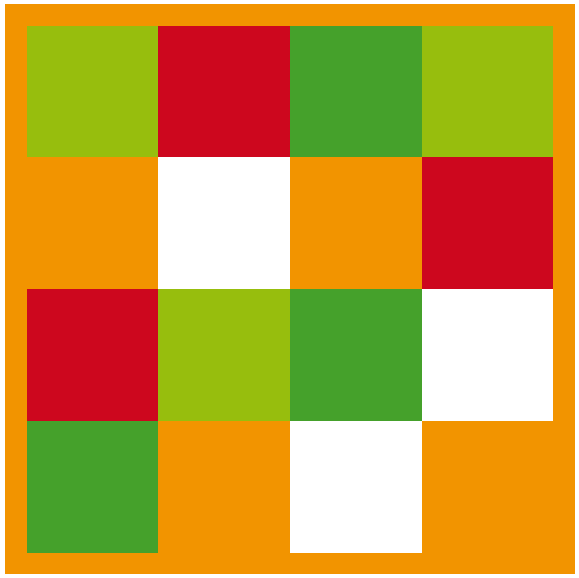

Part I Unity

Unity

I Introduction

This book is about life sciences in the Netherlands – past, present and future. It looks back at what has been achieved, and ahead to what the life sciences may mean for our society and economy in the future. But most importantly, it takes a close look at ourselves – scientists, researchers, business men and women, entrepreneurs, citizens, consumers, innovators – and to what we can do to build on today's strengths and deliver tomorrow's promise.

This book is about innovation. It is about policy. It is about partnership. In the life sciences, you will not achieve much on your own. Life sciences innovation involves a chain of connected activities that typically takes more than fifteen years. Knowledge must be *generated, translated* into practical applications, and *delivered* in the form of products, processes and services that are actually used in real life. This chain stretches from basic research in academia to R&D in corporations and start-ups, to safety and efficacy tests, to prototyping, regulatory approval, production ramp-up and up-scaling, market introduction and more. To be successful, you need partners.

This book looks at the entire chain, but with a particular focus on where partnership has come to play a vital role: public-private partnerships. Since the turn of the century, the Netherlands has seen collaboration between academia, business and government occur on an unprecedented scale. In these public-private partnerships (PPPs), science and business come together. Basic science is translated into practical applications that can then be delivered into the hands of private and professional users, thus realizing social and economic value. Accounting for 40% of all PPP investment in the Netherlands, the life sciences exemplify the purpose, character, successes and failures of the public-private partnership model.

This book itself is a testimony to partnership. Much of the life sciences community has come together to write it. The book embraces many shapes and sizes, with (scientific) disciplines, market sectors, and public and private players uniting in a shared vision of the future, and of what public-private partnership can do to help make that future a reality. We invite you to join the discussion and share in our commitment to achieving the social and economic value that the life sciences promise.

Before we embark on our journey through the life sciences and the public-private partnerships of yesterday, today and tomorrow, we will provide some background: the life sciences and the socio-economic challenges they address, public-private partnerships, the concept of a single "bioregion" and the setup of this book.

A. Life sciences

We have entered the life sciences age. Increasingly, living organisms and biological processes are used to develop and deliver products, processes and services that improve our quality of life. This, in itself, is nothing new. We have used yeast for thousands of years to make bread and beer. But in the last 40 years or so we have made vast leaps in our understanding of life and its building blocks: cells, the molecules that make them, the proteins that are their workhorses and especially the DNA that is the code of life.

Our definition of life sciences
The studies of living organisms and biological processes and their use to develop products, processes and services that have social and economic value

The next wave of entrepreneurial activity

In 1953, James Watson and Francis Crick described DNA's double helix structure. Scientists have since unraveled its genetic code, have learned how to change and reproduce it, and how to insert bits and pieces into various organisms. This has created an undreamed-of toolbox that can help us manipulate and utilize (parts of) organisms for the benefit of humankind.[1] The use of this toolbox is that part of the life sciences called biotechnology.

The applications are many. The first biologically made drug was approved in 1982: human insulin produced in genetically modified bacteria. Today, about 120 biopharmaceuticals have obtained market approval and two are among the top 10 drugs sold today.[2] Tailored microorganisms are now used as small factories in a range of industries, producing products like chemicals, biofuels, pharmaceuticals, cosmetics and food ingredients. In 1997, the first weed and insect resistant crops made their way to the market. Today, crops improved through breeding techniques which were made possible thanks to the life sciences grow throughout the world.

Food, health, agriculture, chemicals & energy – all of these sectors are served by the life sciences. Together, these sectors account for over EUR 200 billion, well over a third of total GDP in the Netherlands. Their application of the life sciences is growing rapidly and is often combined with other new and existing technologies to develop and deliver products, processes and services. Worldwide revenues of dedicated biotechnology companies alone exceeded USD 85 billion in 2007 and are growing by 17% per year.[3] That is just from companies doing nothing but biotech. Factor in the widespread use of fermentation in large chemical companies, or the biologics divisions of big pharmaceutical companies, and the total commercial application of the life sciences is extraordinary. If the 90s belonged to Silicon Valley and dot.coms, then the 21st century belongs to life sciences entrepreneurs. It is the next big wave of entrepreneurial activity (Figure 1).

Addressing the big questions together

Food supply, chronic diseases, energy security and climate change – these are the major challenges of our time. We need to find ways to feed a world population that is projected to grow to more than nine billion by 2050, when nearly one-sixth of today's 6.8 billion are already hungry and undernourished.[4] We need to care for and treat an ageing population, increasingly suffering from chronic diseases like cancer, diabetes and dementia. In the Netherlands alone, current trends point to rises of up to 40% in major chronic diseases by 2025.[5] Our energy demand is expected to grow by 44% from 2006 to 2030, while fossil resources are limited and often come from unstable parts of the world.[6] Last but not least, all of this places a huge burden on our environment. We need to meet our food, health and energy needs responsibly – i.e. safely and sustainably: protecting ecosystems, humans and animals, and reducing energy consumption and greenhouse emissions.

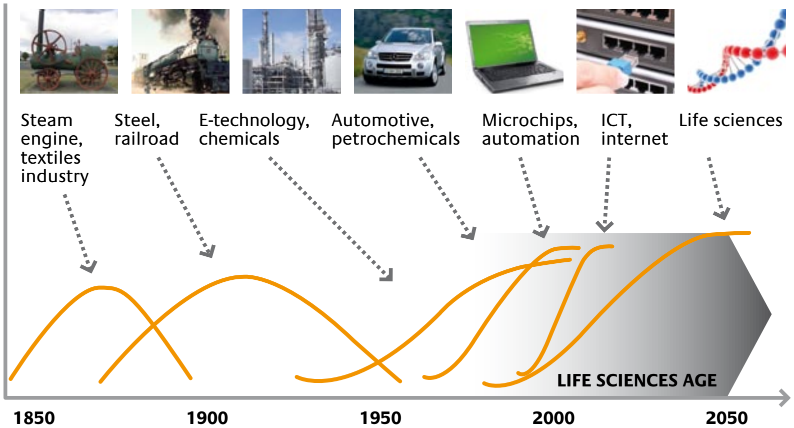

Figure 1: Waves of entrepreneurial activity

Life sciences promise to play a major role in overcoming these challenges. They are revolutionizing plant breeding in agriculture, building resistance against climate and disease and increasing yields while reducing the need for fertilizers and pesticides. They are improving the taste and nutritional value of food. They are increasingly employed in the discovery, development, testing and production of new diagnostics, drugs and medical devices. They are an important enabler in the sustainable production of energy, chemicals and materials, with less energy use and less harmful emissions of greenhouse gases.

These are not separate challenges. They impact each other and none can be resolved in isolation. What is more, they require multidisciplinary solutions in which several sectors work together utilizing the full breadth of their technology base. A good example can be found in the health challenges we currently face. As healthcare depends increasingly on prevention (e.g. diagnosing risk factors, countering and containing them), diet has become a major factor. Food companies can make healthier foods, or better tasting healthy food. The health sector can help food companies better understand and tailor their foods to dietary needs. Agriculture also plays a role. A recent Dutch innovation

The importance of social studies

The life sciences not only provide solutions to challenges of today and tomorrow. They also, like many new technologies, raise new questions and create new risks – many of which we cannot foresee today. The effects of the new life sciences and technologies (including benefits and risks, but also possible changes in social relations) need to be identified as quickly as possible. Once identified, scientifically-founded and democratically legitimate and acceptable policy choices can be made. We propose that “social programs” accompany all life sciences initiatives. Such programs begin with the observation that knowledge, risk and benefit mean different things to different people and in different contexts. By exploring such multiple meanings and interests, social programs will generate debate on the social impact of life sciences innovations. Innovations cannot exist without being embedded in society, and interactive involvement of various relevant social groups in such debates will improve the success rate of innovations. This does require a joint, multidisciplinary and public approach in which the innovators take the lead, but in which they are prepared to listen to outsiders and to consider adapting their designs.

grew tomato with a high concentration of antioxidants that may play a preventive role against cancer.

That same multidisciplinary approach is needed to secure our energy supply and petrochemical industry while preserving the environment. There are many sustainable alternatives to fossil resources, but neither sun nor wind contains the molecules needed to make chemicals and materials. Biomass is a promising solution. It can be eaten, turned into energy, fermented into biofuels or separated through biorefinery into building blocks for pharmaceuticals, base and specialty chemicals, and materials. This requires a joint approach by the agriculture, chemicals and energy sectors, combining life sciences technologies with others, like catalytic and separation technologies, thermochemical conversion and process engineering, and resolving competition issues with the use of biomass for food supply.

A blend of colors

These four sectors – food, health, agriculture and chemicals & energy – are not only connected by their application of life sciences, they are also united by the technology itself. All base themselves on the same (biological) principles and processes. All employ the same toolbox of genomics (genes), proteomics (proteins), metabolomics (cellular processes), bioinformatics (data processing), systems biology (integration) and more. As such, they are all "biotech". The use of life sciences techniques in health is commonly referred to as "red biotechnology", in chemicals & energy as "industrial" or "white biotechnology", and in agriculture and food as "green biotechnology" (although in this book we shall distinguish between "dark green" agriculture and "light green" food to reflect both their commonalities and differences).

However, as clear as the similarities or the need to collaborate may be, an integrated approach is far from simple. Sectors have very different dynamics. The chemicals sector is based on large-scale industrial processes and carefully optimized, global supply chains, whereas agriculture relies on local environmental conditions and is accustomed to wide supply variations due to seasonality and unpredictable harvests. Even within sectors the dynamics can vary. The health sector, for example, is tightly regulated and dominated by (semi-)public institutions. But within this sector, medical devices must satisfy other criteria than drugs for market approval. Food companies wishing to introduce healthy foods may not relish the thought of having to first undergo lengthy trials. On the other hand, they operate within a consumer industry more exposed to (bad) publicity and fickle tastes than others.

These sectors are thus united in diversity. Bound together by applications and underlying life sciences, but each with its own path to take and story to tell. This book presents both.

B. Public-private partnerships

Innovation is a lengthy and risky process requiring large investments over time. This holds especially true for the life sciences, where the path from scientific breakthrough to marketable application is typically 15 years or more for all sectors. Chances of success are often low, investments high and the range of knowledge and competences required wide and varied. It is all but impossible for a single company or research group to realize a life sciences innovation from beginning to end alone. Cooperation is vital. Note that for simplicity we often sketch a somewhat linear process of innovation. In reality, it is not linear at all. It is an iterative process, it branches, sometimes steps are skipped, sometimes repeated and knowledge from innovations on the market is used for the development of others. This last characteristic has made some people refer to innovation as a cyclic process.

Innovation is sometimes described as a three-stage rocket: you need basic science in the first stage to achieve lift off; in the second stage you apply science to real-life problems, propelling you into the "orbit" of markets and companies; and in the final stage the "payload" – a new or improved product, process or service – is delivered to end users. In the Netherlands, the first stage, basic science, is first rate. Dutch science ranks in the top three worldwide in terms of scientific impact – and fields relating to the life sciences are among our top performers.[7] We are, however, not so successful in the final stage: delivering innovations to markets, realizing their value to users and society and making money off of them. Here we are a follower at best,[8] and this may be due in part to failings in the second stage.

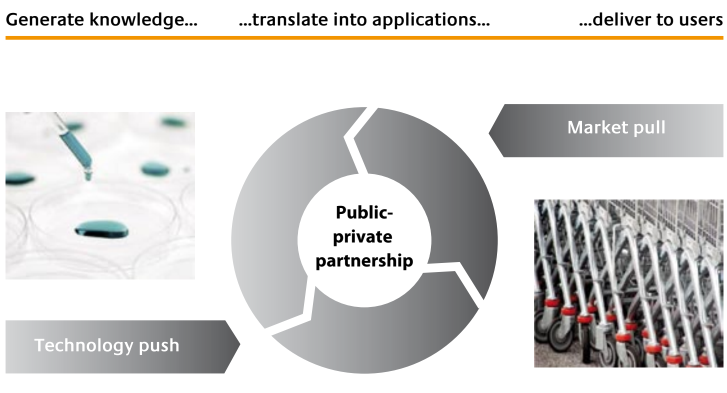

Figure 2: Public-private partnerships combine technology push with market pull

Basic science is the domain of academia: universities, university medical centers and (semi-)public research institutes. It is public and publicly funded. Markets and (large-scale) production are the province of industry – the private sector. To develop and deliver innovation successfully you often need both, and the second stage, where scientific knowledge is translated into marketable applications, is where they meet.

The second stage is absolutely key. You cannot just give ready-to-use academic knowledge to industry. It has been tried. It does not work. It is too much like trying to force a square peg into a round hole. You need more than a simple handover, which is why the second stage must in some sense be transformative, creating practical applications of cutting-edge science and technology that are of value to real people. That means combining the technology push from academia with the market pull from society and industry (Figure 2). It also means (intense) collaboration between public and private players. This is never easy, and results are neither certain nor predictable. Innovation is more intractable than that. However, if not a sufficient condition, it is a necessary condition that the public and private domains of science and enterprise meet and interact.

It is in the space of this second stage that public-private partnerships were conceived. Over the last decade these so-called PPPs have taken major leaps in the Netherlands.

In PPPs, academia, industry and government join forces to translate basic science into marketable applications with social and economic value. Public-private partnership can take many forms: it can be one-on-one; it can involve many parties, from large corporations to small and medium-sized enterprises (SMEs), from universities to (semi-)public or private research organizations, from charities to governments; it can be physical, co-locating teams of researchers on a single campus or in a single building; it can be virtual, combining the efforts of researchers from different organizations and locations; or it can be something else entirely. Although there is no single definition of PPPs and we will not attempt to develop one, all PPPs share a number of traits:

- They are **collaborative** – one partner does not simply pay another for a piece of research or to do a job; rather, partners work together and contribute knowledge and resources;
- They are **precompetitive** – research has clearly progressed to a focus on commercial application, but not to the point where a single company will demand exclusivity;
- They are **partnerships** – partners share the risks and the rewards, all contribute their share of funding (be it cash or in kind) and all receive their share of the intellectual property generated.

PPPs serve different purposes and have different advantages and disadvantages for individual stakeholders. Typically, for industry, they involve a trade-off between leverage (government matching of funds) and exclusivity (pre-competitive, sharing IP). In academia, a balance must likewise be struck between opportunities for additional funding and the threat of withdrawing scarce resources from basic research. Government, meanwhile, wants to see the different parts of the innovation chain connected and resources concentrated on areas that are important for society. It wants to give direction without infringing on the judgment and entrepreneurship of either academia or industry, and without creating a “subsidy fest”.

PPPs are especially suited to the life sciences, with their long development horizon, multidisciplinary nature and collaborative, “open innovation” paradigm. More than EUR 2 billion has been committed to Dutch life sciences PPPs over a period of approximately five years. That is more than 40% of all PPP investment in the Netherlands,[9] which is why the life sciences are a good place to study PPPs as a model for innovation. Now is a good time, too. The life sciences PPPs are gaining momentum and starting to deliver results. Other countries are taking note, following the Dutch model as a best-practice example.

In this book we review the history and origins of PPPs, draw lessons from our collective experience in setting up and operating these PPPs, and describe the challenges we see ahead of us. Although it may be too early for a final evaluation of the PPP model, we believe both the life sciences themselves and society at large will benefit from the critical review in this book. Government has played a crucial role in realizing the PPPs, matching the investments made by academia and industry. That is tax money. It is time that we explain what we are doing with it and why we think it was wisely invested. Moreover, we hope that our successes and failures, and the lessons and recommendations we present, will be of value to government in future policy and funding decisions.

C. One bioregion

The Netherlands is well-positioned to play a leading role in the life sciences age. As we pointed out before, our knowledge base is excellent – among the best in the world. What is more, the industry sectors impacted by the life sciences have a strong presence in the Netherlands. Our plant breeding industry is a global leader. We are the petrochemical gateway to Europe, with one of the strongest chemical and energy sectors on the continent. Our medical infrastructure and academic hospitals are world-class, and we have a dynamic and fast-growing pool of biotech entrepreneurs. We are home to some of the most innovative companies in food and food ingredients. Uniquely, all of this is located on just 42,000 km^2. That is only about double the Bay Area, the Massachusetts life sciences cluster or Denmark's "Medicon Valley". The Netherlands is packed with not one, but several life sciences-intensive sectors, thirteen universities and an unparalleled number of public-private partnerships. In this book we will argue that the Netherlands should be seen as one "bioregion": a single cluster, with a strong tradition of (multidisciplinary) cooperation.

The Dutch polder model is being renewed and applied to innovation in the life sciences PPPs. One lesson of successful (innovation) clusters is not to try to do everything, but to concentrate energy and resources on a select few topics. This creed is commonly summarized as "focus and mass". That is the future we see for the Netherlands: the life sciences polder. A small country with excellent science, strong sectors and real partnership in a multidisciplinary field with huge social and economic promise. In this book we will show why that is both desirable and achievable, and we will set out the routes to reach this goal.

D. This book

This book is about life sciences in the Netherlands. It is about partnership. It is about what can make a small country great. Obviously, we will talk about more. The life sciences cannot be seen in isolation from other technologies or the industry sectors they serve. Public-private partnerships should not be separated from the larger innovation system of which they are part. Basic research is crucial. Its excellence needs to be sustained and its interaction with and participation in PPPs secured. Industry needs to take an active and leading role to take PPP results and bring them to users and markets. (Small, new) entrepreneurs will be a major factor in realizing innovations through new ventures and new business models. Nor are we alone. The life sciences field is an international field, with other countries, companies and universities both competitors and potential partners. But like the life sciences, we have chosen focus and mass: *life sciences PPPs in the Netherlands*.

This is a book in two parts. This, the first, reflects on the impact of life sciences on our lives and the past, present and future of Dutch life sciences PPPs. Chapter II will sketch our world in 2020. What will life be like if the life sciences deliver on their promise? This chapter will be a pastiche of images. Not predictions or ironclad guarantees, but likely future applications and directions. We are not attempting to be 100% accurate or exhaustive. Chapter III is devoted to a case study of Dutch life sciences PPPs. Where did they come from? What have we learned? What challenges await? We will describe successive generations of R&D and innovation policy, draw lessons, point out trends and next steps, and lay out the main recommendations. Chapters II and III are each self-contained and can be read independently from each other. We invite you to read them in the order that you see fit, or pick the one that most interests you.

After these "overview" chapters, individual life sciences sectors will present their perspectives in Part II of this book. Part II will describe in more detail where the sectors are going and how PPPs may help them get there. Each life sciences sector (food, health, agriculture and chemicals & energy) will tell its own story. These stories are bound together by "cross-links" – common elements that unite and span the sectors: enabling technologies, education & training, valorization and social aspects. Each cross-link has its own chapter in Part II. The book concludes with a postface written by Herman Wijffels. Throughout this book, stakeholders from politics, industry, academia and society are invited to share their thoughts about this book, the life sciences, PPPs, or anything else they wish to share.

This book is both a tribute to and an exercise in partnership. It is a polder or an ecosystem in itself, inhabited by different "breeds" and perspectives and benefitting from both their unique contributions and collaboration. We hope this book shows both the unity and diversity of the life sciences. Many people from the many sectors of the life sciences field came together to present a single vision and ambition, to paint the future. Even if not everybody sees it in the same shades or agrees on all details, this book provides a clear and shared sense of direction and a powerful base and stimulus for (continued) collaboration. It is meant to unite and inspire.

Finally, this book is dedicated to you: our fellow citizens, our prospective customers, the people we hope will benefit from the innovations we foresee. We will account for the public funds entrusted to us. We will tell you how they are spent and why we think they are well-spent. And we will offer our experience to the government. Throughout the book we will share recommendations and lessons learned in the hope that this may inspire and support future decision makers in setting policy and allocating funds for innovation – whether in the life sciences or beyond. We invite everybody to join the discussion and contribute to realizing our shared vision.

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A job half done

This is an important book. This book shows that impressive results have been achieved in stimulating innovation in the life sciences in the Netherlands in recent years. There is every reason for Dutch policymakers, Dutch knowledge institutions and private companies to congratulate themselves on half a job well done. Through cooperation and investments from all parties, the groundwork has been laid for a sector that may well develop into the preeminent bioregion in Europe in the years to come. TNO is a proud member of many of the public-private partnerships that together form this Dutch bioregion. Its mission, to help turn fundamental research into innovations that benefit society, aligns perfectly with the mission of life sciences PPPs. In the next phase of the life sciences PPPs, TNO aims to expand on its ambition of valorizing the scientific results obtained in PPPs.

The main value of this book is, however, that it reveals that the job is only half done. The groundwork has been successfully laid, but unless we keep fostering innovation in the life sciences, we will not reap the rewards. Continuity of commitment and investment and the willingness of all partners to keep cooperating are key to future success. This book shows how we can successfully finish the job we started. We all, government, knowledge institutions and private companies, should follow its advice and recommendations. ”

Tini Colijn, Member of the TNO Board of Management

Diederik Zijderveld, Director of Research at TNO Quality of Life

Quote from Tini Colijn ...

... and from Diederik Zijderveld

Unity

II The finished picture

It is 2020. A man walks along a country road. Inside his body, a new kidney takes the place of the old one that failed. It was grown outside his body from his own cells over a biodegradable scaffolding and was not rejected after implantation. He walks past a field where a farmer tends his crop and feeds the non-edible waste into a small biorefinery unit that breaks it up into different parts, including fibers that are used by the paper industry to partly replace wood pulp. In the distance, ships pull into to the port of Rotterdam to deliver their biomass cargo to producers of biofuels, fine and bulk chemicals and materials. Shipments of palm oil have markedly dropped since edible oils were first extracted from algae.

Other parts of algae supply farms like this with fertilizer. The vegetables grown here have been carefully bred to not require any pesticides. The man stops to wave at the farmer before he reaches his destination. He then goes through a door with a DNA lock that recognizes him through the same technology that is used by forensic investigators. He sits at his lab bench and begins again the work to develop the enabling technologies that help make his modern world possible.

Ten years ago, these were just tantalizing possibilities. Who can say what tomorrow might bring?

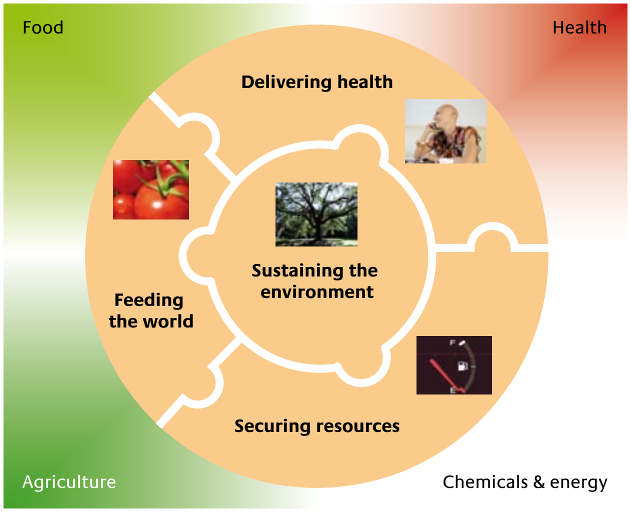


Figure 3: Socio-economic challenges and the life sciences field

If we return to this story in 2020, will it prove an accurate prediction? It may well. Though much work needs to be done, none of the examples given are beyond a reasonable extrapolation of the state of technology today. We will not solve the world's problems by 2020, but between now and then we can make significant progress on some of the most pressing issues. In this chapter, we will examine the main socio-economic challenges facing us in 2009 (Figure 3) and how the life sciences can help address them:

- **Delivering health** to an ageing population with an increasing prevalence of chronic diseases;
- **Feeding the world** and its growing population;
- **Securing resources** for growing energy, chemicals and materials needs; and
- **Sustaining the environment**.

These challenges cannot be solved in isolation. They impact each other. For example, using biomass as the base material for chemicals & energy impacts the environment, as well as the food supply. Comprehensive strategies to tackle these challenges require various disciplines, sectors and ministries to work together. The life sciences will play a major role in that collaboration.[10]

Let us paint a picture of 2020, of what the future could look like if the life sciences deliver on their promise. Mind you, it is an impression, not a prediction – and it is by no means comprehensive. However, it is not that far-fetched either, as the examples of ongoing PPP projects in the boxes throughout this chapter illustrate.

A. Delivering health

In 2020, almost 3.4 million Dutch men and women are over the age of 65, one-third more than in 2009.[11] Compounded by an increasingly unhealthy lifestyle (little exercise, bad food choices, increasing obesity) this has caused the prevalence of chronic diseases like cardiovascular diseases, cancer, diabetes and dementia to rise.[5] Increasing demand, higher expectations and a shrinking workforce have weighed heavily on our healthcare delivery system: costs were rising and personnel in short supply.

But by 2020, the rise in new chronic cases has slowed, patients enjoy a much improved quality of life and costs have been effectively contained. The life sciences have helped do this by enabling early diagnosis, personalized treatment, regenerative medicine, less but better testing, prevention and home care, and increased attention to diet and lifestyle choices.

The life sciences enabled us to see and understand processes in the body on a very small scale by observing biomarkers. From there we started to diagnose and treat (chronic) diseases in a very early stage, before symptoms showed and even before the onset of the disease. The focus has shifted to prevention guided by genetic predisposition. Diet and lifestyle are integral parts of both diagnosis and treatment. When a disease cannot be prevented, its early detection increases the chance of cure and/or reduces its impact on the patient's quality of life. For example, we now can look into white and red blood cells to see whether they are likely to clot, block the flow of blood and cause a stroke or heart attack. This we can then prevent or delay. We can also quickly differentiate between Alzheimer's and less severe causes of memory loss. Immediate treatment slows down the development of dementia in Alzheimer's patients considerably.

The life sciences have also increased the efficiency of treatment by making it personalized, specific to the exact disease and to the individual suffering from it. For example, by looking at the biological characteristics of both lung cancer and patient, we have learned which combination of therapies and dosage work best. Breast cancer treatment has been similarly personalized. More and more, medication delivery itself is targeted – i.e. delivered directly at the tumor site. By 2020, innovative, low-cost sequencing methods have flooded the market, and it has become quite common to have one's genome sequenced. Through systems biology, life scientists have taken large steps in relating genes to processes in the body and their outcomes. Enormous amounts of data and tissue, blood and urine samples from both patients and healthy individuals are collected and stored in data- and biobanks. Bioinformatics techniques have made it possible to process and correlate this information and to better understand predisposition, expression, risk, the effects of diet and lifestyle and prevention and treatment options, truly personalizing healthcare.

WORK IN PROGRESS

Understanding Alzheimer's disease

Age-related memory loss imposes an increasing burden on ageing Western societies. Memory loss is often regarded by patients as an indication that they may have Alzheimer's disease (AD), although in practice it is also a symptom of many far less serious conditions. An important challenge is to differentiate those patients who will and will not develop full-blown AD with dementia. One of the projects of the Center for Translational Molecular Medicine aims to develop new instruments with which to make an earlier and more reliable diagnosis of AD and create tools to evaluate novel medication. This will be achieved by identifying and quantifying biomarkers that indicate AD and developing technologies to make these visible.

Center for Translational Molecular Medicine, www.ctmm.nl

When early diagnosis and personalized treatment are not enough to prevent or stop disease progression, the life sciences offer a range of medical devices and tissue engineering techniques to heal or replace damaged tissue. Regenerative medicine developed, for example, an innovative biomaterial that when applied to damaged bones assists these bones in repairing themselves. And in 2020, the large-scale application of stem cells is not just a dream, but a growing reality. Stem cells have the ability to become any tissue and heal or replace damaged organs. Companies that use stem cell technologies have full and promising pipelines, and the first stem cell therapies have already reached the market.

WORK IN PROGRESS

Preventing kidney failure

Due to ageing, the worldwide incidence of kidney failure is expected to increase rapidly. Current replacement therapies are life saving but fall short of long-term efficacy. Therefore, the development of therapeutic strategies that prevent kidney failure at an early stage and promote functional kidney repair is crucial. The ambition of one of the projects of the BioMedical Materials program is to generate an implantable device that orchestrates the kidney microenvironment to promote the recovery of the kidney and prevent kidney failure.

BioMedical Materials program, www.bmm-program.nl

The life sciences have also impacted the development of health innovations themselves, reducing the need for animal testing and making clinical trials smaller, more accurate and cheaper. Cells have been developed in which the safety and efficacy of medication can be tested. Researchers have found ways to identify the exact subgroup for which a therapy is expected to yield the best results and focus clinical trials on them instead of on random samples of healthy people and patients. All of this helps keep medical innovation in 2020 effective, safe and affordable.

WORK IN PROGRESS

Improving drug dosage for children and elderly

Pharmacokinetics (PK) explores what the body does to the drug: the mechanisms of absorption and distribution, the rate at which drug action begins and the duration of the effect. Pharmacodynamics (PD) explores what a drug does to the body: the mechanism of drug action and the relationship between drug concentration and effect. By modeling the interrelationships between PK and PD based on preclinical and clinical data, predictions can be made on drug efficacy and safety in humans. This allows, among others, for more efficient clinical trial design and improved dosing schemes for patient groups like children and the elderly for which limited clinical data is available. Furthermore, the mechanism-based approach supports the study of drug effects on disease progression. In a project of the Top Institute Pharma, six big Pharma companies and four Dutch academic groups collaborate, yielding mathematical models that are based on existing data to predict among others drug dosage. In this way, an unprecedented knowledge base is created containing models that are based on very rich, multi-partner datasets.

Top Institute Pharma, www.tipharma.nl

Prevention and home care have done the same for healthcare delivery. By 2020, people have become used to (early) diagnostic tools and preventive techniques. Periodic checkups, kits for home care and attention to diet and lifestyle help keep people healthy and out of the hospital. Innovative medical devices that combine life sciences with ICT and nanotechnology allow patients to stay at home and undergo treatment and monitoring from a distance. Healthcare has thus become better, cheaper and more responsive to the needs of patients.

In keeping people healthy, the boundaries between the food and health sectors have blurred. Obesity is one of the main risk factors for chronic diseases and these can be prevented or delayed through lifestyle and diet choices. Our understanding of the relationship between food and health has vastly improved. We better understand our metabolism and what a food component, like a vitamin or sugar, does in our body. We can now predict what genes it will activate, what protein will be produced, what cascade a protein will start, and what consequences that will have for the body. Biomarkers allow us to observe these metabolic processes and signal potential issues. Science-based claims for the impact of food products on health can now be made, and the public can make informed decisions about what to eat and what not. If in 2009 we had the notion that omega-3 fatty acids might reduce the risk of heart disease, in 2020 we know exactly what they do and how and, consequently, when to take them.

WORK IN PROGRESS

Relating food and diabetes

Using a molecular and genetic research approach, new insights can be obtained into the role of food components like fatty acids in regulating organ function and human metabolism and disorders therein. Metabolic disorders are at the onset of major diseases. Insulin resistance syndrome, in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells, greatly increases the risk of cardiovascular diseases. One of the projects of the Nutrigenomics consortium aims to understand the impact of fatty acids on gene regulation in the liver and identify biomarkers in the liver for insulin resistance syndrome.

Nutrigenomics consortium, www.nutrigenomicsconsortium.nl

Food companies have used the life sciences to introduce so-called "functional foods", products that improve health or lower health risks. Certain additives help maintain muscle function and mass in older people. Specific proteins reduce blood pressure and the incidence of cardiovascular diseases in groups at risk. Overeating is addressed by developing food products that satisfy at lower quantities. We have learned how to make healthier foods taste, look, smell and feel like their "bad" alternatives, or even better. Nanoscience and life sciences combine to improve texture. Food products are also used to influence the number and type of microorganisms in our digestive tract, to boost resistance or assist in nutrition uptake. These microorganisms outnumber body cells by a factor ten. Life sciences (particularly systems biology) have taught us much of how they function and function together, enabling new prebiotic and probiotic products. Often these (functional) foods are developed for and tailored to a certain population group, and some even expect this to lead to the food equivalent of personalized medicine. That may be a bridge too far, but even so the products on the market in 2020 are only a first step.

WORK IN PROGRESS

Increasing muscle mass and function with dietary strategies

Skeletal muscle mass and function decline with ageing. This is accompanied by reduced physical performance, loss of functional capacity and an increased risk of developing chronic diseases. Age-related loss of skeletal muscle mass has been attributed to a reduced response of the machinery that synthesizes muscle protein to protein ingestion and/or physical activity. One of the projects of the Top Institute Food and Nutrition investigates this reduced response and defines effective nutritional interventions to stimulate muscle protein synthesis and as such increase muscle mass and function in elderly.

Top Institute Food and Nutrition, www.tifn.nl

Our increased understanding of the relationship between food and health is helping us improve food safety in 2020.

WORK IN PROGRESS

Developing alternatives for antibiotic usage in livestock

This research program of Immuno Valley develops alternatives to antibiotic usage in livestock. One of the objectives of this program is to develop a vaccine against Staphylococcus aureus. This bacterium causes inflammation of the udder of dairy cattle and also threatens humans (MRSA). Two other objectives are phage therapy against Streptococcus suis infection in pigs and the application of peptides and herbal extracts that improve the natural defense system of chickens and pigs.

Immuno Valley, www.immunovalley.nl

Food is now preserved through tailored targeting of decay mechanisms rather than filling them with additives. An important aspect of food safety is microbiological safety with livestock. The majority of new human infectious diseases originate from animals. Infectious diseases are still a continuous health risk for humans and animals in 2020. Early warning systems and sensitive diagnosis have reduced the threat by carefully monitoring epidemics throughout the world (e.g. influenza). Integration of genomic data of variants of microorganisms (viruses, bacteria and parasites) allow timely and effective vaccination of relevant populations of animals and humans. The “One Health” concept, where animal health is integrated into human healthcare planning, is up and running in 2020 (e.g. for Q-fever). Antibiotic resistance is still a threat but can be controlled by efficacious alternative treatments, for example in the fight against MRSA.

The life sciences play a major role in producing all of this safe and healthy food. Through advanced breeding techniques, like genetic modification or marker assisted breeding, livestock that produce healthier products, like unsaturated milk fat, have come within reach. Similar techniques are used to grow vegetables with higher concentrations of health-promoting ingredients. In 2020, we can really set microorganisms to work to control and enrich our food – and not just food, but these organisms produce pharmaceuticals as well. In production, the boundaries have also blurred between food, health and agriculture.

B. Feeding the world

In 2020, the world is shared by 7.7 billion people; this number is expected to rise to 9 billion by 2050.[4] At the start of the 21st century, food shortage was mainly a distribution issue; enough food could be produced for all but it was not easy to get it where it needed to go. Since then, population growth, the limited availability of arable land and dietary shifts in emerging countries (from vegetables to meat) have made production limitations a growing issue. Meat production places a much larger strain on our production capacity because animals need to be fed and cared for. The agricultural sector has therefore been looking for innovative solutions to increase food and feed supply.

We have seen a revolution in crop breeding strategies. This includes the reduction of production losses. More and more plants are being bred to be resistant against diseases, weeds and insects. The life sciences not only provide invaluable understanding of the exact disease mechanisms inside a crop, its natural defense mechanisms and the genes associated, but also biomarkers to monitor plant breeding and optimize the process. Phytophthora, or potato disease, has been all but exterminated. Some plants are even bred to secrete substances that repel harmful insects and preclude the need for pesticides.

In 2020, tougher crop strains have also been developed to survive harsh conditions like droughts, floods and high salt concentrations. With climate change and rising sea levels, such conditions have become more common. But thanks to the life sciences, yields on less fertile ground have increased and harvests have become more predictable and less vulnerable to weather fluctuations. For example, breeders can select lettuce types that are less sensitive to variations in the availability of water and nutrients and can grow under "low-input" conditions. Mushrooms have been bred with low sensitivity to bruising, allowing (cost) efficient mechanical harvesting methods. We have also managed to increase the efficiency of plant light uptake, making them grow faster and bigger. A tomato plant has been bred that can perform photosynthesis (turning carbon dioxide into carbohydrates using energy from light) 24 hours a day in greenhouses. Yields have increased significantly from these and other innovations, mitigating, if not eliminating, the problem of food scarcity.

Livestock produce a major proportion of the world's food. The life sciences have also impacted animal stocks. By analyzing DNA, animals that are resistant to certain diseases can be selected for breeding. Animal health solutions enabled by the life sciences, such as vaccination, also reduce production losses and increase yields. Breeding strategies have enabled the development of highly productive livestock variants. Another life sciences strategy to secure food supply is to match cattle with feed. By studying their metabolism, we have increased the efficiency of food uptake in animals, achieving maximum nourishment with minimal feed. This not only increases the output per acre, but also reduces the acreage needed to grow plants for

WORK IN PROGRESS

Making potatoes disease resistant

The potato is the number one vegetable crop in the world. Like its close relative the tomato, it is one of the few food crops that can be grown virtually everywhere. The Netherlands is the global leader in the breeding of potato varieties. One of the aims of the Centre for BioSystems Genomics is to create resistance to the disease late blight. This disease costs several billion Euros in crop losses annually, despite several billion Euros which are spent on fungicidal sprays. Methods like market assistant selection and the classification and mapping of all resistance genes in potato are used to achieve necessary plant resistance to this disease.

Centre for BioSystems Genomics, www.cbsg.nl

WORK IN PROGRESS

Shedding light on tomatoes
For optimal growth, fruit vegetables like cucumber, tomato and sweet pepper need 4, 6 or 8 hours of darkness per day. Thus photosynthesis does not take place for 17, 25 or 33% per day. If these vegetables could be grown under continuous light, a substantial increase in production is expected. However, continuous light causes severe problems that lead to poor production or even the loss of the crop. This project aims to understand why the current tomato cultivars show deleterious effects in continuous light and develop markers for breeding lines with a significant increase in yield under continuous light conditions.

Technological Top Institute Green Genetics, www.groenegenetica.nl

WORK IN PROGRESS

Improving milk production
The aim of the Milk Genomics Initiative is to identify genes that contribute to natural genetic variation in milk-quality traits, in particular milk-fat and milk-protein composition. The program provides tools for improved breeding programs to exploit natural genetic variation in milk-quality traits and contributes to the knowledge base needed for innovative dairy products. The initiative combines expertise in the fields of dairy science, quantitative genetics, genomics and bioinformatics.

Milk Genomics Initiative, www.milkgenomics.nl

animal feed. On the demand side, our understanding of human metabolism enables us to improve the efficiency of nutrient uptake in humans and reduce the quantity of food a person needs. Life sciences research is also looking for alternatives to meat, such as algae; ways have even been found to grow some strains in the desert.

In the early 21st century, much was made of the competition between food and fuel for biomass and arable land. By 2020, a bio-based economy has emerged that uses all of the plant: the edible parts for food and the non-edible parts for chemicals, materials, fuels, heat and power.

C. Securing resources

This brings us to the third socio-economic challenge we saw in 2009. The demand for energy, chemicals and materials has steadily risen as the population grew and emerging countries became more prosperous. World energy demand increased by 20% between 2009 and 2020, driven mostly by emerging countries.[6] Because fossil fuels are finite, and because the majority of oil and gas comes from unstable regions, the search for alternative energy sources has picked up speed and the life sciences have taken a leading role.

In 2020 we are well on our way towards becoming a bio-based economy. In the bio-based economy, biomass, not oil, is the base material for energy, chemicals and materials. Life sciences techniques are employed to genetically optimize biomass production. One example is a higher productivity of food and non-food crops by increased efficiency of the photosynthesis. Another is biomass with higher content of oil or specific compounds to produce higher yields, or lower lignin content for easier processing. Chemical and biological processes are used to convert biomass into fractions that provide the building blocks for a range of bio-based products (food, feed, chemicals, materials) and energy (fuels, heat, power). The process is called biorefinery, by analogy to its petrochemical inspiration.

In 2020, the Netherlands has both larger and small-scale biorefineries that convert both imported (corn stover, sugar cane bagasse, wood chips, dedicated energy crops) and domestic biomass (grass, municipal and garden waste, agricultural and forestry residues). The edible and non-edible parts of the crop are separated, where applicable, and from the non-edible parts all high-value, but low volume fractions are extracted first. These can be vegetable oils, proteins, chemical intermediaries or even pharmaceutical ingredients. Next, cellulosic material is disconnected from the lignin, broken down into sugars by enzymes and fermented to make biofuels. Last, the remaining material (lignin, etc.) is gasified for heat and basic molecules.

Smaller biorefineries are located on farms where they use agricultural residues and on industrial sites where they use residue streams from, for example, paper or chemical factories. The larger biofuel installations can be found in the port of Rotterdam, which in 2020 is the largest hub for biomass and bio-based (intermediate) products in Europe, building on its petrochemical position and infrastructure. A large synthetic gas facility operates in Delfzijl. Several pilot facilities for conversion of algae and seaweed have been built. An open-innovation pilot plant for fermentation technologies was realized in the Delft-Rotterdam region in 2012. Today, in 2020, 25% of the value of European bio-based products now passes through the Netherlands. The goals formulated in 2007 by the Green Resources Platform and the Dutch government have been largely achieved (20% of energy from renewable resources including biomass) or are on track (30% of fossil resources replaced by biomass in 2030).[12,13]

The life sciences have been a driving force behind the transition to a bio-based economy, from the genetic optimization of biomass to conversion technologies that use specialized enzymes and tailored microorganisms to the

WORK IN PROGRESS

Converting waste into biofuels

In addition to its traditional industrial applications (e.g. production of bakers' yeast and yeast extracts, beer and wine fermentation), the yeast Saccharomyces cerevisiae is rapidly gaining popularity as a multi-purpose platform for metabolic engineering. One of the Kluyver Centre projects focuses on metabolic engineering of Saccharomyces cerevisiae for the production of ethanol and more advanced liquid fuels from lignocellulosics from agroresidues and forestry.

Kluyver Centre, www.kluyvercentre.nl

synthesis of bio-based products. Increasingly, living organisms are used as factories for industrial production of chemicals and materials, including food products and ingredients, and (bio)pharmaceuticals. The organisms, like yeast, are genetically tailored to their tasks. For example, so-called lactic-acid bacteria produce a range of ingredients such as flavor compounds, proteins and vitamins. But they also produce enzymes as input for other industrial production processes. Tailored cells multiply (parts of) flu viruses for use in vaccines. Also, plants are increasingly used not just as base material for further processing, as explained above, but also for direct production of end products.

Not just whole organisms, but also specific processes within organisms are increasingly used in production on an industrial scale. Enzymes, our natural catalysts, and the reactions that they catalyze have been studied in great detail. Enzymes have been found that can efficiently synthesize tailored peptides that have widespread use in the health sector. Others break up large molecules into useful building blocks. Often such enzymatic reactions are used in combination with chemical process steps. Many of the bio-based production processes require less energy than their synthetic counterparts. These biological production methods thus simultaneously secure future chemicals and materials supply and contribute to overcoming the energy challenge.

WORK IN PROGRESS

Setting enzymes to work

Production of end products often requires many chemical process steps. Instead of a cascade of process steps, it is also possible for these to take place at the same time. An example of this kind is tandem catalysis, where two reaction steps are combined. The Integration of Biosynthesis and Organic Synthesis program in one of its projects investigates a process where a biocatalysis step, performed by enzymes, takes place parallel to a polymerization step. The knowledge assembled in that project is expected to be used in the production of advanced dyes for MRI purposes (e.g. vein imagery in hospitals).

Integration of Biosynthesis and Organic Synthesis, www.nwo.nl

The biological products developed in the bio-based economy increasingly replace synthetic ones. Polystyrene foam products in construction and packaging are being substituted by biofoams made from polylactic acid. Bioplastics are steadily replacing synthetic. These bio-based products provide us with new functionalities. They are biodegradable, for one. Novel biomaterials used to coat medical devices prevent the body from rejecting them when implanted. We have come to rely on many of these products in our everyday life. What is more, we have seen our economy thrive and our environment improve as we made the transition to a bio-based economy.

D. Sustaining the environment

The growing world population, its increasing prosperity and the attendant rise in demand for health, food, energy, chemicals and materials put a huge strain on the environment in 2020. Fortunately, the world has woken up to the challenge. Worldwide levels of CO_2 emissions have still increased by 16% since 2009, largely due to emerging nations, but Western countries at least have managed to curb their emissions of greenhouse gasses.[6] Energy savings and a move to renewable resources like sun, wind, but also biomass, have made this possible.

The bio-based economy has been key to this transition. CO_2 is a growth gas and the growth of new biomass binds greenhouse gasses emitted in the production of energy, chemicals and materials from biomass. This does not happen with oil or gas. Biological conversion processes using microorganisms or enzymes often require much less energy and produce less waste than their petroleum-based counterparts. Biological products are also typically biodegradable, reducing our waste problem.

WORK IN PROGRESS

Using genomics for sustainable animal breeding

The pan-European project Cutting Edge Genomics for Sustainable Animal Breeding, utilizes the latest techniques in genetic science to develop more economically and environmentally sustainable production systems for cattle, pigs and chickens. The aim is to provide a range of new breeding strategies to improve animal health and welfare, reduce chemical and energy inputs, minimize livestock waste and pollution and maximize food safety and quality. Genomic and epigenetic science will be used to generate new knowledge and apply it in practical breeding improvement strategies.

Cutting Edge Genomics for Sustainable Animal Breeding, www.sabre-eu.eu

WORK IN PROGRESS

Understanding ecosystems

The Ecogenomics Consortium discovers and characterizes new (un)culturable microorganisms in soil and water, with the aim to identify potential genetic markers using GEO and Phylochip technologies as a thermometer of soil health. The consortium also aims to unlock the vast genetic potential of microorganisms to discover and identify new microbial biofunctional compounds (antibiotics, biocatalysts, etc) using metagenomics approaches and HTP bio-screening. Finally, the consortium aims to explore the possibility of using whole genomic information of (in)vertebrates to develop eco-alternatives to animal-based safety assessment of chemicals. The Ecogenomics Consortium recently teamed up with B-Basic to enhance the development of biologically-based, ecologically balanced sustainable industrial chemistry (BE-Basic).

Ecogenomics Consortium, www.ecogenomics.nl

Of course biomass as an alternative to fossil resources is only beneficial to the environment if it is produced in a sustainable way. Sustainable agricultural production, for both food and non-food uses, has become an integral part of any strategy for safeguarding our environment. Cradle-to-cradle and lifecycle approaches have been applied on a large scale to land selection, the machinery used, the efficiency of harvesting procedures, the transportation of biomass to converters and bio-based products to end users, the use, recycling and bioremediation of these products, etc. Here again, the life sciences have played a critical role. Plant breeding has reduced the need for (synthetic) fertilizers and pesticides. Yield increases in both crop and meat production have made it possible to reduce the area used for food supply and have allowed fields to lay fallow and recover. Alternatives for meat, like algae, reduce pressure on the environment. Local pretreatment of biomass destined for biorefineries ensures that nutrients remain on the field and are returned to the soil. Greenhouse crops have been developed to grow under low energy conditions. The list goes on.

The life sciences have also provided us with a wealth of information on how to interact responsibly with our environment. We now better understand the complex ecosystems in which we live and the threats we pose to those ecosystems, like the risk of depleting the soil by “over-farming”, the effects of (ground) water pollution on our ecosystem and our effects on biodiversity. We know how to monitor and manage these risks. Electrochemically active bacteria that produce a current depending on the amount of a certain toxin in water are used as biosensors and enable real-time responses to safeguard sustainability in our daily activities.

Starting in 2009

This could be our future. Of course, the life sciences will have to deliver on their promise to make this future a reality, but it is plausible all the same. Perhaps this future is not as far away as we think. A life sciences legend, Craig Venter, the man behind the commercial sequencing of the human genome, has claimed he will make all discussions of food versus fuel and climate changes obsolete. His company, he says, will in the near future combine the processes for feedstock growth and fuel processing by designing organisms that inhale CO_2 and excrete sugars.[14] Wouldn’t you like to see that?

WORK IN PROGRESS

Finding alternatives to animal testing

One of the research lines of the Netherlands Toxicogenomics Centre focuses on alternatives to animal testing with regard to chemical carcinogenesis. At present, (putative) human carcinogens are identified via testing of compounds in two chronic two-year rodent bioassays, namely with rats and mice. These testing methods have severe ethical drawbacks in that they use numerous animals under stressful conditions, plus they have practical shortcomings and limited reliability. The aim is to identify a set of genomics effect markers that is able to test compounds for their carcinogenic potential and study the underlying molecular mechanisms of chemical carcinogenesis.

Netherlands Toxicogenomics Centre, www.toxicogenomics.nl

Quote from Rudy Rabbinge

“ **The dominating science in the societies of the 21st century**

The life sciences as a common denominator for many impact-oriented scientific domains is rightly seen as the dominating science in the societies of the 21st century. The increased insight, the better understanding and the tremendous perspectives enable innovations in the medical sciences, the chemical sciences and food and agro sciences.

Demarcation lines between and within the natural sciences are fading away and enable the application and use of physical, chemical concepts and principles in biology at various spatiotemporal scales. That will contribute to sustainable development and food security as technological and scientific innovations flourish. ”

Rudy Rabbinge, Chairman of the Council for Earth and Life Sciences of the Royal Netherlands Academy of Arts and Sciences (RAL-KNAW)

Unity

III A case study of public-private partnerships

Public-private partnerships (PPPs) in the Dutch life sciences are a good case study of the workings of collaborative innovation. We have chosen to focus on PPPs in the life sciences for three reasons. First, we believe that PPPs can play an important role in bringing about the future sketched in Chapter II. Life sciences innovation requires time, investment and competencies that are often beyond the reach of individual companies or universities. Especially in the translational stage, collaboration between public and private parties will prove essential. Second, we believe we should account for the investments that have been made in life sciences PPPs thus far. A lot of public money has been bet on their success. These PPPs are up-and-running and are starting to deliver results. Now is a good time to publicly examine what they have achieved at this point, how well they are working and what we can learn from our experiences to date. So we come to our third reason: life sciences are the ideal field to study innovation policy and the role of the PPPs as a policy instrument. They have both the scale (40% of all PPP investment in the Netherlands today) and the scope (different PPP types in different sectors) for such a study. No other field could. We firmly believe that the example of the life sciences will prove instructive for both government and other fields and we are happy to share our experiences.

There is no single definition of public-private partnership. What works in one instance may not in another. There are, however, three characteristics common to all PPPs: they are collaborative, precompetitive and they operate within true partnerships, as described in Chapter I. We will not attempt a formal or exclusive definition. Rather we will examine how they were, are and will be used and what may be learned from their example. We will start with their origins in fourth generation R&D or “open innovation” and Dutch innovation policy. Next, we will analyze life sciences PPPs in practice: their current incarnations in the various industry sectors impacted by the life sciences and the lessons learned in setting up and operating them. Last, we will look to their future and discuss priorities and recommendations. Any definition derived from this chapter will thus be pragmatic.

A. Origins of life sciences PPPs

The background – The evolution of R&D management
Today, we conduct fourth generation R&D. You may think that the way in which research and development activities are carried out has not changed much over time, but you would be wrong (Figure 4). R&D management properly started in the early 20th century at the end of the "second industrial revolution". Whereas the first industrial revolution (18th and early 19th century) revolved around textiles and steam, the second (late 19th century) centered on electricity and chemistry. We are currently in the middle of a third industrial revolution, where knowledge claims an ever more important place next to capital and labor as a means of production.

Our first approaches to R&D management can be called "systematic". Company labs were founded (BASF in 1867, GE in 1900, Bell Labs in 1925), assigned budgets and generally allowed to set their own priorities. Thus organized, R&D could be far removed from the actual business of the company. Many R&D organizations were, in effect, independent fiefdoms – more often than not engaged in basic research.

Second generation R&D emerged around the 1950s and was strongly influenced by technology development in World War II. It began to link R&D with other business functions and introduced a project orientation with cost sharing, matrix organizations and project planning to manage timelines, budgets and outcomes. This was the golden age of corporate R&D, with many famous scientists and Nobel laureates working at, for example, Bell Labs or Philips Natlab.

Around the 1980s, projects gave way to portfolios. In its third generation, R&D became an integral part of corporate strategy. Portfolio management techniques and technology roadmaps were widely used to manage a variety of research themes and projects and to target market demand. Outsourcing made a comeback, and customers and suppliers became

Systematic
- Emerged at the end of the Industrial Revolution
- First corporate R&D laboratories
- Centralized, budget-based R&D function
- Scientific staff with free rein
- Limited long-term alignment and evaluation
- Strong technology push

Projects
- Heavily influenced by military technology innovation during WWII
- Involvement of business functions as R&D's customer
- Introduction of project planning with alignment, financing and steering between business units and R&D
- Strong focus on results

Portfolios
- Technology management in the context of corporate strategy
- Use of portfolio management techniques and technology roadmaps to chart explicit market demand
- Increasing involvement of suppliers in R&D execution – under responsibility and director of the company
- Industry abandons basic research

Open networks
- Emphasis on learning and interaction with the market to fulfill both explicit and latent market demand
- Increasing use of venturing to commercialize technology
- Make-or-buy question central to defining core competences and transferring R&D execution and responsibility outside the company

Figure 4: The evolvement of R&D

Additional reading: P.A. Roussel et al, *Third Generation R&D* (1991); W. L. Miller et al, *Fourth Generation R&D* (1999) increasingly involved. Industrial labs gradually abandoned basic research, leading to renewed interest from captains of industry in what was happening in academia.

This increasingly open model of R&D is now making way for the fourth generation of innovation management. Beyond the researcher, the project and the company, the fourth generation is about networks. Increasingly, companies are working together in (precompetitive) R&D in which they also involve the customer. Companies realize that knowledge does not necessarily have to be developed in-house. “Open innovation” and strategic “make-or-buy” decisions take the place of resource allocation within R&D departments. We are also seeing the rise of the virtual enterprise that coordinates various business functions to serve a market, and just as easily uses alliances or supplier-partners as its own organization to perform these functions. Entrepreneurship is becoming key within organizations as well as in the market, and venturing is gaining ground as a means to develop and commercialize new technologies.

The problem – The innovation paradox
In this fourth generation paradigm, even more than before, an innovation coincides with its use. Only when a new product, process or service is actually used by a person or organization is value created. A patient diagnosed early and following a regimen of diet, exercise and targeted medication lives a longer, healthier and more productive life. A food company extracting edible oils from algae rather than palms or soy beans diversifies its supplier base with a (more) sustainable alternative. A chemical company that makes succinic acid by (biological) fermentation rather than (chemical) synthesis reduces energy costs and CO_2 emissions and may even command a higher price for the green products it enables. A farmer planting a hardier crop in a barren region can look forward to a (more) bountiful harvest. To use an innovation is to realize its (social) value. To deliver it to the user is to reap the economic rewards.

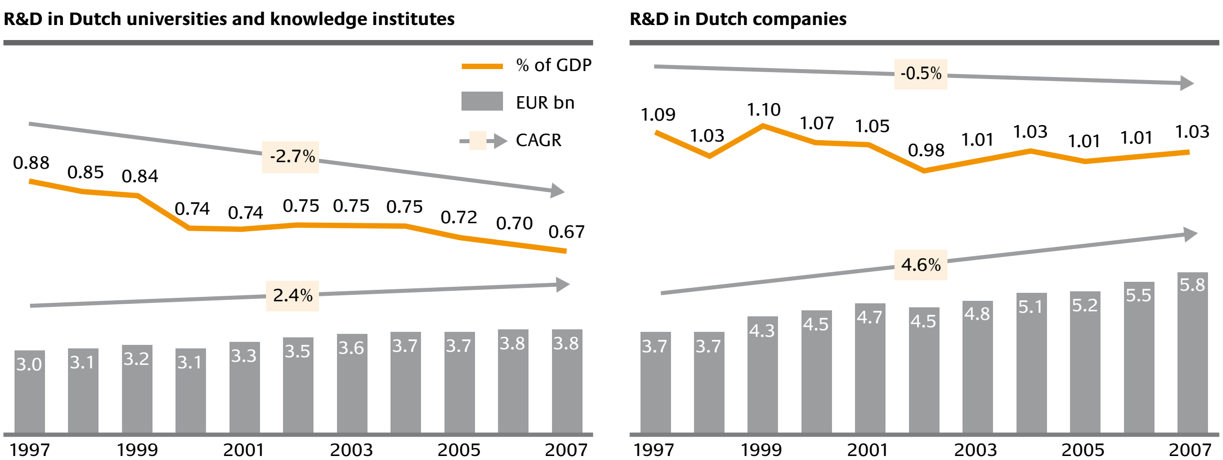


Figure 5: R&D investments in the Netherlands
NOTE: R&D in PPPs is incorporated in these figures. Source: Statistics Netherlands (CBS), Statline Databank

“ Perspective from Brussels...

In Europe, the Netherlands have an excellent reputation regarding research in the field of the life sciences. The participation of Dutch research institutes and related organizations in the different consortia that cooperate under the 6th and 7th Framework Programmes of the European Union is impressive. Particularly in the area of agro-food, Dutch researchers and their organizations are considered to be amongst the best in Europe. The Dutch reputation in this field is confirmed by a high visibility in the quotation indexes. An important bottleneck is, however, the weak link between academia and industry. The Netherlands life sciences scene is just not good enough at transferring the results of research into marketable products. This situation needs to be addressed to ensure that the investments in research pay off and the research system becomes sustainable. A second more general Dutch problem is the underinvestment in research both by the private as well as the public sectors. The fact that the Netherlands remain considerably below the European average in the field of research spending will have negative consequences for the Dutch economy in the medium and long term. A knowledge economy can only be created by investing in it! ”

Robert-Jan Smits, Director DG Research, European Commission

Quote from Robert-Jan Smits

Simply put: invention is nice, but innovation is more. Historically, the Netherlands (as well as Europe) has been good at the former and poor at the latter. In articles per researcher and (scientific) impact per article, we are a world leader,[7] but in innovation we lag behind other Western countries – measured for example as the share of new or improved products in total industrial turnover.[15] This “innovation paradox” has haunted us since the 1980s. There has been limited collaboration between Dutch companies and universities.[7] Spin-offs have been few, and those which do exist have grown slowly.[16] R&D has hardly increased, staying at a low 1.7% of GDP for years (Figure 5) despite ambitions to grow to 3% of GDP as part of a European goal to become the leading knowledge economy.[7,11,17] As recently as February 2009, the annual KIA Photo (*Kennisinvesteringsagenda foto*) showed the Netherlands last in a group of “innovation followers”: at the EU average, outside the top 10 and barely ahead of the pack of Southern and Central and Eastern European countries catching up.[8] Even our excellent knowledge base is in danger of eroding, with public spending hovering at an average level and decreasing as a percentage of GDP, and with other countries rapidly catching up.[7,11]

In private R&D spending, we have been falling behind for years. Even if we correct for the fact that we have a relatively large services sector and that our industry is particularly strong in sectors where R&D intensity is naturally low, such as agriculture and food, the absence of growth relative to GDP (where other countries are clearly showing such growth) is troubling.[7,11] We have a well educated, large pool of science and technology graduates, but we employ few of them in translating our knowledge into products, processes and services.[7,15]

The first stage of our rocket is among the best in the world, but we do not seem to reach the stars. Clearly, that has to change.

A solution – The public-private partnership
The Netherlands is looking to public-private partnerships for part of the solution. The idea is simple: if our excellent knowledge base is not being exploited by industry, let us bring the two together. A recent study by the Innovation Platform identified insufficient cooperation and networking between public and private stakeholders as one of the main barriers for utilizing our knowledge base.[18]

The new paradigm of open innovation is about co-creation. The best way to transfer knowledge is to work together to translate it into practical applications. PPPs were set up, first, to bridge the gap between public and private parties and to induce collaboration; second, to pool knowledge, competencies and infrastructure; and ultimately, to jointly translate this knowledge into concrete applications that are practical and valuable to people and markets. Currently, about 10% of the EUR 10 billion spent annually on public and private R&D in the Netherlands takes place through PPPs.[9,11]

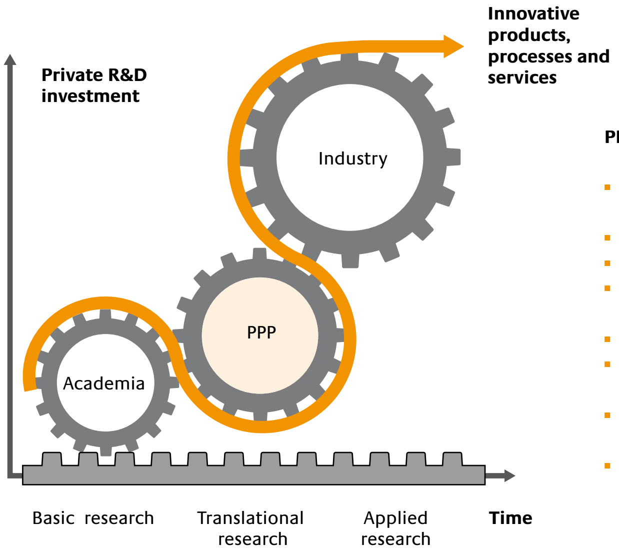
PPPs do something else in conducting what has come to be called "translational" research. They act as a cog in a larger innovation system – conveying momentum from one part to the other. Momentum is greatest if push from technology and pull from social and market demand are geared to each other.

Indeed, PPPs function as a flywheel: multiplying public investment by mobilizing (much larger) private spending. Academia is typically input-funded by the government. It has to be. No one knows what ideas may spring from the brain of a scientist pursuing a line of research out of curiosity. Some of those ideas will be the basis for as yet undreamed-off innovations that make our lives better and increase our prosperity. Industry, however, is privately funded. That is only fair. It puts up the money to reap the rewards. The scale of industrial funding is also much larger than that of academia. An industrial plant can cost hundreds of millions to build. Industry places big bets; academia places innumerable small bets. PPPs connect the two. They take academia's small bets that have paid off (so-far), build on them and, if successful, pass them on to industry for large-scale investment in development, marketing and production. The PPP connection brings academic and industry research agendas in line with each other and with socio-economic priorities – which is why government is also a partner.

All this is a risky undertaking and the funding of PPPs reflects this. Academia and industry typically put up half of the funding for a PPP, 25% each. Government matches this investment in a base formula that has come to be referred to as 1:1:2.

The matching approach chosen by the government is a clever one. Government resists the urge to steer matters beyond its comprehension or control. Instead, it applies the simple logic that if an academic partner sees scientific merit and an industrial partner commercial promise, and both are prepared to invest in joint translational research, then that justifies government help to get them started. The matching approach has huge advantages. For one, it creates a kind of natural selection. Academia and industry must find each other and agree to work together on a certain topic. This means that our strongest and most promising fields become the focus of our efforts. The matching approach also builds mass, mobilizing resources from academia, industry and government and concentrating these on a specific field. Crucially, "focus and mass" allows the government to prioritize areas of particular value to society (e.g. anti-cancer strategies, greenhouse gas reduction, and food safety) without dictating how scientists and entrepreneurs deliver these benefits. This crafting of "focus and mass" is another important function of the PPP.[17]

This then is what a PPP is meant to do (see Figure 6). Each partner within a PPP has its own reasons for joining. For industry, the multiplication factor has obvious appeal: four



PPPs are meant to

- Bridge the gap between academia and industry, induce collaboration and transfer knowledge
- Pool knowledge and resources
- Catalyze innovation through translational research
- Transmit momentum and gear social/market pull to technology push
- Multiply (private) investment
- Align academic and industry research agendas with social priorities and with each other
- Concentrate focus and mass on areas of social priority in which industry and academia are strong
- Increase social and economic returns of basic research

Figure 6: What PPPs are meant to do

times the R&D for the same Euro. Add to that the immediate and extended networks available, the pooling of knowledge and resources and the ability to scout out areas a company would not otherwise explore on its own (too risky, too big, too costly, too distant). For a relatively small investment, a company can monitor and investigate topics with potential long-term strategic relevance, and the PPP provides the groundwork for programs that are of immediate interest. Connecting with academia has become especially important since most companies no longer conduct basic research themselves. Last, but by no means least, finding and hiring the right people is one of the biggest challenges for innovative companies today – PPPs provide access to a large pool of well-trained professionals. This all makes PPPs gateways to Dutch sectors and exerting a force that "pulls" foreign companies.

Academia reaps similar benefits from PPPs: networking, access to outside knowledge and resources and, of course, more funding. PPPs are a way for academic groups to create value from basic research effort. For government, PPPs are a means to influence direction and build momentum for social priorities. The focus and mass built by PPPs also increases the visibility of their work, attracting the attention and activities of international companies and (public-private) consortia.

It should, however, be understood that PPPs are neither the only nor necessarily the right or the best instrument for every instance or phase of innovation. PPPs, and cooperation in general, should never be goals in and of themselves. Instead, they are instruments used to reach a certain goal. Cooperation has downsides, such as the added complexity that may increase costs, as well as upsides; these should be weighed for each case individually. PPPs cannot substitute basic research. In many cases, bilateral contract research agreements between industry and academia will be preferable: the university can be (better) compensated, the company can receive exclusive rights. In joining a PPP, you exchange some freedom and exclusivity for the benefits that matching brings. When you need greater freedom or exclusivity as a researcher or entrepreneur, you must look to other instruments (that should also be available) – such as input funding, direct or through The Netherlands Organization for Scientific Research (NWO), innovation credit or venture capital. Like any instrument, PPPs will not work or will not work well if you seek to use them for purposes for which they were never intended.

The catalyst – Dutch innovation policy

The policy instruments of government have changed with each generation of R&D and innovation management. In first generation R&D, government research budgets were set at a percentage of total spending, to be deployed more or less at the discretion of receivers. It was during this period when TNO and Large Technology Institutes (GTIs) were founded. Second generation R&D ("projects") introduced more market orientation and saw direct support for research at individual companies. Funding organizations such as the Netherlands Organization for Scientific Research (NWO) were born. Instruments like INSTIR (later WBSO) gave tax breaks to corporate research. Trip was the first Minister for Science. In the 1980s and '90s, with the advent of third generation R&D, applied research was transferred from what is now called the Ministry of Education, Culture and Science to Economic Affairs. The Foundation for Applied Sciences (STW) was set up. Innovation-oriented Research Programs (IOPs) were introduced to strengthen academic research in areas where a private sector innovation need was perceived. Such programs improved ties between academia and companies and fostered collaboration between public and private parties.

In 1997, as we made the transition to fourth generation R&D, the Minister of Economic Affairs, Hans Wijers, took the initiative to set up a number of topic-specific, large-scale partnerships between academia and industry. These Leading Technology Institutes ("Technologische Topinstituten", or TTIs) pioneered public-private partnership. Out of a total of 19 proposals, four were selected: the Dutch Polymer Institute (DPI), the Netherlands Institute for Metals Research (NIMR), the Telematics Institute and the Wageningen Centre for Food Science (WCFS), now the Top Institute Food & Nutrition. These institutes addressed the innovation paradox and they created focus and mass on their respective topics. In 2004, the OECD held up the TTIs to its members as a best-practice example, deserving of emulation.[19] Leading thinkers like Michael Porter also applauded the idea. His theory of clusters, in essence, is PPPs taken to the next level. We will come back to that later in this chapter, when discussing future directions.

In 2002, based on the advice of the Wijffels Committee, another important program for public-private partnership was started. The Netherlands Genomics Initiative (NGI) aimed to create a world-class genomics infrastructure in the Netherlands and to set up a number of successful public-private "Genomics Centers". After a successful first phase (2002-2007) with a budget of about EUR 550 m, government, academic and industry partners mobilized some EUR 500 million for the period 2008-2012. 2002 also saw the inception of Advanced Catalytic Technologies for Sustainability (ACTS). Under it, about EUR 100 million from government, industry and academia has been mobilized for precompetitive research in chemistry and chemical technology between 2002 and 2012.

Public revenues from Dutch natural gas fields have been reserved for infrastructure investments in a Fund for the Improvement of Economic Structure (FES) since the mid-90s. In 2004, about EUR 800 million of FES funds were invested in "knowledge infrastructure", specifically to increase cooperation between public and private parties. This so-called BSIK impulse resulted in 37 public-private consortia with a relatively small private participation compared to the TTIs. It followed on two smaller calls in 1994 and 1998, of EUR 113 and EUR 211 million respectively, called ICES/KIS. Most BSIK consortia set up in 2004 are still in operation and will reach the end of their funding in the coming year. They have already passed their mid-term review, in which the *Commissie van Wijzen* (which evaluates funding proposals) concluded that BSIK has genuinely strengthened the knowledge infrastructure and that PPPs – especially in the life sciences – are a valuable instrument.[20]

Since 2004, FES impulse funding for PPPs has become an almost annual event. The scale of the projects returned to and then exceeded that of the original TTIs. First, in 2005, was TI Pharma (EUR 260 million), followed by the Center for Translational Molecular Medicine (CTMM, EUR 400 million), TTI Green Genetics (EUR 40 million), and the BioMedical Materials program (BMM, EUR 90 m). 2007 saw the first and last edition of the so-called SmartMix program that awarded nearly EUR 100 million to seven public-private partnerships. Recently, European policy has started to develop along similar, public-private lines. We will discuss this international dimension later in this chapter, when we turn to future directions.

In the open networks innovation paradigm, a crucial place is reserved for small and medium sized enterprises (SMEs) and especially for new, start-up or spin-off ventures. Technology and its application are not enough. To make the leap from invention to innovation you need an entrepreneur with the right business model to produce, market and deliver a new or improved product, process or service to paying users. The term "valorization" was coined to denote this realization of an innovation's social and economic value.

The government has taken careful note of the importance of SMEs.[17] In 2000, for example, it set up the BioPartner program to provide infrastructure and funding for starting entrepreneurs in the life sciences. After its (much deplored) discontinuation in 2004, life sciences entrepreneurs could apply for the more general TechnoPartner program. In 2004, the STW valorization grant was introduced to stimulate commercial applications of research results of academic institutes through the creation of start-ups. Inspired by the USA where it has been very successful, the government also introduced the Small Business Innovation Research program (SBIR) in 2006. In it, the government subcontracts socially-relevant R&D to SMEs. NGI has helped entrepreneurs since 2008 with pre-seed grants for the first steps in setting up new business in genomics (e.g. for additional research needed for proof of concept or to write a business plan).

More and more, the sectors are organizing themselves. With support from the government, they have initiated broad innovation programs such as Food & Nutrition Delta, Life Sciences & Health (LSH) and the "Innovatietraject Chemie" (innovation route chemistry). These programs are typically directed at the valorization of results from PPPs by stimulating start-ups and spin-offs and by organizing sector representation. The sectors formed coordinating bodies, such as the Regiegroep Chemie and the High Profile Group (LSH).

Focus and mass, furthermore, became the creed of the Innovation Platform established in 2003. Chaired by the Prime Minister, the Innovation Platform brought together leaders from industry, academia and government to reflect on and take or support initiatives to enhance the Dutch knowledge and innovation system. The Innovation Platform championed *Sleutelgebieden* ("key areas"), fields that the Netherlands should focus on and achieve excellence in. Understanding that winners in innovation can neither be picked nor created by government, the Innovation Platform chose to "back winners" – throwing its weight behind emerging successes. In 2006, the Innovation Platform presented the *Kennisinvesteringsagenda* (KIA) that lays out a route towards becoming a real knowledge economy.[21] Progress is measured annually.[8] This book describes how the life sciences and their PPPs contribute.

After this period of generation, when these and several other policy instruments let "a thousand blossoms bloom", the FES call of 2009 concentrated on converging and tightening focus around the *Sleutelgebieden*. Sectors were invited to come up with a single, integrated plan to selectively continue some and end other PPPs, reinforcing the self-organizing principle that had already gained much ground within the sectors. This book is a powerful example, bringing together people from all corners of the life sciences field in a coordinated effort. The life sciences field, certainly, is unifying in diversity – proving that the Netherlands is on the right track.

Interview with Gerda Verburg

“ **1. What do the life sciences mean to you?**

Considering the increase of applications of biotechnology, life sciences are vital to the bio-based economy. I would describe the bio-based economy as a green industrial revolution: a shift in thought and action, from fossil to green. Green resources are renewable, available and less of a burden to the environment and public health. Further, green resources are biodegradable and the mobilization of these resources will generate new economic activities. In order to achieve this transition there is a need for innovation, for which we must all join efforts. Moreover, we can’t exclude a single technology that delivers positive results. The life sciences are of great importance, especially in terms of so-called “white biotechnology” – the technology tailored to the chemical sector. The application of industrial biotechnology within a safe environment is essential in order to maximize the use of biomass. For the development of the bio-based economy and the life sciences we need the contribution and commitment of all parties.

2. What do you think is the biggest challenge for the government in this respect?

I consider it a challenging opportunity to build this complex system of innovation, together with all stakeholders concerned, in a responsible manner. This means indentifying the appropriate role of the government at different phases during this transition. The regulatory EU framework regarding a level playing field is one of these aspects, which requires strong international cooperation. Further, there is also a substantial need for coordination and focus within research programs, in which the government invests in promising economic areas such as in the bio-based economy. Finally, it is necessary, together with social stakeholders, to make the facets of sustainability more tangible. All of this resulting in a solid position for the Netherlands within the bio-based economy.

3. What would you like to say to the field?

A strong bio-based economy also means that sectors need to let go of their traditional ways of thinking. I still sense some sectors holding back. I would very much like to see the agro, chemical and paper industries take steps towards gaining better insight into what they can do for each other. Therefore, I very much welcome this life sciences vision, which offers insight into the commitment and interests of the various sectors with regard to biotechnology. It is now the responsibility of the sectors to take concrete steps forward. ”

Gerda Verburg, Minister of Agriculture, Nature and Food Quality

B. Practice of life sciences PPPs

Any association, virtual or physical, loose affiliation or tight alliance, that brings together public and private parties to collaborate in true, precompetitive partnership can be considered a PPP. We are not interested in marking off boundaries, admitting some and excluding others. In truth, we are not as much interested in what a PPP is but in what it does. It must fulfill a concrete and valuable function in the innovation process, typically in (but not limited to) the translational stage between knowledge generation and market delivery. They should have a “shape-shifting” quality, responding to changing circumstances and priorities and adapting or even dissolving as a consequence. We would argue that when discussions turn to form and when PPPs become (too) institutionalized or a goal in and of themselves, they have outlived their purpose. They are temporary alliances, with function and content – not form – the basis for continuity. If they are not flexible, we risk locking-up valuable resources (researchers, capital, IP) in a fixed distribution over a variety of approaches, some of which may be going nowhere, rather than letting those resources flow naturally towards those ideas that do look to succeed.

Taxonomy – four basic types

There are at least four basic types of PPPs. There may be and probably are more. We can certainly discern hybrids (such as NGI that combines policy and execution under its aegis). However, these four basic types help explain the various functions of PPPs:

1. **Programmatic** – a consortium mobilized around a theme and a research program that is executed by selected projects. Projects are chosen through a series of calls in which public-private consortia apply for project funding. Leading Technology Institutes (TTIs) are the dominant incarnation of this type. Partners within a project typically contribute in the 1:1:2 formula, with academia and industry contributing equally and the government matching their investments. The government approves the program and procedures, not the actual project portfolio. Project selection and execution is left to the public-private partnership.
2. **Executory** – a consortium that executes a program through a number of pre-defined projects. The BSIK consortia are prime examples. Executory PPPs are usually smaller than the programmatic ones and have different ratios of public and private contributions – often more academia, less industry – that reflect the often earlier, more fundamental stage of research on which they focus. Government, in funding them, approves not only the program but its constituent projects and consortia at the outset.
3. **Enabling** – a consortium set up to support innovation (and PPPs) in specific areas, typically aimed at enabling technologies, but also at social issues, valorization and human capital. Such PPPs include NGI’s technology centers. Private contributions are often small, the academic component large.
4. **Infrastructural** – a consortium that establishes and/or maintains key infrastructure for use in innovation projects (e.g. within PPPs). Life sciences examples are biobanks such as the Parelsnoer Initiative and LifeLines and plans to set up an open-innovation fermentation plant for pilot projects. Such infrastructure can be a private, industrial facility or a public asset like the Parelsnoer Initiative, which is owned by university medical centers. Its public-private character can be found in the consortium that set it up and/or in its accessibility to public and private parties (if under strict conditions, e.g. privacy) as a resource for (joint) research.

Incarnations – a rich landscape that spans sectors

We limit ourselves here to Dutch life sciences PPPs – although we think our observations have broader application. The Dutch life sciences are both large and representative enough of (Dutch) PPPs to draw meaningful

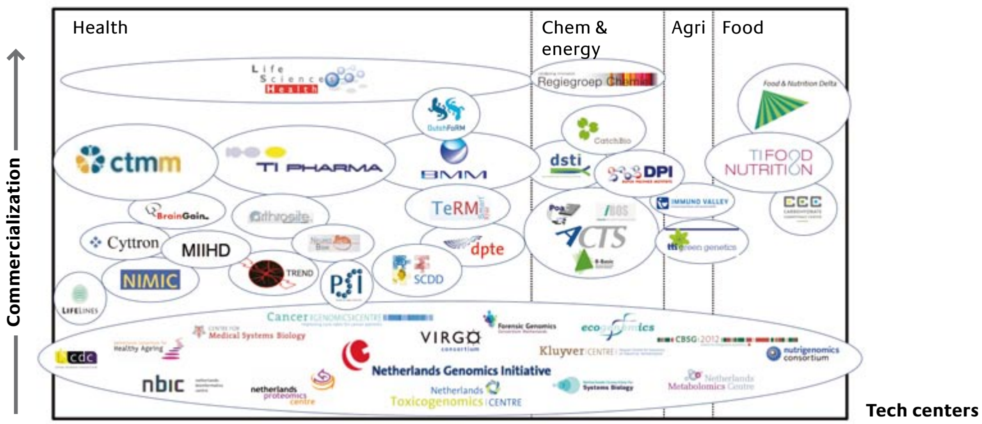


Figure 7: The Dutch PPP landscape of the life sciences – the width per sector indicates the relative PPP investment

conclusions (Figure 7). Between 2003 to 2007, about EUR 5 billion was committed to PPPs in the Netherlands. Some 40% of it, EUR 2 billion, falls within four sectors impacted by the life sciences: food, health, agriculture and chemicals & energy.[9]

FOOD

The food sector has a mature PPP setup that goes back to the Wageningen Center for Food Sciences, one of the original TTIs. Today, as TI Food & Nutrition (TIFN), it aims to develop innovative products and technologies for safe, tasty and healthy foods. The TI Food & Nutrition has been very successful in forging strong ties between academia and industry. It currently combines the strengths of five universities and knowledge institutes, and six internationally leading companies in the food sector. In addition to Dutch companies, in the next phase of TIFN (2011-2014) several international food and nutrition companies will participate, including large players from Europe and the US.

With the valorization activities of Food & Nutrition Delta, TIFN forms the innovation program Food & Nutrition Delta. Since the Food & Nutrition Delta (FND) program started in 2006, it has drawn many companies, especially SMEs, to participate in innovation projects. Several of the SMEs that joined these initiatives had not participated in innovation projects before. Now, in 2009, these projects have generated substantial results, both in terms of novel products and turnover as well as in new jobs. An inquiry into 25 of the over 200 participating companies revealed that these 25 companies generated an additional EUR 126 m in turnover and 248 new jobs, directly attributable to the FND projects.

The public-private Nutrigenomics Consortium that studies the effects of food components on human physiology was part of NGI, but has been clustered with TI Food & Nutrition in the 2009 FES call. Recently, the Carbohydrate Competence Center was added as a regional initiative in the north of the Netherlands. The financial commitment through these PPPs is about EUR 300 m over a five-year period. The 2009 FES call also saw more integration between the agriculture and food sectors, with both sectors submitting plans attuned to each other.

HEALTH

In the health sector, universities, university medical centers, companies and PPPs apply the life sciences to the discovery, development, testing, production and delivery of healthcare solutions like (bio)pharmaceuticals, diagnostics and medical devices. About EUR 1.2 billion has been committed through a large number of BSIK partnerships, two SmartMix

> **A long-term vision is essential to guide innovations**
> I welcome this life sciences vision. Healthcare faces many challenges in quality, accessibility and cost containment. A long-term vision supported by all stakeholders is essential to guiding the innovations that will help us overcome these challenges – together. Our universities and university medical centers are excellent. To translate their research into medical applications and deliver these to patients they must work together with small and large companies, regulators and others. This does not just happen by itself. It takes effort and a real commitment to each other and the common cause. I believe that public-private partnerships are important enablers of such collaboration.
>
> The Dutch government, together with the life sciences and health sector, will continue to stimulate the translation of basic science into medical innovations. If we do not do this, we leave this knowledge unused and miss the opportunity to improve the life of patients, keep our population healthy and, also, strengthen our knowledge economy. Any research group, entrepreneur or consortium that is willing and able to help us seize this opportunity will find a partner in us. ”
>
> **Ab Klink, Minister of Health, Welfare and Sport**

Quote from Ab Klink

consortia, programs that are part of NGI, and three large TTIs. The TTIs are emerging as focal points for three central themes: CTMM for diagnosis, TI Pharma for drugs and BMM for medical devices, with regenerative medicine on the horizon. These themes are supported by a cluster of enabling technology and infrastructure that is emerging around NGI's technology centers and initiatives like Parelsnoer.

For all its diversity, the health sector is exhibiting strong self-organization qualities. FES 2009 demonstrated the consolidation taking place in the sector, with focus and mass centering on the three central themes. For example, the BSIK programs Stem Cells in Development and Disease and the Dutch Platform for Tissue Engineering are merging to form the Netherlands Initiative for Regenerative Medicine with close ties to BMM. Successful BSIK consortia in the early stages of innovation (with limited private involvement) progressed to more application-oriented research, and on average doubled their private contributions. The 2009 FES call also saw an increase in PPPs' use of the technology centers of NGI as partners in innovation.

Further signs of this self-organization can be seen in the Life Sciences & Health innovation program that, with the government, was set up to stimulate valorization and sector-wide collaboration and to coordinate and represent the sector. The sector has also organized a “High Profile Group” of authoritative people from academia, industry and government to informally ponder and provide guidance on future directions. Finally, the three large TTIs are continuously building their combined partnership, having issued a joint call on "image guided targeted drug delivery" in the summer of 2009.

Through PPPs, the health sector has brought together an unprecedented number of public and private parties. For example, the three large TTIs together combine 172 partners that include 102 SMEs, 36 large (multinational) companies, research groups from all UMCs and all but one Dutch university, eight knowledge institutes, two foreign universities, two charities, two interest organizations and the Dutch regulator.

CHEMICALS & ENERGY

The life sciences are being exploited as enabling technologies in many PPPs in the chemicals & energy sector. Public-private collaboration is largely organized through hybrid programs like NGI and ACTS, producing programmatic, executory and enabling PPPs. Research is predominantly focused on industrial (chemical) processes, often involving biotechnology. B-Basic and IBOS are examples. So are CatchBio, which develops chemical conversion processes for biomass to energy and chemicals, and NGI's Kluyver Centre, studying microorganisms for use in industrial fermentation. But DSTI (separation technology) and DPI (polymers), one of the original TTIs, also have a life sciences component. All in all, about EUR 300 m over a period of about five years has been committed to life sciences related activities in PPPs in chemicals & energy. As a result, many strong players in the chemicals & energy sector are now innovating together. For example, the Kluyver Centre connects six universities and two knowledge institutes with ten companies that are part of the Kluyver Centre's Industrial Platform. And the B-Basic program combines the strengths of six universities and knowledge institutes, and five industrial partners.

Chemicals & energy have been combined as a *Sleutelgebied*. Together, chemicals & energy drives the transition towards a so-called bio-based economy. Such an economy is marked by the production of energy, chemicals and materials from biomass instead of from fossil resources like oil and coal, by the replacement or combination of traditional chemical or other industrial processes with biological processes like fermentation, and by the replacement of synthetic products with biological products like bio-plastics. In addition to (and combined with) separation, process and catalytic technologies, the life sciences will play a vital role in enabling this bio-based economy. The new BE-Basic program ("Bio-based Ecologically Balanced Sustainable Industrial Chemistry"), submitted in the 2009 FES call, reflects this evolving focus and concentrates mass by consolidating the preceding B-Basic program and NGI's Ecogenomics consortium.

The innovation infrastructure in the chemicals & energy sector has been well organized for some time. Regiegroep Chemie provides sector-wide governance. It has written a business plan for the sector that government has taken as the basis for an innovation program.[22] The life sciences and life sciences PPPs form a (growing) part of this larger whole.

AGRICULTURE

In the agriculture sector, in five years about EUR 150 m has been committed to PPPs in the life sciences, many with a focus on plant breeding. Public and private players come together in TTI Green Genetics, which aims to develop and apply genetic information for the creation of crops with improved performance and quality. 93 companies and seven knowledge institutes participate in this PPP. The Centre for BioSystems Genomics within NGI develops expertise on plant genomics. A new EUR 40 m PPP is being set up to explore and exploit photosynthesis, bringing together six Dutch universities and 30 partners from industry. These partnerships build on and strengthen the leading knowledge and technology position in plant breeding of the Netherlands.

Another important topic in the agriculture sector is animal health. Immuno Valley is a PPP for research on infectious diseases in humans and animals and the valorization of this knowledge. It is funded by the "Pieken in de Delta" program and has a strong link to the health sector. The 30-partner consortium comprises universities and university medical centers, non-governmental knowledge institutes, local and regional governments, small biotech and large (multinational) Pharma. The PPP works from a regional focus with an international outlook.

Enabling technology in the life sciences
All four sectors are supported and linked by strong, enabling PPPs. Most are hosted by NGI: the Netherlands Bioinformatics, Proteomics, Metabolomics and Systems Biology Centres. The increasing importance of enabling technologies and their integration is illustrated by two initiatives for systems biology. Over five years, NGI has committed about EUR 150 million to these technology centers.

Life sciences technologies not only enable other PPPs to make advances in their efforts, but also contribute to society in their own right. Safety is a good example. NGI's Toxicogenomics Centre (NTC) is devoted to identifying the hazards of chemical compounds and their risks to humans. Together with TI Pharma, NTC participates in a program for assuring safety without animal testing (ASAT). The Forensic Genomics Consortium Netherlands (FGCN) focuses on safety in another sense: the use of genomics technology to analyze DNA traces in crime scenes.

NGI has also initiated research into other social aspects of genomics science and technologies in an independent center with no private involvement. Together with the NGI centers CMSB (medical systems biology), CGC (cancer genomics), Kluyver Centre (industrial biotechnology) and CBSG (biosystems genomics), this Centre for Society and Genomics runs a large social program that includes research, discussion and dialogue exercises, communication and education. The program seeks interaction with the public, scientists, policy makers and decision makers in industry to assess and address the social effects of life sciences innovations in an early stage.

Analyzing DNA traces in crime scenes
The Forensic Genomics Consortium Netherlands (FGCN) has the ambitious aim to revolutionize routine forensic DNA research. From any biological crime scene sample it should be possible to not only (1) match a DNA profile with possible donors (the only currently possible analytical result), but also to identity (2) the cellular origin of the sample, (3) the relative age of the sample and (4) the geographic origin of the donor, and (5) to reconstruct visible characteristics of the donor. And all this from as little as a few cells and within 24-48 hours. For this, the FGCN partners (the Netherlands Forensic Institute (NFI), the Forensic Laboratory for DNA Research of Leiden University Medical Center and the Department for Forensic Molecular Biology of the Erasmus Medical Centre) have defined a realistic research strategy based on the latest available technological genomics research tools. Once implemented, the new diagnostic possibilities will assist in solving a substantially higher number of serious crimes. In this way, the consortium significantly impacts the criminal justice system and contributes to a safer society. Our recent development of a robust method to predict the eye color of a person only based on DNA should be seen as a first step in this direction.

Forensic Genomics Consortium Netherlands,
www.genomics.nl

PPPs from an international perspective
Other countries endorse the public-private partnership approach to innovation that the Netherlands has pioneered. In 1997, the first generation of Leading Technology Institutes was established in the Netherlands, and in 2004 these were hailed as best practice examples in an interna-

Measuring returns of PPPs

So what do you get for investing in a PPP? Well, much of the value of a PPP cannot be measured easily. How do you quantify the potential for future R&D investments, the value of networks created or the value of people trained? Also, it is simply too early for a concrete review of the results of PPPs. The majority of funding committed to PPPs in the Netherlands is in projects that are currently running. And even once these projects are done, it will take years before we see the commercial products that PPP projects contributed to. There is value, however, that can be measured now. Let's consider the following examples: the first phase of NGI,[23] and the 2008 results of TI Food and Nutrition.[24]

NGI 2003-2007; total PPP investment EUR 482.2 m		
	Total	**Per EUR 1 m**
Full time job years	2436	5
Scientific articles	4407	9
Ph.D. thesis	251	0.5
Patent applications	161	0.33
Licenses	67	0.14
Spin-offs	24	0.06
Clinical applications	27	0.4
Non-scientific publications	639	1.3

TI Food and Nutrition 2008; total investment EUR 26.7 m		
	Total	**Per EUR 1 m**
Full time job years	206	8
Scientific articles	126	5
Ph.D. thesis	18	0.7
Patent applications	8	0.3
Licenses*	3	0.12

*Data from the year 2007

tional review by the OECD.[19] Others are following the Netherlands' example. Denmark, for instance, is setting up an institute for pharmaceutical research modeled after TI Pharma. Pan-European partnerships being set up under the European Technology Initiative bear close resemblance to Dutch PPPs.[25]

In the United Kingdom and Germany systematic innovation policies have been developed of which PPPs form an integral part. Germany initiated the Pharmaceutical Initiative in 2007 to give new impetus to its biotechnology and pharmaceuticals industries. The largest part of its annual budget of EUR 160 million is assigned to research in public-private collaboration. Parts of the program are focused on more basic research, other parts on the take-up of technologies by companies.[26] In the UK, this integral approach is being implemented industry-wide. Many collaborations between public and private partners have arisen in recent years that focus on various stages of the innovation value chain. CASE Awards and vouchers foster exploratory research executed by consortia of universities and SMEs.[27] Since 2004, the British government and industry have together invested over EUR 1.2 billion in collaborative research through so-called "Innovation Platforms" that address policy, social and/or market challenges.[28] This demand-driven approach is organized in the form of competitions (similar to calls for

Dr. George Poste about Dutch PPPs
The keynote speaker at the TI Pharma Spring Meeting 2009 was George Poste. During this meeting, a journalist asked him, "What do you think about the Dutch approach?" referring to the three TTIs that have been set up in the health sector in recent years. He answered: "I think it is excellent. I think it is almost unique in the sense of both the scale of investments in terms of the numbers of Euros being invested and the engagement of industry in this which I think is absolutely essential. So I think the three initiatives in molecular medicine, materials and the Top Institute Pharma approach are not only something that I applaud the government for their action but I think other countries would do well to look at it."

George Poste is Chief Scientist Complex Adaptive Systems Initiative (CASI) at Arizona State University (ASU), former Director of the Biodesign Institute at ASU and former Chief Science and Technology Officer and President, R&D of SmithKline Beecham. In addition, he serves as Chief Executive of the consulting company Health Technology Networks, and he is Chairman of Orchid Biosciences and serves on the Board of Directors of Monsanto, Exelixis and Caris Dx.

Source: www.tipharma.com

projects in Dutch programmatic PPPs), such as the current call to develop low-carbon cars. To support these innovation partnerships, about 25 Knowledge Transfer Networks have been set up. These help partners find each other and find funding sources; they also provide strategic information on the sector and innovation.[29] Similar activities are arising in Dutch PPPs and innovation programs like Life Sciences & Health.

Since 2005, French innovation strategy has strongly focused on so-called "Competitive Clusters". As a large country, France tries to create local regions where public and private parties in a specific field of research establish partnerships, create knowledge spillover and gain international visibility. The French government has invested over EUR 600 million in research in these clusters in the last four years.[30]

In the USA, several national initiatives that foster public-private collaboration have arisen around particular themes. One example is the National Nanotechnology Initiative, which heavily funds public-private consortia.[31] State-level PPPs are also being established. In California, four institutes have been built in which a total of USD 1 billion (both public and private) funding has been allocated for research since their inception in 2000.[32] These are actually "physical" institutes, in which public and private partners physically work together to execute research projects.

Each of these countries employs its own forms of public-private partnership as part of its innovation policy that it tailored to the characteristics of the country: from providing shared networking platforms for public and private parties, to governmental funding for research in which public and private partners work together at the same lab bench. In its many manifestations, linking academia and industry is an important step in the global answer to today's – and tomorrow's – challenges.

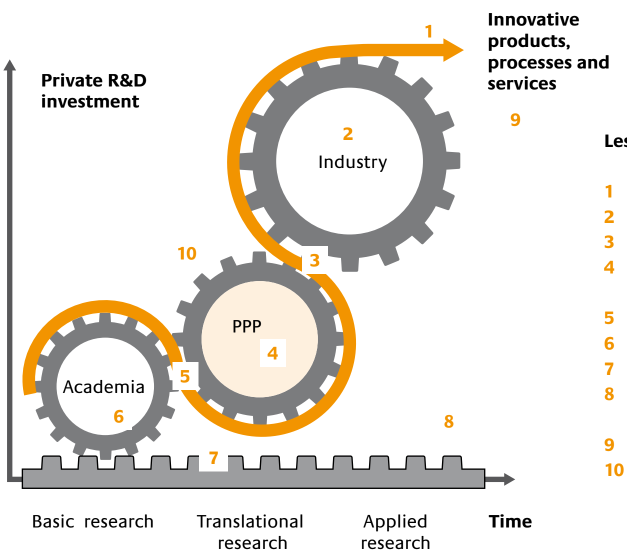
C. Lessons learned from life sciences PPPs

We have gained much experience in setting up and operating public-private partnerships, especially in the life sciences. As these PPPs are now, almost all, up-and-running and producing first results, we can reflect on our experiences and the lessons we have learned. In doing so, it is important not to look at PPPs in isolation. They are part of a broader innovation process that stretches from knowledge generation in academia to the (industrial) delivery of innovations for use in society. We will consider the innovation system in its entirety and identify success factors for PPPs for each element and interface – ten in all (see Figure 8). For each, we will give examples and some tips from people with hands-on experience, which may help others to realize these success factors in practice, when setting up, participating in or operating a PPP.

LESSON 1: Industrial leadership is key

PPPs must balance technology push with market pull to ensure translation. Most PPPs, however, have an academic bias as most researchers come from academia and most research is conducted in academic facilities. PhD students and post-docs are oriented more towards their professors, even if companies pay their salaries. Sometimes, industry contributes little more than cash to such students. Project selection and interim evaluations typically involve an international panel of leading scientists but no or few industry representatives. As a result, research can drift away from industry priorities and industrial partners can lose interest.

For translation to really work, industry must be a driving force on par with academia. It is not so much a matter of academia crowding out industry, as of industry playing its part. It should take an active lead, for example, by putting senior executives who are strongly linked to the business forward to manage PPPs, or by providing experts to sit on scientific review committees or an analogous industrial selection body. Industry representatives could be specifically charged with valorizing PPP results. A triumvirate of general, scientific and valorization directors is proving to be effective in several cases. Excellence is key, in management



Lessons learned throughout the system

1. Industrial leadership is key
2. Industry absorption must be actively managed
3. People are the primary vector for knowledge transfer
4. Dynamic programming makes a PPP more than the sum of its projects
5. Reinventing the wheel in IP causes pointless delays
6. Academic responsibility must balance academic freedom
7. Government should steer PPPs on output and progress
8. A physical research environment and virtual collaboration each have advantages
9. Society should be your yardstick
10. Collectively, we know a lot – let's share

Figure 8: Lessons learned on PPPs

as well as in researchers. If you staff PPPs with first-rate people, you get first-rate results. If you put forward people who are redundant or (semi-)retired, you get poor results.

On a sector level, guiding bodies like the Regiegroep Chemie or the High Profile Group that include people with solid industry experience are a good way to provide visionary leadership. Such "boards" do not need to be formalized. Made up of leading figures from academia, industry and government, they lead by authority and example rather than by hierarchy. They reflect on developments and future directions, take the lead in internal debates, and make a sector more independent from volatile and incidental (public) funding streams by focusing together on a long-term vision.

TIPS

- Install a triumvirate of general, scientific and valorization directors to lead a PPP
- Involve industry in project selection by including them in the scientific review committee or adding an industrial one
- Make sure all partners, and industry in particular, put forward first-rate people
- Set up an informal "board" of sector heavyweights to provide visionary leadership

LESSON 2: Industry absorption must be actively managed

One of the main obstacles for knowledge transfer is the capacity for absorption on the receiving end, industry. Companies that outsource (certain) R&D have long known that outsourcing does not mean that you let go of your own scientists or researchers. If a company cannot absorb science and technology, if it cannot master it, process it, build on it – breakthrough ideas will not find their way into new or improved products, services or processes. This absorptive capacity is equally important when exploring (new) areas. For companies to be able to recognize relevance and opportunity, they must have "scouts" who understand science and its application.

Not surprisingly, one hears mixed reports from companies involved in PPPs. Some are enthusiastic, some mixed, some clearly disappointed. There seems to be a clear relationship between satisfaction levels and absorption. Satisfied companies often put great effort into integrating the PPP into their own (R&D) activities. For example, they match the research team in a PPP project with an internal one of their own, and devote resources to absorbing and building on project results. Some spend the same amount they invested in the PPP on internal and related activities. Absorption works even better if the company contributes researchers and facilities, even IP, to the PPP. Not just cash or older or spare equipment – but expert, scarce resources, human and otherwise, that reflect the importance of the PPP to the company and its dedication to the PPP's success. Active partners have much to gain; passive partners are bound to be disappointed.

In the execution of the research programs, it is important not to solely depend on PhD students and post-docs, but to involve seasoned and experienced researchers from outside academia. For the transfer of results to industry and for industry absorption to really work, it is furthermore important to recognize the important and distinct role that research and technology organizations (RTOs) such as TNO can play in PPPs. These organizations should participate in PPPs not as pseudo-universities, as is often the case nowadays, but contribute specifically towards valorization and industry absorption.

TIPS

- Set up well-resourced shadow programs within companies
- Actively participate in PPP projects through key resources (researchers, facilities, IP)
- Recognize the distinct role that RTOs can play within PPPs to stimulate industry absorption

LESSON 3: People are the primary vector for knowledge transfer

The best way to transfer knowledge from academia to industry is through people: say, a PhD student who joins a company after finishing her work in the PPP. She has developed and applied the knowledge in the PPP and literally takes it with her when moving to industry. This is particularly true for so-called tacit knowledge – knowledge that cannot easily be written down or verbalized and that is consequently hard to transfer to other people and organizations. Tacit knowledge is, however, a major and maybe even deciding factor in the absorption of results by industry. There are two ways to transfer tacit knowledge: it comes with the person possessing it or it "rubs off" on people working closely with that person.

The vital role of exchange of human capital has also been acknowledged abroad. In the USA, for example, research within partnerships has pointed out that cross-fertilization of individuals with experience in the government, academic or industrial sectors was key to their success.[33] This also highlights why it is so important for industry to actively participate in PPP projects (see above) and to hire people from PPPs. In an open innovation paradigm, it is the constant movement and interaction of people that makes for effective knowledge dissemination.

Today, recruitment and human resources are the domain of individual companies and institutes. Many companies find a PPP most interesting as a source of high-quality candidates. However, for PPPs, finding and hiring PhD students and post-docs often implies building an HR function within an organization that lacks the scale and which really should spend the money on something else – the research itself. What's more, universities, PPPs and companies compete against each other for talent. Together, as a sector or even across sectors, companies, universities and PPPs could attract, train and retain human capital much more (cost) effectively.

Imagine, for example, an enabling PPP in life sciences that recruits hundreds of top PhD students internationally, matches them with projects and professors in other PPPs, involves them in industry training programs and at the end of their four year stint finds them a job. This enabling PPP would fast-track visa applications, set up housing and take care of payroll, insurance, etc. That would really attract the best talent to the Netherlands and ensure movement between academia and industry. It would give the Netherlands a competitive edge in the international struggle for human capital – especially if it were part of a comprehensive and integrated (lifelong) life sciences education and training program. It would be a powerful contribution to the ambition of the Innovation Platform to attract 1,000 additional international PhDs and post-docs to the Netherlands.[16]

TIP

Establish a joint recruitment and HR program (including education and training) for a sector or across sectors (possibly in the form of an enabling PPP or through an innovation program)

LESSON 4: Dynamic programming makes a PPP more than the sum of its projects

A PPP must address two inherent risks: compartmentalization and complacency. The first occurs when a PPP is basically a collection of standalone projects, under the umbrella of a single program but not really connected. A PPP can sometimes seem a mere marriage of convenience between consortia to secure government funds and then divide the spoils and go their separate ways until the next funding round. But even with the best of intentions, the silo effect is a risk inherent to (virtual) partnerships. Individual project consortia often work at different sites, with different teams (even if from the same group of partners) on different issues. There may be little or no natural exchange between them. Such a PPP will never be more than the sum of its projects. Indeed, it will always be less, as some of those projects will fail. Therein lies the second risk: if budgets are allocated to multi-year projects from the start, resources can become trapped in projects going nowhere. Successful projects will face budgetary and resource shortages, and the PPP will be unable to help.

The answer to both risks lies in dynamic programming. Cross-fertilization between projects and consortia can be built-in – e.g. by encouraging partners to participate in more than one project, through "passepartouts" that give partners access to all project results, through active matchmaking in project definition and selection stages, and by using shared infrastructure and technology centers. Strict portfolio management should involve periodic evaluations in which underperforming projects are terminated and their resources allocated to promising ones. This not only increases the probability of success, it also "reshuffles" researchers who can contribute ideas and knowledge from terminated projects. Budget could also be held in reserve to spend in subsequent years in line with progressive wisdom or high-risk opportunities. Such decisions require continuous monitoring of progress and results on project and portfolio levels. That may seem obvious, but not all PPPs have such information readily available, if they can produce it at all. Management information systems should be set up from day one.

TIPS

- Build cross-fertilization into the PPP design through multi-project participation, matchmaking and shared infrastructure and technology centers
- Institute strict portfolio management, and as of year two terminate at least 5-10% of projects annually and reallocate their resources to top-performing projects
- Reserve part of the budget for discretionary spending on emerging priorities or high-risk opportunities
- Set up a solid management information system from day one

LESSON 5: Reinventing the wheel in IP causes pointless delays

Intellectual property has no value whatsoever unless it is used. Conversely, without the protection of IP some products will never be made. Pharmaceuticals are a good example. The cost to develop, test, produce and market a new drug is so high that only a period of exclusivity makes it commercially viable. Companies need easy access to IP at a price that reflects the risks and investments they face when turning it into a marketable innovation. Academia and scientists should receive fair compensation for their role in developing the IP.

All parties in PPPs recognize the importance of IP. Still, reaching agreement on IP policy often proves problematic. Many PPPs reinvent the wheel rather than adopt or build on an IP policy that was already developed elsewhere. Issues are being needlessly revisited, delaying the start of PPPs by months, and in some cases by up to a year. The process is further complicated by lengthy negotiations on IP brought in by universities – an issue that is also identified by entrepreneurs who want to use university IP outside of PPPs.[34] Not all parties have a realistic view of the (market) value of their IP. Further professionalization will help. And this is not just a Dutch issue. In the USA, even the extremely successful public-private partnerships have identified IP negotiations as a significant barrier and a continual challenge in the development of new partnerships.[33]

IP policy should be an enabler, not a barrier to innovation. It need not be difficult. The PPPs that are already active today provide a wealth of (best practice) examples, where trouble points have already been resolved. Using their experience – and policies – as a foundation, new PPPs can set themselves up quickly; rather than dealing with every minute issue all over again, they can take general practices from other PPPs and focus on issues specific to their work and needs.

Within an overall IP policy, consortium agreements can likewise be long in the making or overly complex. This is one potential drawback to large (project) consortia with many members. Starting up before agreement is

The two-compartment model of the Kluyver Centre

PPPs come in many shapes and sizes. Choices have to be made when setting up a PPP. Decisions should be guided by a desire to obtain maximum results in the specific environment of the PPP. New PPPs need to learn from existing structures and consider all alternatives.

Most PPPs combine subsidy and matching in individual projects. But this is not the only way. The Kluyver Centre has set up a two-compartment method, separating the subsidy it obtained through NGI from the investments made by private parties. The NGI subsidy is spent in precompetitive research projects at universities in compartment one. The second compartment is directed at application-oriented research, performed and financed by consortia of companies, universities and/or other public funding agencies, without NGI subsidy. All private parties are paying members of the Industrial Platform of the Kluyver Centre. Members are obliged to participate in the second compartment, and company size determines the minimum of participation that is expected.

This construction has interesting IP implications. The IP generated in compartment one is property of the university that performed the research. Members of the Industrial Platform have full insight into all research performed in compartment one and enjoy the right of first priority to negotiate for licenses on patents. This results in (mostly bilateral) agreements for joint projects between academia and members of the Industrial Platform in the second compartment, in which project partners have full control over IP agreements. Where many "one compartment" PPPs have struggled with difficult IP rules in large consortia, this two-compartment method produces smaller consortia that can tailor IP to the specific project and which do not necessarily have to comply with IP boundary conditions from subsidies. As in most PPP models, the two-compartment method still requires a professional university Technology Transfer Office to perform negotiations on IP owned by universities (Part II, Chapter VIII).

IP is not the only reason that the Kluyver Centre chose this model. It also provides the possibility for performing truly precompetitive research that is funded by subsidy, as such research takes place entirely in academia. To connect this precompetitive research to the needs of the Industrial Platform, the portfolio of the first compartment is discussed with the Industrial Platform in advance. The Industrial Platform's access to all precompetitive research encourages cross-fertilization between all academic and industrial groups. This in turn encourages human capital transfer between them, which is believed to be the most important tool for knowledge transfer.

Source: Kluyver Centre

reached almost guarantees conflicts later on when there is IP to fight over. Unresolved or complicated agreements can also make spin-offs or licensing more difficult because it is not clear who owns which rights, and the entrepreneur or licensee has to strike not one, but many deals. Thus, IP can become trapped in the project, where it is of no use to anyone – least of all users. Consortium agreements should be simple and straightforward. They should protect the rights of individual members but ensure that IP can be quickly and easily picked up for further development. And they should be in place from day one.

TIPS

- Use best-practice examples as the basis for a simple and realistic IP policy
- Have simple consortium agreements with straight forward rules for IP transactions, and sign these before starting up
- Professionalize technology transfer at universities

LESSON 6: Academic responsibility must balance academic freedom

PPPs are neither an extension of, nor a substitute for basic research. Without true basic research in universities, the entire system runs dry. Current matching rules, however, have the unintended effect that universities use funding meant for basic research to participate in PPPs. This trend is worrying. The Netherlands is already in danger of losing its leading scientific position, as over the last decade funding for basic research in other countries has grown much faster. The government should therefore take care not to stifle pure, unfettered basic research.

On the other hand, universities themselves must face the fact that choices must be made. PPP funding is not meant for basic research, but to translate basic research into practical applications. Universities must be prepared to pass up an opportunity to attract matching funds if that means locking too many resources away from basic research. It is the responsibility of each individual institute to carefully consider where it participates and where not, and to strike a balance between basic and translational research. Just as government and the taxpayer must ensure that universities retain the freedom to set their own priorities based on scientific merit, so must universities be selective and maximize their impact by excelling in a limited number of relevant fields. In addition to increasing overall funding levels, the percentage available for translational research matching could be capped.

TIP

Make sure that academic participation in PPPs leaves sufficient resources for basic research

LESSON 7: Government should steer PPPs on output and progress

The government cannot evaluate the research conducted in PPPs on content, nor should it. This is not to say, however, that the government should not provide direction. On the contrary, it should be strict on certain criteria. The beauty of PPPs and matching funds is that society, through its government, can quite clearly choose what it wants and will pay for (output), and leave the question of "how" to those qualified to answer. In this system, the government decides on what topics it will fund PPPs to address its agenda (e.g. to fight chronic diseases, develop clean processes, secure food supply or improve our diet). A necessity for this is, of course, that the government has set an agenda (e.g. the Priority Medicines report of the WHO used by the Ministry of Health, Welfare and Sport).[35] Academia and industry submit research programs that they think serve those objectives and which are of both scientific and commercial interest. All proposals must pass a rigorous, independent review by internationally recognized experts in their field on scientific excellence and valorization potential. These proposals should then be ranked on their contribution to specific parts of the government's agenda, the existence of a solid plan, milestones for accountability and a committed, expert consortium. By determining in advance what budget is available for which part of the agenda, the government avoids comparing apples and oranges (or a treatment for dementia and renewable energy) as much as possible.

The matching funds from government should not be a blank cheque. The government can and should steer on output and progress of the PPPs it funds. It can make the release of funds conditional upon the reaching of predetermined milestones, such as having a signed IP policy in place within two months or successfully completing a first call for projects in eight. Funding could also be withheld if a PPP fails to conduct periodic evaluations and manage its portfolio, terminating underperforming projects and reallocating resources to successful or new ones (which could mean that some PhD projects will have to be continued by the university itself – a fine incentive to make progress and show results). When funds have been awarded, momentum can waver and unproductive quarrels arise. Phased release can help keep momentum and focus energies. It has the added advantage of enabling mid-course corrections, rather than supporting after-the-fact evaluations (and regrets).

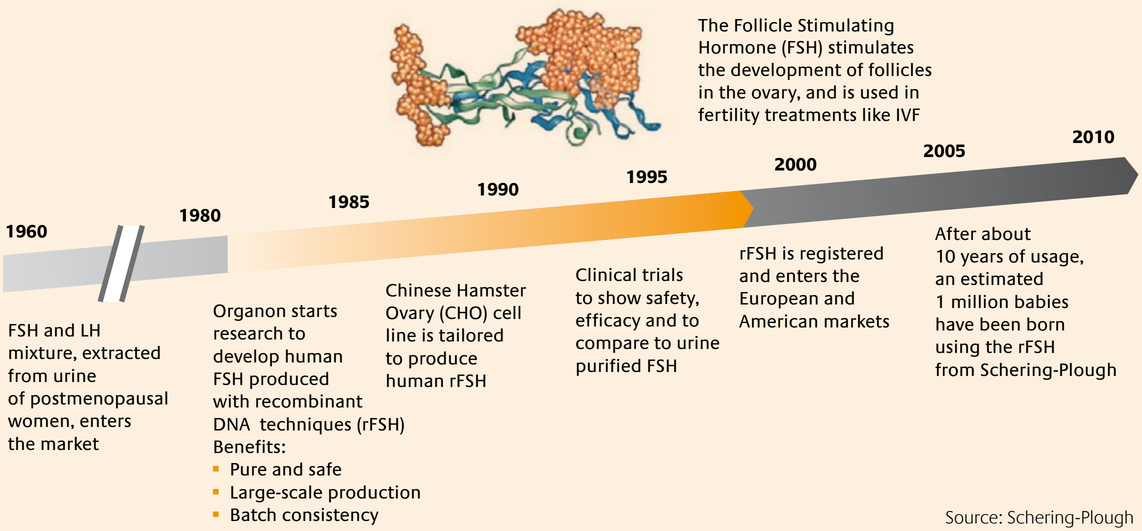
This does, however, require clarity, consistency and continuity in policy on the timescale of innovation (>15 years for life sciences), the timescale on which investments can be evaluated (a UK study estimates the time between the health research and impact in treatment to be about 17 years on average[36]). After all, PPPs are only a part of the long path from basic science to social value. FES 2009 reflected this fact by encouraging consolidation (combining initiatives) and selective continuity (keeping the best, ending others), and left it up to the sectors to agree on how to move forward. Unfortunately, FES 2009 was less effective than it could have been; the evaluation of proposals seemed ad-hoc and not all public bodies involved seemed in touch with the intent and provisions of the call, or indeed the instructions given to applicants. Still, progressive consolidation and rationalization should rightly be among the principles of any long-term policy directed towards innovation and PPPs. This book aims to deliver one essential condition for such a policy: a shared vision of where we want to go. This paragraph touches upon one of the main recommendations of this book (policy continuity), that will be discussed in detail in the next section of this chapter.

TIPS

- Do not try to compare disparate proposals on content – judge them on their merits in their respective fields and on the solidity of their plan and consortium
- Make release of funds conditional upon reaching predetermined output and progress milestones

It takes time to be successful

The timeline of a life sciences innovation is long. Consider the Follicle Stimulating Hormone of Schering Plough, developed in the Netherlands. A success story, used in the birth of over 1 million babies thus far and being the bestselling Dutch biopharmaceutical. The research started in the early 1980s, but the product only reached the market in the late 1990s. And compared to current development timelines, the path of FSH from lab to hospital can be considered short.



Source: Schering-Plough

LESSON 8: A physical research environment and virtual collaboration each have advantages

Thus far, PPPs have been predominantly set up as virtual collaborations. The benefits here are undeniable. Virtual collaboration pools resources from many partners on a scale that is physically unattainable. Partners have access to each other's facilities and do not need to invest in new, joint infrastructure except where it does not already exist. But physical interaction, run-ins in the lobby and informal chats by the coffee machine are few. It turns out that these are important in innovation, maybe more so than we thought. Direct interaction is still the best way to transfer (especially tacit) knowledge, inspire creativity and build trust.

It should be possible to create physical environments for research and collaboration, a "home base" to identify with, a place to (informally) meet colleagues and exchange ideas, to work together and to interact with the public (host tours, exhibitions, school trips, courses). Ideally, such sites would be centered around shared facilities, like technology centers, piloting locations or libraries/biobanks. It could have its core on the R&D campus of a large company or university, with satellites at various partner sites. In Belgium, for example, the Flanders Institute for Biotechnology (VIB) combines a strong central core with virtual programs. Also, the 2009 NWO call in systems biology focuses on physical infrastructure.

TIP

Create a physical research environment where partners and the public can interact

The House of Life Sciences

There are advanced plans to set up a physical meeting place and a landmark for the health sector: the House of Life Sciences. This futuristic building is to be a place where people from all disciplines meet and work together in shared facilities that include labs, offices, and conference and hotel facilities. The House of Life Sciences will stimulate knowledge exchange through informal interaction, discussions, meetings, conferences, shared research, research sabbaticals, temporary (international) research fellows and continued networking possibilities. It is to become a place where public, scientists, industry and policy makers come to be inspired and join in discussions on technology, implications, needs and future priorities.

LESSON 9: Society should be your yardstick

PPPs are meant to address socio-economic challenges important to us all. For the innovations produced by the PPPs to work, these innovations need to be accepted by society. However, society's absorption of knowledge and technology is not always a smooth process. Social groups of citizens, consumers, patients, workers and other stakeholders can change the speed and direction of technology development. The success of innovations is thus primarily measured by the innovations' adoption in society and not by technical criteria: society is the yardstick.

It is crucial to anticipate social support or resistance to new technologies and to explicitly address them during the development process. Research into social issues should therefore accompany science and technology development. In addition to research, education and participatory processes are also important.

Public education is part of an open innovation process, and an integral and crucial function of the PPP. Information should be presented in ways with which non-experts can engage. PPPs can publish (interim) results in popular newspapers, take part in popular science programs, set up websites, visit schools, organize exhibitions, host debates on the ethical issues with new technologies, etc.

But teaching is not enough. Active participation of the public in debates on life sciences issues is important for shaping the PPPs research agenda, for improving innovations, and for preparing the innovation's embedding in society. PPPs should engage the public, experts, policy and political decision makers at an early stage, involving them in exploring and discussing the benefits, risks, and ethical and social consequences of their work.

Finally, the majority of PPP funding is public. PPPs can thus be held accountable by the public. PPPs must earn their credibility and validity. They must demonstrate that they deliver value for money. This book itself is an attempt by all sectors to jointly provide transparency and accountability.

TIPS

- Set up social programs to accompany science and technology development
- Engage at an early stage in interactive dialogue with public, experts and policy makers about all relevant issues surrounding life sciences innovations
- Provide public education for non-experts
- Be transparent and accountable to all stakeholders: general public, partners and government

LESSON 10: Collectively, we know a lot – let's share

The Netherlands now has a long and meaningful history with PPPs. For over a decade, we have pioneered this approach to innovation. We have learned a lot. We have developed best practices in just about every aspect of setting up and running a PPP: from IP to legal structures, to IT infrastructure, to knowledge management, to executing project calls, to selection and evaluation procedures, to portfolio management techniques, to HR, to public affairs and many more. Within sectors, these practices are increasingly shared. Even across sectors we see early attempts at knowledge sharing. But as mentioned before, many new PPPs have a tendency to reinvent the wheel. That is a waste of time, resources and energy. Everything it needs it can obtain from others.

It would therefore be a good idea to develop a starter-kit for new PPPs, and to use existing PPPs to help in the roll-out of new ones. For both existing and new PPPs, a centralized location for exchange of best practices would be invaluable. This would be an important step towards further integration of back offices within and between sectors – meaning

Reboot

Statues of Marjolein Kriek and Erasmus at the event of the 10th Reboot speech, by Pieter Lemmens.

Reboot was a philosophical art project held from October 2008 to October 2009 in Rotterdam's Grotekerkplein, a square where the statue of Erasmus, great humanist and philosopher, is located. Reboot was created and organized by Bas van Vlijmen.

Reboot consisted of two parts. First, a statue was placed in front of Erasmus as a technoscientific challenge to our humanist tradition. Second, a series of speeches took place, given by Taco Noorman, Roel Pieterman, Chris Aalberts, Liesbeth Levy, Carel Peeters, Leo Molenaar, Atze Bosma, Corien Prins, Carla Hoekendijk and Pieter Lemmens.

The challenge to Erasmus consisted of a print of the sequence of the genome (the DNA code) of Marjolein Kriek, a clinical geneticist at LUMC. She is the first woman to have the complete genome determined. The genome was printed per chromosome pair on a weatherproof canvas. The prints were folded and placed on a pile. This pile was then placed on a replica of the pedestal of Erasmus' statue.

Photographer: Lucrees van Groningen

Statues of Marjolein Kriek and Erasmus. Reboot was executed during the renovation of the square to emphasize the fact that people and technology are in flux.

The speakers were asked to consider the relationship between humans and technology in the light of the great challenges of our time, ranging from poverty to social unrest and misunderstanding to climate change.

Source: Bas van Vlijmen; www.basvanvlijmen.com/reboot significant advantages in terms of professional quality and cost. Ultimately this could lead to the consolidation of all IP, IT, management, valorization, education & training, HR and social expertise and resources into a single "backbone" that provides continuous support to PPPs that are redefined as programs that "click" onto the backbone over the course of their lifetime.

Technology centers can play a particularly important role in knowledge and best-practice sharing and cross-fertilization between PPPs. Their enabling technologies should make them preferred partners for all or most life sciences PPPs and ideal vehicles for circulating knowledge, experience and people between PPPs and across projects. We are already seeing such cooperation between technology centers and other PPPs, but it should become even more natural and widespread.

TIPS

- Establish best practices exchange for (life sciences) PPPs
- Develop a PPP starter-kit and use existing PPPs to quickly and efficiently set up new ones
- Use technology centers to achieve cross-fertilization and knowledge exchange between and across sectors

D. The outlook for life sciences PPPs

PPPs have emerged from the fertile grounds of fourth generation R&D and Dutch innovation policy and from the challenges of the innovation paradox. They have taken their place among the instruments for innovation. Life sciences PPPs of all stripes populate a rich landscape that spans the food, health, agriculture and chemicals & energy sectors. Lessons have been learned that will benefit new generations of PPPs in the life sciences and beyond. So, what is next? Where will we go from here?

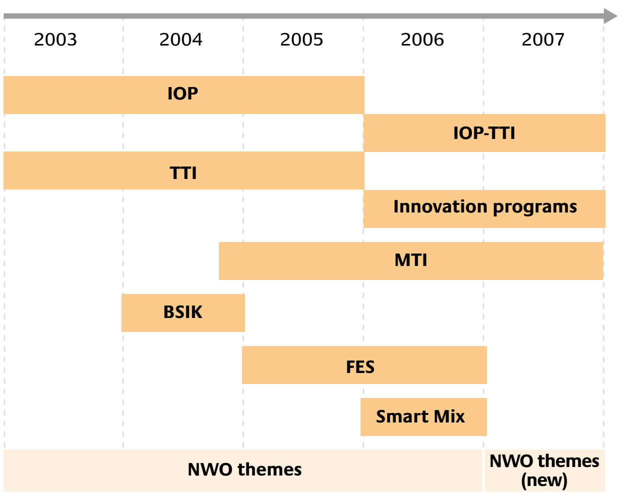
PPPs are short-lived parts of a larger whole. They serve a purpose in advancing innovation from one stage to the next, but they are neither sufficient nor a goal in and of themselves. PPPs are mostly limited to the translational stage between knowledge generation and market delivery. Their partners are involved in one or the other, or both. To look at PPPs is to look at the innovation system as a whole and its constituent stages. That is not to suggest that innovation is a simple, linear process. Stages run into one another, are linked by feedback loops, are revisited in iteration upon iteration and inspire (new) ideas in both later and earlier stages. However, simplification into linear innovation "stages" helps distinguish between upstream and downstream activities and explore what is needed in each stage to create the optimum conditions for success. We have narrowed that down to three overall priorities for the life sciences field, which are the main recommendations of this book: provide policy continuity, build on strengths and position the Netherlands as a single bioregion.

1. Provide policy continuity

Innovation is dynamic, even chaotic. It involves many parties in ever changing coalitions. The reason PPPs are so well-suited to an open innovation paradigm is that they are inherently flexible, adaptable and responsive – if they avoid institutionalization and actively engage with the world around them. Partners within PPPs are innovators

Major national programmatic policy instruments 2003-2007

Policy programs over time



Value of policy programs

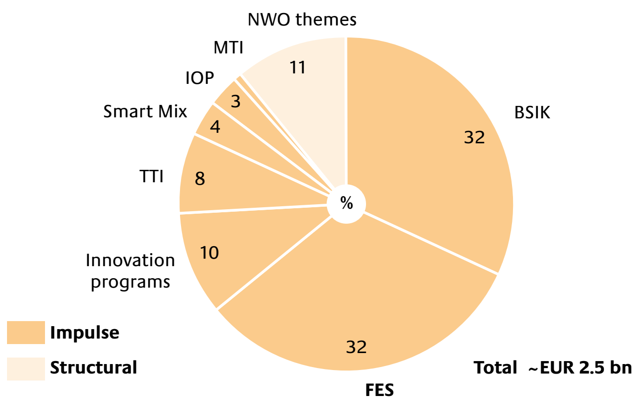


Figure 9: The dynamics of national programmatic policy instruments
Source: Advisory Council for Science and Technology Policy (AWT), *Weloverwogen impulsen* (2007)

themselves, and part of other consortia, PPPs and networks. When they have done their part, PPPs dissolve and partners reappear in new configurations. In a field this dynamic, policy and regulation must provide stability.

Policy continuity is the single most important factor in the success of the life sciences. Long-term commitment to the life sciences and a stable business and regulatory environment on the timescale of life sciences innovation (about 15 years) are essential for mobilizing the large private investments needed. Thus far, however, most public investment in the life sciences has consisted of one-time impulse funding for limited periods of about four years (Figure 9). When reviewing these instruments, the Dutch Advisory Council for Science and Technology Policy (AWT) concluded that innovation policy in the Netherlands lacks a long term strategy, coherence and continuity.[9] Impulses wear off, and even this year's (2009) FES call will not change that. The majority of committed funding will end next year and will

Committed/spent investment in life sciences related PPPs as of start 2009

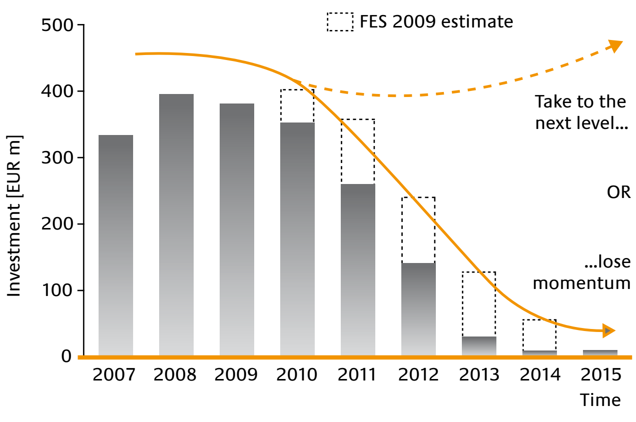


Figure 10: Committed investments to life sciences PPPs – estimates
Source: Estimated using data from PPP websites and Ministry of Economic Affairs

drop sharply from 2011 on (Figure 10). Even assuming that a significant part of FES 2009 will be awarded to life sciences PPPs, we will lose momentum in 2011 and the gap that occurs in 2012 will be about EUR 200 m with respect to 2009 investments. With a lag of at least one year between issuing a FES call and PPPs receiving resources, only a significant investment program issued in 2010 can overcome the losing of momentum and the dramatic decline in funds in 2012. Waiting for after the elections in 2011 before issuing a new call would be devastating. However, new funding sources are uncertain at best.

"You need to think in much longer terms"
Minister van der Hoeven asked Fred Hassan, the CEO of Schering Plough, what the Netherlands could do to remain attractive to the pharmaceutical industry. Hassan later told the Financieele Dagblad: "I praised the knowledge infrastructure, but also emphasized that the government must clearly demonstrate whether the country is committed to investing in the life sciences field for the long term." Of the hundreds of millions currently being invested, Hassan said: "That is for four years. You need to think in much longer terms".

Source: FD, June 9, 2009

FES funding procedure has been highly criticized for being unclear, not transparent, erratic, bureaucratic, and contaminated by short-term thinking, departmental hobbies and lobbying. The *Commissie van Wijzen* – one of the two bodies that evaluate the proposals – faces an impossible task, having to compare the scientific and socio-economic merits of a completely incomparable set of proposals from areas as diverse as energy, the creative industry and health. When independent peer reviews were available, they were not always given due consideration. Even if we allow for the disappointment and frustration of those that saw their plans rejected, it is clear that the current process falls short. The *Commissie van Wijzen*, in its mid-term review of the BSIK impulse (part of FES), urges unequivocal, coherent and transparent procedures, and investment on the basis of a long-term strategic agenda.[20]

Impulse funding has an additional, undesired effect. Because funding periods are limited and nobody knows if and when they will next have the chance to apply, everybody jumps on the first “pot of money” that comes along. Any coordination between applications is lost, programs are written to satisfy ad-hoc criteria, and much energy is wasted on these periodic feeding frenzies. Longer-term continuity (with a limited number of funding instruments and the timing, size and criteria of calls more or less fixed) draws out better, more considered proposals; instead of manipulating content to fit the call, consortia can choose the call that best fits their content. Quality and cohesion will be much improved, and consequently so will the odds of eventual innovation success.

On a four-year timescale, return on investment cannot be expected. Returns require that the four-year investment be part of a long-term strategy. This implies a clear focus on social priorities over 10 or 15 years, preferably tied to existing or new *Sleutelgebieden*. This focus should translate into innovation policy that is consistent, stable and continuous over the entire innovation system, from science to society and markets – including the part that involves PPPs.

Funding itself need not be awarded (to individual consortia) for periods longer than four years. Lessons from previous PPP experience even suggest that phased and conditional release of funds over such four year periods could produce better results (see Lesson 7). It is the long-term strategic framework in which all PPPs should operate that is missing. Again, individual consortia do not need to have the money guaranteed for years to come, as long as they can be reasonably certain of additional funds if they are successful – rather than seeing them redirected to other priorities or whatever makes newspaper headlines then.

But as mentioned earlier, initiatives need to show progress and promise by achieving predefined milestones to be eligible for continued or new funding. Continuity in policy means that such evaluation parameters stay the same, not that you will not be regularly evaluated. The same goes for the policy instruments themselves. For example, if as much as 90% of the initiatives launched under a certain policy instrument have not reached their milestones at an interim evaluation, these initiatives should be discontinued and the policy instrument itself should be phased out (the 10% of initiatives that are on track should be continued under the same conditions). This requires monitoring on the level of the policy instruments, the initiatives launched under them, and the projects in the portfolios of each initiative.

Every innovation and every stage of innovation are different. Each has its own requirements. This does not mean, however, an endless list of policy instruments and funding arrangements. It does mean picking the right tools for the job and arranging a seamless transition from one stage of innovation to the next: from input funding for basic research at universities, to matching subsidies for precompetitive research at PPPs, to deferred loans and tax measures for competitive research in private companies (Figure 11).

Instruments must fit the stage of innovation. One example is the extension of a partnership into a commercial venture to create a soft landing place for promising concepts emerging from PPPs – one is currently being set up to develop an artificial kidney, another to fight neglected tropical diseases. In such public-private enterprises (PPEs), subsidies are exchanged for (deferred) loans and public and private contributions take the form of equity stakes.

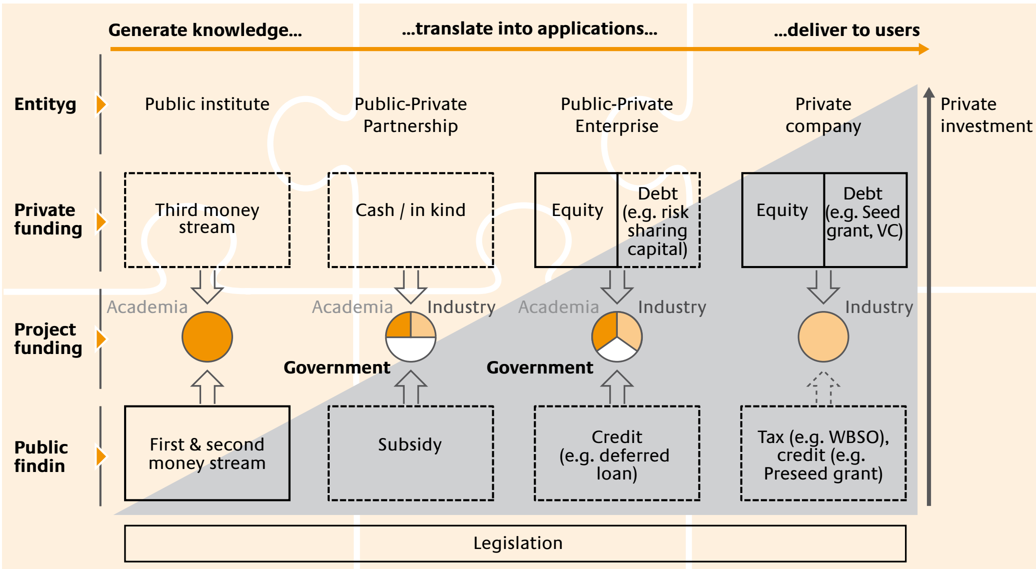


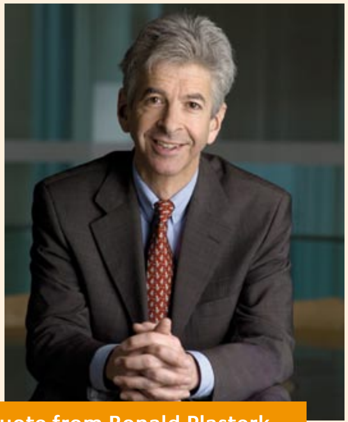
Figure 11: Matching the appropriate instruments to the phases of innovation

As (technology, development) risks recede and the prospects for returns increase, so does the private share of the investment. Public stimulus of corporations and SMEs takes the form of tax breaks (e.g. WBSO). The government may also offer advance purchase agreements, and needs to keep regulation straightforward, stimulating and (at least) on par with neighboring countries. Early stage ventures (coming out of PPPs, academia or existing companies) can get innovation credit: deferred loans that lapse if the technology fails. Smaller companies that have less to gain from joining a PPP (too small to be a primary partner or engage in precompetitive, longer-term research), are better served by help with attracting early stage capital and with striking bilateral agreements with academia for use of IP and research facilities (e.g. through innovation vouchers). Some innovation programs have arrangements to support bilateral cooperation and connect to facility sharing initiatives like Mibiton.

Thus, for every stage and purpose there is a vehicle (public institute, PPP, PPE or private company), a structure for private funding (fees, cash/in-kind contributions, equity) and a range of government instruments (input funding, matching subsidies, loans/credit, tax measures, advance purchase agreements, regulation, etc.). Variations are easily made when needed. The important thing is therefore not to introduce new instruments, but to turn those that exist into an integrated and structural system for innovation support. Thus each initiative at each stage of its development can find the right combination of standard instruments to suit its needs. Such stability creates the best possible conditions for a steady stream of innovations.

The importance of policy continuity and connected policy instruments has been recognized in recent publications by the Innovation Platform and the government program “Nederland Ondernemend Innovatieland”.[17,18] Another promising step was the recent decoupling of the FES budget from fluctuations in natural gas income.

Of course, policy continuity is not a matter for the government alone. In the past, academia and industry often let funding run out and then complained bitterly about the fickle, unreliable government. But changing political priorities are a part of democratic life. Indeed, how can we expect politicians, civil servants and society to steer a steady course if we, as experts, fail to advise them of where



Quote from Ronald Plasterk

“ **It was obvious that after four years the financial backing should be continued**
One of the first things as minister of OCW that I had to do in the area of science was to defend the value of a second term for NGI. NGI was established as an attempt to place the Dutch genomics field at the international fore. When NGI started, genomics was a new field which was conducting promising research and where new techniques were being developed. The results of NGI's efforts were very convincing, and it was obvious that after four years the financial backing should be continued. The expertise that is assembled in initiatives such as NGI must remain available, especially in the Netherlands, for research and for those who can apply it, whether in medicine or in the chemical, agriculture, food or forensics sectors.

Before us lies the vision of the life sciences, a plan written by the public-private sector. Many want to become a Partner in the Polder. In this sense, the polder stands for working together, securing a good relationship between fundamental research and the people who will apply it. And something that is also important to me: this polder is not one of mediocrity, but should lead to the upholding of the quality which has already set this research apart. ”

Ronald Plasterk, Minister of Education, Culture and Science

we think we should be going and why? Only when the field provides sufficient information to politicians and society, shows clear progress and results from its activities, and manages to gather enough support within society, can the government maintain a more or less steady life sciences course in the long run.

This book itself can serve as an example: the sectors have taken up the challenge to lay down their vision of the future of the life sciences and PPPs, between funding rounds when there is no money to be pursued that might corrupt the process. This book represents a first step towards giving society and its elected representatives the means to make informed decisions. If society broadly agrees on its priorities, new governments may change emphasis or degree, but not the fundamentals of policy. Continuity requires a clear, common goal. If you have that, the road may twist and turn, but you will always progress in the right direction.

RECOMMENDATION Provide continuity in innovation policy for 15 years or more

- Clearly articulate where the life sciences field wants to go and what it needs to get there (starting with this book) ***Life sciences field***
- Formulate long-term (>15 years) social objectives to guide innovation policy, in consultation with the field ***Government***
- Keep innovation policy largely constant over the same period: priorities, regulation and the set-up, timing and criteria of funding instruments ***Government***
- Deploy the right (mix of) instruments in each stage of innovation ***Government***
- Track results of innovation policy (instruments and initiatives) over an entire innovation cycle ***Field & government***

!

2. Build on strengths

Against the background of such policy continuity, we can build towards a comprehensive and integrated infrastructure for innovation in the life sciences. The translational stage is now firmly in place and the many PPPs that have been set up are starting to produce results. Our first priority, therefore, is to make sure that these results will eventually reach end users and realize social and economic returns. Next, we need to consolidate the PPPs and take them to the next (European) level. At the same time, we cannot take the excellence of our science base for granted. It must be constantly updated and expanded or it will erode.

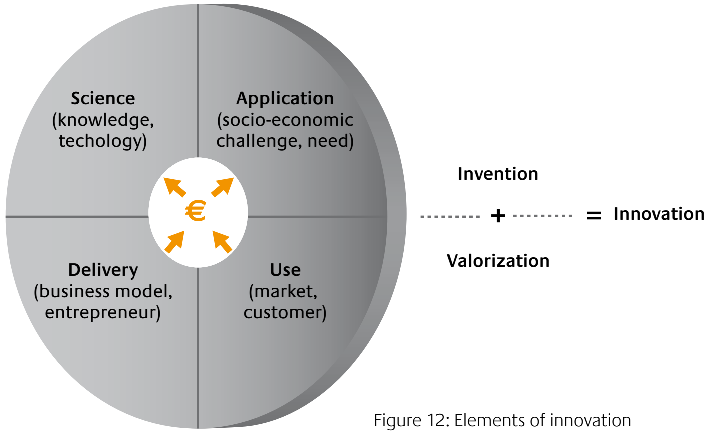


Figure 12: Elements of innovation

Realize returns

An invention becomes an innovation only when it is used. Only when a crop is harvested, a food eaten, a disease prevented or an industrial process introduced does the innovation fulfill its social function and create value for its user (farmer, consumer, patient, company). Part of that value is also then released to whoever delivered it to the user (the plant breeder, food company, healthcare provider, engineering company) and distributed throughout the value chain to suppliers (of knowledge and technologies).

The first returns can be called social valorization, the second economic. Sometimes the two are mistakenly thought to be independent from each other or even contradictory. In fact, economic valorization is a derivative of social valorization. They come together. An innovation that finds no use in society has no economic value. Yet its inherent social value will never materialize unless a way (i.e. business model) is found to organize and pay for its production and delivery – either collectively as a tax-funded public service or privately through an entrepreneur. An innovation, then, must be used and it must be delivered. Neither is trivial. Let us take a closer look at the interplay between user, entrepreneur and government.

A **user** must be willing and able to use an innovation. This requires that he first knows about it, that he has a use for it and that he understands its potential benefits and risks. Life sciences innovations can needlessly fail because of unwarranted fear or moral objections, not only on the part of the user but of government, the general public, regulatory bodies or pressure groups. In its recent report The Bioeconomy to 2030: Designing a Policy Agenda, the OECD concludes that one of its principle policy recommendations is to: "create an active and sustained dialogue with society and industry on the socio-economic and ethical implications, benefits, and requirements of biotechnologies".[10]

Early involvement of all these parties in the work of a PPP has the combined benefit of incorporating their wishes, concerns and ideas into the development process, getting the word out on new products, services or processes and enabling stakeholders to make quick and informed decisions about (allowing) their use. That can make all the difference in the speed and success of market introduction. To create value from a new treatment, for example, a patient must know to ask her doctor for it, the doctor must be familiar with it and comfortable with prescribing it, the

Quote from Peter Wierenga

“ **Let us raise the bar and aim for high impact**
This book once again shows that the Dutch scientific community is perfectly able to join forces and define an inspiring vision and strategy in a particular field. Up till now, we have been less successful in striking the right balance between exploration and valorization that actively involves partners from industry. Also, we are not yet fully utilizing the opportunities which can be found by seeking collaborations with adjacent domains to increase the likelihood of breakthroughs. In the case of the life sciences, this could be high-tech systems or medical technology.

Let us raise the bar and aim for high impact, scientifically as well as for society. ”

Peter Wierenga, Chairman for the Commission for Technology and Innovation at VNO-NCW

regulator must have approved it and the health insurer must have made it part of basic or supplementary coverage.

An **entrepreneur**, too, must be willing and able to deliver an innovation. The development of an invention to the point that any value can be got from it requires a lot of work and money. Such effort takes vision. It takes guts. In other words, it takes entrepreneurship. By that we do not mean start-ups or SMEs alone. Entrepreneurs can be found in large corporations, government and academia. We cannot stress enough how important it is to have entrepreneurs who have the belief, the drive and the perseverance to take promising concepts or inventions and turn them into real innovations – even if that means leaving the safety of university tenure, taking out a second mortgage or betting the company. Entrepreneurship is the single most powerful force in turning ideas into novel products, processes and services. To quote our national philosopher, Johan Cruyff: “You have to shoot to score.”

As with users, however, it is not only about willingness. The entrepreneur must also be able to pick up promising ideas, finance their development and launch the resulting products, processes and services into the market. This requires easy access to knowledge and IP, ample availability of (venture) capital, the absence of unnecessary regulatory constraints and a well functioning market.

Today, entrepreneurs (both outside buyers and spin-offs) find it difficult to obtain IP from academic institutes. Increasing the quality and professionalism of Technology Transfer Offices (TTOs) and greater collaboration to harmonize rules, speed up procedures and facilitate identifying and combining IP from different institutes should have high priority (Part II, Chapter VIII).

A major hurdle for entrepreneurs is the availability of capital,[18,37,38] especially in that part of the innovation process that has come to be referred to as “the valley of death” or “innovation gap” between lab and practice. In the chemicals & energy sector, for example, the life sciences may lead to processes that are revolutionary, or just so new that no previous experience in developing them to commercial scale exists – and what works in the lab more often than not will not work outside it. But venture capital or industrial investors are not keen to invest before proof of concept on a pilot scale. The investment and risk are both very high. The health sector has the same problem between preclinical proof and proof of concept in first patients. We need government and industry to come together in venture funds that help companies cross the innovation gap and to jointly invest in open-innovation facilities where new processes can be proven through pilots. Innovation requires an integrated chain of funding instruments that make capital available at each stage of innovation.

Misguided or excessive regulation will delay an innovation or even kill it off entirely. For example, processes that are more efficient in terms of energy use and greenhouse emissions may not be cheaper unless the cost of environmental damage is included in the prices of competing, "dirtier" alternatives. The absence of a system that certifies respectable sources of biomass or allows for reasonable health claims for food products will make entrepreneurs think twice. If regulation or business climate (including market conditions, logistics infrastructure, taxation, etc.) are more favorable elsewhere, entrepreneurs will start or relocate their businesses there, and those countries and their citizens will be the ones benefiting from their efforts. The importance of policy continuity comes up here, as well: if policy and regulation change every four years, industry will not invest hundreds of millions in production and distribution, to say nothing of riskier development phases.

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Reward innovation and innovators

Globally, the life sciences evolution is in full swing. The Netherlands have great opportunities to play a leading role in this evolution, also in the biomedical field. Pharmaceutical companies invest annually around EUR 500 million in R&D in the Netherlands. A large part of this sum is shared with SMEs and scientific institutions (e.g. in the current public-private partnerships). To keep the Netherlands attractive for R&D in the future, improvements in the business climate are absolutely necessary. Some of them are visualized in the long-term vision, the theme of this book. These measures are primarily aimed at further development of public-private cooperation. However, this is only one side of the coin. Next to measures to stimulate the creation of innovations, it is essential to improve access to these innovative products after evaluation. It currently takes too long for new diagnostics, drugs and biomaterials to reach the market, and consequently the patient.

We are in favor of the development of a National Innovation Pass, whereby innovative medicines, diagnostics and biomaterials are made available for a limited period. This will significantly shorten the time-to-market and reward innovators of biomedical products. The position of the Netherlands as launching country within the EU for new, innovative products will then be strengthened. And that of course will be both beneficiary for individual patients and for society as a whole. A society that acknowledges the positive impact of innovative biomedical products on people, families and communities and also on cost development in healthcare. We seriously hope that the era of "tunnel vision", when focus was solely directed at costs, will come to an end and that we can begin to focus on the revenues of modern healthcare. „

Michel Dutrée, Managing Director Nefarma

Quote from Michel Dutrée

Government can do much to ensure that the conditions for use and delivery of innovations exist. It can facilitate public education and fast-track regulatory approval. It can make it easy for entrepreneurs to pick up knowledge and ideas and attract funding. It can provide a stable and competitive regulatory and business climate.

Government can even help create a market for a new product, process and service. One way is by acting as a launching customer and agreeing to buy, for example, the first 5,000 office chairs made from bioplastics. With this "advance purchase agreement", the entrepreneur can go to the bank for a loan. Such an approach reduces market risk but leaves the technology, development and financial risk where it belongs: with the entrepreneur. It is the most effective way to direct innovation. Government does not have to evaluate whether a subsidy was legitimate and well-spent after the fact – it only pays for results. If results do not materialize, the funds reserved flow back into the public coffers. If they do, however, the innovation is immediately thrust into the spotlight. Seeing first examples at work in real life inspires new sales to companies, public organizations and private citizens, especially if these new products, processes and services are temporarily exempted from VAT or their purchase made tax deductible.

Government should also make the policies and regulations that govern testing and market entry competitive in an international context. For example, government could tie advance purchase agreements to a stricter testing regime. The additional time and cost to the entrepreneur would be offset by the reduction of market uncertainty and the knowledge that approval in the Netherlands (under the strictest testing regime) could guarantee all but automatic approval in the rest of Europe. That would give the Netherlands a competitive edge as a testing and first-use market for innovations and make it the natural entry point into the European market.

To strengthen our case and support theirs, we would like to quote the OECD report *The Bioeconomy to 2030: Designing a Policy Agenda*.[10] The first quote regards one of the principle policy conclusions of the report, reducing barriers to biotechnology innovation: "Identify factors that can prevent the development of competitive and innovative markets for specific biotechnology applications. Evaluate possible policy actions that could free up markets and access to knowledge, including encouraging public research institutions to adopt intellectual property guidelines that support rapid innovation and collaborative mechanisms for sharing knowledge". The second one regards the different layers of policy: "The bioeconomy offers technological solutions for many challenges facing the world… but achieving its potential will require appropriate national, regional, and in some cases, global policies". The third quote regards the scope: "In the longer term, the emerging bioeconomy will be significantly influenced by technological developments, regulatory conditions, intellectual property, human resources, social acceptance, market structure, and business models… addressing these needs to start today".

The overriding priority for life sciences innovation in the next decade is to realize returns. All the investment in earlier stages of innovation will come to nothing if the concepts generated have nowhere to go, no market to land in and no users and entrepreneurs to turn them into innovations.

Consolidate PPPs

The innovation infrastructure in the Dutch life sciences is beginning to take shape. Most PPPs are up and running, many starting to deliver results. The next step is to progress in both scale and scope – to consolidate existing centers and consortia into clusters and communities and expand to the European level.

The PPPs themselves represent a first stage of consolidation. Individual research groups from academia and industry

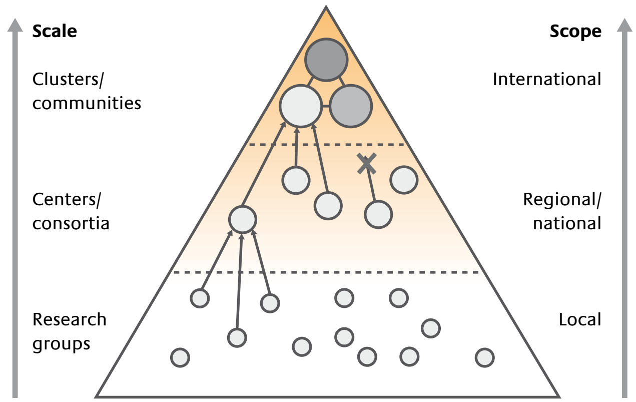

Figure 13: Consolidation and international upscaling

have joined forces in regional and national consortia for (translational) R&D. They realized the first concentration of focus and mass on a limited number of themes and, in doing so, took a step towards even greater collaboration in years to come. The Netherlands now hosts more than 40 PPPs in which the life sciences play a role. This early phase of generation must now be followed by one of selection and the evolution of more advanced forms. We envision their consolidation into about 10 clusters of PPPs that coincide with both the *Sleutelgebieden* identified by the Innovation Platform and the sectors in this book: food, health, agriculture and chemicals & energy. Each sector vision in Part II will present its role in the direction this will take.

Greater collaboration and consolidation must also take place in the back offices. Duplications and overlaps can be eliminated and cohesion and efficiency improved. PPPs will evolve into more dynamic programs if they share a single "backbone" per sector or even for the entire life sciences field. This "backbone" organization could provide continuity (of expertise, facilities and resources) without impacting the autonomy of the PPPs using it. This reduces the danger of institutionalization of PPPs. We are already seeing increased cooperation between existing back offices, and even some mergers. As a general rule, new PPPs should link to existing organizations (giving them a running start, saving on overhead and paving the way for additional clustering).

PPPs will not just connect with others and merge into larger clusters. They will also increasingly connect with other parts of a sector's innovation system (basic research, delivery, policy making) and across sectors to jointly develop and use common facilities and instruments (educating and training professionals, valorization and entrepreneurial support, public education and debate, sector representation, etc.). Part II of this book, in addition to the sector visions, contains visions for these cross-links that explain their role in tying together sectors and the life sciences as a whole. Clusters will fuse into communities that connect and align the entire system.

A start was made in FES 2009. The food sector submitted a plan that clustered TI Food & Nutrition and Food & Nutrition Delta with the Nutrigenomics Consortium. It was closely geared towards the agriculture sector plan presented by TTI Green Genetics. In chemicals & energy, the life sciences related PPPs B-Basic and Ecogenomics clustered in the new BE-Basic program centering around an open innovation pilot plant and close ties to separation technology (DSTI) and catalysis (CatchBio) PPPs. Several life sciences PPPs in the health sector organized themselves into four clusters around focal PPPs, merged some consortia and established a forum for ongoing discussion on focus and alignment.

Innovation programs like Life Sciences & Health and the Food & Nutrition Delta further illustrate this increasing integration and alignment. Established and operating in close collaboration with PPPs, they take up activities like innovation credits for entrepreneurs and educational programs that are important to the entire sector.

Go European

The upscaling into clusters and communities will coincide with expansion to the European level as a first step towards becoming truly global. Limiting PPPs to (research activities and spending in) the Netherlands has always seemed a bit impractical in a globalized (knowledge) economy and an open innovation paradigm. However, the absence of a European dimension has in fact allowed the Netherlands to pioneer public-private partnership at home and position its PPPs as attractive partners in the cross-border opportunities that are now emerging. Europe, like the Netherlands, suffers from the innovation paradox and is following the Dutch in acknowledging the value of PPPs as an integral approach to tackling it. Dutch PPPs should make maximal use of European opportunities to acquire both funding and expertise.

The Seventh Framework Program for Research and Technology Development (FP7) will spend a total of EUR 50 billion between 2007 and 2013 with the aim of bringing together academia and industry. The main portion (EUR 32 billion) is explicitly devoted to cooperation. Europe is becoming a major source of funding for Dutch innovators, including PPPs. If history is anything to go by, we should do well. The Netherlands ranked fifth in awards under FP6, achieving a net gain on its contribution as a member state and outperforming all others in the success rate of its proposals.[39] Competing on our showpiece (PPPs), the Netherlands should have the ambition to do at least as well in FP7.

The European Institute of Innovation and Technology is promoting the creation of so-called knowledge and innovation communities (KICs). Through these KICs, public and private partners from across Europe will come together both virtually and physically to form an integrated “chain” from higher education and knowledge generation to valorization and markets: from principle to product. It is the natural home for Dutch PPPs, and the natural next step in their development, especially because the KICs follow the same philosophy that is behind the Innovation Platform’s *Sleutelgebieden*. With their experience in building and managing consortia, their expertise in translational research and the emergence of sector communities, Dutch PPPs are well positioned to play central roles in the KICs and host some of the physical “nodes”. The European level offers not only funding but access to knowledge, facilities and talent on a scale to match the next step in their evolution.

Also of interest are the European Technology Platforms (ETPs). These are European associations of public and private stakeholders within technology-intensive fields that develop joint visions, strategic research agendas and action plans to boost Europe’s competitiveness – with industry at the helm. Since 2003, about 40 ETPs have been set up. Relevant examples include Food for Life, Farm Animal Breeding and Reproduction Technology, Plants for the Future, Global Animal Health, Sustainable Chemistry and European Biofuels Technology. For ETPs that promise breakthrough technological advances, that have achieved sufficient scale and scope and that would benefit from more organized collaboration, resources are available to set up a Joint Technology Initiative (JTI). A JTI is a large-scale PPP, very similar to and in part inspired by the Dutch TTI model. Currently, six have been or are being set up. One, the Innovative Medicines Initiative, is of particular interest to the Dutch life sciences, and PPPs in the health sector are closely involved. TI Food & Nutrition has played a leading role in Food for Life and by combining strategies has opened the way for its own European expansion and the establishment of a JTI.

The Netherlands actively participates in ERA-NET, the European policy instrument for the coordination of national research programs in Europe. In an ERA-NET, cooperation and coordination between European funding sources, like the NWO in the Netherlands, takes place. NWO with ACTS and NGI are the secretaries of several ERA-NETs in the life sciences, including Plant Genomics and Industrial Biotechnology. Also, so-called Joint Programming is being set up, where European member states align their public strategic research agendas on pan-European challenges (e.g. ageing), cooperating on such topics instead of competing for scare resources.[40]

There are more opportunities. The European Strategy Forum on Research Infrastructures (ESFRI) aims to create a pan-European research infrastructure, aligning policies and sharing resources. Dutch life sciences initiatives have been recognized as best-in-class standards in the Biobanking and

Biomolecular Resources Research Infrastructure (BBMRI). Bilateral collaborations are valuable too, as when a Dutch PPP supported the establishment of a PPP in Denmark.

Europe is the next step for the Dutch life sciences, both in scale and scope. However, playing a leading role abroad depends to a large extent on the quality of the infrastructure and collaboration at home. That home base and collective positioning will be key. Moreover, the evolution from local research groups to national centers to European clusters and communities is an ongoing process. New initiatives will spring up, and the best will consolidate and mature into existing clusters or new clusters of their own. The combined experience and capabilities of the Dutch life sciences PPPs give new initiatives a head start. The future is in Europe, but only if we continue to build on and preserve our strengths – in PPPs and in the underlying science base.

Secure the science base

It has been said many times, in this book as well as elsewhere. The Netherlands is blessed with an excellent base of scientific knowledge. We rank third in the world in impact per scientific publication and our scientists are among the most productive.[7] Breaking the figures down further shows that the life sciences are important contributors to that excellence (Figure 14). In the closing decades of the twentieth century, our relative share of leading scientists placed us sixth in the world overall and third in biology, a core life sciences discipline.[41] Usually, such considerations are left at these figures and attention turns to discussing why we are not getting all we can out of that base in terms of valorization. However, it would be a big mistake to take that scientific excellence for granted. We risk building on historically strong, but crumbling foundations.

There are no (clear) indications that the life sciences knowledge base in the Netherlands is eroding. Current citation impact scores are based on seminal articles often published years ago. It would be interesting to compare the development in citations over time between past masters and those we expect to take up their mantle. There is,

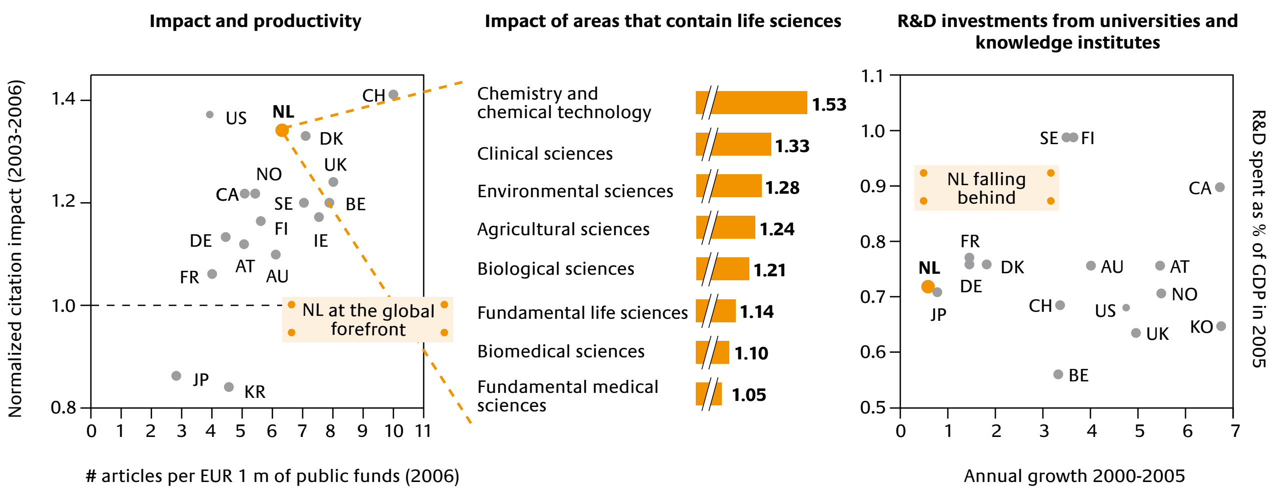

Figure 14: The characteristics of the Dutch research base

Source: Netherlands Observatory of Science and Technology (NOWT), *Science and Technology Indicators Report* (2008) however, cause for concern. While funding may not be the only or even best predictor of scientific success, our lead is slipping. At 0.7% of GDP, Dutch spending on public R&D is average for Western economies, but its growth is lowest of all (Figure 14).[7] Growth in public R&D spending is even below GDP, meaning that as a percentage of GDP, investment in basic science is actually declining and has done so over the last decade (Figure 5).[11] What does that mean for the government's ambition to increase overall R&D spending in the Netherlands to 3% of GDP and public research spending to 1%?[17] It has recently been suggested that this ambition be lowered to the level of average R&D investment in the OECD. This means almost halving ambitions to about the level that we are actually at right now

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Nothing to grumble about?

Great book, but is there really nothing to grumble about? Sure, the landscape looks fine. Dutch biomedical science ranks at the top worldwide and the infrastructure is in place to convert this know-how into new, useful products. But how about basic research? The book emphasizes its importance – "Basic research is crucial" – but also shows how Dutch public investment in biomedical research has shrunk in recent years. We are not only falling far behind our competitors, but also falling short of our own lofty goals, as formulated in the KIA (*Kennisinvesteringsagenda*).

So, should we not consider redirecting some of this PPP money to basic research? Is it really smart to put more money into PPPs than into investigator-initiated research? Are top-down-enforced government-funded PPPs the best way to stimulate the use of new academic knowledge for creating Dutch prosperity? Is it really smart to force our best academic investigators to dance with slow-moving industrial giants? How about facilitating start-up companies by academics, as the Americans do? How about the example of the Swiss, who are very successful in biotech, without ever funding PPPs? They choose to fund their academic research generously and trust that private industry will find new knowledge where it is locally generated.

Great book. It makes a strong case for more Dutch investments in innovation and research in the health sciences. I support the vision, but let us not forget that the reputation of the Netherlands as a "bioregion" rests on the excellence of our basic research, not on PPPs. "

Piet Borst, Staff member and former Director of The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Emeritus Professor of Clinical Biochemistry and Molecular Biology, University of Amsterdam, Member of the Dutch Innovation Platform

Quote from Piet Borst

and have been for years. Wouldn't that be a bitter example of discontinuous policy?

It is inevitable that other economies are catching up – although there is no reason why we should fall behind the USA, UK, Japan or (Northwest) Europe. Strong universities and excellent researchers are vital to educating future generations of life sciences professionals, attracting scientific and commercial talent and investment and sustaining the absorption capacity to quickly seize upon and use the results of scientific research, even if that research was not conducted here. Education is the engine of our economy and society, and innovation is carried by educated people (Part II, Chapter VII). Basic science is literally fundamental to the entire business of innovation, and sufficient resources are necessary if scientists are to go where curiosity leads them and make new discoveries, even purely by accident. To maintain, let alone improve, our leading knowledge position, public investment must be significantly increased.

Resources must be carefully balanced between unconditional research and that which occurs in PPPs and other research arrangements that require matching from university funds. Choices will have to be made. That is the responsibility of researchers and university administrators, although government may want to consider how far it can go in tying basic funding to contract research and public-private performance.

Funding of basic research, however, also comes with the responsibility to make sure that the results of that research find their way to entrepreneurs willing to develop and deliver innovations based on them (Part II, Chapter VIII). The focus there should be on ensuring knowledge (and IP) is picked up, not on negotiating a high price for it. Universities have already been paid for their research and should be required and enabled to devote the necessary resources to making it available to entrepreneurs.

RECOMMENDATION: Build on the strengths that have been developed

- **Create the best conditions for the use and delivery of innovations: easy access to knowledge and IP, ample availability of (venture) capital, the absence of unnecessary regulatory constraints, well-informed and critical citizens and a well-functioning market** ***Life sciences field & government***
- **Consolidate the over 40 Dutch PPPs in which life sciences play a role into ten or fewer clusters that are part of international networks** ***Field***
- **Continue to invest in (clusters of) PPPs** ***Government***
- **Increase investment in the basic research in academia needed to preserve the Netherlands' leading knowledge position** ***Government***
- **Make it easy for entrepreneurs to acquire and build on the knowledge and patents of academia and PPPs** ***Field***
- **Invest in higher and public education to deliver the scientists, entrepreneurs, investors and informed citizens of the future** ***Government***

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3. Position the Netherlands as one bioregion

A connecting theme throughout this chapter has been ever-increasing collaboration: as a natural consequence of open innovation, as a cornerstone of the PPP concept, as a lesson drawn from our own experience and as a challenge for the future. Unity in diversity may rightly be considered the central theme of this book. It all comes together in the third and last main recommendation: to position the Netherlands as one bioregion.

Much has been made of clusters and regional competitiveness. With the life sciences, people tend to think of the San Francisco Bay Area, the Boston area or Medicon Valley in

“ **Make the Netherlands the world’s Life Sciences Polder**
Over the next decade or so, life sciences/biotechnology can offer the world hope. It can help us meet the global challenges that threaten our future, challenges relating to nutrition/water, health, climate change and energy.

As the world enters the life sciences age, the Netherlands has almost everything going for it to become the “Silicon Valley” of the global life sciences/biotech community. On just 42,000 square kilometers we combine an excellent knowledge base with a very powerful chemical and agro-food industry that includes some of the world’s biotech pioneers –including our own company – and a very highly developed logistics infrastructure. On top of that, our country is the pioneer of public-private partnerships, in which industry, academia and the government join forces to turn science into marketable applications with social and economic value. Such partnerships are crucial in a high-risk, high-reward, long-term-oriented sector like the life sciences.

The only other ingredient needed for a flourishing life sciences field and bio-based economy is a firm commitment from all stakeholders involved to help make the Netherlands the world’s “Life Sciences Polder”. I hope and trust that our country will make this commitment. ”

Feike Sijbesma, CEO Royal DSM

Quote from Feike Sijbesma

the Øresund region of Denmark and Sweden. The Bay Area hosts four world-class research universities (and many more of less renown) and about 1,400 companies employing over 100,000 people in the life sciences. It covers an area of about 18,000 km^2.[42] With 20,000 km^2, Medicon Valley is slightly larger and includes five life sciences related universities (out of a total of 12), six business parks with a strong life sciences component, and 32 hospitals – including 11 university hospitals.[43] Each cluster presents itself as a single region and speaks with a single voice, despite internal rivalries and competition. As such, they realize economies of scale in attracting talent, business and investment from around the world.

In the Netherlands, almost every region and province claims the life sciences for their own and articulates the ambition to become a hub on a European or global scale. Most of these clusters, valley and delta’s consist of one university and/or university medical center, a single business park, a regional investment company and 10-20 life sciences companies. On an international scale, however, few of these impress the competition. Unfortunately, national and European regional development programs like “Pieken in de Delta” and EFRO have long encouraged this practice.

A single region within the Netherlands can hardly expect to compete on the international stage. As *one bioregion with local hotspots*, however, our position is promising. The

Netherlands is only about twice the Øresund or Bay Area, but that space is packed with 13 universities and strong food, health, agriculture and chemicals & energy sectors with leading multinationals, a host of SMEs and a large and growing number of start-ups. With the Port of Rotterdam as the petrochemical gateway to Europe, backed by strong industry and research groups, few regions are better positioned to become a major hub in the bio-based economy. Every major agriculture company in the world seeks out Dutch plant breeders. Our food sector has some of the most innovative food and food ingredient companies. The medical infrastructure with its universities, university medical centers and biobanks is world class and could be ideal for clinical trials.

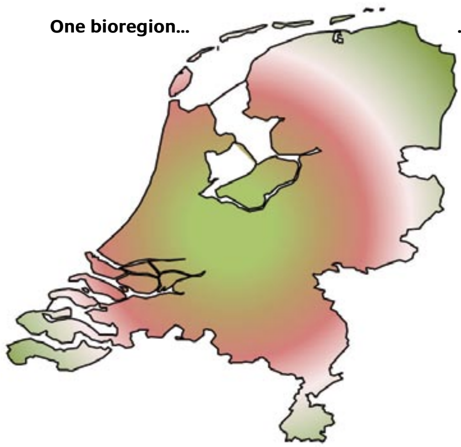

Figure 15: The Netherlands as one bioregion

In the life sciences, collaboration and knowledge exchange take place at multiple spatial scales simultaneously. Local hotspots are important, as spin-offs and start-ups tend to locate near their "mother" organizations; regional is therefore the logical scale for incubator activities. Similarly, knowledge passed around the coffee machine is to a large extent a local phenomenon that can be stimulated by the presence of dedicated science parks. Research collaborations typically require an (inter)national scale. Few organizations can find all the knowledge and resources they need locally. Innovation policy, research funding and (venture) capital are national or even European in scope.

If we combine our local strengths and position them as part of a larger whole, we have a much more powerful message to send to international talent, companies and investors. The Innovation Platform has come to the same conclusion. It is proposing to replace previous fragmented marketing campaigns with one story to attract 50 international companies and 1,000 PhD students to the Netherlands.[16,44]

We have seen before that the life sciences connect sectors through technologies and applications. We all need to work together to address the socio-economic challenges of today and tomorrow. Where better to do this than here – with all that expertise and infrastructure so close together and a long tradition of collaboration and partnership. The Dutch invented the polder model. We pioneered PPPs that are recognized internationally as best-practice examples of collaborative innovation. The Dutch are a nation of traders, an open society ideally suited to an open innovation paradigm. No other region can claim all of this together (Figure 15).

We must come together as one region. Not just to position ourselves on the world stage, but to take that integrated approach that is needed to achieve structural innovation. To take it to the next level and expand into Europe to have access to the resources, knowledge and competences that our neighbors can offer. To join forces in education and training, valorization, technology development and other cross-links that will reinforce the sectors and each other. To breed informed citizens and create an appetite for life

Life Sciences Forum

The writers of this book will continue their collaboration and formalize it in the Life Sciences Forum. It will be open to other participants, meet several times a year and will initiate actions (like developing this vision) that are of cross-sectoral interest. The Life Sciences Forum will have no budget or authority. Both will have to be supplied by its participants and those they can mobilize into action. Its vision is this book. Its mission is to inform, inspire and incite. Its ambition is to make optimum use of the life sciences and the innovation infrastructure to deliver social and economic value to the Netherlands.

Its activities will include:

- Taking this vision to the political and public arenas
- Facilitating debate on the vision (e.g. by placing it online as a "wikivisie")
- Building a life sciences portal, www.lifesciences.nl
- Setting up best-practice exchange within and between sectors
- Reinstating the annual monitoring of economic activity in the life sciences lost with the demise of BioPartner
- Encouraging the establishment of social programs to study and discuss the impact of life sciences innovation
- Helping new PPPs (in the life sciences and beyond) get started and thrive

sciences innovations that will enable us to reap the social and economic rewards of past and future investment. Take for example the Dutch life sciences technology centers: when writing this book, they jointly decided to set up a coordinating body to boost cooperation between them (Part II, Chapter VI).

The life sciences in the Netherlands have demonstrated increasing cooperation between different players from all corners of the field, exemplified by the many PPPs in operation. This book is a further step towards greater collaboration and convergence as a single bioregion. We have jointly laid down our vision for the future and will continue this collaboration as a platform for joint initiatives. (In)formal leadership bodies from individual sectors will meet and in time create rudimentary governance. In the life sciences, we are comfortable with gradual evolution. There is no need to rush integration or impose top-down hierarchies. The advantages of greater collaboration are clear and collaboration will naturally lead to integration as and when it becomes expedient. We will continue to focus on what binds us and to value what makes us different. This book's theme – "united in diversity" – is dedicated to both.

RECOMMENDATION Position the Netherlands as one bioregion

- **Position the Netherlands internationally as a single bioregion with local hotspots** ***Life sciences field & government***
- **Continue the cooperation begun in writing this book, share experiences and set up (informal) coordination wherever useful** ***Field***
- **Help future PPPs take advantage of the lessons learned and existing back offices** ***Field***

Quote from Jan Wisse

“

Biotechnology: a driving force in the Dutch knowledge economy

The 21st century is gearing up to become the age of the knowledge- and bio-based economy. Biotechnology will help us translate a rapidly growing body of knowledge of natural processes into innovations in areas such as healthcare, nutrition, agriculture and industrial production. In doing so, it will add to human and animal health and open up avenues towards sustainable production. Now largely dependent on crude oil, industries will become more environmentally friendly by switching to green, renewable resources.

In this “3rd industrial revolution”, the Netherlands will be able to play one of the leading roles. Key building blocks are already in place: well-educated knowledge workers that know how to build stable partnerships, first-rate science and (bio)technology companies used to conquer global markets. With all of this in a relatively small geographical area, the country is well-positioned to turn itself into an international hot spot for biotechnology.

Both the private and the public sectors have invested heavily in biotechnology over the last decade. Investment levels should be maintained for years to come, because in biotechnology it typically takes more than 10 years to turn ideas into profitable products. Nevertheless, times are approaching in which we will be able to reap the fruits of our labor.

The Dutch biotechnology sector is determined to do all it can to bring in the harvest. At the same time, the sector counts on the Dutch government to also keep up the pressure. Public-private collaboration will be one of the instruments; targeted innovation support will be another.

Only by joining efforts can the Netherlands retain its prominent place among world competition. By working together, we will lay down a knowledge- and bio-based economy as the foundation for a more healthy and sustainable world. ”

Jan Wisse, Managing Director of Niaba

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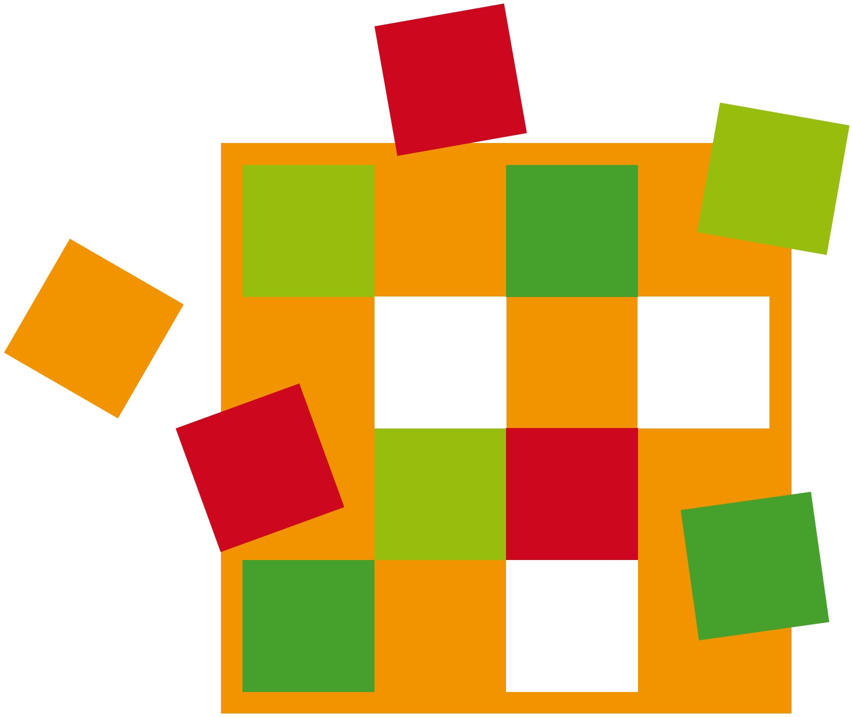


Part II Diversity

Diversity

I Introduction

The first part of this book presented a joint and unified vision. In Part II, each sector and "cross-link" tells its own story, providing its own take on the future of the life sciences and the role of PPPs. The food, health, chemicals & energy and agricultural sectors are all impacted by the life sciences, but in different ways. These sectors differ in size, dynamics and the (type of) companies and institutions within them. Technology, education, valorization and social aspects span all sectors of the life sciences but differ in focus: development, teaching, commercial potential and social acceptance.

Each of the following chapters has been written by experts from the sectors or cross-links themselves, with input from and endorsement by their colleagues. Each chapter presents its own perspective and can be read independently. The teams have read each other's drafts and commented on them. They have joined in sometimes heated debate on each other's views. The various interpretations, expectations and opinions reflect the rich diversity of the life sciences. However, there is broad consensus on the outlines and on many of the details of the way forwards, and all agree that these perspectives constitute a strong basis for further cooperation across the life sciences field. That is what we mean by "united in diversity".

Let us briefly introduce you to each of the chapters.

Chapter II: Food. In the Food chapter, a picture of 2020 is painted in which the life sciences have enabled the development of healthy food and have made food supply more sustainable. In 2020, we understand "healthy" much more than we do now; we understand what makes us healthy, the factory that is our digestive tract and the gatekeeper function of our mouth. We target food products accordingly and are able to make sufficient health claims on these products. In that future, food production is based even more on advanced science than it is now. The role of PPPs in that future is substantial, and PPPs increasingly extend into Europe. Clear national ambitions for the food sector have been defined – health and sustainability – and the sector and government are steadfast in their pursuit of these goals. The government in 2020 provides structural support for this pursuit, and SMEs have become more actively involved in innovation.

Chapter III: Health. The Health chapter argues that a sustainable healthcare system and an economically viable health sector go hand in hand, and that (life sciences) innovations are key to both. Taking the Netherlands' strengths and limitations as starting points, the authors of this chapter look towards a future where healthcare demand increases and delivery adjusts accordingly. A future where the life sciences enable innovations that meet patient needs and delivery requirements. A future where all stakeholders cooperate and innovate in an international open innovation structure and where the innovation and entrepreneurial climate in the Netherlands is favorable. The public-private innovation infrastructure plays an important role in this future, bringing clear focus, a healthy pipeline, strong support and true partnership. Such partnership extends into Europe and receives structural backing from the Dutch government.

Chapter IV: Chemicals & energy. In the Chemicals & energy chapter, the building of a sustainable bio-based economy for the Netherlands is described, an economy in which biomass is a primary source of energy, chemicals and materials. The bio-based economy is the way towards energy security and environmental sustainability, and brings with it considerable economic opportunity. This transition requires technological innovations in several areas, and the life sciences field is one of the critical enablers. This transition also requires collaboration: collaboration in research, technology development and piloting and testing facilities at a shared innovation campus/center. PPPs play an important role in this collaborative transition. PPPs increasingly consolidate and cooperate on an international scale, and receive long-term support. Key to this transition are (1) a portfolio of opportunities ranging from intimate academic-industrial collaboration to proactive Venture Capital Funds for seed capital, and early as well as later venturing, and (2) secure access to sustainable local and global biomass.

Chapter V: Agriculture. The Agriculture chapter paints a picture of 2020 in which the world is standing up to the challenges of feeding its citizens, maintaining the health of animals and humans, supplying energy and basic resources and sustaining the environment. In facing these challenges, agriculture plays a critical role by the primary production of (healthy) food and base material for energy, chemicals and materials, while interacting sustainably with its environment. Achieving this future relies on life sciences innovations and builds on the strong knowledge base and industry that already exist today. This means safeguarding and expanding the strong knowledge infrastructure of the sector. It requires focus and mass on competitive and distinguishing technology in several fields. It requires stakeholders to come together in an open innovation system with public-private partnerships. And finally, it requires technology that is sustainable and acceptable to society.

Chapter VI: Technology. In the Technology chapter, the road to the future is paved by enabling technologies (from the life sciences and other areas) which fuel the development of new products, processes and services in sectors such as food, health, energy & chemicals and agriculture. The Netherlands can build on an already strong infrastructure of enabling technologies, like proteomics, metabolomics, systems biology, bioinformatics, microscopy, bionanotechnology and biobanking. The road towards this future is one of coordination, with a nationwide body of technology centers. It is a road of cooperation, where technology centers work closely together with the sectors and the PPPs therein. It is a road of convergence, where technologies increasingly come together and are combined. Finally, it is a road of stability, with dedicated structural funding that enables expert communities and necessary infrastructures to be built.

Chapter VII: Education & training. In the Education & training chapter, a way forward for life sciences education is sketched. The crucial functions of education and the diversity of the life sciences and its application are central to this vision. Education not only empowers academia, industry and government with what may be their most important asset – educated professionals – but also creates informed citizens who can make life sciences choices in everyday life, like using green energy or buying a certain food product. This chapter describes a future where primary and secondary life sciences education brings examples from student’s everyday life into the classroom. A future where higher education in life sciences consists of a top-quality, diversified curriculum with solid fundamental research training and strong market orientation that continues into lifelong learning. A future enabled by structural funding for life sciences higher education, by valuing top education similar to top research, and by involving the professional field in the life sciences curriculum.

Chapter VIII: Valorization. The Valorization chapter provides an outlook for 2020 where the results of life sciences research are optimally exploited in creating new products, processes, services and commercial activities that see to our needs. This outlook takes into account the many stages and ways of valorization, but with a focus on the role of universities, in particular in direct technology transfer to existing or new companies – a key activity in valorization that requires much attention. The future is one where academic institutes see valorization as their third mission, receive dedicated funding for valorization activities and have professional technology transfer offices. Where resources such as Seed Funds are readily available for entrepreneurs who pick up IP from academia. Where industry and universities have long-term strategic relationships, and where policy, like tax benefits or public procurement, stimulate valorization throughout.

Chapter IX: Social aspects. In the Social aspects chapter, an independent committee stresses that social research must accompany (life sciences) innovation, and the committee draws conclusions for future directions. Science and society mutually influence each other. New developments bring new social questions, and innovations only find use when embraced by society. In this chapter, it is argued that early-stage exploration of the social aspects of innovations is indispensible for a strong life sciences field. This is done through Ethical, Legal and Social Aspect (ELSA) research, which uncovers the plurality in life sciences discussions and anticipates the field's impact. ELSA activities include facilitating the right checks and balances between stakeholders and organizing interactions with and between them. It is argued that sufficient social research requires a budget of about 3-5% of that of the life sciences, and that ELSA research and scholarly activities demand different modes of organization, both embedded in and independent from PPPs.

Authors

Jan Sikkema, TI Food and Nutrition
Wim Verhoog, MGMC

Food

Future food, grow it now

II Food

This chapter takes an outlook on the food and nutrition sector in 2020, the impact that the life sciences have and the role of public-private partnerships. The chapter starts with a short prologue where we describe the changing role of food in our life. Eating is nowadays not so much a matter of survival to the next day, as it is a matter of reaching an old age while staying healthy. In section two we describe the challenges we face with relation to food. Life sciences can assist in overcoming many of these challenges and its role is described in sections three to six. Finally, we end with an epilogue describing the main conclusions and recommendations.

Throughout the chapter you will find boxes in which we will describe examples, explore subjects in more detail or tell related stories. Let us now dive into the world of 2020 and look back at the route we have taken.

A. Prologue

How did primitive humans deal with their food? They probably were not very picky. They had to use what they had to achieve their primary goal – survival for another week, another month or until next year. The reason we nowadays like sweets or fat has everything to do with what our remote ancestors regarded as "functional" food. Such food provides us with lots of calories, and builds a store of body fat against bad times to come. The calories melted away soon enough anyway, thanks to the healthy exercise provided by hunting buffalo.

The diseases of old age as we know them now, let alone any relationship between them and nutrition, simply did not figure into the equation. Such ills were held at bay simply because death came at a relatively early age: our remote ancestors commonly died before their 40th birthday.

The last century saw us living in an increasingly prosperous part of the world. We did not worry about whether we would eat or not. Large portions of cheap, tasty products were on offer at every street corner. The food industry's very survival came under threat thanks to its own success.

Our lifestyle changed, with the result that we started to look at food differently. We had to: the trick for us was to stay healthy in the midst of such excess, during the much longer lifespan allotted us. Diseases such as obesity, diabetes and cardiovascular conditions, started to become more common.

Whereas *medical science* had previously been preoccupied with the fight against diseases, we were starting to look increasingly at food as a route to long-term health and an investment in the future. Not just by cutting out things that are "bad for you" (fats, sugar and salt), but with an increasing focus on the way food could contribute actively to health.

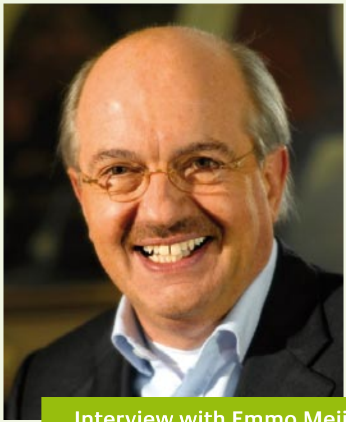
Even though hunger no longer gnawed at us, in our growing prosperity we still had that gnawing feeling telling us that the world was bigger than our own little area and that we should raise our gaze beyond what we had here and now. Of course it would have been naïve to think that the issues of food supply and sustainable food production could be resolved purely by turning to science and technology. But insofar as innovations in food and nutrition were able to contribute to solutions in these areas, then of course they were more than welcome.

All in all, then, around a decade ago scientists and food producers had enough challenges to keep them busy. There was also complete confidence that we would advance in these areas. Partly thanks to a series of successes that had already been achieved, it was clear that the life sciences offered tremendous opportunities in the food and nutrition field. Moreover, that conviction carried over to parts of society that were less directly involved. All of which goes to explain the advances made to the present day, in 2020.

“

We are only at the beginning of learning

Food and nutrition is the area where life sciences will have the biggest impact on the development of knowledge, processes and products” says Prof. Emmo Meijer (senior vice-president global R&D of Unilever). “In the years to come a great deal of the complexity of the interactions between food (ingredients) and the body will be elucidated by the deployment of advanced genomics and metabolomics tools. So far food and nutrition research has been impeded by lack of proper tools as only a few mechanistic links between nutrients and physiological effects could be established. With the increasing technological possibilities many more biomarkers for e.g. metabolism of food components, for interactions between microbiota and gut epithelium will further substantiate the contribution of food and nutrition to health.”



Interview with Emmo Meijer

Emmo Meijer, who is a biochemist by training, compares the studies of the body and its interactions with nutrients with the cell biology he was taught during pre-graduate classes. “At that time we were able to accurately describe the cell and its organelles, but did not have a clue of the complexity of processes taking place in the cell and between cells.”

“Over the last ten years the food industry has made large investments to gain knowledge in the role of specific components of our diet in our body. The impact of single components in our body can already be monitored fairly accurately: for several food ingredients we do know their mechanism of action. However, we are only at the beginning of learning how food and nutrition products affect our body on the middle and long term. Life science research will make the difference in accomplishing this.”

“The collaboration of many different disciplines in ‘life sciences’ have the advantage of obtaining faster, knowledge leading to impressive breakthroughs and a multitude of applications. Associations, such as public private partnerships of which we have a couple of successful examples in the Netherlands, are necessary to organize both the required research and the necessary transfer of results to the food industry. Which, on their turn, could provide consumers with healthier and safer foods with a desired taste. However, to be able to grasp the real profits, emphasis in these partnerships needs to be put on areas that have the biggest improvements or opportunities for our society and industry. ”

Emmo Meijer, Senior Vice-President Global R&D of Unilever

B. Looking back at the challenges

The size of the obesity issue was completely clear at the start of this century, including the associated, greatly increased risks of chronic disease. There could be no doubt: this was the front line for the prevention of disease, which the government, science and the food industry sought to do by means of nutrition.

Dangerously obese

In the Netherlands between 1998-2001, 55% of males and 45% of females aged between 20 and 70 were overweight. We expected, with some trepidation, that the numbers would increase by half within the next couple of decades.[1] The WHO spoke of an alarming trend in the European region, in particular because of the way obesity was affecting children, with a tenfold rate of increase compared to the 1970s.

There was – and still is – every reason to regard this as a major problem. Obesity increases the risk of a great number of chronic conditions: diabetes (diabetes mellitus type 2) as well as cardiovascular diseases, biliary diseases and motor system conditions, including arthritis. There is also an increased risk of a variety of cancers, including those of the large intestine, womb, kidneys and oesophagus. According to WHO estimates, in 2007 obesity in Europe was responsible for more than 1 million deaths annually, while causing more than 12 million life-years of ill health.[2] In different parts of Europe, obesity was related to 2-8% of health costs.[3]

At the start of the century we knew that in 2050 there would be more elderly (65+) in the Netherlands than young people. This is a group that would then suffer significantly from chronic disease due to obesity but which, due to age-related changes in consumption and the uptake of nutrients in the gut, would also suffer from deficiencies of certain nutrients, sometimes even leading to underweight.

The simultaneous malnutrition in a significant portion of the world was the consequence of an uneven distribution of prosperity and resources and was thus a political problem. In a situation like this it was painful to see the amount of loss down the line. Crops infected on the land, poor logistics and spoilage of raw materials and food led us to see that only two-thirds of the food produced was actually consumed. The rest disappeared or spoiled prematurely. This demanded a solution, especially in light of a steadily growing world population.

Faced with the prospect of a global population growing towards an estimated 9 billion in 2050, we knew that we wouldn't be able to make it just by increasing production, coupled with improved measures to prevent losses. The efficiency with which we used raw materials could be dramatically improved.

The food chains – animal and vegetable – had to be optimized for sustainability and efficiency, and the range of products had to be widened to include products distinguished by their contribution to consumer health as well as their taste and convenience.

We understood that we had to focus on the consumers' needs. The consumers were becoming increasingly aware that a healthy lifestyle, framed in terms of nutrition and exercise, was essential, including as it did the prospect of a healthy old age, the costs of healthcare and the insurance premiums needed to pay for it. But there were also less rational impulses where food was concerned – one of which was that food had to taste nice. We had to improve our knowledge drastically, especially where it related to the appreciation and acceptance of food.

Even in comparison with other countries in our region, we were well placed to contribute solutions right from the start. In doing so, we cherished the ambition to consolidate our

The Dutch food sector 2009

The food industry is the largest industrial segment in the Netherlands and one of the most important export industries.[4] The food industry proportionally makes up a larger share of national industrial production in the Netherlands than it does in other countries in the EU. With a share of about 1% of the total number of enterprises, including around 4000 SMEs, the Dutch food industry provides 2% of total employment, 3% of total value added, 4% of total turnover and even 8% of total Dutch exports.[5]

Characteristics	
Size of the Dutch food sector	EUR 63 bn (2007)
Turnover by SMEs	EUR 25 bn
Number of employees	118,000 (2007)
Number of companies	4000

Five of the world's top 100 food companies are based in the Netherlands (Unilever, Heineken, FrieslandCampina, VION, CSM). The Dutch food industry is among the top three contributors to Dutch GDP and demonstrates leadership in many fields. For instance, after the USA, the Netherlands is the second largest exporter of agricultural products in the world and number three in global dairy product exports, behind Germany and France.[6] Ranking sixth among EU food and drink producers (about 5%), the Netherlands is a major exporting country within Europe with a share in total intra-EU food and drinks exports of 17.3% in 2006.[7] In those years the total export value of food products from the Netherlands was around EUR 25 bn.

leading, innovative position in the important key area of food and nutrition, or even to extend our lead.

At the same time we also saw the need to combine forces. Innovations are found precisely on the border between research disciplines. We also wanted to forge more public-private partnerships, with a far greater number of parties than before. The issues were so complex that we understood that we – research institutes, universities and businesses, alone or in bilateral coalitions – often did not have the necessary knowledge and resources available. Government investment in a powerful knowledge infrastructure ensured the necessary continuity for the collaborations. In these public-private consortia we had already seen the benefit of sharing the rights to the basic knowledge that was jointly developed. We dared to go for it because we dared to share. In this joint approach we looked beyond our national borders for possible collaboration abroad when we needed to acquire the basic knowledge needed for innovation.

Now in 2020, we may conclude that the food sector has been able to profit from rapid developments in the life sciences, giving us healthy food, tasty food, affordable food, safe food, convenient to prepare and consume, produced more efficiently and sustainably – a number of examples of which are presented in this chapter. The programmed approach adopted by the public-private partnerships in the food sector has led academic research to focus more on those themes that are important to the industry. Joint forces (industry, universities and research institutes) have led to significant breakthroughs. In this regard, the web-based expertise finder[8] was a great help as it allowed those commissioning research to rapidly track down the scientific and technological expertise they required, as well as the necessary facilities. Moreover, in recent years several hundred scientists have passed through PPP programs to food businesses, which is possibly the most direct, most efficient way to transfer knowledge.

“ **A concentration of forces is clearly necessary**

The development of the life sciences is still very much in an exponential phase. To be able to play a role of significance in this field, a concentration of forces is clearly necessary. With a strong foundation, (international) collaborations are easier to put in place. Movements in this direction are visible everywhere in the world. The European Technology Platform “Food for Life”, for instance, has indicated the areas on which research should concentrate, but not where it should be done. From the point of view of industry, working with the best is a clear advantage in this era of “open innovation”, and it makes life easier if the best are close together. A second aspect, which should be emphasized even more strongly, is the fact that although applications in pharma, food and biotechnology still differ, these fields are coming closer and closer together. This is logical, since the biochemical and physiological base is the same, and their targets, human and environmental health, are similar. The vision illustrated in this book fits very well with these developments. From the existing strong foundations in the Netherlands, through increased collaboration and continued support, a unique position might be obtained. ”

Peter van Bladeren, Director Nestlé Research Center, Switzerland

Quote from Peter van Bladeren

C. What is healthy? What makes us healthy?

The relationship between health and nutrition has been known about for some time, but it was difficult to define it precisely. In the past, we were also hampered by a rather indirect research methodology. We studied the health of population cohorts with different diets and attempted to draw conclusions from the comparisons. This treats the human being – with the exception of a few insights, such as the role of cholesterol, folic acid or anti-oxidants – as a black box: food went in and the result was more or less healthy people. The question remained: was the total picture we observed the result of diet rather than, say, lifestyle? Above all, we found it difficult to define "health" with any precision. Was a person healthy if he/she wasn't overweight, if a number of blood indices were OK and he/she wasn't ill? Or should we be able to express the optimum physical state in terms of a number of favorable metabolic processes, which would also open the way to "feeding" those specific processes?

In that last sense, we have now, in 2020, made enormous progress. We know the clusters of genes that form the script for the major metabolic processes in our body. Moreover, we can determine whether those groups are switched "on" or "off". In fact, we know which compounds (proteins, metabolites) are formed in the processes and we can measure them very precisely, even at low concentrations. In the past decade, the Metabolomics Centre, a PPP set up under the Netherlands Genomics Initiative, has developed and utilized many of the most important analytical methods for measuring the digestion and metabolism of foodstuffs. This way, using biological markers, we are able to state for a given foodstuff whether it has an influence on the expression of certain groups of genes, which might give reason to manufacture food products in which these components are available in higher concentrations or are even absent, if our concern is with less favorable processes. This line was taken up as early as 2009, when we discovered evidence that the fish oil claim was plausible. Omega-3 fatty acids seemed to activate gene clusters in the liver cells which play a significant part in the mechanism by which humans digest fats. We then looked at whether we could describe and predict the ultimate effect at the tissue level. From then on, this was the way we wanted to be able to substantiate every health claim made for food products.

A major step on the road to a more mechanistic approach to nutrition research had already been taken when the Nutrigenomics Consortium was founded in 2004. This consortium comprised the most important research groups studying nutrition at the molecular level, together with industrial partners collected in the Top Institute Food & Nutrition. As the Netherlands had been an early investor in this new research field, we were able not only to build up a strong position but also to play a powerful, coordinating role in the European Nutrigenomics Organisation, which started up in 2005. In the past 15 years, the Nutrigenomics Consortium has shown its worth many times in the analysis and interpretation of the complex interactions between the human body and nutrition.

The new approach did not replace epidemiological research, incidentally. On the contrary, we attach great value to the prestigious LifeLines program that we set up in 2006 to follow the health of an exceptionally large group in the Dutch population for a number of decades. We, together with TI Pharma and the Center for Translational Molecular Medicine (CTMM), allowed our biomarkers to be used, plus the newest, fastest, low-cost non-invasive measurement techniques to collect data from the samples provided regularly by the participants in the program. Rather than comparing groups, we were able to track individuals and thus acquire more specific knowledge and information on the activity of nutrients and diet. We discovered how the results measured by our new parameters and techniques relate to medium-term health aspects as were previously measured in the classical way.

Fighting the fat

Healthy, functional food has not allowed us to reverse the tide of a rapidly growing population suffering from obesity – the nightmare scenario in 2009 – but we have been able to slow it down in 2020. Compared to a decade ago we can now manufacture far more products that assist consumers in regulating their food intake – foods, for example, that give a feeling of satiety even in smaller portions. And we have succeeded in limiting or even repressing the formation of unwanted fatty tissue using specific ingredients in a special product composition.

A side effect of our increased knowledge of human metabolism is that we have started to see obesity as less of a black-and-white issue, without in any way trivializing it. Around 2009 we came to know a lot more about fat storage in the body thanks to improvements in non-invasive imaging techniques (meaning we were able to look inside the body without penetrating it with equipment). Our conclusion was that where fat accumulates is also important. It is harmful if it accumulates in the organs or in tissue other than adipose tissue, as it leads to poorer performance. (In this regard, heavy people can even be healthier than their thinner peers, although overweight remains a risk.) Several years ago we were able to use foodstuff components, linked to a more active lifestyle, to drive adipose distribution as well as to influence other adverse effects of overconsumption. As early as 2009 we had our eye on dozens of regulating compounds (the adipokines), the concentrations of which determine whether or not extra calories are stored in the appropriate fatty tissue. Now, in 2020, we have made far more progress in this area, although much work still has to be done to ameliorate the effects of the obesity crisis. The major European obesity projects, too, like the Diogenes Project (Diet, Obesity and Genes), which is coordinated from the Netherlands, have proved their worth. They have taught us about the great variation in the genetic background as well as diet in the various countries of Europe, and the consequences this has for the incidence of obesity. Inter-country differences have taught us where we should take action to prevent obesity in the future.

It is good for those affected by obesity that we can use a number of biomarkers to concretely show that they are making real progress in their health through diet and lifestyle, even if their scales are not yet reflecting any change.

Naturally, the biomarkers we found have contributed greatly to improvements in disease diagnosis, and treatment monitoring so now one can see very quickly whether a treatment is having an effect. Besides that, we have gone over to a more dynamic type of diagnostic measurement. We look at the body's responses, its resilience. We do that by following metabolic processes rather than seeking to establish a state of health from an instantaneous snapshot. We have progressed far beyond the time when we tested for diabetes by determining the glucose and insulin levels in a blood sample. Just as our present diabetes tests follow the body's response to the administration of sugar, we also subject other metabolic processes to comparable, dynamic tests.

So we now know a lot about components of the diet, what they do with human metabolism. We have improved foodstuffs thanks to our knowledge and made them extremely functional. Besides that, foods have also been developed for specific target groups, such as athletes, pregnant women, people at risk of diabetes or brittle bones

Preventing fatal cardiovascular disease
Thanks to extensive public health research that involves blood tests and cardiovascular system imaging, we have identified natural substances in the body that tell us whether vascular damage has occurred, *even before* the person examined falls ill. Dietary information collected during the research also offered clues into the compounds that – either by their presence or absence – influence the interior lining of the arteries. We were then able to characterize the underlying mechanism. This is how we came to know how to alter the fat composition of the blood favorably via diet in 2020. Since there were continuous interactions between leading academic researchers and scientists working for our industrial partners, the new insights could rapidly be translated into products that contributed to an important degree, for example, to lowering blood pressure.

Graded health claims
Thanks to our advancing knowledge, we were able to emerge from the era of vague health claims. Some years ago, however, the government in particular was starting to go too far when it demanded research-based, scientific substantiation of such claims. It seemed as if the standards would be set so high (as if medicines were involved) that only a few producers would be prepared or even able to invest that much in a product. It was, after all, by no means certain that consumers would want to buy the product.

Fortunately, at that time a way out of the problem was found in a system of graded claims, qualified with the adjectives "possible", "convincing", and "sure". From that point on, producers were able to market their added-value products after the preliminary research phase. This gave them the opportunity to earn money for research that would further substantiate the claims made for a successful product. The Netherlands was successful in lobbying Brussels to this end at that time. If success had not been achieved, nutrition-related innovation in the industry would have been seriously impaired: it might even have come to a halt.

and the elderly, all of which is appropriate to their bodies and what they need to support them. Special foods for nursing infants and young children have been on the market for a long time, but even that segment has seen immense progress in the last decade thanks to our rapidly increasing understanding of the role of individual dietary components and our diet as a whole in the development and maintenance of our physical functions.

The next step, in the eyes of some, is *personalized* nutrition, linked to an individual genetic passport. Some think that is a step too far, however. Another question is whether it's even necessary. We already have a great deal of information – with unequivocal messages about beneficial and adverse effects – on the contribution nutrients and diet make to our health. For people who are open to it, this has already contributed a great deal to healthier diets. One may doubt whether advanced, personalized dietary advice would contribute much more.

D. The factory that is the digestive tract

With about 25,000 genes – in itself rather disappointing for such a smug being – it turned out at the start of the present century that we were not able to explain our functioning. The metabolic potential that our bodies exhibit is in part thanks to other beings: a sizeable number of flora in the gut. This flora (frequently called microbiota nowadays) is composed of organisms that transform compounds in our food into a range of metabolites, such as the health-promoting metabolite butyrate. Thanks to them, we have a wide range of compounds available which we ourselves could never extract from food: "microbe mediated gut metabolism". The number of microorganisms we house is ten times larger than the number of cells in our body. We are married to the useful microorganisms. We communicate with each other. As early as 2007, we were able to demonstrate that lactic acid bacteria affect gene transcription in epithelial cells in the intestine. Our intestinal cohabitees are even partly responsible for alerting the intestinal epithelial cells to the presence of harmful organisms. We are talking about a substantial part of our immune system here, since 50% of our immune cells are located in and round the intestines (which, incidentally, is the second most enervated organ in our body, after the central nervous system). What goes on in our gut, including our interaction with the microbiota, is thus an extremely fascinating process which we only began to understand better when we were able to consider the totality of epithelial cells, receptors, immune cells and bacteria. Insights into their operation and exchange also offered us for the first time a view of possible interventions into some of the problems associated with food allergy, which is actually the body's erroneous response to certain components of the diet.

We knew a decade ago that we had to cherish our gut flora (microbiota). That went further than just not consuming spoiled food so as to avoid flooding our innards with an invasion force of disease-causing organisms. Even at that early date we had started to experiment with ingesting useful organisms (probiotics) to balance the microbiota optimally. We even offered nutrient fiber (prebiotics) to the useful organisms we host, as substrates on which they could flourish. We have come a long way since then.

The "second human genome"
Around 2007, after a lot of research had shown the importance of the microbiota composition in a number of diseases, a number of countries started an initiative to sequence the composite genome (DNA sequence) of the microbiota present in organisms. This metagenome, as it is called, of the intestinal microbiota has also been called the second human genome. The European MetaHit project, in which groups from the Netherlands participated, mapped the functional bacterial genes and their proteins. In this they differed from their American colleagues in the Human Microbiome Project, who were attempting to map the metagenome as completely as possible. As MetaHit participant and winner of the 2008 Spinoza Prize Professor Willem de Vos put it, "It makes no sense to enumerate and name all the species. There are just too many."

Source: NRC Weekblad, *Ze zitten overal (They're everywhere)*, 18 July 2009

By 2007, we had started to characterize the activity of the more than 500 bacterial species in the large intestine and investigate the effect of their activity on intestinal health by offering them substrates labeled with stable isotopes. We now know of more useful organisms, the metabolites they produce and the part these play in our body in terms of our digestion, metabolism and immune system. This is the origin of the wide range of live food we find on the supermarket shelves, which we take orally to enrich our gut flora. We are now also discovering the benefit of the wide range of prebiotics, based on a knowledge of the specific needs of certain useful organisms in our intestines. We now have the possibility to allow our intestinal flora to develop a favorable equilibrium and to maintain it there. In the area of infant nutrition we know how to mimic the structure and function of the natural oligosaccharides that occur in mother's milk and colostrum. This means we can contribute immensely to the development and strengthening of the infant immune system.

What is also important is that about 15 years ago we started to realize that our ancient scientific method – dissect and analyze – does not always lead to an explanation of the way this system works as a whole. Not too surprising in the case of the intestinal flora,as the organisms engage in all kinds of mutual relationships, where one organism may produce a compound that another will process in a subsequent step. Isolated in a petri dish, this sort of production comes to a standstill, or the organism displays a biochemical reaction for which it may be difficult to see how it might be beneficial to the human body. Experiments with populations of 10 to 15 different bacteria were important exercises in an approach based on *systems biology*. We had to understand the whole complex, so increasingly *whole-system* measurements were done to map out the genetic properties (gene sequences) of the entire microbial population, in common with all compounds (proteins, metabolites) associated with the processes for which this community is responsible. Bioinformatics came to our aid, allowing us very quickly to distil results from the soup of data. We have now been able to capture the human intestinal flora as a complex with clear parameters. Moreover, systematic biological research on different cohorts of human subjects has revealed the system's characteristics for nursing infants raised on breast milk and their bottle-raised siblings, as well as for healthy and less healthy adults who are overweight. (As early as 2005, we had the first clues that in obese people far more nutrients are released from food in the intestine for uptake by the body.) The accruing body of literature showed us the way we had to steer our total flora using our diet. We are now increasingly able to depict interventions virtually: the system's biological data is incorporated into models with which we can do experiments "in silico" first.

In brief, the possibility to do "human friendly gardening" in our own digestive tract has increased spectacularly. In 2020, taking care of your body has achieved a whole new dimension.

A firewall for young and old

Over the course of the last decade we have been able to develop new food components that support the immune systems of young and old.

Improved hygiene meant that the young no longer had the time to build up a resistance to viruses and bacteria. By adding specific nutritional components to baby and toddler foods we can now build up in the young adequate and, we anticipate, long-term resistance to general pathogens. The fundamental knowledge on which this is based was gained in Dutch PPPs and European collaborations (such as the major proEUHealth project). Our national input put us in an important position. After this collaborative phase, of course, came the competitive one, with businesses collaborating bilaterally with research institutes to develop the relevant claims. Now that these products have come into use, we see fewer infectious diseases and we hope in time to see fewer "modern" diseases such as Crohn's and colitis.

The elderly appear to particularly benefit from the series of new food components, especially those that stimulate the immune system. It appears to be possible to slow down ageing and the associated reduction in the pool of immunologically active cells. Compared to two decades ago, the elderly feel better longer, they suffer from fewer diseases and they can stay at work longer.

E. The mouth, a unique gatekeeper

Healthier, more functional food is great, but do people actually eat it? In increasing numbers, people want to invest in their body's future, but sadly they encounter resistance – from themselves. When it comes to valuing foods, little seems to have changed from the days of our remote ancestors. Even though more sweets and fat are readily available to us than are good for us, our taste buds tell us a different story. Nor do our brains stop rewarding our bodies with the euphoric feelings that sort of food gives us. Finally, our own lazy nature – creatures of habit that we are – means we're not overly susceptible to reason.

Of course it was tremendous that highly convincing, well founded health claims were made for a variety of food products. There was praise too for the uniform labels that food producers agreed in 2012 to help the customer choose with ease. And of course it was good that schools devoted greater attention to nutrition and health education, explaining new developments, some of which were probably regarded as "creepy". Happily, though, we realized early on that more was needed if people were going to opt *en masse* for healthier food. We were never blinded by the functional aspects of a healthy diet and we never assumed that good information would convince people on its own. We also made choosing the healthy option attractive by making the new products at least as tasty as or even tastier than the traditional ones.

10 to 15 years ago, we in food and nutrition also started to look at the perception of food. What makes people evaluate food in a certain way? Which textures are good to eat? How does the tongue discriminate taste? How does the "retronasal experience" work? (Aromas that reach the nose via the mouth are a factor in our perception of taste that should not be underestimated.) And what tells us we are full at a certain moment? What measurement systems do we have to tell us that, at various spots in our body, from the mouth right down to the cells in the gut and liver?

Less sugar and salt

In 2008, a project began that sought to develop strategies to reduce the salt and sugar content in foods without degrading their taste perception. It worked. The project demonstrated that natural aromas, serum release in the mouth and the concept of taste contrast can be used to enhance the perception of sweetness and saltiness. One of the directions in which a solution was sought – taste contrast – uses a surprisingly simple mechanism. In fact, we found it was fairly simple to cut the total quantity of salt or sugar in a food if we distributed the substance through the food, not homogeneously but heterogeneously. The many salt or sugar peaks experienced by our tongue with such a distribution appear in the aggregate to afford the same sensation as the earlier one, but with 25% less added salt or sugar. These results generated great interest in the food industry, which was under pressure to drastically reduce salt and sugar levels in foods and beverages.

The Diogenes project (www.diogenes-eu.org) was the first at that time to supply data to the food industry which allowed them to start work on tasty products that could give us the same feelings, but in smaller portions and with fewer calories.

The knowledge we gained on the perception of food turned out to be exceptionally useful. Yes, we were able to give the innovative foods the right sensation, even when the balance of substances was shifted in favor of health, or when certain substances were added, subtracted or replaced. So no one had to choose between taste and health. Even as we were innovating we were able to indulge that creature of habit, the primeval human.

This takes nothing at all away from the new culinary experiences we have provided for people: new combinations of texture and taste, expressly conceived out of our knowledge of perception. In fact, we were able to predict with reasonable accuracy those new creations that would appeal to people's tastes.

Of course, taking advantage of perception demands that we must be able to *manufacture* a food to give a certain experience. But, as we show below, we now have vast knowledge and great talent on the manufacturing side.

F. Food production – high science

In recent years, in our efforts to achieve healthy, functional, tasty, safe and affordable foods, we have developed an impressive array of food production techniques.

It all starts with the raw materials. In recent years, the life sciences have made major contributions to the improvement of resources we have used for eons, such as milk and wheat. For decades, the emphasis was on productivity, but in the past decade we have learned to influence specific components of the raw materials. The breakthrough in milk production came after the bovine genome was clarified so that the components and properties of milk could be related to the cow's genetics. For instance, genes were identified that linked with the contents and composition of dairy fat and proteins. Selective breeding then allowed us to achieve a significant increase in the unsaturated fatty acid content (www.milkgenomics.nl).

Some components of the diet can be associated with serious complaints in a limited group of consumers, such as celiac disease (an intolerance to the gluten in grains). In the case of wheat, this is caused by specific proteins that have a toxic effect. Thanks to pioneering immunological research we succeeded in identifying the mechanism underlying the toxic effect as well as the specific toxins. Ten years ago we incorporated this information into selective plant breeding programs. Nowadays, thanks to this, we can produce wheat with a far lower concentration of toxic celiac proteins (the alpha gliadins in particular), while still retaining satisfactory technical properties.

We also looked at raw materials beyond the traditional ones. By now we had methods available that permitted a rapid search for suitable compounds plus selection of the associated processing stages needed to turn them into products. This screening can be done so rapidly because we can now understand the reactions leading to structural changes in the proteins involved, which we can control far better. This was beneficial for industry, since a far wider range of raw materials was made available to manufacture a given product (flexible manufacturing). A range of new tools is now available to us in the production process to change the

Carbohydrates: sweet and functional

Vast quantities of sugars have been used in large numbers of products for a very long time, thanks to their many functional properties, including sweetness, texture, body and structure. Now, in 2020, we have cut back considerably on that sort of use. As a consequence, the energy density of foodstuffs has also declined a great deal. Other, more complex carbohydrates belonging to the class of dietary fibers and prebiotics have taken over a number of the functions played by sugars. We were able to incorporate dietary fiber into foodstuffs and obtain outstanding sensory properties. New generation prebiotics with specific functions have gained their place as ingredients in our foods thanks to their health-promoting and antimicrobial effects in our digestive system. The same holds for specific, complex polysaccharide structures that can help regulate our immune system. The Carbohydrate Competence Centre (CCC) has developed processes for enzymatic modification and controlled biosynthetic pathways to give us a wide range of tailor-made polysaccharides with a range of functionalities, including structure forming (gelling, consistency, viscosity, texture) and component encapsulation (packaging vulnerable or ill-tasting components, releasing them only at the site where they should become active, such as the stomach or the large intestine).

Nutritional value of micro-algae

The nutritional value of algae has been known for a long time. A technical report published by the FAO in 1996 contains analytical data on protein, carbohydrate and lipid in 16 species of micro-algae.[9] Protein turns out always to be the major constituent, often closely followed by lipid, especially docosahexaenoic acid (DHA), an essential fatty acid for optimum growth and brain development in nursing infants. Expressed as a percentage of dry weight, the protein content varies from 12 to 35%, the lipid content lies between 7.2 and 23%, with carbohydrate between 4.6 to 23%.

It says a lot for the changes we have experienced that today in 2020 it is the context within which these figures are placed which seems so astonishing to us. The species here are micro-algae, commonly used in aquaculture to fatten young fish and crustacea. Nowadays it is the algae themselves that make our mouths water.

structure and thus the properties of the molecules in the basic material. (A classic example is the production of modified starch.) We can now call upon a steadily increasing collection of enzymes, which can introduce very specific changes to make proteins more soluble, for example, to create better meshes, or to stabilize emulsions.

Advances in production technology also allowed us to look at organisms to supply raw materials that we would have previously rejected for food production, such as algae, grasses and other relatively simple organisms which are responsible for primary production in the food chain. Our motivation was to produce high-quality food without necessarily always involving animals as the obvious intermediate in the food chain. Bringing these new food chains into being led not only to an infinitely flexible choice of raw materials, but also to more consumer choice. Among the primary producers we now have good candidates for basic protein and specific nutrients such as unsaturated fatty acids and B-complex vitamins. We also know how to deploy a number of grasses and algae to the best effect.

A modest start has been made on marketing the products we can make: a well-known pizza manufacturer has announced that a cheese substitute will soon be included in the product. Cheese-tasting vegetable protein was available as early as 2000, but this manufacturer has succeeded in preparing a vegetable protein product with the same texture and nutritional value as the dairy product.

It is also suggestive that the name “fish oil” for omega-3 and omega-6 fatty acids is slowly lapsing into disuse because the compounds are now extracted directly from algae or incorporated in food products.

We had, incidentally, involved simple organisms in our food production far earlier. Just as our digestion gets help from our sizeable intestinal flora, there are enough microorganisms that want to take possession of the food even *before* we’ve taken a sip or a bite. In a number of cases we were delighted to accept that wonderful offer when we made our yoghurt, cheese, beer, bread and other fermented products. The life sciences have turned out to be a source of rapid innovation in this area – also, incidentally, in case we seek to protect our food against undesired microorganisms.

The vast range of yoghurt-like products we know today in 2020 thanks its existence to changed processing conditions and the assistance of new or modified strains of microorganisms. Some of these products no longer even give you the idea that you should put sugar on your dessert to sweeten it. Our microbe management was also the key to making cheeses that are even tastier, with better structure, taste and aroma. (It was not for nothing that salt started to lose ground as a ubiquitous seasoning.)

It also turned out to be a great inspiration to use microbes – since they are going to tackle the raw materials anyway – to create special, functional compounds for our metabolic and

Demand-led chains

Ultimately the consumer is in charge, so what we need is to build up demand-led chains. Chains driven by the availability of raw materials or processes may easily fail to find a place in the market.

Naturally, every chain has to serve typical consumer demands: those of perception, moment of consumption (need a meal or just a snack?) and price. Since many members of the public are also preoccupied with health and such ideals as sustainability, animal welfare, ethics, environmental friendliness and equality of distribution, it might be expected that the innovative chains would enjoy an advantage precisely in this respect among a considerable group of customers.

The very novelty of these products, however, can also be a reason why innovation does not get off the ground. The consumer just has to get used to, for example, relatively unknown dietary resources, such as grass, algae, mealworms or grasshoppers. Or maybe it's because people have embedded many habits in their cultural background, and food is an important cultural component. On the other hand, it may be possible to make use of food resources from different cultures to gain more rapid acceptance of "new" raw materials. Even when the consumer is regarded as the basis upon which the chains are built, success will still depend partly on an integrated approach, involving such disciplines as communications science and psychology.

immune systems. To achieve considerable concentrations of these compounds in the final product we succeeded in changing the manufacturing conditions, as well as utilizing modified organisms, different ones, or new variants of the ancient ones. For instance, in 2007 scientists at TI Food & Nutrition and the Kluyver Centre developed a process for simultaneously producing a mixture of vitamin B12 and folic acid in yoghurt. A 200-mL portion contained the daily requirement of these vitamins, in the correct ratio. For a dozen years or so now, there have been products on the market based on this process, including special versions for pregnant women (containing a higher proportion of folic acid) and a variant specially for the aged to prevent a deficit of vitamin B12.

Navigating through the metabolic landscape of fermenting microbes

As long ago as 2007, Eddy Smid, Project Leader at TIFN, explained enthusiastically what he was doing: "Our efforts have resulted in a structural approach that supports industry in optimizing fermentation processes. We have constructed a metabolic model for lactic acid bacteria which can easily be adapted to other kinds of bacteria. This model can be compared to a traffic navigator which guides us through the metabolic landscape of fermenting microbes. Briefly, we have designed roadmaps that represent the metabolic routes present in lactic acid bacteria. The roads on these maps stand for the metabolic reactions that take place within the organism, while the cities represent the metabolites that can be produced. With these maps as a starting point, we did several calculations, including the amount of traffic each road can handle and the quickest route from one place to another. This is how we have been able to discover the best way to use bacteria to increase the production of vitamins and flavors, and to optimize growth media."

A few years after that, they succeeded in building similar computer models for the metabolism of several organisms in culture, such as yoghurt. Changing the variables in these models led to the discovery of new processing options and new products.

Taking a step further, one could even view the human being as an interplay of various types of human cells and many microorganisms which can be modelled to allow a better understanding and prediction of the effect of dietary components on our body's metabolism.

Food safety and preservation

By 2007, mild processing techniques had become very popular since they are good at preserving the sensory and nutritional quality of food products. However, under these processing conditions, pathogenic and spoilage microorganisms like *Listeria monocytogenes* and *Bacillus* cereus had a better chance of surviving the process, resulting in a shorter product shelf life. Fortunately, we identified and elucidated the mechanisms underlying their survival strategies, such as cold tolerance, strain diversity, population heterogeneity and the formation of endospores (i.e. temporary “survival pods” that can germinate and grow out to new populations once the preservation or disinfection treatment has finished). To do this, we used state-of-the art genomics techniques and identified several biomarkers and targets for intervention to prevent preservation stress survival. Our new processing techniques were mild, but hit the enemy right at its weakest point!

Since one of the things we looked at in our preservation processes was the heterogeneity of bacterial populations, we attained an even greater safety benefit than the old, coarse methods, like pasteurization. In the main, a *combination* of mild methods turned out to be more effective than the old methods, where we regularly found that a population contained tough individuals that were able to resist any single method, no matter how crude it was.

Nothing is completely safe, of course, but now, in 2020, it can justifiably be stated that, thanks to our improved knowledge and control, the safety of soft cheeses from non-pasteurized milk is nowadays equivalent to the safety of cheeses made from pasteurized milk in 2010. Pregnant women and the elderly thus have nothing to fear from these products.

In our fight against food decay, it is odd when we look at the improbably radical methods we used for ages to conserve our foodstuffs. Overkill just to make sure, which meant we suffered the associated loss of product quality and the degradation of important nutrients.

Nowadays we control food safety not so much at the final production stage; rather, we stay in control throughout the entire process (food safety management). We can do this monitoring thanks to the methods available for the rapid identification of organisms, including the nature and intensity of their activity. We know where the Achille’s heel of these organisms lies and, using subtle, targeted conservation measures, we can frustrate their purpose.

G. Epilogue

Looking back to a decade ago, we were at an important point. We could see the breakthroughs ahead of us, all the more because we had tasted the first practical fruits of what the life sciences could mean for food and nutrition. We also knew that the universities and research institutes would start to move fast as the life sciences developed closer ties with other disciplines. Skills which we had started to invest in early on – genomics, system biology and related research competence, such as proteomics, metabolomics, not to forget bioinformatics – rapidly became integrated into food and nutrition research. Because we entered the field so early, the Netherlands changed over sooner than other countries to a more holistic approach. Moreover, thanks to a highly detailed human phenotyping operation, we were able to zoom out from the molecular level to effects manifested at the tissue level and even to the functioning of the entire body.

In the midst of this all, we had already realized that we had to develop an international "language" to exchange data and lay claim to our successes. We made international agreements, for instance, on sets of important biomarkers and agreed inter alia on data standards and research protocols. The leading regional role played by the Netherlands took nothing away from our awareness that an integrated approach, in pan-European initiatives, was needed to further extend the skills industry required. We therefore sought collaboration with universities and institutes abroad, jointly building pan-European initiatives. The representatives of the Food & Nutrition Delta, thanks to their strong proactive disposition, also played a major pioneering role in European initiatives. The Joint Technology Initiative "Food for Life", which started roughly six years ago, has made major contributions to the scientific underpinning and development of technologies for the sustainable production of healthy, tasty, safe foodstuffs (ETP Food for Life, Strategic research Agenda 2007-2020). In both the seventh and eighth core programs of the EU, important ETP recommendations were adopted when defining the research programs.

RECOMMENDATION Extend national consortia into Europe – In 2020, a significant number of innovative activities are undertaken at the EU level

With the life sciences, we were actually able to achieve major innovations in food and nutrition because the people surrounding us realized the importance of the developments. Besides the business community, government too supplied a substantial flow of funding in the form of both structural support and earmarked funding. Innovation was high on the agenda, after all, and for the Netherlands – traditionally a force in agriculture – there was a new opportunity to play a leading role in nutrition. This is why the government accepted a share of the responsibility for this *Sleutelgebied*, with its importance for the economy and society at large.[10]

RECOMMENDATION Formulate clear national ambitions and stick to them – health and sustainability

Scientific institutes were so confident and enterprising, incidentally, that they went further than just "paid research", daring to risk relatively large investments. Their participation in public-private enterprises (PPE) allowed the institutes to market their accrued knowledge rapidly and efficiently within the PPEs.

Databases and toolkits developed in the PPPs were brought into PPEs, which took care of their maintenance and expansion. This avoided giving an advantage to certain parties when exploiting the knowledge and information acquired in the PPPs. An example was the Dietome database, developed by the Netherlands Nutrigenomics Consortium. This database became a repository for a large number of relationships discovered between diet and its effects at the cellular and tissue levels. The database started to operate as a treasure trove of innovation for predicting the effects of dietary intervention and/or the composition of foodstuffs. While the application of knowledge in innovative products or services is the responsibility of businesses, the government remained an interested party of course. Government's interests lie in improving the climate for innovation and the benefits to society supplied by the concrete output of that innovative effort. This interest found expression in the past 15 years of investment grants. All parties involved recognized the importance of broad participation in innovation: the grants should reach not only the larger but also relatively small businesses. (In terms of volume produced, SMEs are collectively at least as important as the big players in the food industry). In practice, though, SMEs were relatively less involved in innovation. 15 years ago we saw opportunities to get SMEs to participate far more, to innovate and make a profit. A public-private organization like Food and Nutrition Delta was able to act as a bridge, drawing these businesses closer to the sources of both knowledge and funding.

! **RECOMMENDATION Build and expand a powerful knowledge infrastructure with active encouragement of SME involvement**

A decade ago, we clearly saw the way ahead: science, the business community and government all made the right choices. That's why we now genuinely have much healthier, more functional, tastier and safer food. We have achieved the ambition set down in 2009: more than ever – as an independent and indispensable partner in European initiatives – we are playing the leading innovative role in food and nutrition.

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Prof. dr. Stanley Brul, University of Amsterdam; Dr. Jan Dekker, TI Food & Nutrition; Dr. Kees de Gooijer, Food & Nutrition Delta; Prof. dr. Lisette de Groot, Wageningen University; Prof. dr. Rob Hamer, TI Food & Nutrition; Dr. Henk Hendriks, TNO; Dr. Ronald Henry, University of Maastricht; Dr. Martin Hessing, Podiceps and Nutrigenomics Consortium; Dr. Geert Houben, TNO; Prof. dr. Jeroen Hugenholtz, NIZO food research, University of Amsterdam and Kluyver Centre; Prof. dr. Jan Kok, University of Groningen; Dr. Paul van der Logt, Unilever; Dr. Luc van Loon, University of Maastricht; Dr. Jan Maat, Unilever and TI Food & Nutrition; Dr. Diederick Meyer, Royal COSUN; Prof. dr. Michael Müller, Nutrigenomics Consortium and Wageningen University; Dr. Arjen Nauta, FrieslandCampina; Prof. dr. Wim Saris, DSM, University of Maastricht and TI Food & Nutrition; Prof. dr. Huub Savelkoul, Wageningen University; Dr. Patrick Schrauwen, University of Maastricht; Dr. Lolke Sijtsma, Wageningen University and Research Center; Prof. dr. Coen Stehouwer, University of Maastricht; Prof. dr. Fons Voragen, Carbohydrate Competence Center; Dr. Paul de Vos, University Medical Center, University of Groningen; Prof. dr. Willem de Vos, University of Helsinki and Wageningen University; Dr. Jan de Vries, CSM; Prof. dr. Harry Wichers, Wageningen University and Research Center; Dr. Ger Willems, FrieslandCampina; Dr. Diederik Zijderveld, TNO; Prof. dr. Marcel Zwietering, Wageningen University.

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Authors

Roland Lageveen, Chair of the High Profile Group
Peter Luijten, Center for Translational Molecular Medicine
Daan Crommelin, Top Institute Pharma
Emiel Staring, BioMedical Materials Program
Edvard Beem, ZonMw
Jorg Janssen, Life Sciences & Health

Health

Partnering for Health

III Health

This chapter outlines a vision for the health sector. We start by looking at the big challenges and opportunities in healthcare. We will argue that a sustainable, excellent healthcare system goes hand in hand with an economically strong health industry, and that innovations are key in both. Innovations enabled by the life sciences.

Section B details our starting point: the current unique selling points of the sector and points for attention.

In Section C, we describe where we are going. A positive outlook towards 2020, when, thanks to innovations enabled by the life sciences, healthcare delivery has adjusted to meet a changing demand. Where the sector cooperates in an open innovation structure and is thriving. Where, thanks to the government, the climate is favorable to entrepreneurship and investment.

Section D focuses on the role of the life sciences and public-private partnerships (PPPs) in the health sector. In these PPPs, translational research is performed by academia and industry. The term translational research is somewhat confusing in this sector. In health, this term refers directly to linking bench to the bedside, lab to clinic. In this chapter, as throughout the book, the term is used in a wider context, as in translating basic knowledge from academia into applications that industry or healthcare institutes (together) can further develop, test and deliver to users (patients and doctors). In this chapter, the enabling role of life sciences public-private partnerships and their way forward are described. The path is based on four pillars: clear focus, healthy pipeline, strong support and true partnership – together bringing health and wealth to Dutch society. We conclude this chapter with summarizing our main recommendations.

A. Setting the scene: big challenges, big opportunities

Our healthcare demand is changing through ageing, changes in lifestyle, the rise of chronic diseases and new technologies. In addition, we demand higher quality and safety of healthcare. This increases the burden on our healthcare system and drives up healthcare costs. At the same time, the working population is decreasing.

Technological developments in the life sciences provide opportunities to meet this changing demand with innovations that improve healthcare. These offer great benefits to society. Who does not want to live longer, healthier and more independently? We all do. The life sciences can play a pivotal role in this. However, society's willingness to share the burden of all of our care is decreasing.

The healthcare system thus faces the challenges of increasing demand and rising expectations while facing constraints in human resources, costs and solidarity. These challenges cannot be solved by one party alone. They require politics, the healthcare system, industry, medical centers and academia together to improve healthcare while keeping the system sustainable. The political arena must discuss individual versus collective responsibility and how to pay the costs. Healthcare providers need to bring care closer to the people, reducing dependence on healthcare professionals and institutes like hospitals. Industry and academia together need to ensure the supply of tailored, innovative healthcare solutions that not only improve quality of life and safety of patients, but are also labor and cost efficient. Facing today's challenges requires a constructive dialogue and a joint approach between all of these stakeholders.

! RECOMMENDATION Organize a continuous, constructive social debate on life sciences innovations in healthcare to align the priorities, goals and ambitions of all stakeholders

On the other hand, these developments offer strong economic opportunities: an increasing demand for new, innovative solutions, and the opportunity to supply this demand in cooperation with the end user (doctors, patients and government). Health and healthcare are becoming an ever more important economic activity. An economic sector driven by research and innovation is an important driver of a knowledge economy. On a macroeconomic scale, improved health of a society increases its human capital: healthy people work longer and more efficiently. Investing in health solutions is thus an economically viable strategy.

The Netherlands wants to seize this opportunity for its knowledge economy and play a leading role in the innovative health industry, and, at the same time, provide its citizens with good but affordable healthcare. There is a "creative" tension between these two ambitions: healthcare pursues containment (quality, labor, safety and cost), while economy seeks expansion and growth. Looking closer, however, these ambitions go hand in hand and in fact completely rely on each other. Without innovative, cost effective products and approaches, healthcare systems will not prove sustainable. Healthcare providers thus need industry that is strong. Companies need to stay closely connected to healthcare providers to test innovations and to ultimately reach customers.

Both excellent and affordable care and a strong health industry rely on mutual innovations, and thus on the underlying technology base that enables these. One of the main drivers is the life sciences that seek to understand and influence normal and dysfunctional processes in our bodies. The life sciences associated or applicable to human health we will call "life sciences and health". The challenge in innovation is to translate basic knowledge into applications to be delivered to doctors and patients. This is where we believe an important role is set for a strong innovation infrastructure in which public and private parties each have their role to play, and at the same time work together with one objective: providing innovative healthcare solutions for health and wealth.

B. Point of departure: promising

The point of departure towards our goals for 2020 looks promising for the Netherlands. Its unique selling points are a strong knowledge base, a solid infrastructure of university medical centers (UMCs), a growing life sciences enabled industry that is strong in selective areas and has a large diversity of SMEs, a unique innovation infrastructure of PPPs in which stakeholders work together, an open, international attitude, and a government that has demonstrated strong commitment to the sector. However, in absolute numbers our industry is still small compared to other countries and in danger of losing value to other countries. Also, continuity of government commitment to what is needed for a flourishing life sciences and health sector is uncertain. Furthermore, our testing and delivery policy for medical innovation does not fully match that of international competition.

Academia and UMCs

One way or the other, all innovations in life sciences and health start from or build on basic knowledge. A strong knowledge base is therefore crucial in this sector, and is one of the unique selling points of the Netherlands. Dutch academia is home to a world-leading knowledge base in life sciences and health. The quantity and quality of articles is high.[1,2] Dutch academia is supported by a unique infrastructure of eight UMCs, created by the mergers of medical faculties and academic hospitals, bringing knowledge from the bench to the bedside. The citation score of Dutch UMCs is 40% above the world average.[3] Three of the top 10 European institutions in clinical medicine are Dutch UMCs, including the number one on the list.[4] The Netherlands furthermore hosts various top clinical hospitals.

UMCs facilitate a quick uptake of life sciences research in healthcare and a strong infrastructure to test innovations. They work together with regional hospitals, spreading knowledge and innovations. Also, they host a strong information base, including a national biobank program with strong potential. All are supported by dedicated funding organizations like ZonMw.

Our strong knowledge base is, however, too often taken for granted. Investments in academia have lagged behind with other countries, which risks losing our leading position,[1] a situation that can be avoided.

Industry

In 2008, the Dutch healthcare system had a turnover of EUR 74 bn and accounted for about 14% of total Dutch employment (medical care and welfare services).[5] Healthcare providers use a range of treatments and tools that have their basis in the life sciences and are supplied by an industry that we call the life sciences and health industry. In the Netherlands, this industry is promising and growing, hosting about 1,000 companies with a total turnover of about EUR 16 bn and about 55,000 FTE.[6]

The life sciences and health industry is often considered synonymous with pharmaceuticals. While drugs are an important part of this industry, its landscape – especially in the Netherlands – is actually much more rich, encompassing medical devices and biomaterials as well. Here, innovative diagnostic tools ranging from large MRI scanners to tiny lab-on-a-chip blood tests are developed and produced. Or implantable devices like pacemakers and materials that regenerate tissue. Also the drugs section of the industry comprises a range of products, like traditional synthetic drugs, upcoming biological drugs, vaccines and drug delivery solutions that have a strong link to medical devices. In short, the sector is very versatile. The commonality is the increasing usage of life sciences in understanding health and diseases, in the discovery, development, testing and production of medical solutions, and as the end-product or its application. But many other scientific areas and technologies like micro- and nanotechnology and ICT are widely applied in this industry.

The life sciences and health industry is very R&D intensive. In the Netherlands, an estimated 20% of its employees work in R&D.[6] The estimated share of this industry in total private R&D in the Netherlands is around 12% in 2006, an increase from around 9% in 2002.[7] The sector is therefore greatly important to the Dutch knowledge economy.

Compared to countries like the USA or Switzerland, the Dutch life sciences and health industry is relatively small. However, it has several focal points that are internationally competitive. One of our main strengths is molecular imaging for medical application. We host a world leader in this area, Philips, which is increasingly focusing on healthcare. Through Philips, for example, the Netherlands is a world leader in the number of patent applications in this area.[8] We have other strengths in the medical devices area of life sciences and health industry. For example, we host major R&D facilities of the world-leading medical technology company Medtronic. Our pharmaceutical industry is strong in biopharmaceuticals, with special attention to vaccines. We host large divisions of a major pharmaceutical company, Merck-Schering Plough / Organon, and renowned companies like Solvay, Genmab and Crucell. Finally, the Netherlands is strong in biomaterials, such as in the biomaterial coatings in medical devices. This is one of the life sciences focal points of DSM, next to the production of pharmaceuticals and food ingredients.

Small- and medium enterprises are very important. A significant part of the innovation in this sector is carried out by SMEs that often work together with larger companies, here and abroad. A strong knowledge base, unique medical infrastructure and cooperative large companies provide fertile ground for high-tech spin-offs and start-ups, like Progentix, Prosensa, and Agendia, to name a few. The number and quality of start-ups in the sector is high.[9]

Open innovation: Public-private partnerships

Innovating in health is becoming increasingly multidisciplinary, and the road to success is long. Cooperation between academia, industry and healthcare providers is vital. Compared to countries like the USA, Denmark or Switzerland, the Netherlands seems inefficient in utilizing its strong knowledge base. This does not only hold true for life sciences and health. The Dutch Innovation Platform identified critical issues that need to be addressed to overcome this so-called innovation paradox, which includes insufficient collaboration and networking between stakeholders.[10]

While the Innovation Platform has meanwhile appointed a committee to ensure implementation of necessary actions for the issues identified, in the health sector especially the issue of collaboration and networking between stakeholders has already received much attention. In fact, the Netherlands has recently set up a unique infrastructure of public-private partnerships in this sector in which academia and industry meet to translate basic knowledge into healthcare solutions – essentially, to innovate together.

A collection of life sciences and health PPPs covering a range of topics were initiated with the start of the Netherlands Genomics Initiative (NGI) in 2002 and the BSIK impulse (one-time governmental funding program for PPPs) in 2004. In the years after, with the initiation of three Leading Technology Institutes (TTIs) – Center for Translation Molecular Medicine (CTMM), Top Institute Pharma (TI Pharma) and the Biomedical Materials Program (BMM) – a focus on three complementary application areas has emerged: on diagnosis and imaging of biomarkers; on drug discovery and development; and on devices building upon biomaterials, with regenerative medicine on the horizon. Furthermore, enabling technology and infrastructure partnerships have been initiated to support innovation in and outside PPPs, including the technology centers of the NGI and the “Parelsnoer” (String-of-pearls) Initiative, a national biobanking partnership between the eight UMCs.

How this vision came about

The High Profile Group (HPG) made the first steps towards a sector-wide vision with it's Cahier no. II. It was presented to the sector in May 2009 with an appeal to provide feedback on the book and join the further development of the vision. Many stakeholders in the sector have answered this call and provided input. We would like to take the opportunity to thank everybody for this. The authors of this chapter have used the draft vision of the HPG and the input on the cahier from the sector, and combined that with their own thoughts and expertise. This is the result, a next step towards a vision supported by the entire sector.

In this way, the health innovation pipeline is filled with initiatives that secure the entrance of the pipeline with top level basic research (e.g. NGI, the 'Build' stage) and initiatives that have a focus on bundling exploratory research with industry (e.g. the three TTIs, the 'Bundle' stage).

In the summer of 2008, the innovation program Life Sciences & Health (LSH) started. It aims to enhance the innovation and investment climate in the sector, for SMEs and for the value creation of knowledge that results from PPPs and academia (the 'Benefit' stage). Coupled to this program is the High Profile Group (HPG) of the sector. A group of experts who – in a personal capacity – think about the future, launch ideas and add force behind the voice of the sector. The HPG, in fact, initiated the first developments of the health vision that you now read here.

These programs were initiated with the help of strong government impulses. Over a period of about five years, from 2003 to 2007, approximately EUR 1.2 billion was committed in equal parts from the government and the sector to PPPs in life sciences and health.

It is too early to assess the full value of PPPs in terms of output. We still need years for that. However, what we do know is that they have been very successful in mobilizing private research efforts and connecting a wealth of public and private parties that now innovate together (Figure 1). This was the first goal in setting up the PPPs and a very important step for the Dutch knowledge economy and patients. We are proud of that. We believe that the innovation infrastructure, with its public-private platforms for cooperation, is a unique selling point for the Netherlands.

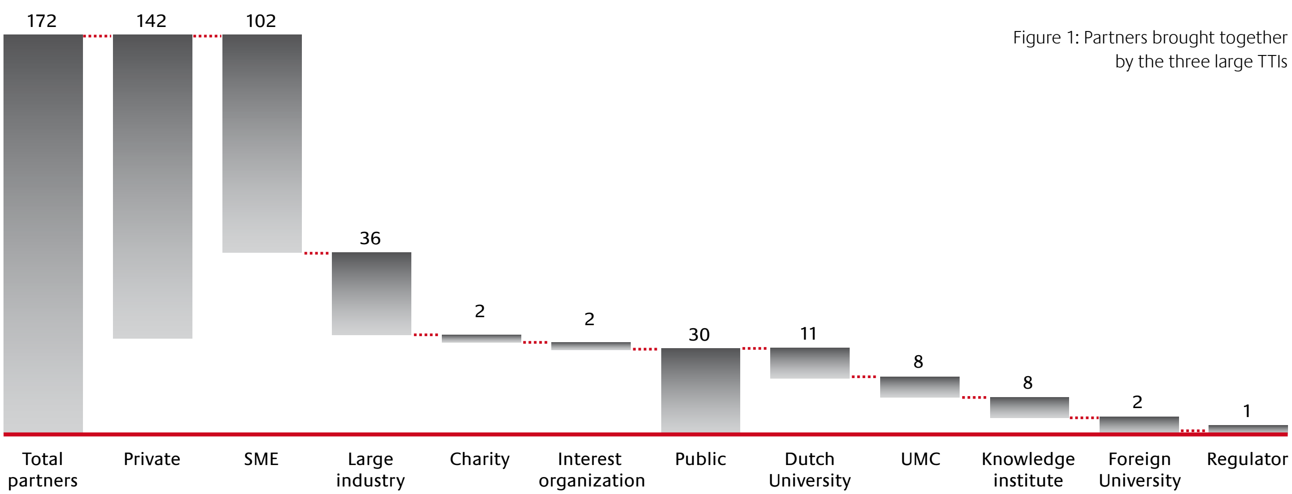


Figure 1: Partners brought together by the three large TTIs

International focus

The Netherlands is part of the global economy. We do not have all competences in the Netherlands. Innovation in the health sector requires cooperation with companies and universities outside our borders, and the application markets are global. Dutch universities and UMCs collaborate extensively with top institutes all over the world. Analyses of publication output consistently show a stream of collaborative publications in the leading journals of the life sciences. According to impact measurements, their quality is very high. International PhD students and professors are attracted to our country, though sometimes face considerable bureaucratic difficulties.

Dutch companies work together with foreign based companies. They make deals on shared product development, creating inflows of funds (e.g. the USD 80 m Progentix deal with NuVasive, www.progentix.com), buying resources or whole companies (e.g. Crucell and Berna Biotech AG, www.crucell.com), or getting bought (e.g. Organon and Schering Plough – now Merck, www.organon.nl). In recent years, several large foreign logistics, production and manufacturing companies in the field of life sciences and health have established themselves here, including Merck Sharp & Dohme (MSD), Glaxo Smith Kline, Danone, GenMab and Pfizer. In the fall of 2008, MSD started a new vaccine product line in Haarlem. Biotech giant Genzyme, with its European headquarters in the Netherlands, is also expanding. Open innovation incubators like the High Tech Campus Eindhoven, started by Philips, and Chemelot of DSM attract activities from abroad. A very recent example is the company TiGenix, which announced that it will build its new factory for a cartilage cell-therapy on Chemelot.

Inflow yes, but how does this compare to outflow of activities? There is an ongoing debate over brain and value drain, mainly regarding the pharmaceutical industry. The product pipelines of large pharmaceutical companies have become thinner in recent years, while development costs have risen. In addition, patents of many blockbusters are coming to an end. This has created a wave of mergers and acquisitions (and cooperation) to maintain short-term revenues and fill long-term pipelines. We do not have a “big pharma” company of our own, but foreign “big pharma” is buying here. Are we not losing value in this way? The Dutch pharma champion Organon, for example, was first bought by Schering-Plough, and is now involved in the merger of that company with Merck.

Mergers and acquisitions may lead to relocation of activities. Where newly formed companies locate their R&D and production facilities depends on company culture, as well as on the innovation infrastructure offered by the Netherlands. If the value of a company comes in part from its embedment in and strong ties with the Dutch innovation infrastructure and network, activities will likely not be moved abroad. Activities might even be expanded here if we play the game well. Take, for example, the new R&D site of Danone at the Utrecht BioSciencePark. The flux of activities over country borders offers a strong opportunity. Winners make sure they offer a unique value proposition to companies and investors here and abroad. We believe the Netherlands has this value proposition to attract activities of large and small life sciences companies. We already do, as evidenced above.

Policy

The inflow of activities thus requires that the best conditions are created in the Netherlands. As argued here, we have some unique selling points, like our knowledge base and innovation infrastructure. By building on these strengths we can achieve a sustainable inflow and minimize the outflow. Policy and regulation can help in this: they create the conditions for maintaining our strong knowledge base, they create the conditions for building further upon

“

An attractive climate

It is no coincidence that Genzyme has its European headquarters in the Netherlands. The Netherlands is strategically positioned as a gateway to Europe. It has high-quality clinical and scientific expertise, globally renowned medical centers and policies encouraging innovation. This provides an attractive climate for foreign biotechnology companies to invest in the Netherlands. However, there is also room for improvement: further stimulating market access legislation can strengthen the life sciences innovation climate in the Netherlands. A long-term commitment from the government will be essential to maintaining momentum. ”

Henri Termeer, Chairman of the Board, President and CEO of Genzyme Corporation

Quote from Henri Termeer

our unique public-private innovation infrastructure, and help assemble “launching customers” (doctors, insurance companies, etc.) for the sector to deliver its innovations to patients. Through policy and regulation the Netherlands thus has the potential to attract, or push away, innovation activity. Dutch policy and regulation should be competitive in an international context to obtain the maximum economic and healthcare benefit from the innovations developed. This is not always the case, especially for testing and delivery of medical innovations. Prosensa, for example, had to take clinical trials for its Duchenne Muscular Dystrophy therapeutic abroad. And the process of uptake in insurance packages in the Netherlands can provide internationally uncompetitive delivery hurdles, like for the breast cancer diagnostic tool MammaPrint of Agendia.[11]

C. Health sector going into 2020: seizing opportunities

Now that we have described the as-is in 2009, we will take a look at the sector going into 2020. How do we foresee the future, and how do we want it to unfold? We will talk about health and healthcare going into 2020 in terms of society (demand and delivery), science and technology (life sciences, ICT, nanoscience, etc.), the sector (industry, medical professionals, academia, etc.) and the investment and innovation climate in 2020 (politics and policy).

Society going into 2020: increasing demand, adapting delivery

In 2020, the Netherlands will have 3.4 million people over the age of 65, up by about 1 million from today.[12] Demand for healthcare increases sharply with ageing. Obesity is on the rise. Blood pressures and cholesterol levels grow. These developments will result in a steep increase in chronic diseases like heart and vascular diseases, dementia, COPD, diabetes, cancer and depression (Figure 2), boosting demand for (new) medical solutions. Similar developments can be seen throughout the Western world.

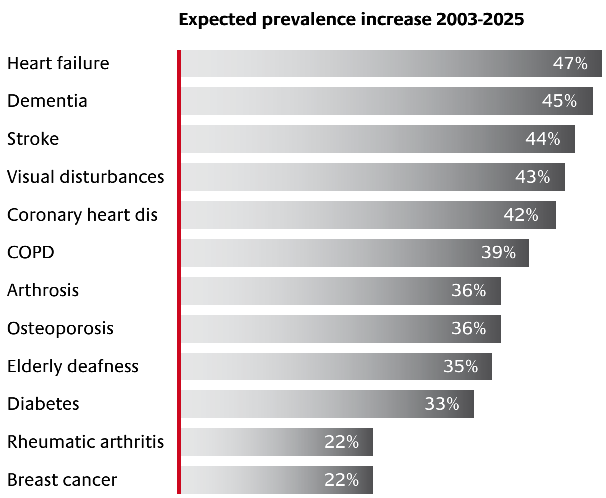


Figure 2: Predicted increase in prevalence of selected chronic diseases in the Netherlands.[13]

At the same time, we are demanding better, safer and faster healthcare. Patients expect minimal side effects and discomfort from treatments and maximal independence. We get increasingly used to solutions tailored to our specific situation.

Calls for sustainability and social responsibility are growing, also within healthcare. Animal testing is increasingly opposed, and we expect industry to dedicate itself to diseases which are highly relevant to our society here or elsewhere in the world (e.g. the so-called neglected diseases, like dengue fever and schistosomiasis).

There is a price tag on this changing and increasing demand. Healthcare costs will increase, maybe even by 50% by 2020.[14] Healthcare delivery needs to adapt to this new situation to maintain the sustainability of the system. Cost control and willingness to pay more for each other are necessary elements. We need to understand the social benefits of healthcare and regard healthcare not just as a cost, but as an important driver of our knowledge economy.

To maintain control over chronic diseases, we need to intervene in a much earlier stage of disease, even before people get sick. A major role of healthcare in 2020 will be prevention. Risk factors of groups or individuals will be identified, monitored and preventative measures taken, like diet or other lifestyle changes. Actual diseases will be diagnosed in a very early stage. Treatment will be tailored to the individual and the exact disease type based on patient stratification using advanced diagnostics, so-called personalized medicine. Starting in an early stage and personalizing therapy significantly improve treatment outcome and reduce its intensity and overall cost. Therapies will be minimally invasive, increasing the quality of healthcare and patient life, while at the same time improving the patients' functioning in society and the economy. Treatment will be monitored more accurately and adjusted to maximize efficiency and prevent overmedication. After regaining health, continued monitoring will intercept reoccurrence in an early stage, and the cure/care cycle starts again.

The Dutch workforce will have decreased by about 2% in 2020.[12] In combination with the labor intensity of hospital care and the high costs that are associated with it, healthcare will need to decentralize towards care close to patients, moving from intramural to extramural care. Ideally, as much care as possible will be placed into the hands of the patient or into the patient's immediate environment. Patients will be monitored from a distance to secure the safety and efficacy of at-home care. They will have 24-7 access to digital interaction with healthcare providers. Maximized patient independence is the goal. This reduces cost and increases the patient's quality of life.

The healthcare system going into 2020 needs to become more innovation sensitive. Besides system innovations that increase the efficiency of healthcare and reduce costs, technology-intensive product and service innovations will need to find their way into healthcare provision. With the products and services available now, the 2020 demand will not be met in a sustainable manner. Prevention and early diagnosis do not only require the development of innovative tools. For their uptake in medical practice, people need to come into contact with medical professionals and/or tools before a disease manifests itself to the patient.

The replacement of lengthy, intramural, costly care for chronic patients with (partly extramural) preventative measures, early detection and minimally invasive personalized treatment will enhance their quality of life as well as decrease the burden, in terms of cost and personnel, on the healthcare system.

Technology going into 2020: life sciences enabling innovations that meet demand and delivery requirements

Innovations will be key to anticipating the changed and increased healthcare demand and keeping delivery sustainable. The life sciences will play a major role in this, and will be applied together with other technologies like ICT and nanotechnology. Life sciences and health innovations will enable an efficient care cycle, from prevention through diagnosis and treatment, back to prevention.

The identification of risk factors and the resulting preventative measures will be further enabled by life sciences and health. Breakthroughs in genetics, bioinformatics and systems biology (an approach to biological processes where the entire system is considered, from molecule and cell to organ and human) will make it possible to read and interpret our DNA code more accurately. More and more, people will have their DNA sequenced and know the impact of their genetic profile in terms of their health (risks).

New imaging and lab-on-a-chip technologies will make it possible to follow molecular-scale processes in patients by looking at specific biomarkers. Biomarkers are genetic or biochemical indicators related to a disease, and can be measured in patients or patient material. This allows us to find the slightest abnormalities, enabling early diagnostics and detailed treatment monitoring.

Deepened understanding of disease progression, the exact disease subtype and the genetic code (and consequences thereof) of an individual enable treatment to be tailored to the individual patient or patient group. Personalized medicine will boost treatment outcome and reduce its invasiveness.

By providing tools and knowledge to diagnose the exact problem and solution, personalize the treatment, and

Quote from Hans Bos

“ **An unanticipated revolution**
In the past 25 years, the life sciences have undergone an unanticipated revolution, in part driven by technical innovations. New discoveries have paved the way to new approaches. Just think of small interfering RNA. Only discovered in the last ten years and currently considered a completely new way to target disease. In cancer we are continuously confronted with new concepts that radically change our views of how to treat metastatic cancer in the future, from global killing tumor cells by single drugs to personalized and targeted therapies of tumor initiating cells using multiple drugs for each tumor. Due to the large variety of cancers this may require the development of a large number of new drugs either based on small molecules, antibodies or new entities, like small interfering RNAs. As a result, new diagnostic tools are required to discriminate between cancers. For the future, there are no signs that the developments will slow down and certainly the scientific landscape and thus the opportunities will change continuously. Strong fundamental research into biological questions supported by technological innovations will remain at the basis of these developments. Therefore, investments in fundamental research as well as in research education are vital for our knowledge infrastructure to make public-private partnership maximally profitable. ”

Hans Bos, Professor at Utrecht University and Director of the Cancer Genomics Center

monitor and adjust therapy, life sciences and health will enable more efficient, less invasive care. This does not only hold for diseases in an early stage, but also when diseases have progressed. Breakthroughs in stem cell research and tissue engineering will make it possible to replace or repair damaged tissue in a minimally-invasive manner.

Technological breakthroughs will not only deliver innovative healthcare solutions; they will also speed up the innovation process itself and reduce costs. For example, cellular systems are being developed in which first testing of safety and effectiveness can be conducted. This enables early elimination of medical compounds in the R&D process that would eventually have failed in animal or human testing. This reduces the amount of animal and human tests and decreases development costs. Also, as medication is increasingly tailored to a certain population group and/or disease subtype that can be identified through DNA and other biological markers, the subject group in clinical testing will be more and more tailored to the exact target group. This increases the chance of success in clinical trials, also reducing development costs.

Innovations will aim at comprehensive solutions for illnesses, linking prevention, diagnosis, cure and care. To achieve this, various disciplines such as imaging, genetics, systems biology, bioinformatics, pharmacology, (medicinal) chemistry and (bio)materials sciences will have to join hands. This requires not only technological excellence, but also working together on an unprecedented scale. Such interdisciplinary effort will result in closer ties to fields outside of life sciences and health. The ICT sector is crucial for large-scale data storage and sharing, which will become ever more important with the increasing information that genetics and systems biology gather. Only with micro- and nanotechnology, ICT and life sciences together, can we develop smart devices for home cure and care. The food sector is also an important partner in prevention. Many chronic diseases like heart and vascular diseases and diabetes are related to food. The food and health sector together, through the life sciences, can pinpoint the exact relationships between food, metabolism and diseases, and define preventative measures for groups at risk (see Chapter II). The future perspective is an integration of the various life sciences technologies and the link with fields like micro- and nanotechnologies and ICT.

2009 Spinoza Prize winners join forces against migraines

Physicist Albert van den Berg, neurologist Michel Ferrari and mathematician Marten Scheffer met for the first time when they were told that they won the Spinoza price of 2009. They figured it would be great to do research together. The migraine research of Michel Ferrari, combined with the lab-on-a-chip activities of Albert van den Berg and the descriptive knowledge on transitions of Marten Scheffer have now joined in the struggle against migraines: real-time measurement of patient blood values in a noninvasive way using lab-on-a-chip technology, modeling the transition from normal levels to the point when the migraine develops, and using this to develop a treatment against migraines. A perfect example of the interdisciplinary approach to developing innovative healthcare solutions, the cooperation required for this and the vital importance of basic research in academia.

NRC “wetenschap interview” July 4, 2009

The sector going into 2020: open innovation networks that develop, produce and deliver healthcare solutions to patients

The innovation process in life sciences and health is changing. More and more, companies are looking for activities outside their own walls. The sector is moving towards “open innovation”. Here, companies spin-off promising, but less strategic research to be developed outside. They partner with others on product development. They buy strategically important research or competences.

Many companies will specialize. Replacing the single company – with everything under one roof, from fresh idea to the market – will be companies which focus on one or few of the successive steps in the innovation chain: technological development, clinical development, testing, production and marketing and sales. Players will work together to develop new products and services or improve existing ones. National borders will not form barriers for cooperation. Large companies form centers of such (international) networks, around which specialized start-ups and spin-offs evolve.

This is not just an industry network. It also implies increasing cooperation with the customer. In the case of the health sector, this means patients and healthcare providers, but also insurance companies and even government. Open innovation will clear the way to increased cooperation with academia, which is becoming more important as a provider of basic knowledge and technologies as large industry moves away from such activities.

The Netherlands is perfectly positioned to become an example of an open innovation structure in the health sector. Many stakeholders already work together in the innovation infrastructure. In 2020, cooperation will be the standard: academia will be a natural and widely appreciated provider of knowledge, technologies and concepts for applications; UMCs and hospitals will work together with

Philips as an example of the movement towards open innovation

In recent years, Philips has opened up to the innovative world outside of its own company borders. Here are a few examples:

- At the High Tech Campus Eindhoven, Philips innovates together with other companies and institutes
- Philips participates in a range of public-private partnerships
- Philips developed the blockbuster coffeemaker Senseo with Douwe Egberts
- Philips acquired a set of medical devices companies to obtain knowledge and technology in this area of strategic importance
- Philips spun-off its semiconductor business NXP in a strategic repositioning
- Philips involves customers to discover new product demand and opportunities through the website leadusers.nl

industry and universities to test potential innovations and provide patient and disease information through biobanks; regional networks of healthcare providers will perform many large or specialized (multicenter) trials; healthcare providers and patients will be involved in early R&D phases to articulate demand and increase the innovation sensitivity of healthcare; insurance companies will enforce a more directive role in healthcare, applying pressure to develop high-quality, cost-effective medical solutions.

Through this open innovation network, the Netherlands will pool significant Dutch and foreign R&D capacity, both public and private. This will be greatly facilitated by a strong innovation infrastructure in which all stakeholders come together. It serves as an entryway to finding partners for cooperation, it pools knowledge and technologies, and it educates R&D professionals capable of finding their way in business, academia and healthcare, cross-fertilizing between different partners.

Next to creating a vivid R&D base, the Netherlands also has good opportunities in advanced production of medical innovations. High-end medical devices and individualized treatment call for smaller, non-bulk quantities of production. To maintain production cost, these will need increasingly innovative high-tech production solutions, an area in which the Netherlands has much potential.

Marketing and sales of healthcare products in the future will be mostly performed by large, international companies that operate in many cross-national, open innovation networks. Dutch multinationals like Philips and DSM should be kept here. This requires a favorable innovation infrastructure and climate in which to thrive, and to increase their chances of success in a highly competitive, international environment. This will also attract foreign-based conglomerates to the Netherlands to innovate here and take up important roles in the network. Under these circumstances, we will be able to breed several mid to large-sized companies. SMEs that specialize in niche markets have the opportunity to grow to sizeable proportions and cooperate with, instead of being bought by, foreign conglomerates. When hitting a future blockbuster technology, it is possible that a Dutch life sciences SME grows into a large multinational.

The sector foresees a clear brain and value gain. But we only know whether we are draining or gaining, and in which areas, when this is monitored accurately. Only with that knowledge can we effectively act. Our monitoring of this must be improved. The sector itself is responsible for that.

The sector strives for the Netherlands to be used to pilot healthcare innovations. We have the strengths for that. Our market is large when considered a gateway to Europe. The open innovation system described above is also perfectly suited to cooperation with healthcare providers and hospitals that hold the testing grounds. But all this requires policy and regulation which supports a favorable entrepreneurial and innovation climate.

Quote from Pauline Meurs

“ **Involve patients and medical practitioners early**
The road from discovery to actual use of new products and services in daily patient care is often long and unpredictable. The sooner the perspectives of patients and medical practitioners can be taken into the process – discovery to translation to use and application – the more likely the innovations can actually be implemented and the sooner patients can benefit from them. ”

Pauline Meurs, Chair of ZonMw

The climate going into 2020: creating a strong entrepreneurial and innovative climate that facilitates the Dutch health sector
The life sciences and health industry can only thrive in a (business) climate which is entrepreneurial and innovative. As we look towards 2020, business costs for R&D need to be kept low and the tax climate favorable. Academic knowledge needs to be picked up easily by entrepreneurs. Only by having internationally competitive policy and regulation can we take the sector to the next level. Innovating in the Netherlands should be at least as rewarding as abroad (a level playing field) – but preferably more rewarding.

Creating a level playing field does not mean lowering standards on safety, for example, or just copying international standards verbatim. It implies creating an innovation route that is on par with our neighbors. Although international standards should be adopted as much as possible, a higher safety demand can for example be compensated by a faster uptake in medical practice. We could consider a system of temporary acceptance for urgent medical innovations, where the innovation is piloted in medical practice while studying efficacy in more detail. The innovation process takes about fifteen years, and policy and regulation need to be consistent over such periods. An entrepreneur or investor does not want to run the risk of being surprised by short-term policy and regulation changes. In a favorable climate, entrepreneurs will come here to innovate and pilot their medical innovations. If we play our cards right, the Netherlands may become the portal to Europe for medical innovations. Quick, reliable and with an endorsement that opens up the large European market.

RECOMMENDATION Develop internationally competitive testing and delivery policy for health innovations that guarantee both safety and speed of introduction !

Policy instability creates uncertainties for stakeholders. Participants in Dutch PPPs, for example, have no clue whether PPPs will still exist in a few years, irrespective of results. PPPs have been set up with typical four year impulse funding without a plan for after. We want to stress that we are not talking about continuity for an institute, but for a program or for a platform for cooperation. It is not about continuation of a back office or a name. It is about continuing to encourage the joint R&D effort of public and private consortia to search for innovative solutions to problems important to society.

The government and sector together need to develop consistent, continuous policy and regulation. The sector should clearly state what it wants and needs. The government should develop policy and regulation it can keep up for longer periods. Intense communication is vital. If policy changes are on the horizon, the sector should be notified well in advance. Government should move away from fragmentizing impulse funding. It needs to be clear which subsidy programs will be there in the years to come. Funding instruments need to be consistent and continuous, and agreements on continuity of programs for periods of over ten years need to be made through agreements on milestones, deliverables and associated go/no-go evaluations.

! **RECOMMENDATION Introduce a sustainable, flexible, but continuous funding structure for public-private partnerships**

In some form, basic knowledge is at the heart of each innovation. It is therefore an integral part of a strong innovation climate. In the run-up to 2020 we have to safeguard our strong knowledge base, and that requires continuous investment in basic research. Capitalizing on this Dutch knowledge base can only be done when knowledge transfer between universities and entrepreneurs is easy. PPPs are just one of the routes for this knowledge transfer: the route of working together. Direct IP transfer is another and an especially important one for start-ups. Universities recognize such direct transfer as an important activity, and they will receive additional funds for this as of this year.[10] However, this process needs to become more effective and efficient. This requires building awareness and commitment and creating incentives and professional Technology Transfer Offices, and more (see Chapter VIII).

The Netherlands in 2020: capitalizing on knowledge for health and wealth

In 2020, the Netherlands has seized unique opportunities in the health sector. The strong knowledge base in life sciences and health has driven the development of many an innovation. Rising demands provided the business opportunity for the sector. The adopting healthcare system provided the gateway to the customer and became a partner in innovation. The open innovation structure is a natural way for Dutch stakeholders to obtain knowledge, technologies and services from each other, here and abroad, and to offer their business, utilize the fundamental knowledge base, and cooperate with healthcare providers, patient organizations and insurance companies. This is supported by a strong innovation infrastructure that, together with stimulating policy and regulation, attracts business and R&D.

The Netherlands in 2020 is regarded as a breeding ground for capitalization on knowledge for health and wealth. The industry is doing well, has grown in added value by 50% since 2009. It creates jobs and contributes to economic growth. Start-ups find fertile ground here and flood the sector with knowledge and technologies for medical innovations.

Facilitated by a strong entrepreneurial and innovative climate, the Netherlands has succeeded in keeping its large companies within its borders, grown sizeable new players, and attracted the R&D of large companies from abroad. These companies work together, with each other, with innovative start-ups, with academic groups, with healthcare providers, patient organizations and insurance companies.

Pioneering science prospers, and has the attention of those abroad. The Netherlands is firmly positioned in the global top-3 in life sciences and health. Academics often work together with the business community. Such partnerships are business-as-usual in this world. Many academics are involved in the startup of new companies.

The medical innovations developed here see to our growing needs, save lives and enhance the quality of life, while maintaining the sustainability of our healthcare system. These, as well as innovations from abroad, are effectively transferred into our healthcare system, which is a strong partner in innovation and safeguards the cost effectiveness of innovations. The Netherlands is regarded as a good place to pilot innovations and a gateway to the European market.

D. The way forward: enabled by a strong innovation infrastructure

We need to innovate to create an economically strong life sciences and health sector while at the same time maintain a sustainable healthcare system. This requires the translation of life sciences and health knowledge into medical innovations. This process is facilitated by a strong innovation infrastructure. The basis for this infrastructure has already been laid. The way forward is to build further on the strengths of this foundation and make it fit for a pivotal role in the future by building on four pillars:

I Clear focus: The innovation infrastructure needs a clear focus on content: application types and diseases. Doing too much will yield fewer results than focusing on select areas. Stimulate areas in which the Dutch health sector is strong, both in academia and industry, and which are of social (public health) and economic relevance.
II Healthy pipeline: The innovation infrastructure needs to form an integrated chain of instruments, using the right tool at the right stage of innovation. This keeps the pipeline of medical innovations healthy and filled throughout.
III Strong support: The innovation infrastructure needs to be founded on strong support activities. Medical innovations require enabling technology and infrastructure throughout the innovation process and all steps in the process rely on highly educated people.
IV True partnership: The innovation infrastructure has to be a true partnership between all stakeholders. Here and abroad, from academia to patients, all have their role to play in optimally facilitating the translation of knowledge to medical innovations that land in the hands of patients and practitioners.

Here we pay special attention to public-private partnerships as part of the innovation infrastructure.

Pillar I: Clear focus

Focus should be dictated by the strengths and priorities of all stakeholders. UMCs, universities and organizations like ZonMw and NGI have set and articulated the focus of academia, from basic research to medical innovation at UMCs. For example, UMCs are strong in particular disease areas, like cardiovascular diseases and cancer.[4] Currently the UMCs, together with the Ministry of Education, Culture and Science, are developing an overview of their individual areas of scientific excellence which may foster further decisions that complement and support existing excellence. This exercise will be connected to priorities in patient care.

PPPs are a good instrument to create focus on areas where both academia and industry are strong. They align public and private research activities from the bottom up on the basis of mutual strengths in which society, through government matching, is willing to invest. In the health sector, Dutch PPPs have already done this. With the setup of three large TTIs (CTMM, TI Pharma and BMM), the sector has chosen three themes: diagnosis, drugs and devices (the latter based on biomaterials and, in the future, on regenerative medicine). It was an intensive process of consulting stakeholders in the sector to achieve this threefold focus, after which stakeholders themselves defined the actual project portfolio from the bottom up. Government matching criteria steered the outcome towards social priorities like those described in the Priority Medicines report of the World Health Organization.[15]

Diagnosis focuses on the development of early diagnostic tools by identifying and imaging biomarkers. Drugs focuses on innovative treatments tailored to the patient's body, lifestyle and the exact disease. Devices based on biomaterials and regenerative medicine focus on healing or replacing damaged tissue using tissue engineering or stem cell technology. Within these application areas, a limited set of disease areas has been chosen (Figure 3). And within these still broad application and disease areas, public-private consortia perform those activities where both the science base demonstrates excellence and private parties see possibilities.

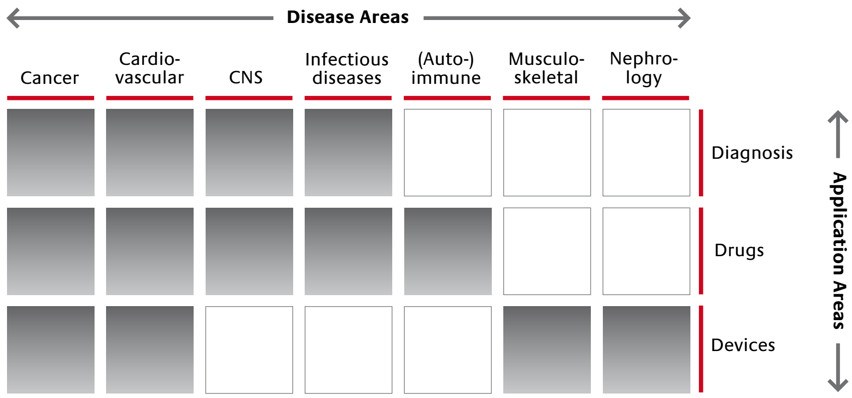


Figure 3: Strengths of the Dutch life sciences and health community, and the focus of the three large TTIs

The three application areas together form an integrated strategy. They come together at the doctor and patient: early detection, recovery with personalized therapies and, if disease progresses, regeneration of damaged tissue. The application areas reinforce each other as well during R&D. They build on knowledge of the same disease areas, and applications from one area are used in the other (e.g. diagnostics are required to assess therapies). A clear technological interface between them exists in terms of achieving precise drug delivery using imaging techniques. The joint call for proposals by CTMM, TI Pharma and BMM reflects this interface in the area of imaging guided and targeted drug delivery. Such interfaces combine strengths and are therewith unique opportunities. Another interface is advanced home-care devices that combine diagnostics, medication and monitoring. These interfaces between application areas offer exciting opportunities to be explored in the future.

As innovations in this sector take about fifteen years, the credo is to build on existing focus while consolidating and rationalizing efforts. A good example of this is the sector's application in the FES 2009 call. The sector consolidated and aligned about ten health PPPs into clusters around the three application areas, with the large TTIs as "centers of gravity". This was not done blindly: new opportunities in which academia and private parties both saw great promise but which did not entirely fit the existing focus where not

Joint call: Imaging Guided and Targeted Drug Delivery
CTMM, TI Pharma and BMM all focus on the translation of research findings into proof of concept for new products and services in healthcare, each with its own special focus. The common denominator is personalized medicine: treatment tailored to the individual patient to optimize efficacy, outcomes and patient comfort.

Many innovations rely on simultaneous applications of technology developed in the three different programs. For example, the discovery of biomarkers of heart failure and arrhythmia (CTMM) will provide better patient triaging to select candidate stem cell therapies (BMM). Molecular imaging and the use of companion diagnostics (CTMM) will greatly enhance the efficacy of targeted drugs (TI Pharma). New scaffolds or nanoparticles (BMM) may be used for the local release and targeted delivery of high concentrations of medicines (TI Pharma).

On June 25, 2009, a joint call for proposals for research focused on the interface of the three institutes was opened: Imaging Guided and Targeted Drug Delivery. The scope is restricted to technology platforms that can be used to control or monitor the targeted and/or controlled (e.g. triggered) delivery of a particular drug or regenerative substrate.

For more information see www.lifesciences.nl/jointcall overlooked, like those that exist in the devices area at neuronal disorders. Focus is meant to create critical mass around promising areas; it is therefore dynamic and by no means places strict boundary condition.

The innovation infrastructure will increasingly focus on output related goals. We care more about the solution to a medical issue than about which science enabled it. Within the current Dutch strengths, goals for breakthroughs can be defined around which public-private consortia in the future emerge. An example could be advancing the moment of intervention for cancer, or the replacement of a specific organ when damaged. Or a home care device for a certain illness. Defining goals for breakthroughs sharpen the focus and make it easy for society and government to participate and embrace a certain program. They help align efforts and open doors to more intense cooperation with other sectors, like food for prevention and ICT for extramural care.

Pillar II: Healthy pipeline

An innovation has a long way to go before it can be applied in daily medical practice. Ideas often develop over the course of fundamental research. If an idea has potential, then academics and industry may work on it within PPPs or in bilateral agreements. Existing companies, spin-offs and start-ups may develop the promising concept further, alone or together, and bring it to the patient through hospitals and insurance companies. The entire trajectory takes about fifteen years.

The innovation infrastructure needs to form an integrated chain of instruments so that the right tool is used at the right stage of innovation. This keeps the pipeline of medical innovations healthy and filled throughout: in the Build, Bundle and Benefit stages. Note that we use the word pipeline in its broadest sense. The route is not straight, it branches, and steps are skipped and traced back. It is iterative and there has no definite beginning. Ideas emerge at all stages. The process is often called cyclic, to highlight that innovations on the market provide information for the next. The bottom line is: the innovation process needs to be encouraged, not just at one stage, but during all of its stages.

The chain is as strong as its weakest link. It can only work if the basic input, fundamental research, is funded in a way that top quality science is continuously generated. This knowledge then must be able to flow to private parties and healthcare providers, either directly or through PPPs. Finally, these parties must be able to deliver innovations to users. Missing links stagnate innovation.

One point of attention in the innovation process is the smaller technology start-ups that are crucial to the system. They make sure that patents and publications are not the end of a research project. They struggle with the high investments needed to pick up discoveries and bring them closer to the market. The risks are high, and finding risk-bearing capital is difficult. This funding gap needs to be closed. This requires an integrated chain of funding instruments. Pre-seed grants for feasibility studies, seed grants for the first stages of the start-up, (venture) capital to grow and invest in expensive clinical trials, tax breaks to reduce R&D costs and a launching customer that reduces risk will simplify the securing of capital. To set up such an integrated chain, the different “owners” of the instruments, like different Departments, funding organizations and other institutes need to work together. A recent example of that is the sector wide Pre-seed grant that is being set up in a joint effort of NGI, LSH and ZonMw.

PPPs must fulfill their specific role in keeping the pipeline healthy. First of all by doing their job: stimulating parties to work together on promising, precompetitive research. Then by connecting supply and demand: between academia and industry, but also by connecting with end users like

Life Sciences & Health Innovation Program
In the summer of 2008, the sector and government started an important enabling initiative as part of the innovation infrastructure which strongly supports our shared journey forward. The role of the Life Sciences & Health Innovation Program (LSH) is to *facilitate* the sector and help *accelerate* the pathway of innovations to the market. LSH is set up by the sector and the sector determines the program. Below is a sample of LSH's activities:

- Facilitate the realization of a sector-wide vision
- Provide credit facilities for SMEs in the life sciences and health industry
- Provide a course catalogue for professionals
- Set up programs for executive education
- Market the Dutch life sciences and health sector abroad
- Provide an international portal to the sector (www.lifesciences.nl, to be expanded beyond health in collaboration with the other life sciences sectors)
- Set up a B2B portal with a life sciences wide company database (not just health)

For these and other activities of LSH, please refer to www.lifescienceshealth.com. Most of these activities are specific to life sciences and health, but some are life sciences wide. In the future, LSH will increasingly cooperate with sister programs in other life sciences sectors to learn from each other and to launch joint projects.

patients. They also need to remove redundancy by making sure the various PPPs in the pipeline fit well together, interact and complement each other. This can be facilitated by joint funding applications. Also, PPPs provide a platform for long-term strategic dialogue between stakeholders in the sector, aligning interests throughout the pipeline.

PPPs need to perform sound portfolio management to keep the pipeline healthy. Set targets for projects in advance, and halt projects that do not reach their milestones. In so doing, poor performers are pulled out of the pipeline. The resources that become available should be used to accelerate projects that are doing better than expected.

Pillar III: Strong support
Within and across application areas, enabling technologies and infrastructure are crucial to the development of medical applications. The innovation infrastructure already has a cluster of enabling technologies and infrastructural support. This cluster includes the technology centers of the Netherlands Genomics Initiative (NGI) and biobanks like the Parelsnoer initiative and LifeLines that collect and save clinical material of patients. The initiatives in this cluster increasingly work together with PPPs in the application areas, supporting them in developing medical innovations. Although cooperation is growing, there is a lot to gain in intensifying this cooperation (see Chapter VI). Much efficiency and cross-fertilization can be achieved when these initiatives really become the preferred suppliers of technology to PPPs.

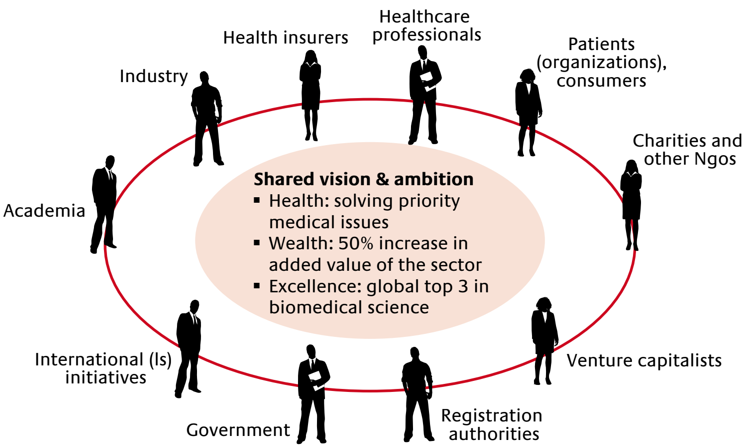
PPPs in the innovation infrastructure face many challenges. Intellectual property (IP) between partners must be settled, contracts signed, project and financial administration handled, ICT infrastructures set up, conferences and workshops organized and lines of communication established with government and society. This process support is increasingly becoming a joint effort. An example is the increasing use of two existing IP models by new initiatives instead of starting new negotiations over and over again. This trend needs to continue: jointly develop and share best practices, while taking into account the differences between specific parts of the sector. Such work may move gradually towards a single backbone of process support for the whole innovation infrastructure.

Such support also provides opportunities for sector-wide valorization support instruments like pre-seed grants, access to shared R&D infrastructure and funds for bilateral, competitive collaboration. Technology Transfer Offices (TTOs) also play an important role here. Any university IP that is transferred to companies or brought into a PPP requires a professional TTO with which to work.

Highly educated knowledge workers are crucial building blocks for the innovation infrastructure and all parties operating therein. The sector needs multidisciplinary researchers who are not only brilliant scientists but also who have entrepreneurial and business skills and the tools to share knowledge with others and build bridges between universities, companies and the clinic. They should be flexible to regularly changing job environments as an essential part of (tacit) knowledge transfer. A strong education and training program that teaches content as well as business skills facilitates the development of such researchers.

The foundations for this must be laid at higher educational institutes that need to take into account the demand for multidisciplinary professionals in shaping their curricula (see Chapter VII). But the sector is responsible for continuous learning. Solid steps towards a joint education and training effort for professionals have been taken. LSH has set up a catalogue of available courses for researchers. Furthermore, it initiated a life sciences MBA together with the Nyenrode Business University. Such strong education and training infrastructure assists in drawing foreign students and knowledge workers, bringing knowledge and experience from abroad within our borders. This is important, as one of the challenges for innovative sectors is to find and retain talent.

The innovation infrastructure does not just support education of professionals through shared training programs or MBAs. The working together in PPPs might actually be its most important educational tool in creating multidisciplinary professionals who make knowledge transfer possible. With the current funding impulse, PPPs are training around 500 PhD students. Keeping them in the Netherlands after graduating requires absorptive capacity and thus real industrial, hospital and academic R&D infrastructure. This should be facilitated by investing in infrastructure like open innovation laboratories and pilot plants. Expanding our physical R&D infrastructure is vital.



Academia
Wish list:
- Knowledge, technology and facilities
- Valorization of own results
- Funding for science
- ...

Added value:
- In-house knowledge, technology and facilities
- ...

Industry
Wish list:
- Knowledge, technology and facilities
- Increased quality, market success, and lower time to market of applications
- R&D professionals
- ...

Added value:
- In-house knowledge, technology and facilities
- Capital
- Market access
- ...

Health insurers
Wish list:
- Cost-effective therapies that improve quality of care
- Impact on research agenda
- ...

Added value:
- Data on disease burden
- Accessibility of applications
- Gatekeeper function
- ...

Healthcare professionals
Wish list:
- Fast access to new, top-quality therapies
- Higher efficiency
- ...

Added value:
- In-house knowledge, technology and facilities
- Easy uptake in med. practice
- ...

Patients/ consumers
Wish list:
- High quality therapies tailored to patients' needs
- Improved quality of life
- ...

Added value:
- Personalized information
- Demand for new solutions
- ...

International PPPs
Wish list:
- Knowledge, technology and facilities
- Increased span
- ...

Added value:
- Knowledge, technology and facilities
- Increased span
- ...

Charities & other NGOs
Wish list:
- Cure and care solutions
- ...

Added value:
- Funding & knowledge
- ...

Government
Wish list:
- Healthy population
- Wealthy economy
- Scientific excellence
- ...

Added value:
- Subsidy
- Stimulus legislation
- ...

Registration authorities
Wish list:
- Safety and efficacy of new medical solutions
- Efficient procedure
- ...

Added value:
- Fast registration
- Efficient and low-cost testing
- ...

Venture capitalists
Wish list:
- Investment opportunities
- Risk sharing
- ...

Added value:
- Capital
- Identification of commercial opportunities
- ...

Figure 4: Stakeholders work together towards the same goals that support the individual wish list of partners. Lists are illustrative, not comprehensive

Pillar IV: True partnership

The best way to innovate is by joining forces. All stakeholders need to participate in a joint approach to translate knowledge into medical solutions, facilitated by an innovation infrastructure where they all come together. In joining in true partnership, all will benefit, as illustrated in Figure 4.

Current PPPs are mostly set up as virtual institutes. This has led to cooperation between people with diverse backgrounds, and in changing circumstances. The value of such cooperation is undeniable. However, knowledge transfer is strongly facilitated by direct, physical interaction that is also key to building trust. True partnerships, built on trust, cover both forms of cooperation, virtual and physical. We already see a trend towards more such direct interaction, encouraged by the use of shared, central facilities such as biobanks, enabling technology PPPs and other research infrastructure. Open innovation sites, like the High Tech Campus Eindhoven, are important tools for bringing partners physically together.

The sector should speak with one voice, in the Netherlands as well as abroad. No conflicting notes, just a single sound that rings loud and clear, focusing on the unique selling points of the Netherlands. The sector is increasingly giving this role to LSH. The sector would benefit from an all-encompassing brand name. Active, univocal communication and a well-recognized brand name increases partnership, provides international recognition, and draws attention to the Netherlands as a place for life sciences and health activity.

! **RECOMMENDATION** **Actively map and clearly articulate the unique selling points of the Netherlands**

Attracting 50 companies
The Dutch Innovation Platform published a report in 2009 on attracting 50 foreign companies to the Netherlands.[16] A quote from the report (quote is translated from Dutch): "Around 15 national and regional organizations have sent various messages into the world that the Netherlands is a place of business. Around 180 trade delegations have arisen, independently, in order to attract foreign companies. The costs of these fragmented campaigns total around EUR 200 m each year. To go out with one story about the power of the Netherlands as a place of business, and to approach interesting companies together, puts us in better shape to attract the companies we want." We are sorry to say that this sector has participated in articulating a fragmented message, and are on our way to change this.

Partnership has to go European, which is where our future lies – or even further, worldwide. Europe is a strong source of funding, competences, knowledge and other resources. We have to scale up our PPP effort to European proportions. Several programs are currently active to create a "pan-European" infrastructure for translational research, like the European Strategy Forum on Research Infrastructures. The Netherlands has the potential to become a premier league player in this process. By leveraging our strong innovation infrastructure, we are currently positioning ourselves as a primary participant in several European programs. For example, the Netherlands is setting the standard for best-in-class biobanking infrastructure with the BBMRI program and operational procedures in translational research with the EATRIS program. European up-scaling also implies doing everything in our power to put our stamp on pan-European TTIs like the European PPP, the Innovative Medicines Initiative (IMI).

We do not necessarily need European instruments to scale up our innovation infrastructure to the European level. We have to consider direct collaborations with other small countries or regions around us, like Nordrhein-Westfalen, Belgium and Denmark, aligning or even consolidating our national innovation infrastructure and policy with such partners. Acknowledging the value of our PPP efforts, Denmark is setting up a PPP in the drugs area according to the Dutch model and will be operating in close collaboration with its Dutch counterpart.

RECOMMENDATION Embed the innovation infrastructure in Europe !

Realizing true partnership does not happen overnight. It requires long-term commitment from all parties involved. To match the timescale of innovation (about fifteen years) with that of the government (about four years), stakeholders in the sector and the government need to work closely together. Commitment duration between partners should not be linked to the period of a typical four-year governmental grant, but to the timescale of innovation.

A vision has to grow on people. This chapter is part of an ongoing initiative to unite the sector in a shared vision. Fully aligned with and building further on what the HPG started in Cahier no. II. Slowly but surely, the vision is taking hold. It is a continuous process, however, and should be periodically updated so that it corresponds to the momentum of the entire sector.

E. Main recommendations

In this chapter, many ideas on what the future of health can look like and how we can get there are presented. Five recommendations we find of particular importance:

- Organize a continuous, constructive social debate on life sciences innovations in healthcare to align the priorities, goals and ambitions of all stakeholders
- Develop internationally competitive testing and delivery policy for health innovations that guarantee both safety and speed of introduction
- Introduce a sustainable, flexible, but continuous funding structure for public-private partnerships
- Actively map and clearly articulate the unique selling points of the Netherlands
- Embed the innovation infrastructure in Europe

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Authors

Luuk A.M. van der Wielen, Isabel Arends and Sef Heijnen, Department of Biotechnology, Delft University of Technology
Johan P.M. Sanders and Elinor Scott, Wageningen University and Research Center
Andre P.C. Faaij and Bert Weckhuysen, Utrecht University
Dick Janssen and Bert Poolman, University of Groningen
Sascha Kersten, University of Twente
Marcel Wubbolts, DSM White Biotechnology
Jos Keurentjes, AkzoNobel Industrial Chemicals
Jan van Breugel, Purac International
Dirk den Ouden, Avantium

Chemicals & energy

Building a sustainable bio-based economy
for the Netherlands: 2020 & beyond

IV Chemicals & energy

Executive summary

The Netherlands is ideally positioned to benefit from the integration of its rich research culture in many topics relevant to the bio-based economy, with national and international innovations. Our country offers world-class innovations in the agroforestry field, as well as an advanced logistics and industrial position. Sustainability of local biomass production and of the import of biomass streams is critical to a responsible and effective implementation of the bio-based economy. The challenge lies in translating early Dutch initiatives (Cramers criteria) into a dynamic certification sector, and in achieving a proactive attitude while helping emerging world markets develop. In overcoming this challenge we can combine our environmental responsibility with economic benefits.

Dutch scientific research in the fields of industrial (white) biotechnology, chemical catalysis, energy and process technologies is in a leading position globally. At the same time, (multi)national chemicals and energy companies based in the Netherlands are embarking on a transition to more bio-based, low-carbon manufacturing. Connecting the academic and industrial worlds with investments in piloting facilities as well as proactive venturing will help bridge the innovation gap (or rather, the “innovation valley of death”) even better. The consolidation of proven successful R&D initiatives will guarantee our continued lead in science and technology. It will also generate a much needed stream of innovations with social and industrial benefits.

The time to act is now!

A. Introduction

Bio-based energy, chemicals and materials options are a daily reality for billions of individuals on this planet and have been so for as long as we can remember. An illustrative example is the use of wood stoves. Natural biomass (wood) and a simple technology (stove) are used to create energy: bio-based energy.

Energy production through a traditional wood stove represents a small-scale process. The small scale fits well with the distributed nature of biomass and the dispersed distribution of users in small rural communities. Yet, it should be realized that even this "natural" form of energy production from biomass is far from optimal or efficient. A modern version of the traditional wood stove uses approximately 80% less fuel, and produces 90% less smoke and 99% less contaminant emissions[1] at a constant effective productivity.

This example illustrates the challenge in balancing sustainable biomass production and biomass conversion in advanced processes, leading to products such as energy, fuels, chemicals and materials.

Quote from Rein Willems

"**The Netherlands is in an excellent position**
To capture the full economic and ecological benefits of the bio-based economy for the chemicals, fuels and energy sector in the Netherlands, technologies based on lignocellulosic biomass streams are critical. This is underlined in the business plan of the Chemistry Board (RegieGroep Chemie) and supported by recent macroeconomic studies. The Netherlands is in an excellent position to benefit from the bio-based economy: leading chemical players that lead the sustainability index, world-class biotechnology and chemical scientists, as well as a tradition of close, successful industrial-academic collaborations (DPI, B-Basic, CatchBio, IBOS and others) and a key position as the logistic gateway to Europe. The substantial governmental as well as private and public investment have contributed to this top position.

But it is not a time to sit down and relax: proof-of-concept in an industrial or academic laboratory requires experimentation at relevant (pilot scale), industrial targets for continued "greening" of production. Such production requires the development of supply chains of sustainable biomass with the necessary certification and access to world markets. Job creation requires that hundreds or thousands of engineers, scientists and technicians become educated in building and operating this new branch of industry. And finally, a proactive financial sector is needed to invest in sometimes seemingly risky opportunities.

The Chemistry Board has strongly supported this bio-based development and will continue to do so. The Chemistry Board will inspire and stimulate its industrial, academic and institutional members to continue investing NOW, and calls strongly upon the Dutch government to do the same."

Rein Willems, Chairman of the Dutch Chemistry Board, former President of Shell Netherlands

B. The 2009 status quo

In 2009, bio-based production provides about 10% of the global energy portfolio of roughly 450 exajoule per year. Most of it (roughly 40 exajoule per year) relates to highly inefficient biomass combustion in open fires in developing countries. The energy loss in these processes exceeds 90%.

Large-scale efforts are taken in the USA and Europe to replace fossil resources with bio-based ones. Asia is expected to follow. In Latin America, with its rich history in biofuels, an increased effort is underway to remove bottlenecks (transportation) and further scale-up sugar cane and eucalypt production.[2,3] While the debate on exact fossil reservoir volumes and timing of "peak oil" continues,[4] the arguments to justify these efforts are environmental considerations in view of carbon dioxide budgets, the need to be independent of (insecure) oil import, the need for rural development and other economic or employment advantages as triggered by the increasing oil prices. This aspect is described in the following paragraph.

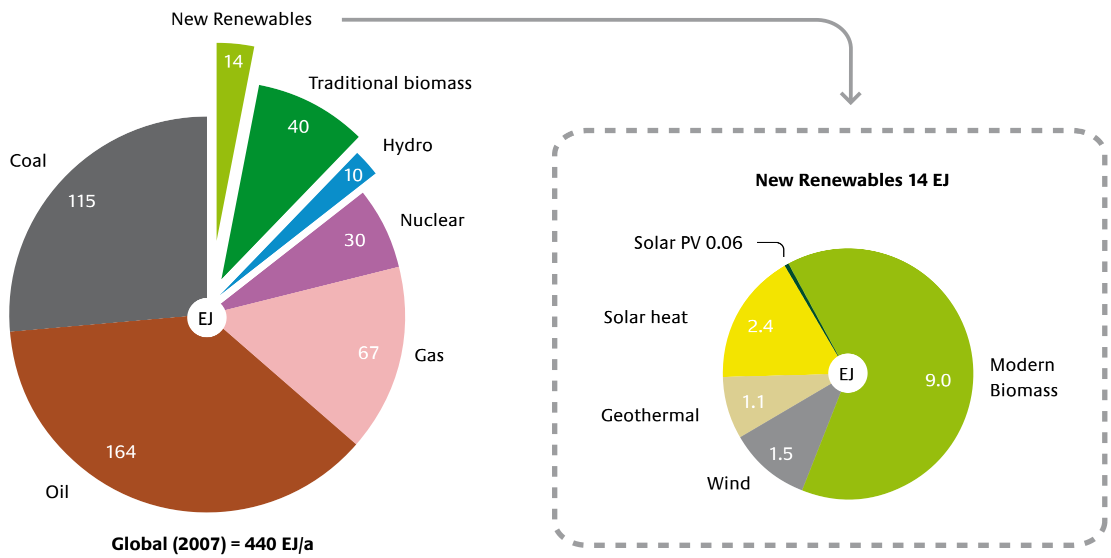

Figure 1: Energy consumption rates (in EJ/a or 10^{18} Joule per year) per energy source in 2007. Biomass amounts to 49 EJ/a or 10% of the global energy consumption. Source: Science 315, 808 (2007).

Global and local drivers for the bio-based economy
Specifically, the common drivers for the development of bio-based options can be divided into socio-economic drivers and energy-related drivers:[5]

Socio-economic drivers

- **Environmental considerations:** Greenhouse gas (GHG) emissions cause environmental and climate change. International environmental policies aim at closing the cycles of minerals, sulfur and nitrogen. This policy favors low-sulfur biomass systems (< 1% compared to 1 to 5% for coal)
- **Employment considerations:** On average, 11 jobs are created per MW installed biomass conversion capacity. Thus, 5% bio-energy in the EU leads to 160,000 additional jobs (Wright report)
- **Regional and agricultural considerations:** The EU has 20 million ha agricultural land and 10-20 million ha marginal land available for non-food production in 2000. Decentralized bio-energy stabilizes rural employment and regional development
- **Security of supply:** Without an EU policy, the external energy dependence will reach 70% before 2030, and 90% when it concerns oil imports
- **Energy costs:** Fluctuating and specifically rising costs for fossil fuels

Energy-related drivers

- **Co-firing of biomass** with coal to directly produce heat and/or steam to generate electricity is an attractive, scale-independent and, in secure areas of Europe, a well-developed option with a relatively low need for additional investments
- **Gasification** offers excellent options for high efficiency, large-scale electricity and chemicals production
- **Biofuels are for the next decade(s) the only option for a substantial replacement/supplement** of the transport fuels pool, without major infrastructural adaptation. Scale of biofuels requires fast development of 2nd generation biofuels from agroforestry residues that do not interfere negatively with human food chains
- Biomass is the **only renewable feedstock for the chemicals industry**, ranging from intact fibers to fermentative production of monomers and polymers. Therefore, sustainability can only seriously be evaluated in an integrated manner for energy, fuels and chemicals sectors. Note that the Netherlands is one of the few countries in the world where the use of fossil resources for the full chain of the chemical industry is more than the consumption of fossil fuels for transportation

1. **E-security**
2. **Economic opportunity**
3. Rural support
4. Greenhouse gas savings

Art: Kevin Kallaugher, *Economist*

Figure 2: Overview of common reasons to develop biofuels.

C. The big challenges for 2020 and beyond

Current developments in the direction of a bio-based economy will continue and intensify, leading towards a more sustainable situation in 2020 and beyond. With biomass taking care of about 10% of the global energy consumption rate (49 EJ/a) in 2007, a doubling of this number in 2050 seems a reasonable minimum scenario. Some researchers predict a possible increase in this century of up to 700 EJ/year. Based on these numbers, 300 EJ/year appears to be a median prediction (see the very recent WAB Biomass Assessment study that compiled all leading international literature in the field and which explicitly takes into account the key sustainability concerns with respect to water, biodiversity, competition with food production, etc.)[6]. Specifically, in 2020, three big challenges are (being) met:

1. The efficiency of existing industrial chemicals, materials, fuels and energy production in terms of ecology and economy are improved through a portfolio of superior technologies including industrial biotechnology
2. New processes and products based on bio-renewables with improved climate and economic impact are developed, leading to better resource security for energy and materials
3. Large-scale climate mitigation and adaptation technologies are developed especially for climate sensitive areas such as the Dutch delta but also worldwide (industrial biotechnology in context)

These challenges have been met with a major sense of urgency: infrastructures are provided, initiatives supported and implementations tested in order to accelerate finding and implementing significant solutions.

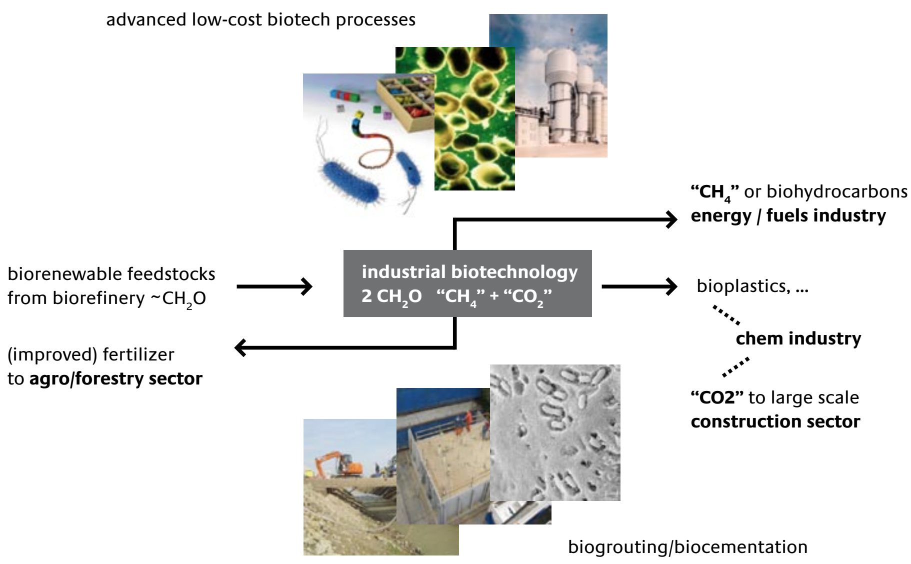

Figure 3: Most 2nd generation (lignocellulosic) biofuels processes produce dilute, water miscible (ethanol, butanol) or mixed ($CH4/CO_2$) biofuels leading to (1) high purification costs, (2) relatively low net carbon savings, (3) incomplete mass utilization of carbon, and (4) substantial CAPEX in large volume processes. B-Basic/BE-Basic (TU Delft, Deltares and partners) develops alternative biofuels that automatically phase separate and put value to carbon in large-scale construction markets, via low-cost bioreactor technology.

D. From 2009 to 2020

STRATEGY, IMPLEMENTATION AND IMPACT

To double energy production through biomass, it is critical to gain insight into how the global, generalized drivers for the bio-based economy translate into local (national/regional) implementation, since "the devil (and the costs) is in the details" of regional measures (R&D programs, investment stimulus, biomass logistics and handling, certification criteria, regulations, etc).

For instance: where 300 EJ/year seems to be a reasonable, potential biomass estimate for 2050, the established regional biomass transport capacity in developing countries is 40 EJ/year, and global transport capacity is available for the equivalent of approximately 9 EJ/year only. 300 EJ/year at an average 15 PJ/MT requires 20,000 MT biomass/year. To transport this quantity requires an equivalent of 50 ports the size of Rotterdam. The development of a bio-based economy therefore requires massive logistic capacity for biomass or its derivatives, with an associated certification infrastructure to guarantee sustainability. It is evident that for open economies with modest biomass production potential such as the Netherlands, a proactive policy with respect to biomass (and derivatives) imports and free global market access is essential.

An integrated macroeconomic/ecological study was recently issued by the Platform Groene Grondstoffen to evaluate the quantitative impact on the gross domestic product (GDP), employment, greenhouse gas (GHG) emission and energy security of various realistic scenarios of a responsible implementation of the bio-based economy in the chemicals, materials, energy industries and on trade/logistics. In the independent study, performed by researchers at Utrecht University and Wageningen University, several scenarios were investigated.[7] The scenarios differ on the one hand in the level of technological development of (biomass) conversion technologies, and on the other hand in terms of international trade:

- In the **national scenario**, limited sources of biomass are available from EU countries only
- In the **international scenario**, there are global biomass suppliers with the Netherlands as hub through its seaports at full capacity (Rotterdam, Amsterdam, Delfzijl, Terneuzen)
- In the **low-tech** scenario, existing 1st generation biomass conversion technologies are used until 2030
- In the **high-tech** scenario, advanced 2nd generation technologies substitute current technologies from 2010 onwards

The conclusions for scenario extremes under the assumptions of the study are indicated in Table 1 (full details and assumptions will be published elsewhere). The numbers in brackets are relative to 1990.

Preliminary results	Greenhouse gas reduction	Fossil energy avoided	Net effect on balance of payments
Low-tech/national scenario	-8 MT/yr (5%)	113 PJ/yr (4%)	+2 billion €/yr
High-tech/international scenario	-56 MT/yr (30%)	833 PJ/yr (25%)	+4 billion €/yr

Table 1: Impact of implementing the bio-based economy – scenarios

A All scenarios show substantial economic and ecological returns, with actual GDP contributions that are multiples of the numbers above
B The environment benefits strongly from the (high) technology investments
C There is a clear need for substantial biomass imports (realistic production in the Netherlands seems limited to 10-30% of total)
D Lignocellulosic (2nd gen.) technologies are essential for full effect (>50%)
E It is important to focus on sectors with high-added value per ton such as bulk and fine chemicals as opposed to energy (fuels, power) only

From the study, it is clear that the realization of the bio-based economy has substantial economic and ecological impacts, with international trade (and certification) key to such impact. The low-tech scenarios are moderately economically attractive but less attractive with respect to environment and energy security than the high-tech scenario. Current investments in the Netherlands, of around EUR 7 billion, are mostly directed towards low-tech 1st generation technologies. The high-tech investments offer substantially better economic, energy security and ecological returns, but are relatively risky in terms of technology development and implementation. As a result of that:

- The rate of implementation depends on (public) technology investments and initial market development (launching customer role for government);
- Technology winners for energy and chemicals sectors are probably different and depend on market position: this implies a need to support consortia with industrial partners and leadership, as well as to stimulate new start-up creation (venture capital portfolio, tax facilitation, incubator facilities, etc.).

INNOVATIONS IN THE TECHNOLOGY LANDSCAPE

In order to achieve the ambitions for 2020 and beyond, the current technology landscape needs to evolve.

RECOMMENDATION Technology innovations in four areas are urgently needed and represent opportunities for the Netherlands. These areas are: (i) an increased connection between bio-based chemicals, fuels and energy production, the agroforestry value chain and the logistic hub position of the Netherlands; (ii) development of better biomass refining (fractionation & depolymerization) technologies; (iii) chemo, thermo and catalytic conversions; and (iv) systems integration.

!

In the following paragraphs, we address each of these innovations.

(i) Connecting to the green (agroforesty) value chain

Recent literature reveals an explosion in biorefinery concepts: the fractionation and conversion of complex biomass streams into valuable products, integrated with the nutrients returns to the fields. Existing food-oriented refineries (starch, protein, oils) or fiber-oriented refineries (paper, clothing) usually target a small (edible) fraction of the produced biomass, producing considerable (mostly lignocellulosic) residue streams More modern concepts focus on the residue streams of specifically-grown energy crops, targeting the chemicals, materials, fuels and energy industry.

Residue streams

Co-products from agricultural activities and other biomass residue streams can be used for energy purposes. Clearly, the use of biomass for the production of energy and

Utilizing Dutch waste

Taking the Netherlands as a typical west-European case, not much land has been taken out of production and no large role has been assigned to the cultivation of biomass for energy purposes. On the other hand, energy production in the Netherlands is greatly decentralized in large to medium-size units, and it can benefit from it logistic gateway position to Europe. The high degree of urbanization results in a large amounts of organic waste, which is well-suited for energy production. If one considers waste as a residue stream from humans, then the Netherlands produce 65 million tons annually; 5 million tons of this waste are burned and partly used for energy production; 4 million tons are landfilled; the remaining 57 million tons are reused. In terms of waste treatment, this policy is very effective. Nevertheless, the above figures indicate that further utilization of waste is possible, and much could be gained by further increasing energy conversion efficiency. Another important aspect is that most Western European countries have outstanding facilities for supply and transfer, as a result of which the treatment and processing of biomass could lead to new developments.

chemicals should not interfere negatively with the main product of agricultural production: food. Additional biomass streams are made up of residues from maintenance work in parks, thinning wood from forests, grass from shoulders and agro-based processes such as industrial starch and biofuel. There is also waste from households, industry and industrial processes in general such as vegetable fruit and garden waste, demolition wood, slip, saw dust, cocoa nuts and coffee waste.

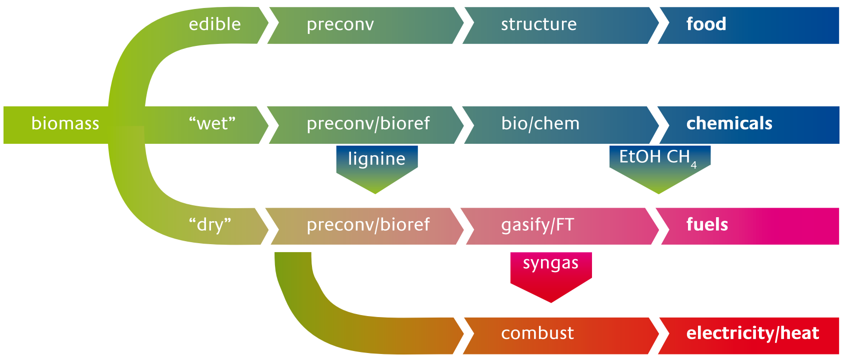

Figure 4: Simplified diagram of common biorefinery concepts to utilize biomass for food, chemicals, fuels and energy. More complex schemes can be drawn that have advanced cascades of biological, thermochemical and fractionation steps in them – this requires significant integration of the various scientific and technological fields.

Energy crops

For specific energy crops, obviously, only fast growing plants with a high yield per hectare are of interest. Typical examples are perennials such as Miscanthus, Sweet sorghum, Poplar and Willow. Algae are interesting because their growth requires no land, but sweet or marine water instead. Reports on biomass and specific (lipid) products production rates vary, but are of sufficient interest to merit continued investigation. For chemicals purposes, growth rate and yield as well as specific chemicals expression are crucial – but one has to realize that markets depending on specific “chemicals crops” may become instable upon productivity variations (diseases, weather).

Well-controlled plant biomass production is the basis of a bio-based economy. In essence, two complementary strategies need to be followed: **sustainable extension of suitable crop area** including water supply and erosion prevention, as well as **increasing crop yield and quality**.

Extension of crop area: marginal lands

Current biomass components for the conversion into liquid fuels (sugars, vegetable oils, etc.) are also essential components of the human diet. In the future, the availability of water, arable land and phosphate (in this order) may become a limiting factor in the production of both food and bio-energy. One option to prevent competition between food and fuel on the resource level is to reserve current arable land primarily for food production, and design crops and crop systems to allow all (edible and non-edible) biomass production on marginal soils or harsh environments.

Crop optimization for the bio-based economy

A rather extensive management of crops can be pursued with, for example, drought tolerant crops having a high photosynthetic capacity (e.g. C4 characteristics) combined with the ability to fixate nitrogen and CO_2 more efficiently. Also, insight into plant-bacteria associations is needed to enhance the exploitation of available soil nutrients such as phosphates.

An important research goal is the improvement of the yield potential and quality of plants already growing in the target ecosystems. Target crops for research are C4 grasses (low ash level, improved cell wall characteristics), succulent crops (e.g. improvement of seed oil and latex production in Euphorbs), perennials (improving yield perspective of seed oil producing Jathropha) and N-fixating trees. Crop production systems also need to be designed based on integrated insights into ecosystems, agronomy and crop characteristics.

Extension of crop area: aquatic production

Shortage of land and fresh water can be overcome with algae and cyanobacteria. Algae and cyanobacteria can be cultivated in the open sea at very high productivity levels, the latter requiring even less or no nitrogen. Some algae can accumulate up to 60% of their dry weight in various types of fats, and some cyanobacteria are reported to excrete significant amounts of small molecules. However, very little is known of the genetics of algae in order to directly synthesize specific components under various growth conditions. Furthermore, the processing of algae should be executed at or close to the (off shore) production site because algae contain so little dry weight. This puts some serious constraints on separation process development.

Improved storage characteristics: C and N-partitioning

The quality of plants is primarily judged from their suitability as a food crop. The composition, quality and value of crop plants is primarily the result of C-partitioning processes: the allocation of C and N into soluble or insoluble storage compounds (amino acids, proteins, sugars, sugar polymers, oils, cell walls, etc.). When plant biomass is used as starting material for fuels or chemical feedstocks, other C and N-partitioning processes become relevant, both over metabolic pathways and cellular compartments.

For instance, channeling of C and N into proline (building block for aromatics), lysine (building block for N-functionalized aromatics), carboxylic acids (O-functionalized building blocks for solvents and polymers) or some proteins are more attractive when biomass is used as a source of base chemicals. These molecules are already produced in plants, but only as intermediates in metabolic pathways, and normally do not accumulate in substantial amounts.

Therefore, an important research goal is to gain better understanding of the mechanisms controlling C and N-flux into specific metabolic pathways, and compartmentation and sequestration of these molecules into specific cell organelles. The present state of knowledge on plant and microbial metabolic processes, genomics proteomics and metabolomics will provide a sound base for improved understanding of the role of cellular transport in compartmentation and sequestration of useful compounds.

Improved storage characteristics: breeding approaches

Classical breeding approaches have not been fully exploited to improve storage capacities for special compounds. Preliminary screening of germplasm revealed ample natural variation that may be used in breeding, preferably combined with up-to-date marker technologies.

Another strategy is directed molecular breeding using genes from plants and microorganisms. Plants and microorganisms use different mechanisms to accumulate economically interesting compounds in high quantities. Whereas most industrial microorganisms export their overproduced metabolites into the medium, plants generally accumulate molecules in plastids, cytoplasm or vacuoles of specialized cell types. Relatively little is known about the allocation of metabolites over the different organelles in plants and microorganisms. Elucidating the genomics and physiology of membrane transport mechanisms in both types of organisms will result in an improvement of biomass yield and quality.

(ii) Biomass refining technologies

To optimize the use of renewable raw materials (or biomass), and to be able to generate a respectable net income from a crop, as many components as possible should be utilized (in the broadest terms: food, heat, fuel, chemicals) by employing an efficient biorefinery process and subsequent conversion technology.

Bio-conversion technologies

Whereas conventional fermentative production relies on cheap C6-carbohydrates, many efforts are made to completely utilize lignocellulosic feedstocks to enable the use of residue streams from the agro-sector and waste recycles from households. When fuels become essentially bio-based, the large volume of car-associated chemicals such as motor oils, lubricants, surfactants coatings and other materials, may have to become bio-based as well. So far, the latter challenges have not been met but provide an important stimulus for the chemicals industry.

The N, P and S containing fractions of bio-based feedstocks can represent significant value both for food (e.g. proteins) and non-food (chemical) applications. Fractionation of bio-based feedstocks following the biorefinery concept potentially lead to an increased economic margin and reduced carbon emissions potential, compared to separate fuels and chemicals manufacturing.

Sugar-based platforms

Although lignocellulosic material is rather resistant to enzymatic hydrolysis, it is expected that in the near future a combination of physical/chemical treatments such as acid or alkali hydrolysis, high temperature and pressure together with cheaper enzymes will result in an economical biomass hydrolysis process. The hydrolysis of especially hemicellulose leads to a mixture of hexoses (mainly glucose) and pentoses (xylose, arabinose) which must serve as feedstocks for fermentative production of ethanol. In order to be economical, the hexoses as well as the pentoses in the hydrolysate should be fully converted into valuable products. Routes to recycle specific elements such as sulfur, phosphor and particularly nitrogen should be developed as well, which can significantly reduce these waste streams and capture the energy content (maintain redox state).

Although smaller in volume than biofuels, the conversion of biomass via hydrolysates in bulk chemicals is a truly large-scale challenge as well. Classic fermentation products such as lactic and glutamic acid are being revisited, and serve as an (updated) model for newer products such 1,3 propanediol, hydroxypropanoic acid and possibly acrylate.[8,9,10]

Chemical conversion technologies

Efforts to produce chemicals with constant quality and performance currently focus on the use of carbohydrates as raw materials and the use of biotechnology for conversion. The development timescales involved are very long. Where the use of bio-based raw materials, instead of fossil raw materials, to prepare (or use in) current (chemical) products has taken place, implementation has been more rapid. For example, a glycerol by-product from bio-diesel production was utilized in the production of epichlorohydrin (Epicerol®) by Solvay. Another example is the wide portfolio furans and related compounds as developed by Avantium.

As can be understood by considering the enthalpy changes involved in the petrochemical processes, conversion of oil to other hydrocarbons is an energy efficient process. The use of hydrocarbons in the production of chemicals functionalized for example with amine or carboxylic acid functionalities, however, is not. Bio-based raw materials already contain many functionalized components such as oils, carbohydrates, lignin and protein. These can act as a platform for chemicals of a desired functionality, thus limiting energy loss during conversion.[11]

The thermochemical route

Thermochemical treatment of (fractions of) the biomass provides cheap feedstocks for use in large-scale biotechnological processes. Some of these proposed feedstocks are presently produced from petrochemicals at low cost. For example, methanol and especially glycerol due to 1st generation biodiesels are currently relatively cheap and attractive feedstocks for fermentation processes. These clean substrates are completely miscible with water and provide good carbon and energy sources for a large variety of microorganisms such as bacteria and yeasts. In the 1960s, ICI and Shell succeeded in converting methanol from fossil resources to single cell protein for animal feed on a large scale. Two oil crises made this process uneconomical. The scale-up in biomass utilization via thermochemical treatment promises to produce substantial volumes of additional feedstock components at low cost.

(Bio)catalyst screening, construction and development

The production of building blocks, and the availability of cellulose hydrolysates, requires the design of new synthetic

Connecting bio and thermochemical systems.
Research funds are required to investigate the strategic option to reduce power and energy by using methanol and equivalent low-cost components from thermochemical treatment of biomass (or still from petrochemical sources) as a source (co-substrate) for fermentation processes aimed for the production of reduced aliphatic and aromatic products.[12] These novel feedstocks will require genomics-based research to obtain the appropriate organisms. Metagenomics data pool harvesting, synthetic biology, population studies instead of individual organism studies, and the use of naturally occurring processes will be important elements in this research direction.

The studies will also address stress and zero-growth aspects because the large-scale operation typical for biofuels production crucially requires a very low surplus production of the organism. The present technology would still produce huge amounts of the production organism. A zero-growth production strain limits growth and uses the organisms as true cell-factories. This strongly improves sustainability and economics. All of these will enable major engineering research opportunities.

trees. A key requisite for this is the availability of mild and selective catalysts. Enzymes as biocatalysts can fulfill this demand. Biocatalysts have been shown to catalyze a wide variety of reactions, such as the (enantioselective) formation of CO, C-C, C-N and C-H bonds. Enzymes will be evolved and engineered in such a way that they are active and selective for a range of building blocks. This area is largely unexplored, and offers many new opportunities for the exploration of enzyme space.

Current (chemical) catalysts are geared to a number of key transformations (often in the absence of other functionalities). However, by application of bio-derived components as raw materials for the chemicals industry, new transformations will be required. For example, many components have oxygen containing functionalities (in the form of hydroxyl or carboxyl groups) that need to be removed. This is often carried out by dehydration or decarboxylation in the presence of other functionalities, which results in poisoning of the catalyst or a lack of integrity in the structure in the synthetic pathway.

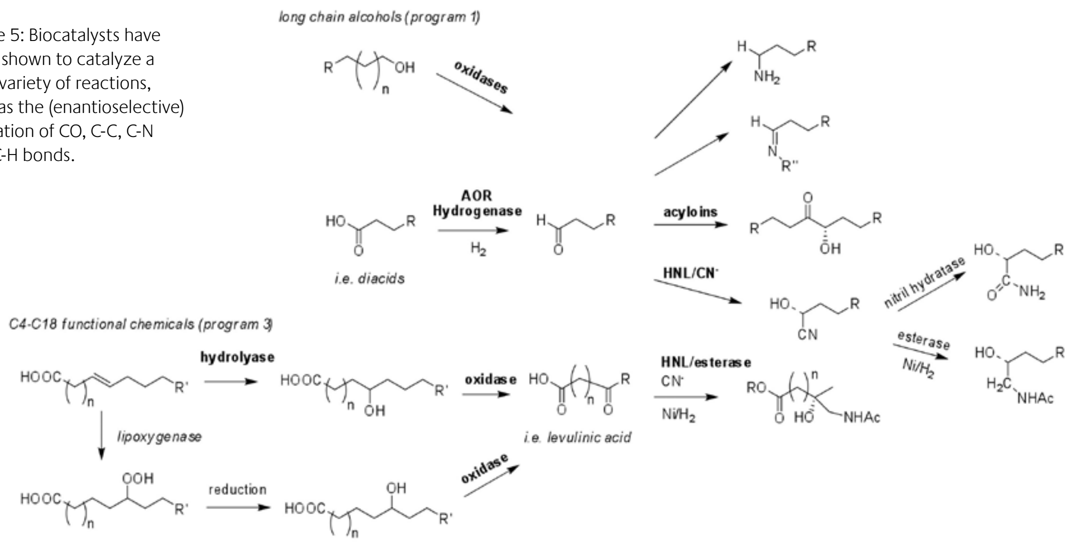

Figure 5: Biocatalysts have been shown to catalyze a wide variety of reactions, such as the (enantioselective) formation of CO, C-C, C-N and C-H bonds.

Another area of importance is the depolymerisation of complex heterogeneous raw materials. This is particularly important in the production of aromatic compounds such as benzene, toluene and phenol from lignin.

Metabolic engineering and synthetic biology

Synthetic biology revolutionizes the use of biological principles and building blocks to generate more effective bioconversion routes, higher rates and robustness of industrial microorganisms. This requires a comprehensive analysis and engineering of the cell membrane and cell wall to improve the performance of microorganisms under conditions where they are exposed to hydrophobic and toxic substances and metabolic end-products, either produced inside the cell or originating in the environment.

Synthetic biology

Microbial transformation of hydrophobic molecules requires efficient uptake and rapid conversions to minimize the adverse affects of these compounds on the cell and its membranes. Similarly, in the production of hydrophobic compounds the excretion needs to be efficient to prevent the membrane from saturating with the molecules with membrane disrupting properties, such as alcohols, isoprenoids, amphiphiles, weak acids and others. Synthetic biology can be used to construct new or redesign existing pathways of membrane transport and metabolic conversion. This requires integration of kinetic, thermodynamic and network analyses with genetic, physiological and bio-informatic approaches.

Bioprocess technology innovations.

The scale of operation and urgency to produce biofuels call for the creative development of appropriate bioprocesses. To meet competitive implementation, a full integration of the fast stream of newly discovered biological options with the latest developments in bioprocessing is needed. In-situ product separation (ISPR[13]), twin fermentation[14] with zero oxygen requirements and heat production using a closed redox balance by simultaneous production of oxidized and reduced products, inherent septic systems and purification in novel (staged) fermentors and integration of functions needs novel approaches. In addition, process integration efforts and high-throughput screening technologies are mandatory.

(iii) Chemo, thermo and catalytic conversions

Thermochemical processes can convert a wide variety of biomass feeds into heat, power, fuels and chemicals. Processes are being developed to completely convert lignocellulosic feedstocks into secondary energy carriers as well as for the downstream upgrading to end-products. Next to lignocelluloses, sugars, lipids and by-products from bio-conversion technologies have been identified as potential feedstocks. Traditionally, dry feedstocks were considered particularly suited for thermochemical conversions, but recent developments have shown that by operating at elevated pressure wet feeds can also be used.

Catalysis will play an important role in the production of bio-based fuels and chemicals, just as it currently does in the conversion of fossil feeds. It is therefore essential to adapt the knowledge related to making fossil fuels to lignocelluloses-based fuels. Additionally, the development of efficient processes requires new concepts for catalysts and reactor technologies. Of special importance are deoxygenation and C-C coupling catalytic technologies, since many natural bio-building blocks such as sugars are too oxygen-rich and too small for many fuels and chemicals applications. Many available catalysts are designed for use with hydrophobic, hydrocarbon-like molecules and rethinking catalytic concepts to fit an aqueous environment with hydrophilic molecules is a substantial challenge.

In the sections below, we will focus on the most important challenges related to thermochemical conversions, which

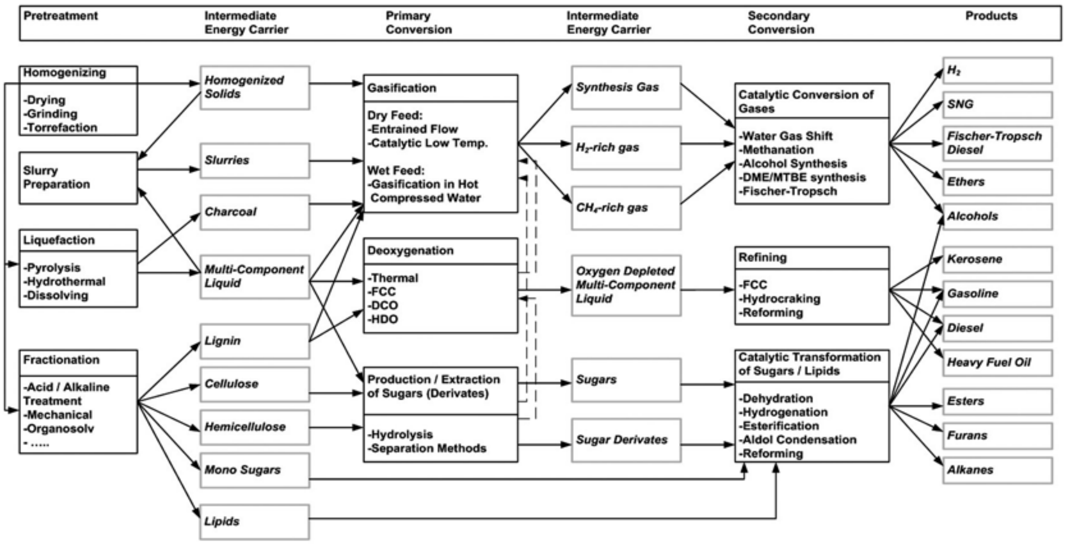

Figure 6: Thermochemical routes for the production of fuels and chemicals.

can be integrated with existing fossil industries and markets. The state-of-the-art in the thermochemical conversion of biomass into energy as well as fuels and chemicals is schematically shown in Figure 6.[5,15]

Pre-treatment

Lignocellulosic biomass needs pre-treatment before it can be processed. Drying, grinding and palletizing are well developed processes. Torrefaction and liquefaction (pyrolysis and hydrothermal liquefaction) are technologies aimed at conversion of bulky inhomogeneous biomass into secondary energy carriers, with improved energy density, that are easier to process in upgrading equipment. Liquefaction, torrefaction and palletizing can be done near the source of the biomass feedstock (e.g. remote, rural areas), with large-scale production of the finished products near the market. Ideally, a large percentage of minerals is recovered at the biomass production site and returned to the soil.

Torrefaction only requires a temperature of 200-300°C. In this process, the feed embrittles, loses its moisture and becomes water repellent too. These improvements are expected to increase the possibilities for co-combustion and gasification. Liquefaction (300-500°C) yields a multi-component bioliquid that can be upgraded to fuels and chemicals via gasification and refining.

Torrefaction and pyrolysis development activities are currently in the pilot/demonstration phase, aiming to increase the robustness and availability of the technologies. Research is directed towards quality improvement of the product. For pyrolysis this partly means making the product (pyrolysis oil) less acetic, more stable and more compatible with refinery streams. The introduction of a fractionation step in the pre-treatment is also sought, thus creating a lignin-rich and a sugar-rich product. Catalysis will play a key role in product improvement.

Fractionation and Separation

Carbohydrates can be extracted relatively easily from 1st generation biomass. 2nd generation lignocellulosic biomass requires more complex fractionation to separate lignin from poly-carbohydrates and conversion steps to depolymerize the poly-carbohydrates. Fractionation is the first and a very important step in the path from lignocelluloses to fuels and chemicals via sugars (i.e. the so-called sugar platform).

Research should focus on cost reduction, minimizing the need for additional chemicals and preventing the formation of unwanted by-products. This will require processes and catalysts that can work under severe fouling and poisoning conditions caused by the complex lignocellulosic biomass. Separations are required in future biorefinery complexes to extract chemicals from bioliquids (e.g. acids and phenols from pyrolysis oil). Water removal/densification technology will become very important in economically utilizing highly diluted feeds like algae for fuel production. Research on these separations is in an embryonic stage.

Combustion and gasification for heat and power

Co-firing is the simplest form of biomass use in a coal-fired power plant. In fact, the biomass is carried with the pulverized coal to the boiler.

Technology development should be focused on increasing the co-firing percentage and preventing maloperation. A development to improve flexibility of biomass input with coal is torrefaction. Co-conversion is a more advanced use of coal, with the possibility that it can also be utilized in gas turbine power plants leading to higher efficiencies. For this application, biomass is first converted to a combustible gas in a separate gasifier, after which this gas is blown and burned in a coal boiler. In this way, the mixing of biomass ash and coal ash can be avoided and there is more freedom in choosing the conversion percentages. However, an investment in a biomass gasifier makes the process more expensive compared to co-firing. As these technologies are still new, it is not surprising that several problems have emerged which challenge scientific research.

Gasification followed by catalytic gas upgrading to fuels and chemicals

This route can be integrated with the current fossil at two levels, namely co-feeding of the gasifier and co-feeding synthesis gas to catalytic converters. Developments in the coal and oil industry have led to three archetype gasifiers: fixed bed, fluid bed and entrained flow. Low-temperature gasifiers without catalyst operate at below 950°C and generate fuel gas (comprising CO, H_2, CO_2, H_2O, C_xH_y, $C_xH_yO_z$, tars), which needs extensive conditioning in the conversion to syngas for the production of fuels and chemicals. In fact, gas cleaning and conditioning is the Achilles' heel of this technology and still requires large R&D effort. As an example: tar removal of even ~99% is still not enough to protect downstream catalysts such as Cu in alcohol synthesis or Co in FT. Research is ongoing on catalytic low temperature gasification for syngas and methane-rich gas. High-temperature (entrained flow) gasifiers operate at above 1300°C and provide a relatively cleaner synthesis gas (CO, H_2, CO_2, H_2O), but require pure oxygen and thus a larger scale of commercial operation. Recent developments have shown that very wet biomass streams (> 80 wt% moisture) can also be gasified. For this new technology, high pressures (> 200 bar) and catalysis are required. Technologies to convert syngas into SNG, H_2, FT-diesel, ethers and alcohols are mature for fossil feeds. Using these techniques for bio-based gas, two approaches are possible: i) cleaning the gas to the desired level, ii) development of new catalysts which are more robust for poisons related to biomass feeds.

Gasification of biomass aiming at fuels and chemicals is in the pilot stage, focusing at de-bottlenecking engineering aspects. From these activities, new scientific research lines aiming at efficiency and operability improvement are emerging.

Refining to fuels and chemicals

Refining is used here as the processing of bioliquids in ways similar to that of processing crude oil. Lipids, primary bioliquids such as pyrolysis oil, black liquor and sugar solutions are the expected feedstocks. Lipids, once extracted, can be converted in mature esterification and hydrogenation technology into diesel and kerosene. Co-processing primary bioliquids together with refinery feedstocks in existing refineries makes use of the available infrastructure, which saves investment costs and generates standard products for existing markets (diesel, kerosene, gasoline). In this way, large amounts of biofuels could be introduced in the near future. The main principle of this route is partial deoxygenation of (fractions of) primary bioliquids (pyrolysis oil, hydrothermal liquefaction oil).

Research focuses on:

- Developing catalytic deoxygenation and C-C coupling technologies and routes (fraction-technology combination) with minimum hydrogen consumption;
- Determining the required quality of upgraded primary bioliquids for co-processing.

The catalytic conversion of carbohydrates into fuels (e.g. alkanes, LA-esters) and fuel blending components (methyltetrahydrofuran) has been studied intensively in the last five years. Research is directed at solving the shortcomings of the current routes which i) consist of too many steps that often operate at different conditions, thus requiring intermediate separations and having a low overall yield (selectivity), and ii) have reaction rates that are generally too low.

Large-scale biomass production

Algae are considered an interesting energy crop because of their high growth rate and high lipid content. For large-scale energy applications, algae growth should not be considered as an agricultural but as an industrialized process. To allow the transition from the current algae growth for nutrients and specialties to energy, the algae production costs should be reduced by a factor 100, which demands a huge R&D program.

(iv) System integration

An important challenge concerns the distributed nature of biomass production related to its widespread use as energy-fuels-chemicals feedstock. The proper balance between large or small-scale manufacturing, transport and mobility, income distribution, biodiversity and community structure and culture is crucial in the acceptance and speed of implementation of bio-based options.

Scaling-up by sizing-down?

With respect to total efficiency improvement, dematerialization and energy densification are key technologies. Large-scale processing of agro-products, inspired by the current petrochemical industry's infrastructure and capital, is a potential route. This will lead to intensified use of bio-based feedstocks, to large-scale, global transport of biomass (derivates). It is technically feasible, but is it desirable? The distributed character and local variation of biomass in relation to the distributed use of the main product volumes (energy and fuels) could also favor smaller scale collection, processing and redistribution.[16] Other alternatives could also be implemented at a small scale, such as combined heat and power plants on the microscale (micro and mini-CHP), fuel cells and photovoltaic panels. Apart from the additional range of scientific and (alternative) technological options, this may lead to a better alignment with the current community structure than the one associated with large-scale energy, fuels and materials sectors. This will enhance the development of completely new social, financial (microcredit) and industrial structures.

INNOVATIONS IN THE PARTNERSHIPS' LANDSCAPE

Public-private partnerships as windows to innovation

The value chain of the bio-based economy ranges from field to forest, via a wide array of harvesting, handling, fractionation and conversion technologies to a similarly wide array of consumer products: chemicals, materials, fuels and energy. Only a few industrial players such as agro-food processors can integrate a significant fraction of the value chain; most others focus on a single or a few elements from the point of view of a market or technology portfolio. Therefore, many alliances are formed to control larger fractions of that chain and to bring the required capabilities together. Open innovation models based on precompetitive public-private partnerships such as B-Basic (NL), Kluyver Centre (NL), Porter Alliance (UK), CLIB2021 (DE) and Energy Bioscience Institute (USA) bring together established, large-scale players and have succeeded in combining fundamental scientific research, technology development and innovation. Similarly, commercial joint ventures (e.g. DuPont-Genencor, DSM-Roquette, Shell-Codexis) are also promising in this stage, but can only work when (i) sufficient R&D capacity is already on board, (ii) sufficient R&D capacity is incorporated via mergers, or (iii) links to the academic world exist. Feeding commercial joint ventures with new ideas is a natural role for public-private partnerships (PPPs).

The Dutch landscape is rich in PPPs that are relevant to the bio-based economy. Examples include industrial biotechnology (B-Basic, Kluyver Centre), chemical catalysis (CatchBio), (bio)process intensification (DSTI, PI, Biorefinery) and bioproducts development (DPI). In addition, a number of enabling programs have been initiated in the "omics"-field (genomics, metabolomics), in molecular sciences and in systems biology. Critical for generating new concepts will also be (more) interfaces between (historically) separate science and technology fields such as biotechnology, chemocatalytics and process engineering. Interface programs between these PPPs are a high priority area, and obstacles should be removed.

It should be recognized, however, that these PPPs are based on relatively short-term programs (4-5 years), whereas the time horizon for the transition to a truly sustainable development in the chemicals and energy field is substantially longer (10-20 years). Furthermore, although the interfaces between these fields offer many opportunities, there are no incentives for the individual centers to collaborate with each other. As a matter of fact, the application and evaluation process favors programmatic focus instead of integration between programs.

RECOMMENDATION The Netherlands, with its rich and high level biotechnology and chemical research culture, is ideally positioned to benefit from long-term support of proven PPPs, which is recommended. It is also recommended to stimulate programmatic collaboration at the relevant and promising interfaces between them. !

Public-private partnerships as start-up engines

New ideas are certain to emerge when young, creative minds are brought together to tackle the big challenges in climate mitigation and adaptation, energy security and economy. Some of the real breakthroughs are among the more risky ones in terms of technology and economy. Large companies may be required to deliver these breakthroughs, but they do not necessarily provide the best, risk-taking framework (inherent dynamics, shareholder value, regulations). Clearly, the R&D and "New Business" departments of large industries are not the proper homes for exciting breakthroughs; instead these risky developments benefit from the small company structure of a start-up.

So far, the (precompetitive) public-private partnerships in the Netherlands have had limited funding possibilities themselves to start or support those (competitive) initiatives, although some have developed mechanisms (B-Basic's Leo Petrus Innovation Trophy) to identify and support proof-of-concept and further. The freedom to create new businesses is also practically restricted by the requirements of national, pre-competitive programs (BSIK, FES), such as the requirement to incorporate an average of 25% industrial co-funding from large corporations with associated IPR control. Apart from a few options (MIBITON, Biopartner, SBIR), a fully functional venture capital culture is lacking in the Netherlands.

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RECOMMENDATION It is recommended that more opportunities for *proactive* venture capital funds are created for seed capital, and early as well as later venturing (including stimulating mechanisms such as *entrepreneurs in residence*), while maintaining the constructive public-private collaboration between academia and existing industries.

Public-private partnerships can provide risk-sharing facilities

The most challenging contributions of the emerging bio-based economy target large-scale energy, fuels and chemicals manufacturing. Success requires the proper combination of sustainable bio-feedstocks, efficient large-scale production technology and significant markets. In those cases, the combination of specific feedstock and large-scale production technology is critical for success, and needs to be developed, tested and demonstrated on a significant scale. This cannot, however, be handled in small-scale experimental equipment (grams to kg per day) at the laboratory, but experiments must be extended to the pilot plant level (100 kg to 10 tons of product per day). Clearly, large-scale technology also generates its own set of challenging scientific questions that can only be answered by researching on a significant (pilot plant) scale. It also requires demonstration on the (semi-)industrial scale, which ranges from thousands to hundreds of thousands of tons of product per year. Scaled-up (experimental) installations are very capital intensive, while in the bio-based economy many options still need to be evaluated. This combination brings high risk, and certainly private sector hesitation to invest in the current economic framework. Sharing risk by sharing facilities, while benefitting from bringing multiple partners together in a stimulating open innovation pilot plant environment, is critical for successful and progressive implementation of the bio-based economy.

So far, pilot plants are always focused on the combination of a single feedstock and a single process. The risks and costs may be acceptable for some of the biofuels (e.g. ethanol from corn stover) but even in these cases the US government strongly supports the critical step via a variety of initiatives. In the Netherlands, with its wide diversity of chemicals companies, it is impossible for a single company to do this, given the costs and time required. Here, availability of open innovation and multi-purpose, not-for-profit facilities are critical for translating laboratory results into commercial processes. Such facilities are particularly indispensable for start-up companies, especially for those in equipment manufacturing, monitoring devices and other associated businesses.

Pilot plant facilities also play an essential role in training new generations of technicians and engineers. Obviously, the facilities cannot be operated full-time and necessarily will have to be idle from time to time. The high safety requirements associated with using recombinant organisms in fermentation processes or tough conditions (high temperatures, hydrogen pressure etc) require a skilled technical support team. Yet, the steadily falling budgets for institutes of higher education negatively impact the creation and operation of these capital intensive facilities. Aligning these various research, innovation and education/training targets into a single combined, not-for-profit facility can share both risk and costs. A public-private partnership setting can be instrumental in governing this. Physically locating piloting and demonstration facilities at an innovation campus, in the vicinity of a port and academic center – such as that projected for Bio-Based Economy/Industrial Biotechnology in the greater Rotterdam-Delft area – will strengthen the Netherlands' strong international position as a key European logistical, industrial and knowledge hub for the bio-based economy. Availability of unique and differentiating facilities will attract new international industrial players, boost start-ups and inspire the next generations of technicians, engineers and scientists.

! RECOMMENDATION **It is recommended to bring research, technology development, piloting and testing facilities into a combined innovation campus/center such as that projected for Bio-Based Economy/Industrial Biotechnology in the greater Rotterdam-Delft area.**

Consolidating the Netherlands' public-private partnerships

Dutch public-private partnerships such as B(E)-Basic and the Kluyver Centre for Genomics of Industrial Fermentation have initiated/tested a model of intimate industry-academic collaboration. The model relates to that of the Dutch TTIs (Leading Technology Institute) such as DPI. That 12-year-old and successful model of mutual respect, drive for quality and joint focus on scientific progress as well as commercial opportunities inspired many of the later public-private partnerships in the bio-energy and biochemicals arenas. The success of the Dutch public-private partnership model is internationally recognized, especially in the area of sustainable (bio-based) production technology. Figure 7 gives an overview of industrial and academic players that partner in one or several of the PPPs involved in climate mitigation and adaptation. Most are centered around the axis of Rotterdam/Delft-Utrecht-Wageningen. This density of innovation programs, as well as commercial and scientific activity, is only matched by the Bay Area's *Silicon Valley* and Boston's *Kendall Square* around MIT and Harvard. An urgent extension in terms of multi-purpose and open innovation piloting and demonstration facilities is needed to bridge innovation's valley of death more efficiently.

It is critical to consolidate this model after 10 years of experimenting with relatively short (4-5 year) programs. One option is to merge successful bio-based programs into a leading technology institute. For the various programs in the field of industrial biotechnology such as B-Basic, BE-Basic, IBOS and the Kluyver Centre, there is an excellent opportunity to integrate the best practices into a Netherlands Institute for Industrial Biotechnology. Similarly, the existing DSTI program, and the planned Process Intensification and Biorefinery Programs could merge into a joint Institute for Sustainable Process Technology.

RECOMMENDATION **It is recommended to consolidate proven and successful public-private partnerships into centers with a longer term funding basis. Examples could include a Netherlands' Institute for Industrial Biotechnology and an Institute for Sustainable Process Technology. !**

Linking (inter)national public-private partnerships

Public-private partnerships with integrated budgets at the scale of several tens of millions of Euros are good size initiatives (B-Basic EUR 10 m/yr, Kluyver Centre EUR 10 m/yr, BE-Basic EUR 25 m/yr, EBI EUR 50 m/yr). Smaller programs lack critical mass; larger programs tend to become

□ Companies	Bio (B(E)-Basic, Kluyvercentre
◇ Institutes	BioSolar
○ Universities	CCS (CATO)
	Process (DSTI, PI)

Figure 7: The high density of industrial, academic and NGO partners in the Dutch bio-based economy compared to Silicon Valley (also pictured above)

(overly) bureaucratic and ineffective. Still, linking them to larger networks is interesting for two different reasons:

- **Scale of knowledge and innovation communities**
  On average, every EUR 2 m spent in a public-private partnership yields a patent, and typical PPPs generate 5-25 patents per year. Thus, the scale of a single PPP is too small to feed a reasonable-scale venture capital (VC) fund of hundreds of millions of EUR/USD, which needs deal flows at the scale of several hundreds per year. By grouping a number of related Dutch public-private partnerships – such as outlined in the previous section – it is possible to achieve a more reasonable foundation. Many of these Dutch PPPs have similar governance structures, and collectively they could act as a large-scale "deal flow generator" for a number of VC funds. Investors could come from the private sector (financial as well as corporate VCs), from the government to accelerate economic development and job creation, as well as from each of the academic and industrial partners. The VC funds can provide a window on the world as well as to add value to research output. A challenging option is to link international public-private partnerships in the same field of activity (e.g. B-Basic/Kluyver Centre plus CLIB2021 (Germany) and Porter Alliance (UK)). In this case, it is recommended to reduce or fully remove regulations that restrict international collaboration.

- **Assessment of social impact**
  Our ecosystems are under pressure from increasing demands for food, feed, fiber and fuel. Large-scale transitions such as the one towards a bio-based economy will significantly impact our society, as the increasing demand for biomass requires sustainable production, responsible use and equitable sharing of resources and products. Energy security and climate change mitigation, rural development and sustainable land use will depend upon rigorous debate supported by the best available fact-based information. Most of the national public-private programs have specific social "work packages" which are necessarily focused and thus have their obvious (regional/thematic) bias. However, the global scale and large thematic breadth of bio-based economy development is such these separate social insights need to be brought together in order to achieve truly new insights.

Global Biorenewables Research Society
Alongside eight peer institutes, B(E)-Basic and the Kluyver Centre have initialized the "Global Biorenewables Research Society". The GBRS will work in an IPCC-format to generate hard facts on and insights into the true sustainability of the bio-based economy. GBRS aims to provide the standard for science-based knowledge for sustainable bio-renewables. The founding partners of the GBRS are scientists from the leading international bio-renewables centers: B-Basic (Netherlands), the Energy Biosciences Institute (USA), Kluyver Centre (Netherlands), Institute for Biotechnology and Bioengineering (IBB) (Portugal), Institute of Advanced Studies of the University of São Paulo (IEA-USP) (Brazil), University of Queensland (Australia), Imperial College (United Kingdom), University of Cambridge (United Kingdom), Copernicus Institute of Utrecht University (Netherlands), Catholic University of Valparaíso (Chile), Indian Institute of Technology Kharagpur (India) and University of York (United Kingdom). Membership is open for additional participants.

RECOMMENDATION It is recommended to support national and international links of public-private partnerships for reasons of accelerating business and job creation, as well as to improve the rational basis of sustainable bio-based economy development. !

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Authors

Huub Löffler, Plant Sciences Group, Wageningen UR
Arno Vermeulen, General Manager Immuno Valley

Agriculture

The future of the agricultural life sciences in the Netherlands
A vision for 2020 and beyond

V Agriculture

Executive summary

Covering nature, agriculture and environment, the agricultural life sciences are fundamental to the very existence of the world as we know it today. In 2020, the agricultural life sciences will continue to play a major role in addressing challenges that require innovative technological solutions. Major issues will be feeding a growing global population with healthy food, mitigating climate change and dealing with energy security while avoiding negative impacts on our living environment. Feeding the expected 7.5 billion people requires more efficient production systems, minimizing losses due to pests and (infectious) diseases. Global health is at stake not only as a consequence of malnutrition, but also due to age-related chronic diseases, food-related disorders such as diabetes, obesity and bowel disease and infectious diseases in human and animal. The agricultural life sciences can play a leading role in answering these global problems.

To be effective, the agricultural life sciences need to be rooted in a sound Dutch scientific infrastructure. The current infrastructure, comprising the academic institutes, social organizations and the private industry such as breeding companies, food companies, biotech and the pharma industry, has gained international recognition and is thus fully able to develop the innovative solutions needed and to market the products throughout the world. Public-private partnerships are an effective tool in bringing this innovation process forward.

Only by capitalizing on the full potential of Dutch agricultural life sciences can we develop the products that bring profit to our industry and sustain the wealth and health of our society.

RECOMMENDATION **To further strengthen its future position, the agricultural life sciences call for:**

1. **A stable and strong knowledge base striving for excellence**
2. **Strong focus and mass on competitive and distinguishing technology in the following fields**
   - **A secure and sustainable food supply**
   - **Animal health**
   - **Biorefinery**
   - **Systems biology**
   - **Micro- and nanotechnology**
3. **Continuity of the open innovation systems such as public-private partnerships**
4. **Technology that is sustainable and acceptable for the society**

!

A. The agricultural life sciences

The agricultural life sciences encompass nature, agriculture and the environment. The agricultural life sciences, therefore, cover organisms such as microbes, plants, animals, human beings and also the many interactions between them. As such, the agricultural life sciences are fundamental to the very existence of the world as we know it. To date, genomics and related technologies have become a formidable driving force within the agricultural life sciences. We now face the challenge of how best to explore the future potential of the agricultural life sciences, in effect, to explore the full potential of nature itself. How will the agricultural life sciences contribute to the quality of life? How can the agricultural life sciences be used to meet major global challenges? What is needed to capitalize on the full potential of the agricultural life sciences? What is the impact that the agricultural life sciences will have on society and how can this become pertinent to decision-making in science, industry and politics?

B. Global challenges

Feeding the world

2020

In 2020, one of the major globally-addressed topics is food security. The global population has reached 7.7 billion and everyone has a right to be fed a balanced diet. A higher agricultural productivity in combination with a better distribution of available food is a major challenge which has to be met. The life sciences meet this challenge with technological innovations. Improved and novel foods, including new protein sources, have been introduced. Insect and aquaculture products like algae are frontrunners of a new and more sustainable food production industry. However, the "classic" animal and plant products are still the major sources of protein. The consumption of animal products in the Western world is decreasing slightly. However, prosperity has grown (e.g. in large parts of Asia). Consequently, the diet of a large part of the Asian population has shifted from a predominantly vegetarian one towards the consumption of more meat and dairy products. This fast-growing demand will put great pressure on the world's resources.

The road to 2020

Feeding more people with an affluent diet calls for considerably higher primary food production. Increasing the agricultural production area is hardly an option in tackling this challenge. The most fertile lands are already under cultivation and exploiting marginal soils demands a considerable input of scarce and valuable resources like energy, water and phosphate. A higher agricultural productivity is therefore the best option to achieve food security. Higher productivity is rooted in three major developments. Firstly, sophisticated plant and animal breeding technologies can increase the potential biomass yield of plants and animals. For example, the efficiency of feed uptake by livestock can be increased by applying the correct combination of animal and feed through the selection for Optimal Feed Conversion Rates (FCR). The potential yield of plants could be increased, say, by improving photosynthetic efficiency. The second intervention is to improve the quality and composition of feed which improves nutrient utilization and total production. The third important action is based on avoiding production losses. Plant diseases, destroying crops both during cultivation and after harvest, can be controlled by advanced agronomic methods. New plant varieties will be developed which are more resistant to pests and diseases. The control of infectious diseases in animals is also of utmost importance in preventing losses in meat and dairy production. Precision agriculture, in combination with well adapted plants and animals, will ensure a high output/input ratio. More predictive approaches (predictive + prognostic tools + early warning methods based on biomarkers) are needed that allow corrective measures to be taken at a very early stage.

The role of the agricultural life sciences

The life sciences are the driver behind all of these developments. A thorough understanding of the functioning of

> “It is a scientific challenge to design four times more ecoefficient agricultural production systems, to ensure that we can feed the world within the carrying capacity of our planet earth.„
>
> **Martin Scholten, Director of the Animal Sciences Group of Wageningen University**

genes and proteins and their interactions with external factors as well as their effects on traits, (micro)organisms, environment and agricultural systems are of crucial importance to this sector. The installation of high-throughput facilities to collect relevant data, and especially, the correct bioinformatics to integrate this data (systems biology) necessitate the development of more predictive and preventive approaches in plant and animal sciences. Through higher productivity, enough food can be produced on the existing agricultural area without jeopardizing nature or existing biodiversity. These technological solutions cannot be met through national incentives alone. Global trade in plant and animal products thrives and the EU, including the Netherlands, is a major producer and must therefore collaborate via national initiatives in larger frameworks to develop these technologies.

Climate change

2020

In 2020, temperature rise is no longer an issue for debate. Climate change is considered a fact, and has affected global agriculture. Although a higher temperature, in combination with an increased CO_2 concentration, may even have increased the yield of vegetable production on a global scale, the regional variations are large. Precipitation patterns have shifted and have resulted in desertification of some formerly productive regions, while flooding others. The gradually rising sea level is causing salinization of coastal zones. These shifts especially impact agricultural systems in developing countries, putting food security at risk. Animal diseases (most zoonotic) are rapidly spreading (Bluetongue, Rift Valley Fever, African Horse Sickness, Crimean Congo Fever, Chikungunya fever) and are having significant impact on animal farming and global health. Likewise, plant pests and diseases have spread to new regions, threatening local agriculture.

The road to 2020

Mankind responds to global warming by trying to neutralize the causes (mitigation) and by modifying life to suit the new situation (adaptation). If livestock can consume feed more efficiently, less waste will be released as methane into the atmosphere. The slogan here is “two times more with two times less” referring to the ratio of production to environmental impact. Farm animal breeding and management can contribute to the decrease of environmental output (e.g. by increasing environmental production efficiency and by decreasing output of gas emissions). Precision agriculture and better digestibility will enable a higher output/input ratio, minimizing waste and also the conversion of fertilizer into the major greenhouse gas N2O. Plants act as powerful CO_2 catchments, purifying the atmosphere of CO_2 and converting it into biomass. In addition, new systems and crops/animals will be developed that are (more) adapted to the new climatic conditions. New plant varieties can survive periods of drought or flooding, and resume growth as soon as the extreme situations have passed. To overcome salinization, new cultivation systems and crops adapted to saline conditions will be established for agriculture in brackish regions. Animals will be selected that can thrive on products from salty soil. Prevention of new diseases needs early warning systems and appropriate diagnostic tools.

The role of the agricultural life sciences

The life sciences drive all of these developments. Both mitigation and adaptation necessitate a fundamental understanding of crops and livestock in modern farming systems. Technological advancements make use of natural biodiversity to select the best adapted animals and plants and can even introduce selective traits into the population. Sophisticated breeding technologies will enable the development of robust crops/animals optimally adapted to the changing conditions. The genetic constitution of organisms and populations determines their potential to respond to changing climatological conditions. These responses, in turn, determine the behavior of farming systems and enable the prediction of crop production systems that are best suited to meet climate change. Both in terms of mitigation and adaptation, the agricultural life sciences are crucial. Correct interventions orchestrated by the agricultural life sciences will help minimize the effects of global warming. The life sciences have the lead in developing new diagnostics and early warning systems on a global scale.

Energy supply and basic resources

2020

In 2020, society can no longer rely fully on fossil resources for energy and industrial raw materials. The bio-based economy has grown to maturity and agriculture has expanded widely beyond its original goal: the production of food. However, this has been shown to create an extra burden on the availability of agricultural resources for the production of food and feed. Energy-neutral (agricultural) production, reuse of waste as fertilizer or as biofuels are, even in 2020, still challenges for the years to come. The focus is on the next generations of biofuels, without jeopardizing food security; biorefinery is in place to maximize the value of biomass. Developing countries, well-suited to the production of biomass, are profiting from renewed interest in biomass.

The road to 2020

The current first and second generations of biofuels competes, with other uses of biomass, for scarce resources like water, land and nutrients. The challenge is therefore to develop new pathways for bio-energy. Exploring the potential of photosynthesis, both for higher biomass production and for the development of BioSolar Cells, is one such new and exciting path and needs to be pursued. Biomass is urgently needed for biomaterials. Where several alternatives to fossil energy are available, the only alternative for fossil-based materials are those originating from biomass. Inevitably, this development will grow in impact over the coming decades, supported by the many new options offered by sophisticated technologies. Biorefinery technologies are needed to maximize the value of biomass. By carefully fractionating biomass into components with different economic values, the overall value of biomass will increase dramatically. Biomass is not used for one or the other application, but for both simultaneously. High-value components may be used for special chemicals; proteins and sugars may be used for food; and the remnants are still a suitable source of energy. This option relies upon advanced technologies and carefully controlled and interdependent processes and production chains.

The role of the agricultural life sciences

New advances in the life sciences open new possibilities for the true development of a bio-based economy. Sufficient production of biomass is a prerequisite for using biomass beyond food purposes. This may be reached either by tailoring crops for growth on what is currently wasteland, or by improving the production capacity of crops in existing systems. Genomics and breeding are key to these developments. The multiuse of biomass calls for new biorefinery concepts and again, for plant varieties that are optimized for broader use. In line with the cradle-to-cradle concept, plants and plant-based systems need to be (re)designed for optimal processing. Animal production systems need to be developed such that waste is no longer considered as waste anymore, but rather as feedstock for further processing. Diminished environmental pollution is an extra pay-off. The life sciences will play a key role in fueling these developments.

Environmental stewardship

2020

In 2020, a sustainable agricultural environment is considered essential for humankind in numerous ways. Animal

“ We face the challenge to increase our agricultural productivity while decreasing our ecological footprint. The agricultural life sciences are excellently suited to address this challenge and I hope and expect that they will have a growing impact on our agricultural systems to the benefit of mankind. ”

Martin Kropff, Rector Magnificus of Wageningen University

and plant production is now an integral part of our environment and is functional as a major economic factor in society. Farming comprises both large-scale animal and plant production as well as smallholders with strong emphasis on biological values giving particular attention to the recreational and educational aspects of the profession. With the increased pressure on biotopes through further urbanization, human infrastructure and agricultural land, biodiversity is under great pressure. Environmental stewardship is the prime responsibility of every individual on earth and governments have called for global approaches in order to preserve our environment. Surely the need for space, energy and food are in conflict with environmental needs. Therefore, technological innovations are essential to meeting this challenge for generations to come.

The road to 2020

Environmental stewardship calls for sustainable production systems without jeopardizing our environment. In ultimo forma, this is conceptualized in the cradle-to-cradle model. In this concept, introduced by William McDonough and Michael Braungart, waste is considered food either for the biosphere or for new production processes. Non-sustainability is not an option, and both ecology and the economy will benefit from this concept if it is consistently implemented. Nature conservation and reclamation need to be pursued to create viable ecosystems where the maintenance of plant and animal biodiversity is optimally guaranteed.

Genetic diversity in plants and animals is recognized as pivotal for many future applications. More and more, plants and lower organisms will be discovered that form the basis for (bio-)pharmaceuticals. Diversity of the intestinal microbiota will be exploited to improve animal health and feed conversion. Diversity will be further exploited in breeding as a source of many important characteristics such as disease resistance and adaptability. Diversity is proving fundamental to resilient ecosystems and adaptive production systems, enabling farmers to respond effectively to a changing environment. Biodiversity is being explored and exploited by local communities to improve their economic situations. Biodiversity is being cherished to save nature as a natural resource of biodiversity. However, the impact of nature reaches far beyond its role as biodiversity source alone. Ecosystems serve as sinks for CO_2, for the production of oxygen, for nutrient cycling and pest regulation, for tourism and well-being, for pollination, for water and climate regulation and so on. The impact of the roles of ecosystems is acknowledged, and consequently environmental stewardship is considered essential for a flourishing future.

The role of the agricultural life sciences

The life sciences play a central role in environmental stewardship. Understanding the complex interactions in ecosystems is essential for maintaining resilient systems. The life sciences will allow us to identify which interventions are possible and needed in order to be able to manage these systems. Modern molecular (-omics) technologies define markers to characterize these ecosystems. The combined genomes of microorganisms present at the interface between animals/plants and their environment form a typical meta-genome reflecting the interaction with this environment. Combined genomic profiles of individual organisms, often referred to as the barcode of life, shows the detailed composition of the ecocommunity. Together they form the ultimate forensic record of life, activity and functioning of ecosystems. The agricultural life sciences are thus major governors of the genetic diversity which is of fundamental importance for a sustainable future of the sector itself and the environment into which it is integrated.

Global health

2020

In 2020, a long and healthy life is now reality for more and more people due to the rapid developments in (bio-) pharmaceuticals and healthcare. Ever more therapies based on advanced biotechnology are available to cure different diseases in animals and man. However, disease prevention remains a global challenge. The "ladder of health" (Figure 1) depicts the steps that the world has taken from 1900 onwards to improve the basic health of its citizens.

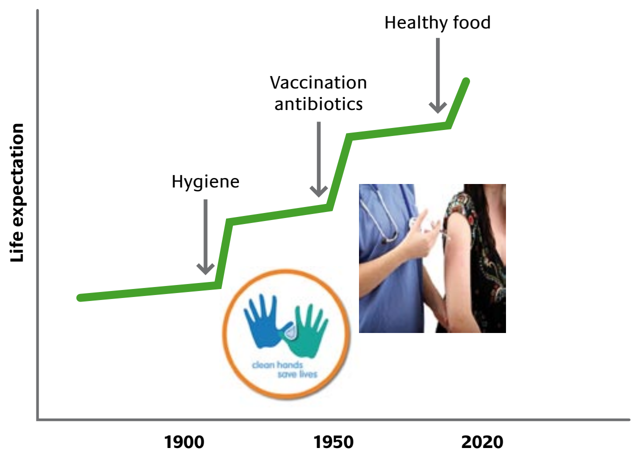


Figure 1: The ladder of health

The impact of hygiene and vaccination/antibiotics has greatly controlled the most common infectious diseases. However, new (mostly animal derived) threats are lurking and still need our attention for the development of new control tools. SARS, Influenza, Tuberculosis, but also Rift Valley Fever, West Nile Virus and others, are not yet under control and need inventive strategies. Food safety is still of utmost importance and will benefit from further innovations in disease monitoring, epidemiology, prevention and treatment. Human and animal risks regarding antibiotic resistance are mitigated by the introduction of alternatives in animal husbandry but are not yet fully under control.

Apart from infections, disorders related to prosperity such as cancer, diabetes, obesity and food allergies have appeared. Although ageing is still a significantly hard to control factor, most of these syndromes are caused by overconsumption of specific compounds like saturated fatty acids or (refined) carbohydrates. This requires novel primary products with less "unhealthy" compounds and more "healthy" nutrients that could even be of beneficial use (healthy food, the next step on the ladder).

The road to 2020

70% of new infections originate from animals and need to be controlled, at the source if possible. Animal health therefore needs to be integrated into human healthcare planning (so-called One Health). Technologies can be developed for exploitation and application throughout the health chain. The animal health industry faces enormous challenges.

Better diagnostics and epidemiological tools are prime for improved control. New strategies need to be developed to mitigate the risks of epidemics and pandemics. Apart from priority listing as is performed by (global) politics, the health sector and industry, new instruments like marker vaccines, anti-virals, immune modulators to broaden efficacy and mass-applicable formulations should be introduced and applied to prevent animals from becoming diseased and spreading the pathogens around the globe. Breeding technologies may enable selection for more resistant animals.

Healthy food can prevent many diseases related to prosperity. Low fat and low sugar foods will help fight obesity and diabetes, and the removal of allergens will avoid allergenic disorders. Foods fortified with "evidence-based" health-promoting components like vitamins, micronutrients and antioxidants will strengthen the constitution of consumers. Breeding and primary production can help the food sector meet these challenges by assuring a healthy supply at the very beginning of the production chain.

The role of the agricultural life sciences

The life sciences are at the basis of the development of global health. The agricultural life sciences are pivotal to human and animal health and the green food sector. The introduction of innovative technologies will result in establishing a sustainable and healthy society. Sophisticated diagnostic and epidemiologic tools will stimulate preventive animal disease management. Systems biology approaches focusing on host-pathogen interactions are key to developing new preventive and therapeutic tools to deal with this challenge. Better understanding of microorganisms is key to developing the appropriate tools. Genomics is at the basis of all of this.

Genomics and breeding technologies can be also be geared towards raising new varieties rich in health-promoting components and free from "unhealthy" compounds. Application of nutrigenomics know-how can develop new animal feeds with a positive impact on animal health, product quality and with a reduced ecological footprint. Not all consumers react to food components in the same way. The diversity of consumers calls for a diversity of food products. Technologically advanced primary production can provide the basic materials needed to establish this variety of next generation healthy foods. As a result, on average, humans will live longer than they did a few decades ago, and in good health.

" The Ministry of Agriculture, Nature and Food Quality encourages the Dutch agro-food complex to contribute to sustainability of future society. For that purpose we need a strong and internationally competitive agro-food economy with respect for the interests of man, animal and natural environment. It is my believe that strong and proactive public-private partnerships in life sciences can and will contribute to meet these challenges of the future by finding innovative solutions. "

Janneke Hoekstra, Director of the Knowledge and Innovation Department (DKI) of the Dutch Ministry of Agriculture, Nature and Food Quality

C. State of the art

The Dutch agricultural sector

Since the industrial revolution, the Netherlands has played an important, often leading role in innovative agriculture. As an open economy, the Dutch strategy is based on innovation. This strategy has been very successful. The Netherlands is now among the countries with the highest land productivity, a global leader despite its small size in a number of agriculture sectors, and with a large percentage of its gross domestic product (GDP) based on agricultural export. In 2007, when primary production is concerned, the Dutch agro-complex accounts for 10% of GDP and provides 670,000 jobs, more or less evenly spread over de plant and animal production sectors (dairy and meat). The Dutch agro-complex accounted for 17% of the total Dutch export and contributed EUR 23.6 bn (60%) to the Dutch trade balance in 2008. These statistics underline the economic importance of the agriculture sector and the international success of Dutch entrepreneurs in the sector. The Netherlands plays a leading role in the plant breeding and plant propagation industries. Dutch plant breeding is highly advanced, well organized and is for a global leader in many vegetables, flowers and potatoes. The turnover of the plant breeding and plant propagation industries in the Netherlands exceeded EUR 2.5 bn in 2008. The sector employs over 11,000 people. More than 40% of all plant breeders' right applications (for registering new plant varieties) in the EU come from the Netherlands.

Animal production plays an important role in European society. Optimized animal production systems contribute to a safe, healthy and diverse diet, help maintain sustainable human communities in more marginal regions of Europe and facilitate reductions in our environmental footprint on the planet. A vibrant and effective animal production industry is instrumental in meeting Europe's future challenges in animal agriculture in a rapidly-changing ecological, economic and social environment. Dutch farm industries are global players and supply competitive markets, both European and global. The Netherlands harbors the largest animal meat producer VION, which has a 57% market share in pig production and slaughtering. With sales of nearly EUR 10 bn in 2008 and over 35,000 employees on the payroll, this is an important company for the sector. Plukon Royale is one of the major poultry producers in the EU, with 2008 sales of EUR 600 m. And the Dutch dairy industry is significant, with FrieslandCampina, DSM and Unilever as major players in the entire food sector. Currently, animal breeding companies in the Netherlands play a dominant role in the world. CRV, Topigs and Hendrix Genetics are at the top of this highly developed industry. They therefore have a major influence in determining the genetic make-up of future animals and hence, on the whole of animal production. Fish farming has firmly set foot in the Netherlands, an industry that is growing exponentially and will contribute to future objectives of animal production.

This important industry can only thrive by having high quality support from animal health knowledge institutes and biotech. The Netherlands is still home to the top of animal health pharmacy R&D (Intervet/Schering Plough

> “Plant breeding not only remains a driving force in reaching food security in the world, plant breeding will also be key in addressing the global changes as we face them today.”
>
> **Hans Dons, Managing Director BioSeeds BV**

> “The global animal breeding industry is consolidating rapidly and technology is a key driver. By acting now, The Netherlands can be a world leader in 2020.”
>
> **M. H. M. Hendrix, President Hendrix-Genetics**

Animal Health), in association with the privatized Animal Health Service that supports the sector in decision making and healthcare issues.

Being the best, rather than leaning against protective interventions, forms the basis of the Dutch vision. An example is the Dutch vision of using vaccination strategies against epidemic diseases rather than eradication strategies based on culling. The Netherlands has been advocating these vaccination strategies for years. This perception is embedded in the Dutch agricultural policy and fits the Dutch ambition to develop its economy to be a leader in the global knowledge economy. The Dutch Innovation Platform was established in order to guide and support this ambition, and identified the agricultural sector as one of the most innovative and promising sectors of the Netherlands. Now it is up to the sector to capitalize on this promise.

The Dutch knowledge system

The Netherlands has strong players in agricultural life science research, both academic and industrial. This excellence concerns animal, plant and environmental research. The Faculty of Veterinary Medicine at Utrecht University is ranked among the top five in the world for the quality of its research and the dissemination of results. The Central Veterinary Institute of ASG-WUR is one of the best equipped centers in the EU for high containment research and clinical trials (Prion diseases, HP-Influenza, Q-fever). Research in infectious diseases has received international recognition, and especially the interaction of animal and human infectious diseases is exemplary. Collaboration within Kennisketen Infectieziekten Dier (KID) but also programs on antibiotic resistance and epidemiology of zoonotic infections connect the Dutch human and animal health institutes. The “One Health” concept for humans and animals is becoming more and more anchored in science (see www.immunovalley.nl). Immunology and vaccine technology is an intrinsic competence of many Dutch knowledge centers, with the Netherlands Cancer Institute, Central Veterinary Institute and Netherlands Vaccine Institute as anchors. The Animal Sciences department of WUR is strongly connected to collaborative (EU) research programs often in PPPs together with the Dutch feed and breeding industry.

The Dutch Plant Sciences research system is excellent, exemplified by its rank as third on the global ESI list of high quality scientific publications. This position is reflected in the number of multinational plant breeding companies with a main office established in the Netherlands and the high number of Dutch plant breeders’ rights applications. Innovation has been, and still is, the key to the international success of the sector. To this end, research institutes and industry closely collaborate in many national and international research programs and networks. The Netherlands initiated and dominates the ERA-NET Plant Genomics and is leading in research on Solanaceae through, for example, the NGI Centre for BioSystems Genomics. The relevance and economic potential of the sector is acknowledged by the Dutch Innovation Platform by appointing "Flowers & Food" as one of the *Sleutelgebieden* (key areas) for future innovation.

Fundamental research is essential for innovation and stimulates the development of new technologies and the translation of these technologies into products on the market. Industrial research is essential for the translation of new technologies into products. This can be applied using various strategies, generating business for the industry and income for academic research (IP rights). Quality of research and education go hand in hand. Industrial research thrives in countries with strong research institutes and an excellent education system that provides the next generation of researchers. A key element is the relationship between academic and industrial research, as demonstrated by the financial commitment of both private and public partners in financing public research at the major institutions for animal and plant sciences. Around 50% of the research in these institutions is acquired from competitive programs involving quality-driven investors. This indicates the important role which high quality research plays in the infrastructure of the agricultural food sector. This relationship can be further intensified by synchronizing the research agenda and by stimulating the movement of researchers from academic to industrial research and vice versa. A better aligned research agenda is expected to result in more outsourcing of research activities from industry to academic research. Having access to top scientists, in combination with efficient research cooperation between academic research groups and industry, will stimulate international companies to establish, maintain and/or increase their research presence and capacity in the Netherlands. The role of new initiatives such as Food Valley and Immuno Valley is clearly to address these issues at the interface of politics, science and industry and to promote further knowledge transfer.

The transfer of technology from basic research to product feasibility and from there to development is of central importance. Early involvement of industry is essential to enable effective transfer. Public funding of research has to include this transferability as part of the funded activities. Involvement of industry can only be accomplished effectively if based upon Intellectual Property (knowledge) and adequate regulatory requirements (policy).

The Dutch agricultural sector operates in an entrepreneurial, research-intensive, international, dynamic, innovative and competitive environment. Research institutes, social organizations, industry and the government join forces to stimulate innovations, scientific developments and education. This collaboration reflects a new interaction in the knowledge structure and is often referred to as the public-private partnership (PPP). In this model, market and social partners are leading in defining the objectives of the research agenda. The research organizations contribute by developing innovative solutions for social and economic questions. The government facilitates these innovations and drives the activities within a political, national and international context. The various parties collaborate within networks, combining the expertise needed to address the topics concerned. To date, many successful research activities are based on this new model.

Flourishing public-private partnerships: Milk Genomics Initiative

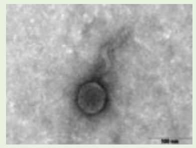
The aim of the Dutch Milk Genomics Initiative is to identify genes that contribute to natural genetic variation in milk-quality traits, in particular milk-fat and milk-protein composition. The program provides tools for improved breeding programs to exploit natural genetic variation in milk-quality traits and contributes to the knowledge base needed for innovative dairy products. The Milk Genomics Initiative combines expertise in the fields of dairy science, quantitative genetics, genomics and bioinformatics.

The industrial partners in the Dutch Milk Genomics Initiative guarantee the utilization of results and ensure a fast diffusion of the relevant knowledge to the practice of dairy cattle improvement and product innovation.

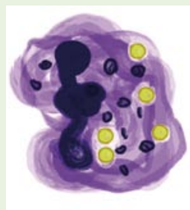
Flourishing public-private partnerships: Immuno Valley ALTANT program

The program was initiated by the Ministry of LNV with seed funding of EUR 3 m, and started on January 1, 2009. The objective is to develop proof of potential for use of alternatives to antibiotics in livestock by December 31, 2010. Immuno Valley has organized this program into four projects:

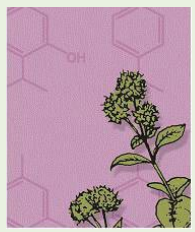
ASIA: anti-microbial peptides



RESUPLYS: phage/lysin therapy against Streptococcus suis



EVAC: vaccine against Staphylococcus aureus



MODIPHY: phytochemicals with immunostimulating, antimicrobial activity

Both public and private partners are incorporated into (international) consortia. Relevant industry has been invited to monitor the program and to join as soon as is feasible. In 2011, a full PPP will be constructed around the most promising projects, involving up to EUR 18 m. Achievements six months in: 1 new patent application, 1 publication

D. The way ahead

The Netherlands has the ambition to develop further as a knowledge economy. This perfectly fits with the European ambition described in the Lisbon Treaty. The Lisbon Treaty acknowledges that, for future economic development, besides the traditional production factors (nature, labor and capital), knowledge will be essential. The establishment of an Innovation Platform and continued support for innovative public-private partnerships show the way as to how the Dutch government intends to achieve this development. This policy needs to be pursued in the future, but focus is needed to guarantee sufficient critical mass. Open innovation will be key in these developments. Companies will profit from combining external and internal ideas to reach new breakthroughs. Consortia willing to share knowledge, as found in public-private partnerships, are valuable instruments in advancing open innovation. It is the vision of the agricultural life sciences to focus on three socio-economic relevant topics (what), to invest in two platform technologies relevant in these topics (how) and do so with impact on society in conducive networks.

Priority: A secure and sustainable food supply

Food security concerns the entire supply chain (Figure 2). National and EU governments make the rules for food safety and human health, as well as guidelines based on global environmental agreements (climate change, stewardship). Regional governments are mainly involved in landscape and environment and in reducing the ecological footprint of food production. The sector is concerned with productivity (profitability) and industrial competition. These stakeholders are influenced by retailers, consumers and others in society. The driving force will be the higher productivity and profitability of the sector framed by demands of society and policy.

The production chain can be influenced at two major points. Firstly, the source material should be optimized to produce optimal yields given the conditions provided (region, climate, requirements). Sustainability is a precondition of the newly developed breeds and varieties. Feedback will occur from the production process drivers (higher productivity, better efficiency) as well as from the health and welfare controllers (more robust, better pathogen resistance), but certainly also from the marketing and sales system (functional food genes, sustainability criteria, quality labels). Selection or developments of such source material is of utmost importance and will require new knowledge and know-how in the field of genetics and systems biology. Secondly, the production process itself can be positively influenced by developing optimal production systems that minimize waste emissions and reduce production losses due to external sources such as weather, pests and diseases. This can be achieved through innovative solutions developed by specialized knowledge centers in close collaboration with biotech and pharma.

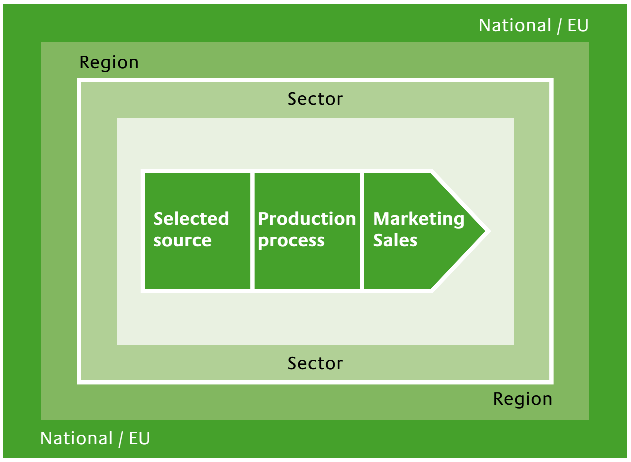


Figure 2: Food production supply chain with its stakeholder environment

> “In 2020 the “One Health” concept, recognizing the (two-way) continuum of communicable diseases between humans and animals, is accepted in its importance and realized in practice.”
>
> **Anton Pijpers, Dean of the Faculty of Veterinary Medicine, Utrecht University**

Priority: Animal health

Animal health is central to global health and will therefore be a major priority for the agricultural life sciences. The spread of infectious diseases is of global concern and needs to be tackled using a contingency plan that applies modern technology in decision-making and control tools. The integral effects of human activities on the planet are continuously changing ecosystems and disease risk management on a global scale. International technology platforms (ETPGAH and DISCONTOOLS) set the stage for developing the basic tools to improve efficacy of vaccines and the new generations of antimicrobials. Together with the results of improved breeding of robust animals, industry has what it needs to integrate this into the next era of animal (and public) health control. Public-private partnerships are at the foundations of such complex integrations.

Priority: Biorefinery

In the future, agriculture will expand far beyond its current core function: the production of healthy food. Sooner or later, shortages of fossil resources will demand the use of biomass as an alternative source of many compounds now produced via the petrochemical industry. Contrary to this negative driver, however, are the large opportunities which biomass offers. Plants synthesize an enormous diversity of compounds that may be used creatively for a myriad of applications. Plants can be bred to produce specialty compounds or to be more appropriate for particular processing technologies. Using biomass as a resource will open new avenues for the production of all kinds of materials. Advanced biorefinery technologies will allow the separation of valuable compounds and enable the multiple use of biomass. The same batch may be fractionated to obtain specialized compounds for pharmacy, for food or feed (proteins), for clothing (fibers) and more. Optimized source materials and production processes will be essential for effective processing further down the production chain, and through this approach, the agricultural life sciences will merge with the white life sciences to capitalize on the new challenges of the bio-based economy.

Priority: Systems biology and the “$1000 genome”

Putting the life sciences to work calls for a combination of disciplines at various aggregation levels (Figure 3). The developments in genomics and related technologies opens new avenues for data collecting that need to be connected to biological characteristics to reveal their complete meanings. The realization of the $1000 genome will open up new roads for crop and breed improvement and must be fully exploited for maximum impact in areas such as biodiversity screening/monitoring, sequence-based breeding and biomarker generation. Systems biology is a new and rapidly developing scientific area that seeks to do so. Mathematics and statistics, modeling and information technologies are key to this development. Systems biology will help predict and explain the functioning of agricultural systems based on all available information. This will enable agronomists, breeders, molecular biologists, veterinarians and ecologists to predict the behavior of such systems and choose whatever intervention may be deemed necessary.

The agricultural life sciences needs to follow this path to profit fully from the scientific potential and assist the search for solutions to global challenges. This will help the switch from a curative to a more predictive agriculture and animal health strategy. The results of these complex analyses should form the basis for stronger interaction within the natural sciences in order to predict social impact of the underlying technologies.

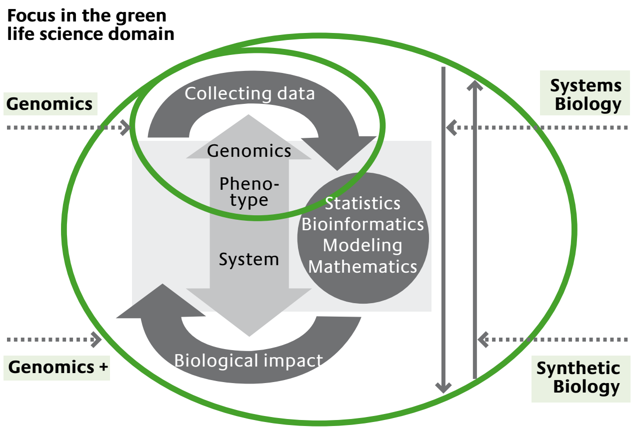


Figure 3: Interacting disciplines and aggregation levels in the agricultural life sciences

Priority: Micro- and nanotechnologies

The application of genomics to investigate important traits in animals and plants will, first and foremost, generate molecular indicators (biomarkers). These indicators can be employed as tools to assist decision-making in the production chain concerning new applications, treatments or destinations (including the destination of biologically active molecules in the body after delivery). As such, these indicators will be essential tools in optimizing quality and sustainability traits. However, this implementation depends on the availability of fast, reliable (and high throughput) detection and monitoring instruments that can be used both in the form of R&D equipment and as detection and monitoring instruments in the production and processing chains. The development of such systems, based on “lab-on-a-chip” technologies, is currently being pursued in the field of micro- and nanotechnology, thanks to the exceptional functional advantages of miniaturization.

Priority: Public-private partnerships

The Dutch agricultural sector is characterized by innovation. Being a forerunner of new developments has been the basis for success and will be the challenge for the future. For both piecemeal and system-based innovations, all relevant stakeholders need to join forces. Science and industry need to collaborate to produce the right answers to the important questions raised, preferably in an open innovation context. The profit-driven industry, however, needs additional incentives to address specific low-profit issues. Politics may help by creating regulatory facilities for emergency problems.

In 2020, public-private partnerships are characterized by open innovation platforms based on actual investment and risk-sharing between large companies, small innovative

“ PPPs perfectly suit the Dutch way of working, they are the ever best investment in our innovation driven economy. Abroad, they envy us... ”

Antoon van den Berg, CEO Hendrix-Genetics

start-ups and research organizations. Large companies will use the PPPs to explore candidate pipeline products and thus consolidate or improve their economic value. The small companies will benefit by expanding specific technology that will enable them to collaborate or merge with the larger established companies. Involvement of social parties is necessary to guide the innovations. A socially non-acceptable innovation is no innovation at all.

Public-private partnerships must continue to provide the opportunity to bring complementary groups (even from different sectors of science and industry) together to work on key innovative precompetitive topics with two primary goals – feed knowledge into industry, fully (pre-)tailored to current and future needs, and feed manpower into industry, fully trained to meet current and especially future needs. Key to success are excellence, multidisciplinary collaboration and critical mass.

Public-private partnerships may be national, but will increasingly have an international character. The philosophy of open innovation is that all parties profit from access to knowledge from other parties. Consequently, the effect of open innovation will be larger when more parties are involved. In addition, public interests often reach beyond national borders. Global issues like climate change, food security or animal health call for international approaches. In fact, the framework programs of the European Union act as forerunners of international public-private partnerships.

In 2020, the public-private partnerships need to learn from each other to a higher extent than they do today. Interaction at the managerial level must be encouraged and facilitated. Whether this requires a central governing board is open for discussion. The Netherlands Genomics Initiative has shown that the partnerships under it benefit from central governance and have resulted in giving genomics in the Netherlands a visible place on the world stage.

Public-private partnerships are characterized by investments by all partners. Public and private parties alike are required to contribute, in whatever form (knowledge, materials, cash, expertise) to the partnerships. However, this only works if all parties are also rewarded. In this way, the stakes are balanced and the co-innovation is shaped. Success tends to be restricted by the limited resources of the public partners like universities and research institutes. A sound knowledge infrastructure, based on core-financing, is therefore necessary for flourishing public-private partnerships.

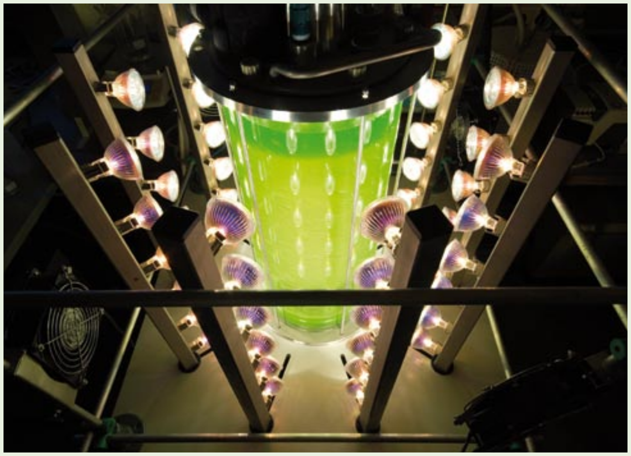
A number of successful PPPs have already gained a dominant position in the Dutch agricultural life sciences. Examples of such initiatives are given in boxes throughout this chapter.

Priority: Impact on society

Consumers must be heard. Society must be involved in shaping social context and in avoiding technical solutions that do not fit social demands. Policy must be involved to frame research within national and international challenges and to monitor and implement relevant scientific breakthroughs wherever applicable. Directed education is needed to raise a new generation of employees experienced in the new innovative technologies.

Animal welfare, animal experimentation, sustainability, genetic modification of living plants and animals and their benefits for society are subjects of public decision making and need to be addressed well in advance. Society cares about animal health, and the culling of animals in cases of disease outbreak is no longer acceptable. Much of this debate can be solved by providing the technological evidence for safety and efficacy, but since risk assessment is often part of the debate, other disciplines such as ethics, anthropologists and sociologists should participate in this discussion. Policy needs to be continually aware of public choice.

Flourishing public-private partnerships: Towards BioSolar Cells



A new, EUR 40 m initiative is a PPP especially targeted to exploring and exploiting photosynthesis. Both higher plant production and new sources for sustainable energy have a common denominator: photosynthesis. It is a major limiting factor in plant production, since only 1-2% of the solar energy that reaches a plant leaf is converted into biomass. Improving the energy harvesting efficiency of organisms will have an enormous effect on biomass production, benefitting food, feedstock and energy supply. Even more challenging is designing systems that allow photosynthetic energy-tapping before the energy is converted into biomass. A thorough understanding of photosynthesis, its hierarchical organization and its underlying mechanisms are essential for capitalizing on these approaches.

To accomplish this goal, a consortium of six Dutch universities, 30 partners from industry, social partners and the Netherlands Organization for Scientific Research (NWO) has formed. This consortium is facilitated by the Dutch government, particularly the Ministry of LNV.

Flourishing public-private partnerships: Technological Top Institute Green Genetics.

tti green genetics

TTI Green Genetics is a EUR 40 m collaboration between research institutes and industry. The central theme is "Innovative plants for sustainable Flowers & Food". The research will enable breeders and growers to use the full genetic potential of plants for optimal and sustainable growth under existing and new production systems. Research topics are demand-driven and prioritized by the industrial partners. Research is carried out by selected plant sciences research groups in close collaboration with industrial partners.

Through the implementation of strategic research projects, TTI Green Genetics helps to position the Dutch plant science research infrastructure as one of the top players in the world. Its main focus is to strengthen research, education and capacity building in the plant sciences disciplines physiology, genetics and pathology.

In total, 93 companies and seven knowledge institutes participate. This intensive collaboration between industry and academia has already identified plant traits that are now being commercialized, for instance through Plant Breeding Rights. In the coming years, it is expected that the focus of TTI Green Genetics will shift from exploring plant genetics, to exploiting plant genetics. Therefore the new focus will be on comparative biology, phenotyping and linking genetic and phenotypic data to predict the performance of plants.

Flourishing public-private partnerships: The Centre for BioSystems Genomics

CBSG 2012
Centre for BioSystems Genomics

CBSG was initiated in 2003 under the auspices of the Netherlands Genomics Initiative as the Centre of Excellence in plant genomics. The partnership comprises 7 knowledge centres and 15 industrial partners. The applied research programme (ca 100M€ / 10 years) has a strong focus on the two most important Dutch vegetable crops – potato and tomato – for which Dutch industry is also leading the world in terms of market share and crop improvement for both consumer and environmental quality traits. Improving resistance to potato late blight and the taste of fresh tomatoes are two key targets for which great progress has already been made and for which results and new plant materials have already gone out to the industrial partners for implementation in their own improvement programmes.

CBSG is committed to facilitating Dutch industry to move to the next level regarding the exploitation and implementation of state of the art genomics technologies as a means to answer sustainability and social issues on crop production. While forming the focal point, CBSG is also used to act as a major research multiplier through initiating many additional bilateral, multi-lateral and international PP research initiatives to a value exceeding 150M€, thus maintaining Dutch research and industry, centre stage.

E. Recommendations

1. **A strong knowledge infrastructure** must form the basis for prolonged investments by industry and decision-making governmental institutions. Continuity in finance and facilitating the corporate intelligence of the Dutch knowledge system is thus essential in shaping the technological future and the impact of the agricultural life sciences, both to the Dutch economy and society as a whole. The policy should choose for quality of the research by investing in topics (and groups) that achieve global excellence. This will fortify our strengths and attract industry to join.

2. **Focus and mass** are necessary, and therefore choices need to be made for the following priorities:
   - A healthy society based on secure, safe and sustainable water and food supply in association with sufficient strategies for prevention of diseases;
   - Biomass production tailored to a bio-based economy. Focus needs to be on the multiuse of biomass and on high-value applications;
   - A "One Health" approach, central to animal and environmental health, is the basis for human health and well-being and requires investment.

   Two technological approaches are needed to develop the priorities:
   - Systems biology will enable the interpretation and use of the enormous flow of genomic data. New high-throughput technologies will further increase the generation of data in the near future, thus challenging the biological interpretation to keep pace;
   - Micro- and nanotechnologies are needed to develop devices for monitoring production processes, detection and monitoring of pathogens (early warning systems), and for individualized health.

3. **Public-private partnerships** are needed to accomplish all of the above, and should be encouraged. All stakeholders need to benefit from them. Science has to be rewarded for IP generation, and industry will only be driven by profitability. Policy needs to create incentives for industry investment, and society must benefit from these investments.

4. **Acceptance and sustainability** of new technologies are pivotal. Social impact of technological solutions must not be overlooked. Stronger collaboration between natural and social sciences are essential to ensuring the right choices are made for the future. Sustainability is the overarching objective and needs to be accomplished by integrating social demands, technological solutions and opportunities, including economic benefit for all stakeholders.

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This chapter could not have been accomplished without the highly appreciated input of the following colleagues, all experts in their fields:
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Examples of solutions

As examples, the following issues and solutions fit the agricultural life sciences vision and recommendations.

- Varieties and breeds of plants and animals, optimized for maximum performance with a minimal ecological footprint
- Animal health tuned into the prevention of notifiable and human-threatening diseases (e.g. Newcastle Disease, Crimean Congo Fever, Rift Valley Fever, MRSA, Influenza)
- Plant health that reduces the need for pesticides in crop production systems
- Controlling transmission of diseases as the result of complex interactions of individual susceptibility, environmental factors and herd immunity
- Robust diagnostic assays, thus reducing the number of animals to be sampled
- Health and performance checks at the individual and population levels (allowing early warning and control)
- Introduction of functional feed and foods to assist in general health perception of animals and humans
- Identification of the origins of animals and plants or their derived products (quality assurance)
- Resilient agricultural ecosystems, reducing production risks for farmers and enabling adaptation to climate change
- Intestinal health as a result of interaction of the animal with its environment (micro and macro)
- Better prediction of response of a biological system (plant/animal) to changes in environment, treatments, etc.
- Precision farming
- Crops tailored to the biorefinery and bio-based economy
- Possibility for social (gamma) sciences to apply risk assessment in predicting the impact of life sciences induced changes
- Sustainable farming

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Authors

Eduard Klasen, Leiden University Medical Center
Ruben Kok, Netherlands Bioinformatics Centre
Luc Rietveld, Netherlands Genomics Initiative

Technology

Technology makes the life sciences flourish

VI Technology

Summary

Progress requires technology
The accessibility of cutting edge technologies is one of the critical factors for innovation in the life sciences. A wide range of experimental and computational technologies are needed to provide answers to essential biological questions of today. Examples are mass-spectroscopy facilities for proteomics and metabolomics, software for processing genomics data, large-scale computational infrastructures, etc. In many cases, such novel technologies fuel scientists to move ahead and ask new, far-reaching questions. In turn, these questions are related to pressing issues in health, nutrition, sustainability and safety. Issues that are important to society at large and that cannot be properly addressed without top-level life sciences technologies.

Technology programs make expert knowledge and infrastructure available
Traditionally, the Netherlands operates right at the front when it comes to new technologies. In recent years, investments in a number of technology areas relevant to the life sciences have been made, resulting in technology platforms and technology centers that have become crucial players in the overall life sciences field. They have ensured the availability and accessibility of state-of-the-art enabling technologies such as proteomics, metabolomics, nanotechnology, (high-throughput) microscopy, biobanking, bioinformatics and systems biology for both the scientific community and industry.

Network of collaborations between technology organizations and research programs
The technology platforms combine state-of-the-art technological expertise and (large-scale) infrastructure essential to the major research programs in the life sciences. Collaborations between the technology platforms and life sciences organizations (such as the Leading Technology Institutes (TTIs), other FES consortia and NGI Genomics Centres) are currently taking shape. Such collaborations also match the trend towards an open innovation research environment in which public and private parties come together, and open up possibilities for large-scale life sciences research approaches. As a result, a close network of developers and users of technology emerges, stimulating scientific progress and boosting the international profile of the Netherlands as an attractive partner in the life sciences.

Technology platforms strengthen international position
The current generation of technology platforms is a clear representation of the quality and critical mass that the Netherlands has to offer in the life sciences. Statements by international review committees and advisory panels support this notion. The Dutch technology platforms are securely embedded in international networks, which gives the Netherlands an excellent starting position when it comes to being involved in or leading international initiatives. It offers opportunities for influencing decisions on funding and topics in the life sciences and on international standards and best practices. Internationally renowned technology platforms also attract private parties to invest in the Dutch life sciences field.

Maintaining and strengthening this favorable position requires continuous efforts to upgrade, advance and extend existing technology platforms and take on new technological challenges whenever they emerge. This is the only way the Netherlands will be able to uphold its leading role in the life sciences in 2020.

Defining organizational standards for technology platforms

Each of the current technology organizations has been built separately, which has led to a range of organization models, especially with respect to (scalable) support structures. A process has started to exchange "best practices" between the platforms to define an organizational standard to facilitate collaborations. The model should also help to turn emerging technology initiatives into functional platforms in a rapid, effective and cost-efficient manner. Of course, the organization of a technology platform will remain dependent on the specific characteristics of the technology and the technological community.

National coordination demanded: LIFT

In the past five years, the Dutch Government, universities and industry have invested in the order of EUR 2 billion in the life sciences in the Netherlands through public-private partnerships (PPPs). In order to capture the full potential of these investments, tuning and collaboration between technology platforms, and between technology providers and life sciences programs is crucial. Coordination of this process on a national scale is a necessity to enhance the return on investment from a scientific, social and economic point of view. Here, we propose to establish a dedicated national organization: LIFT, Dutch Life sciences Initiative for Technology (Figure 1).

LIFT will ensure optimal tuning of existing and emerging technological developments, as well as adoption by the scientific communities. National coordination promotes the integration of the various domains and prevents duplication of efforts. Coordination is a prerequisite for the achievement of focus, excellence and effective technology transfer. Also, coordination provides the opportunity to set priorities. LIFT must be set up as a platform with participation of all stakeholders in the life sciences field. Thanks to the investments in technology platforms in recent years, the Netherlands is by all means ready for such an approach.

RECOMMENDATION To sustain a strong international position for the Netherlands in life sciences technology, we propose to:

1. **Install a national coordination body that fuels effective collaborations in the life sciences field and ensures that essential technology and infrastructures are made available to end users. A working model involving all stakeholders is proposed as LIFT: Dutch Life sciences Initiative for Technology (Figure 1);**

2. **Dedicate structural funding to the technology domain, in order to build expert communities and necessary infrastructures. Include dynamic funding mechanisms for individual technologies, based on demand in major public-private life sciences programs and in industry;**

3. **Tighten the growing network of technology platforms and life sciences organizations, set up collaborative life sciences research projects and boost open innovation in the life sciences to meet social challenges.**

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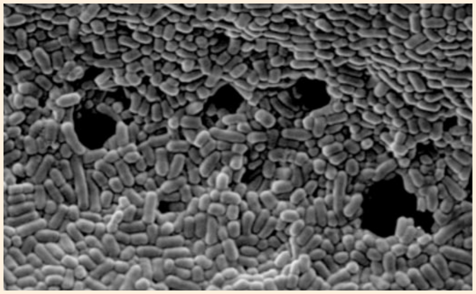
Navigating through metabolic highways for biotechnological applications

Photographer: Jan Dijksterhuis



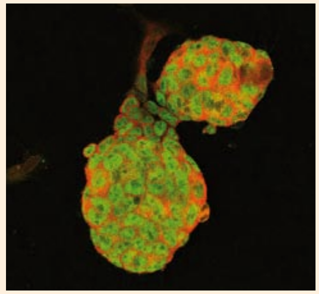
Scanning-electron-microcopic image of Lactobacillus plantarum cells used in many food fermentations.

Using a systems biology approach, researchers from the Kluyver Centre for Genomics of Industrial Fermentation have developed computer models of the complete metabolic roadmap of several microorganisms used in industrial biotechnology. This “Tom-Tom” for bioconversions links genomic information to the chemical conversions that can take place in the organism being studied. The models explore new possibilities for enhanced productivity, and for innovative resources and products.

For the lactic acid bacterium *Lactobacillus plantarum* (photograph), a bacterium used in many food fermentations, Teusink, Smid and coworkers at NIZO Food research developed a metabolic model. It was used for analysis and interpretation of complex fermentation data and successfully predicted the adaptation to novel carbon sources.

Teusink and Smid, *Modelling strategies for the industrial exploitation of lactic acid bacteria*, Nat Rev Microbiol vol. 4, 46-56 (2006); Teusink, et al, *Understanding the adaptive growth strategy of L. plantarum by in silico optimization*, PLOS Comp Biol vol. 5 (2009).

Proteomics helps uncover the mechanisms governing stem cell differentiation



Researchers at the Netherlands Proteomics Centre (NPC), Utrecht University, the Hubrecht Institute, Utrecht and Leiden University Medical Centre (LUMC), have reported a significant advance in the understanding of the molecular mechanisms that control stem cell differentiation. Using proteomics, they studied the signaling pathways that become activated or inactivated when human embryonic stem cells exit the undifferentiated state.

These results by Heck, Mummery and co-workers were published in the high profile journal Cell Stem Cell on August 7, 2009 and shed light on how we should manipulate and program stem cells to specific fates, so that they can become a source of tissue replacement for regenerative medicine purposes.

Van Hoof et al, *Protein staining in stem cells*, Cell Stem Cell vol. 5, 214-26 (2009)

A. Technology as a driving force in the life sciences

The life sciences greatly impact our (future) society

In the year 2020, the life sciences will have a major effect on all facets of life and society. Health, nutrition, industrial production, the energy supply, sustainability and safety all highly depend on the results of research in the life sciences. Various, now successful areas of focus of the Dutch Ministry of Economic Affairs will only remain successful if the life sciences can flourish in the Netherlands. This is particularly true for areas such as chemistry and biotechnology, food & nutrition and life sciences & health.

Dutch treat: large-scale public-private partnerships in the life sciences

Over the past ten years, our country has successfully set up a considerable number of PPPs in which industry, knowledge institutes and the government collaborate extensively in life sciences research programs. Core to these partnerships is the excellent science base our country has built at the universities, university medical centers and private research institutes. Indeed, recent evaluation of the PPP programs underscores that this is a highly successful approach, given the quantity and quality of the scientific output and the added value for industry and society, through the benefits of new products, for example in healthcare.

The Netherlands distinguishes itself internationally with this formula of public-private and public-public collaboration. Apart from their scientific and social benefits, these programs have led to best practices relating to the organization of collaborative research programs, and, for instance to the question as to how intellectual property rights can best be arranged.

Technology revolution continues for the empowerment of the life sciences

The results of the life sciences will only become profitable for our economy and society if novel technologies are rapidly and efficiently made available to the scientific community. A revolution is taking place, in particular in the area of molecular and cellular technologies, as well as in the ICT field. Technologies are being developed and improved for systematic and large-scale analysis of molecular information and biological structures, and for the integration and analysis of information via bioinformatics and systems biological methods. These technologies provide advanced knowledge of complex integrated cell processes and make it possible to extract relevant information.

Currently, the fields of proteomics and metabolomics, nanotechnology, imaging, biobanking, bioinformatics, structural biology and systems biology are rapidly developing. In addition, new technologies are emerging, such as high throughput DNA sequence analysis and (nano) microscopy.

The annex of this chapter gives an overview of national developments in the various different areas of technology.

Technology integration increases the pace of finding solutions

There is a strong movement towards the concerted application of different technologies. Revolutionary development of DNA and RNA sequencing provide essential data at the level of genetic systems, while experimental techniques and databases in proteomics and metabolomics are converging, resulting in better opportunities for the simultaneous analyses of protein and metabolite composition. Imaging and nanomicroscopy technologies allow for the localization and in situ analysis of a system, while biobanking efforts introduce clinical data to be taken into consideration.

Combined experimentation requires a better interoperability of experimental data. To an increasing extent, bioinformatics is in a position to extract relevant information from the various complex data streams thanks to international agreements about data standards and computational infrastructures. As a last step, systems biology produces mathematical models to understand and predict the behavior of biological systems.

In 2020, the combined deployment of the different technological fields makes it possible to better unravel the major biological questions. The complexity of biological systems makes these integrated approaches essential, yet it requires research to be done on a much larger scale. In the coming years, therefore, consortia of collaborative public and private parties will carry out research jointly on the same system using parallel experimental techniques, and using the same experimental biological material. An example of this is the German HepatoSys program. In the Netherlands, research centers such as the Toxicogenomics Centre and the Forensic Genomics Centre already take this integrated approach as the basis to develop innovations for our society. These programs have a strong technological component and directly apply these technologies via close interactions with industrial and social partners. For example, the Toxicogenomics Centre employs genomics technologies to develop alternatives to animal testing (ASAT), by providing a scientific basis for chemical risk assessment. In the near future, many more such “power users” will come into being in the larger international life sciences centers and projects. The Netherlands is well positioned to realize the potential of such integrated approaches, and gain experience through national research collaborations.

Collaboration between 16 biobanks gives insight into lifestyle and genetic risk factors for heart and vascular diseases and diabetes.

The strength of collaborations between biobanks and the use of good infrastructure at the national and European levels, which is the goal of BBMRI and BBMRI-NL, is very well illustrated by a series of publications in Nature Genetics (January 2009) and American Journal of Human Genetics (March 2009). These involve Europe-wide integrated studies of smoking behavior, metabolic disease and glucose metabolism, in the framework of the ENGAGE FP7 project, in which several Dutch biobanks participated, together with other biobanks from abroad.

The two Nature Genetics papers confirmed several major loci determining lipid levels as an indicator of coronary heart disease risk, and glucose levels as an indicator for diabetes. The research involved 20,000 to 30,000 participants, including subjects recruited by scientists from Erasmus Medical Center, the Netherlands Twin Register and the VUMC. The paper on smoking was a collaboration between Leiden, Rotterdam and Amsterdam and identified several interesting groups of genes involved in smoking initiation and persistence.

Aulchenko et al, *Genome wide association study in 16 European population cohort: major loci determining lipid levels and coronary heart disease risk*, Nature Genetics vol. 41 (1), 47-55 (2009); Prokopenko et al, *Variants in the melatonin receptor 1B gene (MTNR1B) influence fasting glucose levels and risk of type 2 diabetes*, Nature Genetics vol. 41(1), 77-81 (2009); Vink JM, et al, *Genome-wide association study of smoking initiation and current smoking*, Am J Hum Genet. vol. 84(3), 367-379 (2009).

B. Collaboration between technology platforms and life sciences initiatives is key

Roadmap for technology must yield communities, not just infrastructure

In 2007 the Dutch Minister of Education, Culture and Science established the Netherlands' Roadmap Committee for Large-Scale Research Facilities, chaired by Wim van Velzen. The Roadmap Committee is linked to the European Roadmap for Large-Scale Research Facilities, the European Strategy Forum on Research Infrastructure (ESFRI). The Roadmap Committee provides advice about the most important areas for investment in large-scale research facilities in the coming five to ten years. In its report published in 2008, the Committee states that scientific progress emanates from a combination of the talent of creative researchers and the availability of good research facilities. In addition, the Committee acknowledges the importance of collaboration and clustering of research infrastructures. The OECD also emphasizes the importance of life sciences technology platforms in its recent publication (2009): *The Bioeconomy to 2030: Designing a Policy Agenda*.

In any event, in 2020 the success of life sciences will be determined by concerted actions of strong international research teams with top quality technologies and facilities. Advanced facilities will lead to a concentration of scientists, to communities of researchers, both users and developers, in the form of dynamic partnerships between people, facilities and capital. This situation is already emerging in the growing network of research organizations and technology platforms that has been established in our country.

A growing network of technology platforms and major life sciences programs

In the Netherlands, the large-scale deployment of the palette of life sciences technologies will be boosted by the growing collaborations between current technology platforms and life sciences consortia in the Netherlands. In recent years, as a result of the establishment of these organizations, extensive experience has been gained with a collaborative approach. Good examples of collaboration have already come into being between technology centers and genomics centers within Netherlands Genomics Initiative (NGI). It takes time to make such forms of collaboration effective for both parties. In the coming years, a broadly based form of national collaboration will come into being, consisting of the generic technology programs with all major life sciences stakeholders, such as the TTIs. This broadening of collaborations is essential to increase the yield of the technology platforms, to boost research of all major life sciences programs, and to reduce duplication of efforts and investments.

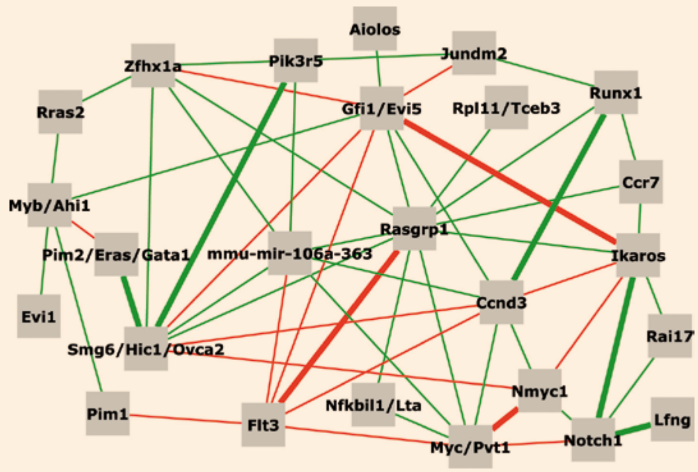
Dissemination and support: making technologies available requires special effort

The generic enabling technologies have applications in all life sciences research domains, whether in health research, plant sciences or industrial biotech. Having the most advanced technology facilities is no guarantee, however, for successful use of these technologies by the life sciences researchers that they should serve. While investing in existing and forthcoming technologies for the life sciences, it will be imperative to make them broadly available to public and private life sciences players in the Netherlands. This must be done in a rapid, efficient and cost-effective manner. Technology platforms must be accessible to the entire field and they all require an active approach in dissemination, training and support. Specialized personnel is needed here, and a dedicated support organization that is scalable in terms of necessary experimental capacity and guidance.

Technology platforms operate as technology providers on a national scale

Existing technology platforms and research institutes have developed a spectrum of models for organization of support. The Netherlands Metabolomics Centre, for instance, has set up the concept of a local *demonstration and competence lab*,

Bioinformatics researchers help identify genes involved in cancer development



Network representing the co-occurrence (green) or mutual exclusivity (red) of the 20 most significant cancer-related genetic elements, as detected through bioinformatics analyses of mouse tumor material.

Combining novel bioinformatics methods with genetic techniques has allowed researchers to identify 250 genes that seem to play an important role in the development of leukemia. The research was carried out at the Netherlands Cancer Institute (NKI) as part of the research program of the Netherlands Bioinformatics Centre (NBIC), in close collaboration with the Cancer Genomics Centre. 'The work performed by the groups of Berns, van Lohuizen, Adams and Wessels has been published in Cell.

Uren et al, *Large-scale mutagenesis in p19ARF- and p53-deficient mice identifies cancer genes and their collaborative networks*, Cell vol. 133, 727–741 (2008).

while the Netherlands Proteomics Centre has installed so-called *proteomics research hotels* at several locations. Under the name of *BioAssist*, The Netherlands Bioinformatics Centre builds a fully distributed support network, backed by a team of software engineers, and making use of the excellent e-science and ICT infrastructure the Netherlands has established through organizations such as SURF, NCF, VL-e and BiG Grid. Besides dedicated support structures, all technology platform parties have experienced that effective dissemination can be reached through joint projects with biologists, whether public-public, or public-private. In such projects, technology experts actively participate in research of partner programs. This allows for tailor-made application of technologies and for training *on-the-job*.

As many of the present major technologies are not yet in a mature phase of standardization and cannot be purchased "off the shelf", we need an active approach in research support. The technology platforms are well suited to safeguard the necessary mechanisms to make technology available, which must be one of their key tasks. Of course, the efficacy of support depends strongly upon availability of resources, and requires active collaboration with all major life sciences stakeholders in the Netherlands. The scale of these efforts make them ideally suited for technology spin-offs, as well as other commercial technology and service providers to find a niche in this process, especially as technologies become more mature. The public-private collaborations of technology platforms and life sciences organizations are an ideal diving board for these commercial service providers.

C. Public investments in the life sciences research infrastructure attract private partners

Public funding needed for basic technology development; private funding follows
In the next decade, technology development will mainly be funded by public sources, including national governments and the European Commission as well as academic organizations. Initially, industry will only invest modestly, with the exception of companies aiming at technology development such as Philips and FEI (electron microscopy). Their entire businesses are based upon the development of technology. Nevertheless, the technology platforms manage to attract a growing number of industrial partners, including technology users, such as Unilever, DSM and the pharmaceutical industry. The investments made by Schering Plough, DSM and Unilever in the Netherlands Metabolomics Centre are a clear example of the expectations of industry with regard to this technology platform. Similar examples are contributions of Schering-Plough, DSM and Philips in the program of the Netherlands Bioinformatics Centre.

Top quality life sciences, including technology communities, is an absolute precondition for continuing investment from the globally operating industries in the life sciences. These concentrations of scientists and facilities are a good basis for close collaboration with industrial parties that can translate the results of research into social applications. It is expected that industrial involvement in the life sciences programs will grow substantially with the intensified collaborations between life sciences programs and the technology platforms. This will lead to a steady increase in public-private collaboration, in which industry invests in projects both individually and in consortia. The TTIs, such as those for polymers (DPI) and nutrition (TIFN) are good examples in this respect. The number of foreign companies that invest in the DPI meanwhile exceeds the number of Dutch companies. In order to reach a similar position in 2020, the Dutch life sciences technology platforms will need to be embedded in national and international networks, so that they form excellent partners for industry.

Strategic alliances of technology supply and demand
The close collaborations with life sciences clusters and with industrial partners keep the technology programs focused on practical applications of their novel technologies: "market demands" determine to a large extent which technological bottlenecks are worked upon. In this way, the research of the life sciences centers largely dictates the direction in which the technology programs are being developed. At the same time, the technology platforms provide state-of-the-art technological expertise and facilities which open up new research avenues. This can be compared with taking part in a car race. The technology platforms provide the advanced vehicle, equipped with the latest technology. The life sciences centers, however, sit in the drivers' seat. Together, the partners define the direction of the research. This essential partnership, whether public-private or public-public, determines the overall quality of the research output, and therefore the chance to win the race.

Thanks to this approach, the Netherlands has gained a prominent international position in the life sciences in 2020, in which technological development and practical applications go hand in hand. In order to reach this state, it is proposed below that a strong level of coordination is implemented, with participation from all major stakeholders in the life sciences.

D. Governance in 2020:
LIFT – Dutch Life sciences Initiative for Technology

The optimum working model in 2020 is one in which national coordination is guaranteed. Here we propose LIFT: Dutch **L**ife sciences **I**nitiative **f**or **T**echnology.

Figure 1 explains the practicalities of LIFT: proposed scope and role, stakeholders, organization and funding set-up.

The rationale for LIFT is as follows:

- The most important objective of LIFT is to ensure the availability of the relevant technology for research organizations in the life sciences. National coordination promotes integration of the various life sciences technology domains and collaboration between the key parties to support joint research and prevent duplication. LIFT provides an overview of available technologies, expertise and infrastructure. It provides the portal that links life sciences demand to technology supply;

- The technologies are lodged in "community platforms" in which the various stakeholders are represented. The technology platforms then set up a core program of technology research and development, including necessary facilities, and take care of dissemination and support as well as training and education. LIFT will strike a balance between guidance and steering, allowing room for new initiatives to be developed from within the field;

- LIFT will provide a stable technology funding base that is linked with joint funding by the various life sciences organizations and programs. It brings together various (existing) funding instruments, so that they operate together towards strengthening a national research infrastructure. As a result, LIFT ensures that generic technologies are being developed and provided on the basis of demand from the field. LIFT also stimulates the building of real infrastructures as part of international research infrastructures, and onto which institutes and industry can capitalize in the longer term. It will enable universities to utilize their personnel and resources more efficiently;

- In turn, the life sciences programs and institutes will entrust a portion of their research to the technology centers and platforms by means of shared research goals and with matching from the technology platforms. In this way, collaboration will come into being in which both parties make their own financial (and scientific) contribution;

- LIFT may form a platform for stakeholders to address issues related to the introduction of various novel life sciences technologies in society, such as legal aspects of introduction of medical technologies;

- LIFT is able to react rapidly to national and international developments. Life sciences technology is preeminently an international arena, which requires a rapid response to take advantage of foreign initiatives and international research programs, for example within the EU. LIFT ensures clear agreements about the moment at which the technology has been developed sufficiently for it to be deployed by the life sciences domains and institutes themselves.

LIFT: Dutch **L**ife sciences **I**nitiative **f**or **T**echnology

Scope and role

Organize technology platforms and infrastructures and facilitate their broad accessibility and use
- Scan for and select upcoming enabling technologies and infrastructures from the international arena
- Organize national communities in selected technology areas
- Support organization of communities of developers and users by using specific funding instruments, such as the establishment of formalized PP collaborations
- Fine tune new and existing funding instruments in the technology innovation pipeline
- Guide platform development, governance structure and IP arrangement (standardized)
- Guide development of dissemination and support programs
- Guard capacity building and efficient tech transfer
- Support embedding of PP platforms
- Safeguard connection to national and European programs for research infrastructure (e.g. van Velzen roadmap, ESFRI)

Stakeholders

Broad representation from the field
- Knowledge institutions (e.g. VSNU, NFU)
- TTIs, NGI and other major life sciences initiatives
- KNAW, NWO, SenterNovem
- Ministries, Innovation Platform
- Industry
- Umbrella organizations

Organization

Light-weight structure with a small central core and distributed technology platforms
- Strategic programming board
- Representation of all stakeholders at central level
- Platforms represented by communities of experts
- International peer review
- Make use of existing organizations

Funding

Establish structural technology funding base for life sciences support with dynamic components
- Sustainable funding from government and knowledge institutions:
  - Platform building, basic expertise development (matching funds),
  - Joining existing funding sources to set up generic infrastructures
- Dynamic “tailor-made” funding from knowledge institutions, NWO, SenterNovem, large life sciences initiatives and industry for:
  - Basic research, specific infrastructures, support and education
  - International embedding

Figure 1: Working model of LIFT, the proposed Dutch Life sciences Initiative for Technology

E. Conclusions and recommendations

Life sciences technologies can only flourish if there is a mechanism of national coordination and tuning between major programs, involving all stakeholders (e.g. technology platforms, the major life sciences programs as clients/users of technology, academia, industry, NWO). This will make it possible to form an effective network of research partners in which the best technology is made available by technology communities well organized to address the most prominent issues from the life sciences domains.

1. Install a national coordination body that fuels effective collaborations in the life sciences field and ensures that essential technology and infrastructures are made available to end users. A working model involving all stakeholders is proposed as LIFT: Dutch Life sciences Initiative for Technology (Figure 1). LIFT coordinates financing, planning and strategy development, and guarantees input from all stakeholders, in particular clients/users of technology. LIFT takes care of the timely integration of new technologies and of the phasing out of technologies that have reached the market.

2. Dedicate structural funding to the technology domain, in order to build expert communities and necessary infrastructures. Include dynamic funding mechanisms for individual technologies, based on demand in major public-private life sciences programs and in industry. Technology development takes place during various phases: from basic science via methodology development through to application. The financing strategy should be linked to these phases. In the earliest stage, financing from public resources is the only option. As a technology develops, the better its chances are for public-private financing. Life sciences technology requires stable public funding. This ensures that at a later stage private resources can be brought in, as soon as the commercial application of the technology becomes feasible.

3. Tighten the growing network of technology platforms and life sciences organizations, set up collaborative life sciences research projects and boost open innovation in the life sciences to meet social challenges. In 2020, the individual existing and forthcoming technologies will be deployed collectively to a far greater extent in order to unravel biological mechanisms and be able to meet social challenges. This will lead to research approaches at a much larger scale, and requires effective collaboration between a multitude of disciplines and parties. The Netherlands' life sciences field must invest to gain further experience in setting up such public-private partnerships, building upon the growing network of technology platforms and life sciences organizations.

In the short term:

- Make life sciences technologies available nationally to all potential users;
- Begin with the national coordination of technology programs and centers;
- Begin with the establishment of national working communities for technologies, together with the major user stakeholders in the field;
- Collect and share “best practices” for organization, management, support mechanisms and intellectual property ownership arrangements.

Acknowledgement

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Annex 1: Technologies for the life sciences in 2020

Biobanks
***Technology organizations:* String of Pearls Initiative (PSI; www.parelsnoer.org); Biobanking and Biomolecular Resources Research Infrastructure-NL (BBMRI-NL; www.bbmri.org); Life Lines (www.lifelines.nl)**
Thanks to the scaling up of research and the increasing importance of “high throughput” technologies, the availability of large numbers of samples is continuously becoming a decisive factor in the success of medical and genetic-epidemiological research. The discovery and development of new drugs and diagnostics is increasingly dependent on large collections of well-documented clinical and biological information and material from patients as well as healthy individuals. Biobanks contain these details about health, diet, environmental and lifestyle factors in combination with biological material. Enrichment with “omics” technologies, such as transcriptomics and proteomics, and applications from bioinformatics and biostatistics, will become definitive in increasing insights into the origin of diseases, particularly multifactorial disorders. The goal is to accurately diagnose illness, cure and perhaps even prevent disease from developing at an early enough stage.

On the European level, the importance of biobanks is acknowledged in the European Roadmap for Research Infrastructures (ESFRI). In 2008, BBMRI (Biobanking and Biomolecular Resources Research Infrastructure, www.bbmri.org) was established, aiming to create a European infrastructure of biobanks. In the preparatory phase in 2008, the Netherlands played a leading role.

The Netherlands has an excellent starting position in this field. The strength of the medical, genetic and epidemiological research and the quality of healthcare have resulted in a large number of well-maintained and unique biobanks in the Netherlands. Dutch experts play important and often leading roles in international biobank consortia.

Our country plays a leading role in future developments in the international biobanking field. University medical centers, private foundations and the Dutch government have invested in the strengthening of existing collections and in the development of new large-scale biobanks. Parelsnoer, LifeLines and BBMRI-NL are three important initiatives that complement each other. The Parelsnoer initiative is a unique collaboration between the eight UMCs in the Netherlands to collect patient details and materials for eight disease areas. LifeLines is a population cohort which is following 165,000 residents of the northern provinces for 30 years. BBMRI-NL connects existing biobanks in the Netherlands, strengthening their competitive power through harmonization and enrichment. The combination of these initiatives is unique in Europe and the Netherlands thus achieves critical mass with enormous potential. As one of the first countries, the Netherlands has begun to prepare itself as a national “hub” for the major European BBMRI infrastructure.

The European infrastructure must be operational by 2013. To maintain its position, continue developments and to reap the benefits in the coming years, the Netherlands must put structural effort into this area until at least 2020.

Genomics: High Throughput Sequencing
Technology initiative: in preparation
Over the past decade, many genomics tools – such as DNA sequencing, microarray technology and high throughput genotyping – have already contributed to our knowledge of the genetic basis of many organisms. With the advent of the next-generation of very high throughput (HTP, or massively parallel) DNA sequencing technology, the genomics field will be revolutionized. HTP sequencing is expected to become the dominant technology in all genomics research areas. The new technology decreases sequencing time of genetic material from plants, animals or humans from several months/years down to one or two

weeks, and at a fraction of the costs associated with the earlier generation of DNA sequencing. In the near future, sequencing speed will increase even further, which opens up a whole set of new genomics applications. This is the reason why internationally, substantial investments are made in sequencing facilities as well as the necessary expertise base to deal with the enormous flow of data produced. In order to maintain the leading position of the Netherlands in several areas of the life sciences, predominantly medical and agricultural and forensic genomics, Dutch research institutes and industry will follow the same path towards implementation and capacity building around this novel technology.

HTP sequencing is an upcoming technology in both basic and applied genomics research. Results from early medical genomics research are being translated into the first generation of medical applications, including diagnostics and therapeutics. Variations of established disease-associated genes are being validated for diagnostic application, for example. Development of the technology will soon allow us to sequence an entire human genome at very low cost ("$1000 genome") and within a short timeframe. In agro-food genomics, next-generation sequencing is currently used to elucidate genetic variation in different animal species (cattle, pig, poultry), microorganisms and plants (tomato, Arabidopsis). The focus is currently on reconstructing reference genomes for a variety of species, which would provide the basic background for identification of markers for characteristic breeding traits, such as disease resistance, nutritional value and production.

While many HTP sequencing efforts focus on creating reference data for large-scale genomics research, the implications for nutrition, health management and safety are numerous. Significant reduction in time and costs will make it the main technology to elucidate the full genetic background of phenotypic variability in various species. This provides the opportunity to resolve common complex human diseases, with potential applications in DNA and micro-RNA-based molecular diagnostics, genetic testing and pharmacogenetic profiling. It also provides applications in forensic genomics, increasing possibilities for identification, privacy and safety. In plants and animals, HTP sequencing will cause a significant improvement in efficiency and productivity of breeding programs, which include traits that improve disease resistance, quality and production.

The impact of this NGS technology has been recognized worldwide, initially limited to large genome centers in the US and Asia. Ongoing international efforts (1000 Genomes Project (human), 1001 Genomes Project (Arabidopsis), Personal Genome Project) aim to establish reference sequence databases for various species. In Europe the Wellcome Trust Sanger Institute (UK) has been well ahead in terms of investments, but governments in Germany and Spain have announced large investments in HTP sequencing technology over the coming period. In the Netherlands, Leiden University Medical Center (LUMC) and the University Medical Center Nijmegen (UMCN) are coordinators and leading partners in a European initiative on medical genome sequencing. Hubrecht Laboratory is deeply involved in initiatives in expression and micro-RNA profiling. Likewise, Wageningen University and Research Centre leads international sequencing initiatives on animal, tomato and potato species.

While HTP technology is currently available in laboratories within most Dutch academic hospitals and research institutes, there is a clear need for exchange of expertise and capacity, and the construction of an effective infrastructure (including bioinformatics data infrastructure). The genomics programs under NGI involving academic and private partners have all started individual HTP sequencing projects, and in collaboration with the Netherlands Bioinformatics Centre (NBIC), a national HTP sequencing community is emerging. Similarly in the medical field, LUMC and UMCN have taken the first steps towards bringing together all university medical centers and NBIC, and towards setting up public-private collaborations, involving Merck/Schering-Plough and Philips Medical Research, with close ties to international projects. Further development of such collaborative initiatives will be vital in the coming years to establishing the necessary infrastructure and expertise base in our country, and facilitating efficient implementation of HTP sequencing technology in the life sciences initiatives in the Netherlands.

Proteomics

Technology organization: Netherlands Proteomics Centre (NPC; www.netherlandsproteomicscentre.nl)

Proteomics comprises scientific research and technology development for large-scale analysis of gene products (i.e. proteins) and their role in biological processes. This involves measurement of protein expression profiles, protein modifications and interactions, related to developments in health/disease and other biological processes. Proteomics is at the heart of life sciences research, an indispensable tool of molecular systems biology.

The long-term implications of results generated by proteomics-related biomedical and biotechnology research will be immense. Improved understanding of biological processes at the molecular and protein levels will allow us to identify new drug targets and thus improve drug therapy, obtain better biomarkers for health and disease, whose analyses may be much less evasive than current medical tests, and improve the application of proteins in plants, animals, food and nutrition. Society at large will benefit from these advances.

The Netherlands Proteomics Centre (NPC) has achieved international recognition and is firmly embedded in national and international research networks with academic and industrial partners. As an example, in 2008, the NPC hosted the HUPO 2008 World Congress in Amsterdam, the annual international meeting of the Human Protein Organization (HUPO), with over 1700 participants and more than 80 industrial exhibitors. Researchers of the NPC are leading European and international experts, with a remarkably high production of scientific publications.

Knowledge dissemination and collaborations in well-defined multidisciplinary research projects, with NGI centers and other high level research groups, are essential for the further development and application of proteomics technology for research and development of innovative products and therapies. In particular, the NPC has established dedicated "research hotels" as facilities for hands-on training and collaboration with other leading academic or industrial scientists. NPC research hotels house state-of-the-art equipment, research protocols and specialized personnel. In 2009, over 300 collaborative projects and trainings have already been performed in the NPC research hotels, which have attracted attention from international funding bodies (Genome Canada, Medical Research Council (UK), Deutsche Forschungsgemeischaft (DFG)) as a role model for knowledge transfer.

Relevant future developments in proteomics include:

- Deeper understanding of the proteome, including all proteins of a cell;
- Innovation in mass spectrometry, allowing breakthrough approaches every 3-6 months;
- A closer link to technologies that enable the determination of dynamics of a proteome in time and place (electron and light microscope, imaging technologies);
- Significant improvement of technologies for "difficult" proteins (e.g. membrane receptors, complex post-translations modifications (phosforylation and glycolysation), low abundant proteins and dynamic and transient protein networks).

The immense technological progress of recent years does not imply that the work is done. Successful developments in this field require a substantial lead time and investments and collaborations should be based on scientific quality and perspectives for applications.

Metabolomics

Technology organization: Netherlands Metabolomics Centre (NMC; www.metabolomicscentre.nl)

The Netherlands Metabolomics Centre invests in technological development to (systemically) study metabolic processes in (individual) cells, plants, microorganisms, animal models and humans. Metabolic processes are key in physiology and thus extremely suitable for determining systemic differences between health and disease states. This higher level understanding provides unique novel methods for better diagnosis and intervention in disease management. In addition, such an approach can be applied to plants and/or microorganisms to more efficiently and economically obtain the desired product.

The NMC makes its developed technology available via its Demonstration and Competence lab through, for example, hands-on training and dedicated experimental facilities. Developed software, bioinformatics and biostatistics are made available via the Data Support Platform in strong collaboration with NBIC. The ultimate NMC ambition is to improve this metabolomics technology in order to be used to answer biomedical questions that are bottlenecks and thus to achieve better personal(ized) healthcare and quality of life.

Internationally, the metabolomics field is one of the younger technology developments in the "omics" family. The field is rapidly evolving with some strong national initiatives present in Europe, Asia, Australia, the US and Canada. The field is organized via the Metabolomics Society founded in 2005, which organizes the International Metabolomics Society meeting. The 2010 meeting will take place in the Netherlands and will be jointly organized by the NMC and CBSG. This illustrates the strong position of the Netherlands in the field of metabolomics. Plant Research International (partner in CBSG and NMC) is world leading in plant metabolomics. The NMC provides further scientific leadership in the metabolomics field via Professor van der Greef at TNO, Professor Hankemeier at Leiden University and others. The leading role of the Netherlands is also revealed in the fact that two of NMC's board members are also board members in the Metabolomics Society. Participants of the NMC have already experienced that metabolomics helps to gain important new insights, for example in disease mechanisms. In addition, it is expected that metabolomics technology will allow the systemic analysis of complex organisms, from microorganisms to plants, animals and humans. In combination with better data analysis and modeling this will lead to better biologically interpretable results to address the current bottlenecks in the life sciences.

Via its founding members, the NMC has an excellent overview of developments within the international food, pharmaceutical and chemistry industries. Industrial partners of the NMC such as DSM, Unilever and Schering-Plough want to apply NMC technology in their product R&D pipelines. In addition, the NMC collaborates with top research groups in the life sciences such as the NGI genomics centers and TTIs. These collaborations are implemented in technology driven and application driven projects, as a part of the NMC research program, which are carried out by the academic and industrial NMC partners. In this approach, the NMC – and thus the metabolomics community – profits from the early presence of companies and university medical centers. Together, the partners share expertise in biomedical questions and the accessibility to samples derived from realistic clinical studies that are being performed as part of their R&D programs. Instrument manufacturers collaborate with the NMC as NMC partners in order to profit from the critical mass in technology development by implementing developed technology in their future product lines.

The NMC focuses on the development of generic metabolomics-based technologies and instrumentation to address current and future challenges in biology, biotechnology and biomedical research in order to improve personalized healthcare and quality of life. In 2020, the NMC will have the technology and tools in house to deliver personalized healthcare using minimally invasive methods.

Internationally, the NMC is one of the largest initiatives in metabolomics. NMC takes the lead in international standardization initiatives in which it participates with other international key players in the field of metabolomics. This guarantees that developed technology within the NMC indeed can be used in day-to-day clinical and industrial practice.

Bioinformatics

Technology organization: Netherlands Bioinformatics Centre (NBIC; www.nbic.nl)

Current experimental technologies have caused an explosive growth in biological information, in ever new data types, much of which is deposited in public databases. With the systems approaches of today, biologists increasingly combine information from current molecular data collections with other types of clinical or experimental data, such as phenotypic patient information, literature or epidemiological data, or with images created by (high-throughput) microscopy. Data-driven systems biology is now an essential part of bioinformatics, as these studies generate an extra level of heterogeneity and complexity of biological databases.

Bioinformatics plays an essential role throughout the life sciences domains to facilitate the design of experiments and data-analysis protocols to maximize the yield of these experiments and the value of the data produced. With the aid of advanced ICT technology and (GRID) infrastructures, bioinformaticians develop new methodology and expertise to help extract essential biological or biomedical knowledge from the complex data collections so that this knowledge can be translated into social applications, whether in healthcare or the food industry. Bioinformatics covers a broad range of disciplines, and contributes to the life sciences by bringing in essential collaboration with fields of chemistry, statistics, (medical) informatics and e-science.

The Netherlands Bioinformatics Centre (NBIC) has been established as the national technology platform to bring together the community of experts. The organization has been set up as an open platform of academic and other public partners, and of industrial parties. In close collaboration with Dutch and international life sciences organizations, projects are being carried out in which bioinformatics technology development and advanced biology research go hand in hand, which has already resulted in work that receives international acclaim. NBIC is a partner in the ESFRI ELIXIR bioinformatics program led by EBI (European Bioinformatics Institute) and in the EATRIS translational program.

The NBIC support program BioAssist is set up to provide bioinformatics support for the Dutch life sciences groups. These activities include strong involvement in international initiatives for data standardization and harmonization. The bioinformatics research infrastructure uses essential Dutch (e.g. BiG Grid, VL-e) and international (e.g. MyGrid, Omii-UK) programs in E-science and WEB technology. BioAssist is set up to facilitate distributed and multidisciplinary collaboration, and allow broad accessibility to bioinformatics expertise, methods and software, and to international data collections as well as computational capacity. Currently, there is a shortage of well-trained bioinformaticians in the field. The Dutch bioinformatics community has taken up an important task of training the next generation of bioinformaticians and biologists, at all educational levels, in order to adequately support the latest developments in the international life sciences fields.

Funding of the ever growing demand for bioinformatics must be coupled directly to experimental life sciences research. A sufficient fraction of the budget for subsidized scientific projects using and creating large data collections should be invested in the associated bioinformatics that is needed for the data to be analyzed. It is essential to install a level of coordination here, to create synergy between programs and to prevent redundancy between organizations.

Systems biology
Technology organization: Netherlands Consortium for Systems Biology (NCSB; www.ncsb.nl)
Systems biology is a fast developing paradigm in the life sciences. The “omics” technologies (genomics, proteomics, metabolomics, etc.) and developments in the ICT field in the past decade will soon give us a close-to-complete list of components and processes in living organisms. However, to understand how biological systems function in a way that we can predict how they behave under specific conditions is still largely impossible. This is due to their extreme complexity. For instance, a living cell contains many thousands of different molecules that interact inside the cell in a very dynamic way. Similarly, organisms such as human beings consist of billions of cells and many different tissues and organs that all communicate and cooperate with each other. Key processes span length scales from nanometers to meters and time scales from microseconds to years.

Systems biology approaches these extraordinarily complex systems by integrating components and processes in mathematical models that have the potential to predict the behavior of biological systems. Predictions can be experimentally tested and results are used to improve the model. This cycle of model –> prediction –> experimental verification –> improved model –> etc. constitutes the very heart of systems biology. This approach is beginning to be used in the biomedical and pharmaceutical worlds (rational design of therapies and drugs) and in biotechnology. Examples are the model of the human heart and the successful engineering of the metabolism of fungi and other microorganisms so that they produce economically important chemicals or deal with pollutants. The steps towards socially and environmentally acceptable alterations of plant metabolism are being made. Exciting biomedical and pharmaceutical applications are becoming possible.

Systems biology requires tight cooperation between disciplines. The expertise of mathematicians, chemists, engineers and physicists is essential to describe and analyze complex systems. Systems biology is not linked to any specific biological system or topic. Rather, it is becoming a generic and systematic approach that is widely applicable in the life sciences.

The Netherlands Consortium for Systems Biology (NCSB) is an NGI program that aims to implement systems biology approaches in ongoing Dutch biomedical, pharmaceutical, agricultural and biotechnological research programs. The NCSB program (2008-2013) comprises a EUR 15 m investment from NGI, matched with an equal investment from the participating institutes: several NGI genomics centers, TI Food and Nutrition (TIFN), TI Pharma, the Netherlands Institute for Systems Biology (NISB) and NBIC.

The NCSB program synergizes with NWO investments in systems biology, which is one of the NWO spearheads. Among others, NWO is initiating three or four national centers for systems biology, starting in 2010.

Molecular and Cellular Imaging
Technology organization: Cyttron (www.cyttron.org)
There are many different technologies for imaging the cellular and molecular components of life. Each technology reveals essential features, and is indispensable for complete understanding of fundamental living processes. However, each also has limits that constrain its specific application. For instance, X-ray crystallography reveals the atomic structure, but requires the sample to be crystalline; NMR reveals molecular structure and dynamics, but cannot handle large molecular complexes; AFM can measure forces on (living) surfaces, but does not allow views of the inside of the sample; electron microscopy reveals the molecular architecture of the cell in nm resolution, but requires the sample to be fixed or frozen; there are many modes in light microscopy that give molecular information on localization and intermolecular distances, but their resolution is limited. All these modes of imaging are complementary and their areas of application only partially overlap.

Cyttron aims to integrate these modes of imaging in a single platform, which requires tuning and optimizing the various constituent technologies and creating a common visualization and modeling platform which allows easy correlation of multi-modal data. The Cyttron consortium focuses on bio-imaging techniques and includes a cooperation between the Universities of Leiden, Delft, Utrecht, Antwerp and London; the Leiden University Medical Centre and the Companies of Bruker-Nonius BV, FEI BV and Key Drug Prototyping BV.

The Cyttron consortium wants to implement a comprehensive, integrated infrastructure for bio-imaging and modeling cells down to atomic detail. The aim is to provide a generic tool for identifying the molecular causes of disease, essential for the prevention of disease and the development of new drug and therapies, and to establish a platform for advanced diagnosis and tuning of individualized therapy, increasing effectiveness in healthcare. The consortium is highly multidisciplinary, with (bio-)physicists, chemists, mathematicians, bio-informatics and image processing specialists, cell biologists, microscopists and medical researchers from various research institutes. 15 research projects are being carried out.

Nanoscopy

Technology organization: The Netherlands Centre for Nanoscopy (NeCEN; www.necen.nl)

The Netherlands Centre for Nanoscopy (NeCEN) is a facility based on a powerful combination of three different types of cryo-transmission electron microscopes (cryo-TEMs) designed specifically to explore the complex structures inside cells at a level of detail unknown until now, and – even more important – in a close-to-native state. Visualization of cellular processes on this scale and under these realistic conditions will lead to scientific breakthroughs and to new possibilities in the prevention, diagnosis and treatment of cancer and infectious, neuro-degenerative and cardiovascular diseases. A recent example of the value of nanoscopy in increasing our understanding of diseases is the discovery of the life cycle of Mycobacterium tuberculosis, a study which will eventually lead to new vaccines and drugs to combat this widespread disease.

On a national level, NeCEN will fuel scientific developments in key areas of scientific research by offering beyond-state-of-the-art nano-scale imaging capabilities.

Examples of these key areas are:

- Life sciences and genomics – current research clusters include the Cyttron-program and the Center for Translational Molecular Medicine (CTMM; early diagnosis and targeted therapies) and the BioMedical Materials Program (BMM; co-polymers, material properties at the nano-level);
- Micro- and nanotechnology/high tech systems – research topics including nano-structures with new functionalities such as bio-compatible MEMS, memory chips and microprocessors;
- Chemistry and energy – in particular research programs aimed at (low cost) photovoltaics and the replacement of fossil fuels by agricultural products (bio-based economy).

On a European level, NeCEN's infrastructure is a response to the EFSRI-initiative in integrated structural biology and the Network of Excellence 3D Electron Microscopy. NeCEN has the potential to become one of the major centers in these and other European research networks.

Renowned TEM manufacturing company FEI is partner in NeCEN and will fabricate in Eindhoven the high-end cryo-TEMs, all based on the innovative Titan platform. Currently only two Titan high-throughput cryo-EMs exist, one of which has already provided us with remarkable results. At NeCEN, three cryo-TEMs will be working together: one will be equipped for high-throughput single particle analysis; the second for high-throughput cryo-electron tomography; the third will be used for the development of new cryo-microscopy methods and instrumental innovations such as better image detectors, phase plates combined with Cs correctors to reduce beam damage and/or increase contrast and resolution. The triple approach is key to the success of NeCEN. Together with the strength of the consortium and its approach to setting up the center, it defines the added value of NeCEN to individual TEM centers in the world. The NeCEN is unique in the world for its capabilities to study infectious microorganisms, and diseases with a genetic component, such as cancer.

Bioimaging and light microscopy

Technology initiative: Dutch Light Microscopy Initiative (NLMI), in preparation

The Netherlands plays a very prominent role in Europe in the area of microscopy. In size, the Netherlands comes in second after Germany.

Microscopy in the Netherlands is often locally organized in microscopy centers facilitated by local bioimaging research groups. The Dutch Association for Light Microscopy is currently working to develop the Dutch Light Microscopy Initiative (NLMI), in association with the European example ELMI (European Light Microscopy Initiative).

A proposal is being developed as part of ESFRI called Euro-Bioimaging, sent from EMBL (Ellenberg/Pepperkok) and Rotterdam (Krestin). It is being deliberately launched as a pan-European, distributed research initiative to reflect the nature of microscopy itself. A few main disciplines are named: Advanced Light Microscopy (coordinated from EMBL) and Medical Imaging (coordinated from Rotterdam). The European initiative includes a number of nodes in advanced microscopy and in medical imaging, and a number of overlapping nodes. The Netherlands is actively participating in this pan-European initiative, which can also stimulate the entire microscopy field in the Netherlands.

Over the last 90 years, an enormous revolution has occurred in microscopy. New techniques with high resolution, rapid image processing, molecular contrast, sensitivity to each and every molecule, new probes and software have all been developed. These involve, almost without exception, various forms of fluorescence microscopy. Alongside these technological developments, the areas of laser technology and detection technology have also seen enormous progress.

The Green Fluorescent Protein (GFP) revolution has given the field a tremendous boost, accelerating in 2002-2004 after the discovery and application of various red fluorescent protein mutants. It is now possible to equip virtually any protein molecule of a genetically coded label with select fluorescent properties. This has led to highly sophisticated biosensors that can report on specific modifications of proteins, metabolites and second messengers with subcellular resolution in living systems. The revolution this has brought about is well illustrated by the Nobel Prize in 2008 for its discoverers Tsien, Chalfie and Shimomura.

Finally, there is an important pillar of the “omics” revolution which allows us to identify systematic gene functions using the microscope. This uses, among other things, RNAi methods in combination with high-content biosensor technology. In recent years, more than half of the funds from infrastructure investment grants of NWO and ZonMW have been allocated to microscopy equipment. These have all been local initiatives.

The international field’s current situation is that there are many different labs where completely new methods are being developed, and with various probes/biosystems used. It is therefore clear that we are still at the beginning of the microscopy revolution. The full potential will only be reached if all forms of advanced microscopy are used in all biosystems with all of the appropriate probes. The advanced light microscope will play a central role in future biotechnological research (together with surrounding laser, detection, image processing, sensor and “omics” technologies), particularly in cellular systems biology. With its strong expertise basis and excellent international position, the Netherlands can play a leading role in this global development in the life sciences.

Bionanotechnology

Technology organization: NanoNed (www.nanoned.nl)

The multidisciplinary character of nanotechnology can perhaps best be seen in the area of bionanotechnology. Physicists, chemists, biologists and doctors come together within this generic theme. Imaging biological processes on a nano-scale can make the study of disease patterns, viruses, cell functions, etc. much more accurate. Various techniques, such as NMR (nuclear magnetic resonance spectroscopy) and AFM (atomic force microscopy), have made it possible to image molecules and to study behavior or abnormalities. Nano-machines can mimic nature, and therefore can be used to store energy or, for example, to transport and deliver DNA structures.

The application of devices such as lab-on-a-chip also falls under bionanotechnology. This includes, for example, the diagnosis of diseases and abnormalities at an early stage. Bionanotechnology is very important in the food industry and for the environment. Possibilities are being studied, and at the same time applied, to make food safer, healthier, tastier and cheaper. Safety, perception and risk play a large role in all of these application areas.

Research groups contributing to the development of this research theme are mainly concerned with biology and biophysics at the molecular and cellular levels, nanofluidics, physics and (bio)chemistry of functional nanoparticles, and pharmaceuticals and cell biology. This research is underway at virtually every Dutch university, the three technical universities as well as the regular universities. The FOM institute AMOLF is also making an important contribution.

Clinicians play an important role in nano-medicine, both in the shaping of important questions for basic research, and in testing applications in clinical practice. There is a lot of self-organization in the field, such as in the CTMM and BMM programs where public and private research groups work together on innovations in nanomedicine, focused, respectively, on diagnostics and devices, or in collaborations between biophysics and medical groups at universities and in academic hospitals.

The Netherlands is home to many companies, large and small, in the area of nanomedicine. Philips is an important global player. This area also includes many SMEs and start-ups. There is much opportunity in this area, much of which is realized: in diagnostics, molecular imaging, targeted and local drug delivery and reconstructive medicine.

In KP7, Europe has reserved a budget for nanotechnology of EUR 3.48 bn for the period 2007-2013. The budget in the first years can be compared to that of KP6, after which the budget doubles. We can especially see nanotechnology subjects returned in KP7 themes like “Nanosciences, Nanotechnologies, Materials and New Production Technologies”, “Health” and “ICT”. In the theme descriptions, there is much emphasis on application, socially and economically driven research by consortia of companies and knowledge institutes, where there is also certain room for basic research. Integration of technologies for industrial application is explicitly named as a theme. Involvement of SMEs and dissimilation of R&D results to SMEs remains an important point of attention in the framework program.

Especially important for nano-medicine is the European Technology Platform (ETP) Nano-medicine, in which European companies and academic institutes have joined efforts under the leadership of Philips and Siemens. Other ETPs relevant for nanotechnology are ENIAC, Photonics 21 and Artemis. ENIAC (nano-electronics) and ARTEMIS (embedded computing systems) have in the meantime become Joint Technology Initiatives, with Dutch co-financing via Point-One.

Author

Leen van den Oever, Netherlands Institute of Biology

Education & training

Education, education, education – powering the life sciences, empowering society

VII Education & training

Education is the engine of our knowledge society. It empowers us with the basic concepts, context and critical skills to be informed citizens and consumers. It equips us for our professional lives and it helps us deal with an ever-changing world, where continuous (re)training, more than any single job, provides security of work and income.

This is especially true for the life sciences. The life sciences play an important role in food production, in cure and care, in manufacturing products, in nature management and in ecological regeneration. These activities require highly educated professionals in a wide range of disciplines (biology, chemistry, physics, geology, engineering and medicine). These professionals fill many different functions: scientists, corporate researchers, developers, engineers, entrepreneurs, managers, teachers, farmers, consultants, civil servants, regulators and more. In 2008, more than half the graduates in biological sciences had a job outside of R&D after one year.[1] These professionals are everywhere. And they need to be, to help generate, translate and deliver life sciences knowledge in the form of new or improved products, processes or services.

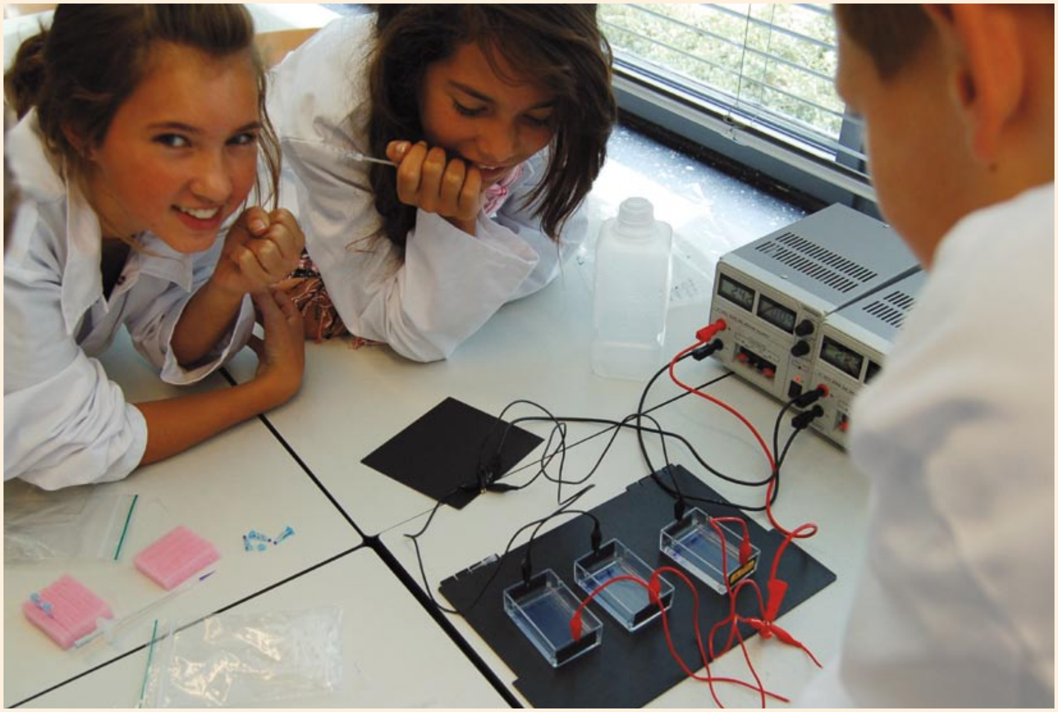
But that is not enough. As earlier chapters have argued, the success of an innovation ultimately depends on its adoption and use by individuals and companies. Before buying or investing in a new drug, green energy, improved crop and livestock, fermentation plant or nutraceutical, mature and responsible consumers will have to know that it is safe and useful. Scientists, business people, regulators, consumers – all need to understand basic life sciences concepts and technology to be able to generate, apply, regulate and use it responsibly, sustainably and to their benefit. Education is a *conditio sine qua non* for innovation.

Life sciences education is as diverse as the life sciences itself. Biology is its main vehicle, especially in primary school. Biology is, literally, the science (logos) of life (bio). But the life sciences increasingly are part of secondary and higher education in chemistry, physics, geology, biotechnology, medicine and other courses. These disciplines are becoming more and more intertwined, not just in their practical application, but also in curricula and teaching. In the Netherlands, the modernization of life sciences education has begun in the last decade. A new curriculum framework was developed for 4-18 year olds. Initiatives were launched to improve vocational and university education and much emphasis was placed on targeting courses to needs in the marketplace.

In 2020 we envision the culmination of these and additional efforts in an integrative, uninterrupted process of life sciences education. Primary and secondary school teaching based on the concept-context approach will provide a large and steady inflow of students to higher education. Higher education in the life sciences is a top-quality, diversified curriculum with a strong focus on fundamental science and its applications. Graduation is but a transition in a process of lifelong learning that continues throughout a life sciences career, whether in academia or industry. Education is a partnership, built on cross-institute collaboration, efficient funding and strong, unified marketing. It delivers highly qualified and versatile professionals to all sectors and citizens that are informed and are able to make personal decisions about what they buy or the care they receive.

From a family tree to DNA and back again

Students working on genetic screening simulation using gel electrophoresis. From dispensing the DNA sample to "running" the gel and staining the DNA.



A. Life sciences education in 2020 – an integrative, uninterrupted process from primary school through university that delivers a large and steady stream of life sciences professionals

Education prepares. It can prepare you for further, more advanced education, it can prepare you for a professional career, but it can and should also prepare you for life – for functioning as an independent, critical citizen. Life sciences knowledge production is fast and includes many disciplines. Thus, education must be integrative and uninterrupted. It must combine knowledge and courses from different fields and link basic science to authentic contexts. Each stage in education must naturally flow from the previous and run into the next. In 2020 we foresee a life sciences education process that connects smoothly from primary education through universities to post-academic and industry training programs and that puts into effect lifelong learning ideals.

A linchpin in life sciences education in 2020 is the concept-context approach taken from primary and secondary biology education.[2] In this approach, practices from student's everyday life are brought into the classroom to illustrate the life sciences to improve how students view the relevance of the life sciences. The approach also links different stages of education. An example: in primary school the concept "animal" is taught by referring to pets like dogs, cats and fish. Education then progresses to the role of animals in producing milk, cheese and meat. In secondary and higher education, the focus shifts to evolution and socio-economic challenges such as animal rights and the effects of dietary changes on food supply. Thus, the meaning of the concept "animal" is elaborated by applying the concept to the everyday life of the student. Understanding of the concept "animal" increases through successive stages of life sciences education by using different practices.

In primary education, the concept-context approach will be centered on daily life, such as eating, cooking and animal care. This introduces the first life sciences concepts – plant, animal, behavior, ecosystem – in a way that children can relate to in their own lives. In secondary education, science and business come in. Life sciences concepts are progressively elaborated (gene, cell, molecule, organ, organism, DNA, proteins) and tied to real scientific and business practices in fundamental research and market sectors (food, health, agriculture, chemicals & energy). For example: the practice of mapping the human genome or that of rice and how that may translate into (economically viable, sustainable) solutions to health problems or food shortages.

RECOMMENDATION Accelerate introduction of the new concept-context curriculum to enhance students' perception of the relevance of the life sciences, and facilitate its implementation by building a strong life sciences education community of teachers, scientists and entrepreneurs

!

In 2020, this setup of life sciences education will deliver a large inflow of students into higher (university and vocational) education. Students will have experienced the wonder and relevance of the life sciences in primary and secondary school, and many will be excited by the field and the prospects of pursuing a career in it. We want to see annual enrollment rise in life sciences bachelors and bachelors with a strong life sciences component (university and HBO levels) from 5000 today to 7500 in 2020 (Figure 1).[3]

Our social priorities (health, food supply, energy security, sustainability) and our economic prosperity all hinge to a

Student influx in Dutch bachelor studies on life sciences or with important life sciences component

University Bachelor	2009 influx	Δ 08-09
GENERAL		
Biology	516	7%
Life Science & Technology	171	37%
Biotechnology	42	17%
Molecular Life Sciences	120	6%
FOOD		
Food and Health	81	8%
HEALTH		
Biomedical Sciences	410	-3%
Biomedical Technology	130	29%
Psychobiology	102	38%
Pharmaceutical Sciences	87	32%
Health and Life	31	-6%
CHEMICALS & ENERGY		
Molecular Science and Technology	102	15%
Chemical Technology	98	1%
AGRICULTURE		
Plant Sciences	22	47%
Animal Sciences	52	8%
TOTAL	**1,964**	**11%**

HBO Bachelor	2008 influx	CAGR 04-08
GENERAL		
Biotechnology	12	19%
Applied Biology	59	0%
Biology and Medical Lab. Res.	1,014	4%
Bio-informatics	61	-5%
Applied Science	108	-1%
FOOD		
Food Technology	110	-1%
HEALTH		
Medical Imaging and Radiotherapy Techniques	362	3%
Biometry	30	4%
Healthcare Technology	22	-18%
CHEMICALS & ENERGY		
Chemical Technology	229	8%
AGRICULTURE		
Biotechnology (Agriculture)	103	27%
Aquatic Ecotechnology	27	-6%
Horticulture and Arable Farming	130	-7%
Animal Husbandry	421	-3%
Animal Management	181	3%
Forest and Nature Management	166	-1%
SAFETY		
Forensic Research	67	18%
TOTAL	**3,102**	**3%**

Figure 1: Number of students and growth in bachelor studies at universities and HBO in the life sciences or with a strong life sciences component. The CAGR represents annual growth. Note that there are many more studies in which the life sciences are part of the curriculum, such as Medicine which had a 2009 influx of over 7000 students.

Sources: Informatie Beheer Groep, *Vooraanmeldingen voor het studiejaar 2009/2010, peildatum 04-07-2009* (2009); HBO Raad

large degree on the success of life sciences innovations. For that, we need a large number of life sciences graduates to work in both science and business.

The concept-context approach acquaints students in secondary education with science and applied science practices and the professionals in these practices. This will increase appreciation of the life sciences and its role in society, and by 2020 will result in a large influx of first-year students into higher education who are better prepared for it. Higher education is in this way an extension of the education they received thus far. There will be no discontinuity in the learning process, as there often is today. Students will know what to expect and what they can look forward to upon graduating. Better motivated students are also less likely to drop out before graduating. Higher intake and higher pass rates mean higher output – a large and steady stream of life sciences professionals.

B. Higher education in the life sciences in 2020 – a top-quality, diversified curriculum with a solid fundamental research training and strong market orientation that continues into lifelong learning

Top quality

In 2020, the output from higher education will have increased – but so will its quality. High-quality university and vocational education is a prerequisite for any knowledge society. In the Netherlands, life sciences education will be excellent. This can be traced back to the quality of teachers and facilities. Higher education institutes have a dedicated teaching staff, continuously trained in didactical skills. Top researchers are part of this dedicated staff, taking responsibility for education as well as performing excellent science. In 2020, professionals at academic institutes are valued for education in the same way as scientific output.

There will be many contact hours and a large amount of practical training and internship. The staff will be supported by guest lecturers such as entrepreneurs, consultants and other life science professionals. PhD students will also support the teaching staff. The teaching activities of PhD students will be valued as much as their research responsibilities. They will no longer see teaching as a low-value side job. They will really learn how to explain their research activities and pass it on to a new generation of life sciences professionals.

Significant investment in high quality teaching with emphasis on didactic skills and methods, research excellence and market orientation, between now and 2020, will result in top schools that deliver outstanding graduates.

Diversified

The life sciences are a cross-disciplinary field. This has multiple meanings. The life sciences are *multidisciplinary* in that they involve knowledge and expertise from more than one area of academic study or professional practice. They are *interdisciplinary* because of the new or extended knowledge that originates between and beyond existing academic disciplines or professions and from their interaction. Where boundaries between the life sciences blur and scientific and professional perspectives are integrated and connected to the practices of users, regulators and other stakeholders, the life sciences are *transdisciplinary* – a term without a firm and fixed definition, but intuitively applicable to the translational research in public-private partnerships.

The cross-disciplinary character of the life sciences implies two things: life sciences professionals must be versatile, able to collaborate on a wide range of subjects with a wide range of partners, and they must be highly-qualified, able to contribute their own specialist knowledge and perspective. The challenge is to develop a curriculum that combines disciplinary depth with cross-disciplinary breadth.[4]

RECOMMENDATION Value top education the same way as top science to create a leading scientific landscape, with top researchers challenging students to surpass limits. Invent a rating system that encourages cross-disciplinary education

!

One advantage that the life sciences have over other multi- or interdisciplinary fields, is that the life sciences are connected in both the science and technology base and end-market applications. Thus, higher education in the life sciences in 2020 will teach a strong life sciences knowledge base in the bachelor phase, including evolution, genetics, cellular biology, molecular chemistry, and systems biology and its application in food, health, agriculture and chemical and energy production. This basic bachelor's program is cross-disciplinary, involving different institutes. Students will work on projects, in teams and with students of all specializations that the life sciences touch upon, such as biology, chemistry, physics, environmental sciences and food sciences. Students will also be introduced to business and entrepreneurial skills. All students, whatever life sciences field they specialize in, must have the same basic background in fundamental aspects of cell biology, biochemistry, biophysics, evolutionary biology, ecology and biomathematics.

In the course of the bachelor's program, students must choose specialist subjects through additional elective courses on top of the standard life sciences bachelor. In subsequent research or business master's programs, this specialism will be more deeply explored to become the student's primary area of expertise (e.g. medical biotechnology, plant sciences, genetics, food technology, climate studies or (bio)chemical process engineering). Minors provide the opportunity for further business and entrepreneurial qualifications, and throughout the curriculum qualities like collaboration, cross-disciplinary attitudes, communication, organization and working on a project basis are stimulated. In this way, in 2020, higher education in the life sciences will deliver versatile specialists with broad foundations across disciplines and a deep specialty in one.

Strong market orientation

It is clear that life sciences (higher) education in 2020, besides having a high-level scientific profile, has a strong market orientation. From primary school on, students are confronted with what the life sciences mean for real, everyday life. They are ingrained with the dual imperatives of unfettered (basic) research to generate new knowledge and perspectives and concrete, practical applications that are useful and have value to society and its citizen-consumers. The broad bachelor's and specialized master's setups, with their many minors and electives, allow students to tailor their studies to their interests and career ambitions. Students are exposed to different job environments early on, so that they can familiarize themselves and make informed decisions. Life sciences professionals from a wide range of academic and professional backgrounds serve as guest lecturers in their first terms. Large companies sponsor or host courses that are part of the curriculum, introducing themselves to and becoming acquainted with the new talent. Small and medium sized enterprises (SMEs) put research questions to schools for higher vocational education (HBO), giving SMEs access to resources beyond their budgets and students exposure to real-life problems in graduate work. Policy institutes, public and private research organizations and companies offer internships and positions to work on final theses.

Students are strongly encouraged to experience at least two different job environments firsthand, like research in academia and industry, or policy and consulting. Even if a student knows early on in which environment he wants to work, experiencing several job situations is important as the boundaries between environments are fading and public and private stakeholders work more and more together. Working together requires professionals to speak each others' languages. A student may, for example, do an internship on R&D policy for a government department and write her final thesis in an industrial biotech lab. In addition, there are research and teaching assistant positions in academia as well as an online job fair where employers in the life sciences field offer “side jobs” to students (e.g. during summer vacations). In this way, most students will already have worked in the field, for more than one organization, before graduating. They learn and earn a bit extra, familiarize themselves with career opportunities and start building a network. Employers in turn get a good, close-up impression of the next generation of life sciences talent and will follow their careers. Thus, even if a first or second job takes a graduate elsewhere, the company he interned with may hire him five years down the line. In this way, higher life sciences education delivers outstanding, versatile specialists who are both well-equipped and well-prepared for the (job) market (Figure 2).

Employment situation one year after graduating for a masters in biosciences

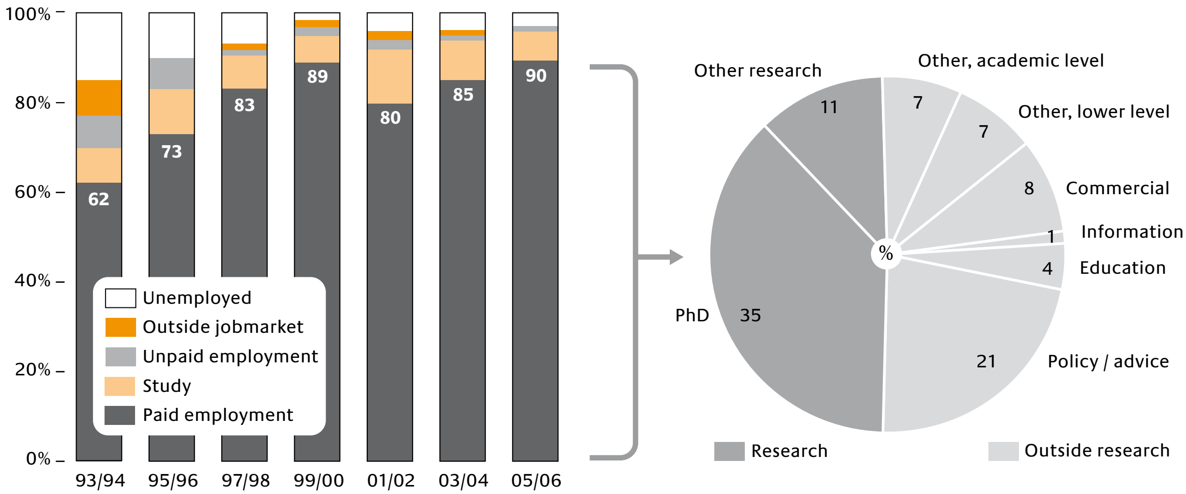


Figure 2: The employment situation of former biosciences students one year after graduating with their master’s degrees
Source: Netherlands Institute of Biology (NIBI), *Annual employment situation inquiry* (2008)

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RECOMMENDATION **Involve the professional field in life sciences education in a sustainable way, making them part of the value chain by offering guest lecturers, internships, graduation projects and side jobs, and giving them excellent professionals in return**

Continuing into lifelong learning

Education in the life sciences does not end with accepting a job. PhD students, post-docs, researchers in companies, PPPs or academia, policymakers, business people and others embark on a future of lifelong learning. This is not a single institute or an common curriculum, but a motley collection of company and industry training programs, postgraduate education, refresher courses, master classes, centers for entrepreneurship, etc. Parties involve and benefit from each other. Companies retain institutes for higher education to provide parts of their in-house training, universities employ sector professionals in topical refresher courses.

Lifelong learning in the life sciences is a reflection of the open innovation paradigm. It is about variety and integration, not consolidation. If a program or a course exists and it is good, other institutes do not try to replicate or subsume it, but connect, collaborate and enroll their own people in it. Every interested can “mix and match” depending on its needs and priorities and add new initiatives. For example, the Life Sciences and Health innovation program first put together a sector-wide training program for PPP researchers almost exclusively from existing initiatives in 2009. In the same year it set up, with and at Nyenrode Business University, a business education program open to all life sciences.

C. The life sciences education system in 2020 – a partnership built on cross-institute collaboration, efficient funding and strong, unified marketing

This vision for 2020 is built on partnership. It could only come about through collaboration by and between all institutes for education and training, large and small, basic and advanced. The same principle applies to both higher education and lifelong learning in the life sciences: collaborate at home, compete abroad. To deliver the numbers of outstanding, versatile and specialist professionals we need, the Netherlands must come together as one bioregion and pool resources. If every university and school for higher vocational education, every disciplinary department within them, and every sector, company and PPP were to build its own independent, proprietary life sciences education and training infrastructure – resources would be wasted and the results would leave us inadequate, weak and uncompetitive on the world stage.

Cross-institute collaboration

The broad life sciences bachelor's program in 2020 is the first cross-institute program of its kind. Students circulate, gain instruction from many different institutes and groups, and receive a joint degree from their "home" university and the collective. They then decide where to specialize in their master's. Although typically centered around a single university, these master's programs also involve other institutes and make the most of their respective research and education specialties. There are partnerships with other leading (European) universities to further broaden and deepen the curriculum. Every institute for higher education has its own focus areas and distinguishing master's programs, but the fact that all are part of the larger Dutch life sciences education infrastructure gives them a distinct edge over competing programs internationally and makes them much sought-after partners.

Efficient funding

The partnership character of life sciences education in 2020 is also reflected in its funding. There is a greater involvement, also financially, of industry – not just in postgraduate or industry programs, but in graduate and undergraduate education as well. (Higher) education institutes allocate dedicated budgets to life sciences teaching that do not compete with research funding. Government supports this practice, for example by providing matching funding that is earmarked and cannot be redirected elsewhere. (Public) funding is tied to student numbers, teaching intensity and the use of expensive facilities like clean rooms, equipment and (bioinformatics) ICT. There is a premium for education that is evaluated as excellent, based on predefined quality criteria that are monitored regularly. Multimedia and online teaching methods relieve the burden on teaching staff and free up resources for contact hours and practical work. A small part of budgets is reserved for education experiments, that, if successful, are incorporated into established, regular programs.

RECOMMENDATION Provide structural funding for life sciences curricula at higher educational institutes, student-number based and which allow intensive practical education using actual life science materials and methods. This funding would not be able to be redirected to other courses or to research

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Strong, unified marketing

In 2020, Dutch life sciences education actively positions itself as a diverse but unified system. It is marketed at home and abroad, individually and collectively by (higher) education institutes, companies, sector associations and government organizations. They speak with a single voice. The Netherlands, as a single bioregion, makes a unified, world-class environment available for education and work in the life sciences.

Talent follows opportunity. The strong science base of the life sciences, the excellent (and lifelong) education, the wealth of job opportunities in business, PPPs and academia and the vibrant, dynamic innovation landscape give the Netherlands a strong proposition to attract and retain the best talent. In 2020, the numbers of domestic and foreign life sciences students in Dutch higher education have increased by 50%. The Netherlands also attracts (researcher-)teachers from around the world, both as visiting or tenured professors. Its universities and vocational schools are preferred partners for leading international institutes for higher education in the life sciences.

Quote from Kerst Boersma

“

Research on the quality of biology education

Without hesitation, I support the emphasis on biology education in this book. Furthermore, I hope that the concept-context approach inspires policy makers in the life sciences, as it did the authors of this book, and that they recognize its potential. Continuing the line of argumentation, I would argue that research on the quality of biology education, and in particular on the quality of its learning and teaching processes, should be considered the engine of high-quality biology education. The urgency of this research, however, is at odds with its present appreciation in the Netherlands. Until recently, the Faculty of Science at Utrecht University housed one of the leading research groups in biology education in Europe. Shortly after my superannuation, however, it was decided to not fill the vacancy of full professor and to terminate our research for financial reasons. From a national perspective, this reduction of research in biology education is not acceptable. The Netherlands requires at least one research group of sufficient extend that focuses on the quality of biology education. Such a research group cannot and should not compete with biological research and should be safeguarded. ”

Kerst Boersma, retired Professor Didactics of Biology at Utrecht University

D. The results in 2020 – highly qualified and versatile life sciences professionals for all sectors, and informed citizens who are receptive to innovation

It is our ambition to deliver, through education and training, a large and steady stream of life sciences professionals to all sectors in 2020. These professionals are the life blood of the life sciences. As blood delivers nutrients and oxygen to organs, so life sciences professionals circulating through academia and industry disseminate knowledge and inspiration. They are the primary vector for knowledge transfer, especially tacit knowledge that is not easily transferred. To the life sciences professionals of 2020, cross-disciplinary, public-private collaboration comes naturally. It is how they were educated. In their studies they learned to operate in different environments (academia, business, government) and to work with people of all life sciences stripes. They are also highly mobile, moving from one position to the next – from researcher to entrepreneur, to business developer, to civil servant, to professor, to investor, and back, and round again.

This also makes the life sciences professionals of 2020 a driving force behind cross-fertilization between disciplines and sectors. They break the language barriers and bring partners from different fields together in innovation. They are pivotal figures in a network of professionals – researchers and practitioners – that they started to build during their formal education: studying at several institutes; working in teams with students of other disciplines and with different (educational) backgrounds; in summer jobs, internships and thesis positions in academia, government and industry. Throughout their career, their collaboration in PPPs, bilateral and other ventures and lifelong learning programs, they continue to meet and work with each other, maintaining and expanding the network.

Finally, the life sciences professionals of 2020 are entrepreneurs, encouraged from the outset to take risks in research and business, to seize opportunities and to be comfortable with uncertainty. They carry that entrepreneurial spirit with them and transmit it to others.

In addition, and by no means less importantly, life sciences education in 2020 delivers informed citizens who are receptive to innovation. Life sciences education educates consumers so that they can make decisions guided by fact rather than fear. This will make them more receptive to innovation, but also protect them by giving them the context and critical skills to evaluate the merits and dangers of new products, processes or services themselves. Primary and secondary education are especially important, but higher education, lifelong learning and public education all play a role.

A lot of marketing power is expended in the food, health and wellness industries. A lot of lobbying and populism pervades discussions on climate, energy and pollution. Citizens need to be able to make their own personal (lifestyle and political) decisions, and life sciences education prepares them for it. As essential as life sciences professionals are, this may be education’s biggest contribution to life sciences innovation.

RECOMMENDATION Have sector organizations set up a network for the life sciences (students and professionals) to organize: marketing, meetings, mobility, social communication and matching of market needs and education

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E. Recommendations

This chapter makes five main recommendations, summarized below. They contain actions that can only be successful when taken up by the field and government together, in a joint approach.

- Accelerate introduction of the new concept-context curriculum to enhance students' perception of the relevance of the life sciences, and facilitate its implementation by building a strong life sciences education community of teachers, scientists and entrepreneurs

- Value top education the same way as top science to create a leading scientific landscape, with top researchers challenging students to surpass limits. Invent a rating system that encourages cross-disciplinary education

- Involve the professional field in life sciences education in a sustainable way, making them part of the value chain by offering guest lecturers, internships, graduation projects and side jobs, and giving them excellent professionals in return

- Provide structural funding for life sciences curricula at higher educational institutes, student-number based and which allow intensive practical education using actual life science materials and methods. This funding would not be able to be redirected to other courses or to research

- Have sector organizations set up a network for the life sciences (students and professionals) to organize: marketing, meetings, mobility, social communication and matching of market needs and education

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Board of The Netherlands Institute of Biology (NIBI)
Bioscience Forum
NIBI discussion platform for Higher Education
Committee New Secondary Biology Education

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Authors

Koen Wiedhaup
Chrétien Herben, NGI, Valorisation Unit
Ingeborg Meijer, Technopolis

Valorization

A vision on value creation

VIII Valorization

A. Introduction

Over the last decade, a lot of public and private money has been invested in research in the life sciences under the assumption that this will generate substantial economic and social benefits.

The life sciences offer technological solutions for many of the health and resource-based challenges that the world faces. Developments in the life sciences can help increase the supply and environmental sustainability of food, feed and fiber production, improve water quality, provide renewable energy, improve the health of animals and (ageing) people, and maintain biodiversity by detecting invasive species. However, the life sciences field is unlikely to fulfill its potential without appropriate regional, national and, in some cases, global policies to support its development and application of ensuing knowledge production.

The impact of life sciences research can already be illustrated with many examples, for instance better clinical treatments, less pressure on the environment, new business activities through spin-offs and the production of new products and services at existing companies. Several applications such as biopharmaceuticals, in vitro diagnostics, some types of genetically modified crops and enzymes are relatively “mature” technologies. On the other hand, there are many applications with limited commercial viability either due to absent supportive policies (e.g. bioplastics, some biofuels), or because they are still in the experimental stage, such as regenerative medicine and health therapies based on RNA interference.

Even though there is a solid scientific foundation for building a strong valorization track record, the Netherlands is still lagging behind in the valorization of life sciences research. This problem has been recognized by the Dutch government, and several important and rewarding initiatives have been taken in recent years. Examples are the BioPartner program (2000-2005), the Technopartner program, and the valorization activities of the Netherlands Genomics Initiative (NGI), the Foundation for Applied Sciences (STW) and Innovative Drug Research and Entrepreneurship in the Netherlands (STIGON; ZonMW).

While these initiatives are primarily directed at strengthening technology transfer out from our academic institutes, the need was felt to also stimulate a closer and more effective relationship between academia and industry and create an open innovation culture. Thus, in all important application sectors of the life sciences, public-private partnerships (PPPs) have been set up, covering a wide range of topics. Examples are the Center for Translational Molecular Medicine (CTMM), focusing on diagnosis and imaging of biomarkers in the health sector, the Top Institute Food and Nutrition, covering research issues in the field of food and health relevant for the food industry, and the Top Institute Green Genetics on research relevant for the plant cultivation industry. These initiatives provide opportunities for the strengthening of our valorization track record in the life sciences.

Government and stakeholders should be fully aware of the typical characteristics of innovation in the life sciences, such as the need for focus and mass to be able to compete internationally, requiring integration and coordination of activities. Another characteristic is the relatively long timespan it generally takes to fully develop a new idea into a marketable product (often more than ten years). Finally, many regulatory procedures may delay marketing approval as well as the actual uptake and effective use of newly developed products.

The innovation programs that were set up by the Ministry of Economic Affairs aim to support the building of critical mass and to work towards an integrated approach to innovation in a particular sector. The life sciences are essential in three of these innovation programs: Food & Nutrition Delta, Life Sciences & Health and the "Innovatietraject Chemie" (innovation route chemistry), all sectors which are covered by this book. Two of these also coincide with the *Sleutelgebieden* (key areas) of the Innovation Platform: Flowers & Food and Chemicals.

In order to fully utilize our country's valorization potential, a stronger entrepreneurial climate at universities as well as in industry is mandatory and needs to be further stimulated and supported.

What is valorization?

The Dutch Innovation Platform defines valorization as "the process of value creation from knowledge by making it suitable and/or available for economic and/or social use by translating it into competitive products, services, processes or new commercial activities".

The process of creating added economic and social value out of research findings is a complex and iterative process: it does not happen spontaneously, but requires a set of dedicated activities relating to the objectives and human and financial resources.

Valorization is, however, not only the dissemination of research findings. It also includes (demand-driven, user-inspired) research programming, interaction with stakeholders during the research and (more indirectly) through network events and transfer to industry of researchers after having finished their degrees, the impact of which is often underestimated. However, ultimately valorization is the transformation of knowledge into concrete new products, services and processes.

Valorization can be realized through various processes in various institutional settings. We can distinguish between valorization processes that lead to new business opportunities of established firms and those that lead to the start of a new company. For the first type, public-private partnerships (PPPs) can be suitable instruments. PPPs are consortia of publically funded research organizations (universities and research institutes) and companies. Collaboration can vary from bilateral to large groups, from one location, to co-location, to even virtual. However, by definition they are collaborative, involve partnerships and deal with precompetitive research. A number of PPPs in the life sciences involve consortia of large and medium-sized companies and research organizations (see the chapters on the life sciences in specific application areas, and that on technology). However, these large settings are not always appropriate: bilateral consortia including only one research organization and one company may be preferred in specific cases to avoid forced partnerships.

Another aspect of valorization is that of technology transfer to companies that are not actively involved in R&D (and for that reason cannot be a partner in a PPP), but will use the results of public research for improvement of their products and production processes.

The universities and the university medical centers (for reasons of readability we will refer to universities and university medical centers in this chapter by "universities") have a central place in our vision, as they are important loci where valorization of research findings starts. Valorization also occurs at other publically-funded research institutes, for instance TNO and the large technological institutes (GTIs). Most of these institutes have committed to the valorization of their newly developed knowledge. While the universities are expected to consider knowledge transfer as one of their missions (in addition to research and education) adequate measures to firmly implement this mission in terms of valorization are still limited at most universities and, as a whole, in this respect, our country is still considerably behind other countries with which we have to compete.

FIGON recommends the Scottish Knowledge Transfer Grants
Recently FIGON, the Dutch Federation on the Innovation of Medicines, presented a series of recommendations to stimulate the creation of new drug companies out of academic research.

One of these recommendations emphasized the need to recognize valorization as a central mission, and consequently, as an unambiguous commitment of universities. To allow Technology Transfer Offices to function on a truly professional level, new money should be made available without requiring matching support from institutes. If not, it would be seen as competitive with core research and teaching activities, and affect academic motivation in terms of validation and commercialization.

FIGON recommended considering the Knowledge Transfer Grants (KTG) implemented by the Scottish Funding Council as a best practice to boost technology transfer.

The KTG have been allocated since 2001 and concern funding on top of what institutes already receive for teaching and research. Annual funding currently amounts to approximately EUR 22 m, of which around EUR 5 m is available for each of the two major Scottish universities of Glasgow and Edinburgh (size comparable to Leiden University, including LUMC). The success of the KTG system is illustrated by the fact that academic productivity in terms of patents, licenses, spin-offs, etc. is four times the average of the ten major universities in the USA and also substantially higher than the UK average.

Taking the Scottish model as a best practice for our country would imply that the Dutch government invest an additional 2-3% of current funding ("eerste en tweede geldstroom") available to the universities, corresponding to an overall EUR 100-150 m annually. While this amount is in line with the more recent recommendation of the Valorization Project Group of the Dutch Innovation Platform, it seems wise to analyze the conditions and the strict monitoring system under which the Scottish government is making this funding available.

Source: FIGON, *Creating New Drug Companies by Empowering Academic Research,* October 2007

It is for that reason that this chapter devotes much attention to the strengthening of technology transfer from academia, realizing that if the valorization process does not adequately function, it will hamper the successful utilization of new knowledge both in the creation of new companies and in PPPs.

This chapter introduces our vision of how valorization will become an integral activity of Dutch universities and other public research institutes by 2020 (section B). In order to draw conclusions and recommend actions that are necessary to reach the desired situation in 2020, we will first describe the current status. Section C presents our vision of what value creation in the life sciences entails, and, more specifically, how this varies among the most important application sectors: health, agriculture, food, and chemicals & energy. In section D, we discuss the barriers that hinder optimal technology transfer and exploitation in the life sciences in the Netherlands. The last section (E) summarizes our recommendations.

B. Valorization in the life sciences by 2020

In order to achieve the vision for 2020, several actions need to be taken to change the culture, to raise commitment and to improve and increase the necessary capacities and conditions. The first steps towards this goal are already in progress; further reinforcements are still necessary and will be presented in section E.

The universities

In our vision, by 2020, optimal exploitation of the results of life sciences research in the Netherlands has been realized through important changes. Our first focus is on the universities where changes in culture, commitment and capacities have taken place. The national government facilitated these changes by creating conditions for structural and long-term support of valorization.

Culture

By 2020, Dutch universities have:

- An excellent base in the life sciences;
- Courses in business development, IPR and marketing to create awareness of the utilization of research results as an integral part of their education/training programs;
- An incentive system that motivates and rewards entrepreneurial researchers;
- A culture that also values making and doing business.

Commitment

By 2020, Dutch universities have:

- High commitment for the valorization of research from people at all levels (executive boards of universities and academic medical centers, faculties departments, research groups);
- Technology Transfer Offices that fall directly under the responsibility of the Executive Board (illustrating this commitment), and striving for coherence with education and research;
- Researchers that exploit their findings through TTOs.

Capacities

By 2020, TTOs at Dutch universities have:

- The capacity for scouting and screening of ideas and knowledge on intellectual property;
- Professionals who are able to develop business concepts (set up a management team, perform market analysis, write a business plan, secure funding);
- Funds for studies to establish the feasibility of a new business concept or start-up company;
- A network of business people who are able to act as coaches for new companies;
- Professionals who are able to negotiate, secure and carry out knowledge transfer deals with new and existing companies;

> “ Ideally, valorization in 2020 looks like this: organization with and around universities is on track, boards of governors realize that valorization is a core task and that they formulate an integrated strategy, providing seniority and expertise in the TTO. Old habits are avoided and TTOs are broadly supported, say, by involving CEOs from companies. ”
>
> **Edward van Wezel, Managing Partner Biogeneration Ventures**
>
> (Quote from telephone interview on June 9, 2009)

- Created an nationwide network of TTOs to exchange know-how and experiences, adopt best practices and pool resources and results whenever appropriate.

Conditions

By 2020, the following conditions have been met for realization of these goals:

- The national government has an explicit policy that universities are responsible for knowledge/technology transfer and exploitation;
- This policy is implemented through policy instruments and related budgets;
- The budget for valorization activities at universities and their TTO's is supplementary to the existing budgets for education and research;
- There are no matching requirements from universities for these budgets for valorization activities;
- This budget is conditional with set valorization targets (in terms of patents, licenses, new companies) that are monitored. Funding will be proportional to output delivered;
- Universities are closely working together in exchanging best practices in technology transfer and valorization, coordinating and pooling activities and expertise on a national level whenever appropriate;
- The above measures are in addition to a governmental policy to maintain an excellent and internationally competitive science and knowledge base at our academic institutes.

The open innovation structure; public-private partnerships

Well functioning TTOs are a prerequisite for both the creation of new start-ups as well as for the establishment of effective collaborations with existing industries. In the Netherlands, the creation of PPPs in a number of specific fields, financially supported by the government, are considered crucial for the development of an open innovation structure by 2020.

Culture

By 2020, open innovation is flourishing because:

- Cooperation between academia and industry is standard in all fields of life sciences;
- Industry and other social stakeholders are able to articulate demand; universities are keen providers of knowledge, technologies and concepts for application by industry;
- Bioregion Netherlands (www.lifesciences.nl) – consisting of regional and countrywide networks and clusters – is accessible to international industry and attracts new businesses.

Conditions

By 2020, the following conditions have been met for realization of this culture:

- Universities and industry consider an entrepreneurial climate as one of their greatest assets;
- Government and stakeholders are aware of the need to focus on excellence and competitiveness within the context of the existing PPPs;
- Sustainable and structural policies are implemented by the government, ensuring full development of new products, services and technologies by newly started SMEs as well as within the context of PPPs;
- Regulatory procedures and measures delaying economic or social use of new innovations have been alleviated;
- An active policy for attracting foreign companies and keeping Dutch companies in the Netherlands (taxes incentives, facilities, free regulation) has been developed;
- The government has developed an explicit public procurement policy (launching customer) similar to the SBIR regulations in the USA;
- The national and regional governments promote the Netherlands as one of the top bioregions in the world in terms of knowledge, partnerships, fiscal advantages, investment climate, geographical location, etc.

C. The Process of valorization in the life sciences

Value creation chain

In our vision, the chain of value creation ranges from awareness to economic and social added value. We reemphasize that valorization is an iterative, non-linear process. This means that valorization is not only transferring knowledge from a university into a new company or new business of established companies, but it also includes (demand-driven, user-inspired) research programming, and interaction with potential users during the research. Here, we will focus on the transfer of research findings into concrete new products, services and processes. These value creation chains consist of eight discrete stages of valorization (see box: "The eight stages of valorization").

The eight stages of valorization

1. **Awareness of utilization.** A continuous awareness of the utilization of research results is required. Rewarding systems (in terms of academic career, but also financially), should also consider excellence in terms of potential benefit for society, and not only in terms of benefit for scientific progress
2. **Scientific creation.** This stage leads to results that are novel and patentable and which are "user-inspired". Excellent and front-line science is the first condition, but needs to be supported with a stimulating environment, excellent facilities and strategic thinking by the university sector
3. **Feasibility.** This stage confirms the potential business viability of the project. This leads to research results that are protected by patents and that have the potential to mature into a project in a PPP or into a product or company
4. **Validation.** This stage leads to the creation of a business plan or a well-defined project. Stimulating and facilitating (potential) start-up companies by financing applied follow-up research and the development of a solid business plan that will attract a team and investors. Resulting in inventions that have proven to be commercially viable, either as a license or as a spin-off
5. **Valorization studies.** These lead to proof of concept results. Once proof of concept is demonstrated, financial and coaching support is necessary in order for it to mature into sustainable business, leading to successful exploitation of knowledge
6. **Commercialization phase I.** Once a project has reached the commercialization phase I (or is well on its way towards that phase), further development will generally be funded by additional PPP funding, private money (equity or debt), via licensing out to another company, a buy-out or by going for an IPO
7. **Commercialization phase II.** This stage includes all large-scale activities needed for introducing the product to the market (e.g. clinical trails, field trails, manufacturing processes, demonstration plants)
8. **Market introduction.** Approval for marketing and reimbursement of costs (in case of diagnostics, medicines, etc.) are subject to governmental regulations and measures that may delay access to the market. Increasing requirements may be costly and can considerably delay introduction

> “ Successful innovation requires that the entire value chain be adapted, and that you strive towards simultaneous and iterative processes: then you'll have much more chance of impact. Innovation success is characterized, for example, by the involvement of people in business development from early on. This way, goals and activities can be much better defined. TTIs can play a role in this. ”
>
> **Emmo Meijer, Senior Vice President of Global Foods R&D, Unilever**
>
> (Quote from telephone interview on June 15, 2009)

Characteristics of valorization in the life sciences

There are a number of characteristics that apply specifically to the life sciences, and which influence the value creation process in this field considerably.

- Time > Long-term developments. For most life sciences innovations, the R&D trajectory and valorization process take more than 10 years, going up to 15 years, such as for new polymers, many food products, pharmaceutical entities, enzymes for industrial processes in downstream sectors and for biofuel production;
- Risk > Risk profiles are very high because of the high failure rates of development. For example, it is estimated that 1 in 5,000-10,000 substances become a marketable medicine;
- Money > The R&D trajectory is expensive due to the cost of field trials for new plant varieties, (pre)clinical trials, the amount of resources to get approval from regulatory authorities, etc. Thus, substantial cash flow is required;
- Regulation > Extensive regulatory requirements to protect consumers exist. The ICH, FDA, EMEA and the GMO, and novel food regulatory guidelines, are becoming more and more complex, especially for the health and food sector;
- Governmental measures that delay uptake in the market (e.g. cost containment in health).

Therefore, the lifecycle of life sciences products is much longer than that compared to, for instance, ICT innovations. This affects return on investment for capital investment providers, who are very aware of the risks and usually choose to be on the safe side. As a result, the only certificate of value during this long and expensive process is the IP that protects findings, and which can be sold to the next investor or company in case of a takeover.

Globalization

In the life sciences sectors globalization is important in two ways:

- As the market of the life sciences is worldwide, multinational companies operate globally, and this holds for acquiring knowledge as well. Multinationals are shopping around for the knowledge they need. As a result, they will benefit from investments in the life sciences and the strong knowledge base that has been built in the Netherlands. For the Dutch economy to profit as much as possible from this, a strong industrial base needs to be present. At the moment this is the case for the agriculture, food and chemicals & energy sectors and the medical equipment sector (that integrates life sciences); in the pharmaceutical sector this industrial base is smaller but growing in size and number of (small) companies.

Agendia's MammaPrint

Established in 2003, Agendia is a company that is pioneering the development and commercialization of validated tests that assist healthcare professionals and pharmaceutical companies in determining the diagnosis, prognosis and therapeutic responsiveness of cancers in individual patients.

In 2004, Agendia became the first company to commercialize a test (DNA chip) that predicts the risk of breast cancer recurrence (MammaPrint). In 2007, MammaPrint became the first in-vitro Diagnostic Multivariate Index Assay (IVDMIA) to acquire clearance from the US Food and Drug Administration (FDA). On the basis of Mammaprint analyses, about one-third of breast cancer patients on average can be treated without chemotherapy and its heavy side effects. The potential market for this DNA chip is very large, as about 200,000 women in the USA and Europe are potential breast cancer patients can benefit from MammaPrint test results.

Market introduction of the Agendia test depends on the validation and acceptance of its tests. In the USA, approval for market introduction by the FDA is sufficient. In the Netherlands however, market approval does not necessarily mean that health insurance companies reimburse the cost of the test. Here, every new, FDA or EMEA approved test or drug must be judged by the Health Care Insurance Board on its cost-benefit profile in order to be included in the basic (health insurance) package and subsequent coverage of the cost of the test. For companies, this last step (or barrier) is important for making any profit on a new product.

For MammaPrint, the decision of the Health Care Insurance Board is still in progress, and thus health insurance companies generally do not reimburse it. This is why at the moment there is a limited use of this prognostic test even though doctors are increasingly convinced of the benefits of MammaPrint.

While many have claimed Agendia's success, it now lacks the support from all those who were so eager to share in its success. According to Bastiaan van der Baan, Vice President of Commercial Applications at Agendia: "The Agendia test is rather new and it costs very much time to inform and convince all parties involved: the Ministries of Public Health and Economic Affairs, the Dutch Healthcare Authority and the Health Care Insurance Board".

Source: *'Bedankbriefjes als beloning' Interview with Bastiaan van der Baan*, C2W Life Sciences vol. 9, May 2, 2009

- Foreign investment or establishment of R&D sites in the Netherlands. The market environment is important for keeping Dutch companies in the Netherlands, and for attracting foreign companies to do research in the Netherlands. Therefore, the generic tax and investment climate is a parameter for valorization that needs attention as well, in order to be able to translate our investments in research into economic and social added value.

It should be noted that an up-to-date global vision is mandatory at all times in terms of policymaking, since most other European countries and the USA realize the importance and potential impact of the life sciences as well. In the spring of 2009, the UK established the Office of Life Sciences, led by the Minister for Science and Innovation, in order to support the UK's life sciences industry as a major growth industry and to help ensure the UK's place as a global leader. Similarly, France and Switzerland have recently expressed interest in reinforcing the life sciences. These developments show that a country has to act aggressively in order to stay ahead of competitors, and needs to have the ambition to become or remain one of the top bioregions in the world.

Government ambitions for the life sciences in France and the United Kingdom

President Sarkozy
I undertake today to ensure that the healthcare industries become a major focus of France's competitiveness. Given the increasing complexity of therapeutic innovation, greater cooperation is needed between publicly and privately funded research. We achieved this in the aerospace and the civilian nuclear sectors. Why not do the same thing in the pharmaceutical industry?

Source: Speech to the heads of R&D of the International Pharmaceutical Research Laboratories, Paris, June 5, 2009

Andy Burnham, UK Secretary of State for Health and Lord Mandelson, UK Secretary of State for Business, Innovation and Skills
We need to do more to ensure that the UK continues to offer an attractive environment for the life sciences companies to do business. The Government has a crucial role to play, helping to remove the barriers that prevent the UK from making the most of its strengths.

Source: Foreword, *Life Sciences Blueprint*, *Building Britain's Future*, July 2009

Differences in the value creation chain in the health, agro-food and chemicals & energy sectors
The life sciences field finds its applications in many industrial sectors. The most important are health, agriculture, food and chemicals & energy; in Europe also referred to as the red (health), green (agriculture and food; or agro-food, as in this chapter the two are discuss together) and white (chemicals & energy) biotechnology sectors. In other chapters of this book, these sectors are discussed in more detail. The innovation processes in these sectors show large differences with respect to R&D intensity, the way product regulation affects the innovation process, the types of stakeholders that are involved, the Dutch industrial presence, etc. This also applies to the valorization chains in the different sectors. They are rather similar in the first five stages, but show the largest differences from the commercialization phase onwards (stage 5-8). Differences that affect valorization are discussed below.

The health sector
The health sector comprises both pharmaceutical companies and those in medical equipment that increasingly integrate biotech-based sensors and diagnostics within their products. A number of PPPs operate in this field including the three Leading Technology Institutes (TTIs) CTMM, Top Institute Pharma (TI Pharma) and the Biomedical Materials Program (BMM) – focusing on diagnosis and imaging of biomarkers; on drug discovery and development; and on devices building upon biomaterials, respectively. Furthermore, enabling technology and infrastructure partnerships have been initiated to support innovation in and outside PPPs such as the technology centers of the NGI and "Parelsnoer", a national biobanking partnership between the eight UMCs. In the spring of 2008, the innovation program Life Sciences & Health (LSH) started. It aims to enhance the innovation and investment climate in the sector for SMEs and for the value creation of knowledge that results from PPPs and academia.

In the health sector many aspects of the life sciences are converging with medical technology. In this book the focus is primarily on life sciences, and does not address medical technology in its broadest sense. In this section we therefore pay particular attention to the pharmaceutical part of the sector. It should be noted, however, that in the Netherlands a range of very relevant medical technological developments are taking place with a huge valorization potential. Examples of these developments are given elsewhere in this book.

The health sector is very knowledge-intensive in all stages of valorization. Excellent research is needed to fill the pipeline, but subsequently excellent technology transfer is the basis of start-up companies and of collaborations with industry, including both SMEs and large pharmaceutical companies. Taking new pharmaceutical entities from a university spin-off through a biotech company phase up to takeover by a large company includes several distinct – capital-intensive – steps.

In order to create value from research to proof of concept and ultimately to the market, large amounts of funding are required. In the first stages of valorization, these funds are provided for by governmental pre-seed and seed facilities. The next phases of development require appreciable amounts of venture capital from different sources.

The commercialization phases are very expensive due to complex international regulations that have to be complied with in order to register a new product. It is difficult to maintain cash flows in fluctuating financial markets, but more funding may come from multinational pharmaceutical companies that are increasingly concentrating on the last phases of product development (clinical research, production, marketing). This, in turn, leads to more and more outsourcing (e.g. through strategic alliances with start-up and biotech companies, and academia to guarantee access to knowledge). As a result, the scale of precompetitive research and open innovation at academic medical centers may increase.

The innovation program Life Sciences and Health offers support to SMEs facing high risks in these commercialization phases. These companies can apply for so-called Innovation Credits and may also be eligible for financial support when partnering on an international scale.

Continuous support of life sciences research in the health domain should be prioritized on the basis of excellence and social demand. Society's expectations of new therapies, diagnostics, prevention and care are high. However, the final stage of valorization, the uptake and use of innovative products and services in healthcare, is heavily regulated as well. Reimbursement of innovative products is often granted on the basis of various regulations and may take another year or two after registration, thus hampering the overall process of innovation and valorization in the life sciences for health in many cases.

“The Pharma industry is transitioning into a new business model in which the early phase of the R&D path is becoming increasingly outsourced. In the public domain, increase of scale and free exchange of precompetitive research are easier. This creates plenty of possibilities for universities and university medical centers.”

Maarten le Clercq, Member of the Board of Directors of Leiden University Medical Center

(Quote from telephone interview on August 18, 2009)

The agro-food sector

The agro-food sector in the Netherlands is dominated by a strong innovative, R&D-driven industrial capacity in several domains: seed, food, food processing and health-related products. Long-standing relations between Wageningen University and large companies like Unilever and DSM have resulted in one of the first PPPs in the Netherlands: the TI Food and Nutrition. This TTI has been able to bridge the gap between basic research and applied research by creating a common research agenda, carrying out a roadmap to define individual strengths, establishing strong ties between industry and academia, conducting research through consortium agreements, and making use of a program-based collaboration rather than a project-based approach.

The PPPs in the agro-food sector have undoubtedly resulted in the creation of new value chains and of business models where supply and demand collaborate. Parallel innovation processes, where all stakeholders are involved in all stages of valorization, are the new paradigm. Companies active in biotechnology in this sector are mostly large and medium-sized companies. Compared to the health sector, there are less small and medium-sized high biotech companies operating in this sector. For SMEs in the agro-food sector that are less knowledge-intensive and innovative, it is less straightforward to have them benefiting from knowledge transfer.

Several issues in the agro-food sector are worth mentioning here. Introduction of new nutritional ingredients in the market is increasingly hampered by stricter regulations on claim substantiation (e.g. cholesterol reduction, blood pressure lowering, weight management), resulting in expensive and time-consuming clinical studies.

Another, major social issue in agriculture is that of GMO plants. Although Dutch food crops breeding companies have moved most of their GMO activities including field trials outside of Europe (except for Spain), this issue also led to the development of alternative breeding techniques such as cisgenese. The major issue in food is the discussion on health food, and the amount of research that is necessary to substantiate a health claim.

In terms of increasing valorization, more focus and delineation in much smaller and sharply defined themes that line up with industries' interests are expected to occur. Since the economic impact is strong in this area, rebalancing of scarce governmental funding is to be discussed.

The chemicals & energy sector

Only a few firms in the Dutch chemicals & energy sector apply bioprocessing. Most of them participate in the PPPs in this field. The positive contributions of bioprocesses that replace chemical processes, and the use of biomass replacing fossil fuels as raw material in this sector lead to more sustainable production processes in the chemicals & energy sector. The Kluyver Centre for Genomics of Industrial Fermentation is an example of how valorization in a PPP in this sector is being managed. In this PPP, participating companies have direct, confidential access to the results of the research activities in the Centre that are performed by academia and financed by the NGI, and companies are allowed to pre-screen research proposals of these projects. This enables companies to rapidly identify research output for valorization. In addition, individual companies can participate in tailormade projects, mostly bilateral collaborations, in which they receive adequate intellectual property protection (Part I, box on page 55).

Patents are important carriers for transferring research findings of university groups to companies. They are used to protect the large investments that are necessary to develop new chemicals or new product processes. There are no differences between the legal requirements to obtain a

“ **Hidden value**

Reliable DNA diagnostics for about 2000 rare diseases have been developed, even while in many cases no sufficient therapy exists. The social value of the diagnosis is tremendously undervalued. The 50,000 DNA tests performed annually provide relief in 80% of the cases. Including the family members that would have had the same genetic disorder, this annually reliefs about 150,000 people, setting them free to enjoy the rest of their lives. Underestimation of valorization potential also holds for therapies for rare diseases. Because of the very well-defined patient population, these therapies and the information/models obtained during their development often play a major role in developing therapies for common diseases. ”

Gert-Jan van Ommen, Head of Human Genetics at LUMC, leader of the Center for Medical Systems Biology (CMSB) and first winner NGI Valorisation Award

patent for an invention in the chemicals or pharmaceuticals fields. Yet chemical patents are different because they can include generic structures (structure of the chemical group the patented chemical belongs to); these are used to make the patent claim as broad as possible.

In addition, an important stage in valorization with the chemicals & energy industry is the development of large-scale production processes for these new chemical entities (commercialization stage). These development processes are very expensive: it is for these reasons that tests are being done on a smaller scale, including the development and testing of the production processes on a pilot scale (100 kg to 10 tons of product per day) and demonstration scale (up to hundreds of tons of product per day).

Except for issues specific to the life sciences, in this sector other aspects also play an important role in the valorization chain, such as certification of biomass, logistics, futures and international trade agreements. Environmental regulations, especially those focused on reducing greenhouse gases, are a driving factor behind innovation in this sector.

D. Barriers to successful valorization in the life sciences

Stage 1, Awareness of utilization
Although business development courses are offered to young scientists in the life sciences at a number of universities, scientists in the Netherlands are still only vaguely aware of the users' value of their research, and more specifically, of the commercial or social value of potential applications of their findings. The culture within most universities is dominated by norms and values that relate to performing high quality research and education. In addition, there is too little awareness of the specific expertise that is needed to create value out of research.

Stage 2, Scientific creation: Third mission
Although many universities and other public research organizations (academic hospitals, research institutes) have institutionalized valorization support activities, there is still little commitment to valorization at the strategic level of these organizations. Missions of most universities are

The success of K.U. Leuven Research & Development (LRD)
K.U. Leuven has become well-known for its approach to valorization and knowledge transfer. Within the university, a separate entity, K.U. Leuven Research & Development (LRD), has the specific mission to promote and support the transfer of knowledge and technology between the university and the industry. In order to do this, LRD offers professional advice with regard to legal, technical and business-related issues. The activities of LRD include contract research, IP management, the establishment of new research-oriented and innovative spin-off companies, access to venture capital, and the promotion of high-tech entrepreneurship and innovation by stimulating networking initiatives.

The main elements of the success of LRD are:

- A long-term commitment: over a period of more than 30 years, researchers and staff have become familiar with industrial innovation and have learned the pros and cons of academic entrepreneurship;
- A decentralized management style: to give researchers and research groups sufficient freedom on the one hand, but stimulate them to compete for innovation in the market on the other;
- The introduction of an interdisciplinary matrix structure within the university: in this matrix structure, research excellence prevails along one line, while valorization excellence is rewarded along another line;
- The introduction of innovation coordinators: to ensure close contact between LRD and the research groups;
- The appropriate mix of incentive mechanisms, targeted to the research groups and to the individual researchers;
- Budgetary and human resource management autonomy within the university: LRD divisions have the autonomy to balance revenue and expenses.

Source: Koenraad Debackere and Reinhilde Veugelers, *The Role of Academic Technology Transfer Organizations in Improving Industry Science Links*, Research Policy vol. 32, 321-342 (2005) formulated in terms of research and education, but not in terms of valorization. Adding to this, reward systems only address research excellence or teaching qualities but do not reward entrepreneurship. Universities and research organizations need clear objectives as to what they want to achieve within the context of their "third mission", which activities and instruments are needed to support the objectives, and a proper monitoring and evaluation system that addresses the third mission as well.

Stages 3/4, Feasibility and validation: Quality of TTOs questionable and patents under pressure
In most universities, Technology Transfer Offices (TTOs) have only recently come into existence. In the first years, they were staffed primarily with officials and were not very integrated into the university/academic medical center organizations. There is still a long way to go before they are staffed with professionals who have a sound relationship with the scientists, and an extensive network with industry, lawyers who have specialized knowledge of patenting and licensing, business developers who are able to write plans for new companies and to negotiate, secure and carry out deals with existing companies, have knowledge of specific markets and who have realistic expectations about the financial returns of their activities. Collaboration and exchange of best practices between TTOs should be stimulated, leading to a network and to pooling of information on patents, etc., whenever required. Such a network could also be instrumental in positioning our country as an attractive bioregion.

At a more general level, there are increasing problems with the patenting system. As mentioned above, patents play a central role as they capture the stock of potential returns on the investments made in science and in the activities to valorize them. However, the patenting system is under pressure as it has been driven away from its original goals: open access to "protected finding" and commercialization of findings.

Deadly sins

- Think your TTO does not need objectives
- Think your TTO will generate loads of money
- Think your TTO will break even in less than 5 years
- Think your TTO can be staffed with "lost" administrators
- Think it's all about money
- Think it is not about money
- Think your patents don't need marketing
- Think no one will notice the scary increase in patent costs
- Think you don't need a lawyer for your agreements
- Think a lawyer will handle the deals

Source: Rudy Dekeyser, *Thinking start-ups grow on trees*, VIB, Belgium (2008/9)

The number of patent applications, especially in biotechnology, has increased considerably over recent years to more than 200,000. This overload of applications has posed enormous problems for patenting bureaus, and one effect has been that they have become less critical and have granted most patents. This also affects the TTOs, since patenting and the marketing of patents are their main activities: when a new finding has to be patented, it takes considerable effort to get an overview of relevant patents and to find out if there is an infringement. In the USA, the market is even more assertive against infringement and in litigation. International organizations have identified the problems with the patenting system and are discussing how to deal with them.

Stage 5, Valorization studies : Lack of expertise
In the life sciences, professionals who know how to create value are scarce. Of course, this has to do with limited entrepreneurial awareness. But there are also a limited number of serial entrepreneurs who have practical experience in biotechnology, and know how to deal with the

Progentix Orthobiology

Progentix Orthobiology B.V. is an example of a successful spin-off company. Progentix was established as a spin-off from Twente University in 2008 by former Isotis founder Clemens van Blitterwijk and Joost de Bruijn, former CSO of Isotis. Progentix develops CuriOs (TM), a unique osteoinductive material for clinical application in bone regenerative surgery. The Progentix product portfolio currently consists of a novel family of calcium phosphate synthetic bone substitutes attracting stem cells after implantation.

Progentix Orthobiology obtained financing from BioGeneration Ventures in early 2008, allowing the accelerated development of its technology. Only a year later, it closed an investment agreement with NuVasive (USD 10 m upfront payment), a medical device company from San Diego (USA) which focuses on developing products for minimally invasive surgical treatments of the spine. Under the terms of the agreement, NuVasive will gain access to Progentix's synthetic bone substitutes designed to accelerate bone healing through a novel microstructure created by a proprietary manufacturing process. In addition, NuVasive obtained exclusive worldwide distribution rights and an exclusive option to purchase Progentix entirely under certain circumstances (USD 70 m milestone payments).

NuVasive's initial commitment allows Progentix not only to grow in the spine market, but also to continue developing its unique family of bone graft materials, and makes the near term commercialization of these products possible. Or in other words, in course of a couple of years, Progentix has developed into a global player and has secured investments as a firm base for future innovation.

Source: www.progentix.com

capital needs and regulatory requirements. Similarly, if transfer to large companies is the objective, proper legal, business and marketing expertise is needed. Thus, if valorization is a true goal, a critical mass of TTO staff is needed, including professionals who understand both business and research, speak their languages, and know their habits and needs. The actual size of staff of several Dutch university TTOs is still far below the required critical mass and desired quality. Within the context of a PPP, industrial partner(s) can provide essential input on market need and business experience.

Stage 6/7, Commercialization stages

An issue related to the commercialization stages in a more general way has to do with the Dutch start-ups' insufficient ability to grow. Only a few reach substantial size or grow into a mature firm; others have chosen for an exit strategy such as merging with or selling themselves to another company in the business. This is mainly due to the absence of long-term consistency in the set of instruments needed to support start-up growth. Various reasons account for this, varying from lack of experienced management able to run a larger company, insufficient focus on the business goals, to lack of funding required to perform relatively costly proof of concept studies.

Small budgets for valorization

One cannot expect valorization to happen by itself: when the objective is to create added economic and social value, specific activities relating to the objective need to be in place. The Netherlands is seriously lagging behind in measures to stimulate the separate valorization stages in the value creation chain. The first phase of NGI (2003-2008) has shown that a separate set of well-balanced instruments is needed in order to stimulate valorization; a number of them were created recently and are now operational. STW also has the mission to stimulate the utilization of research results, and has developed instruments. Yet, compared to the amount of funding that is spent to maintain the excellent, precompetitive knowledge base through PPPs and other programs (currently ~EUR 400 m/year for the life sciences, of which ~50% is matching funds, excluding direct funding from the Ministry of Education, Culture and Sciences, and NWO and STW programs and projects), public funding for the distinct valorization stages is rather limited (see Table 1).

Success and failure factors of academic life sciences spin-offs

Arthur Tolsma studied the results of the BioPartner First Stage Grant and STIGON programs. He made a detailed analysis of all 89 spin-offs that were supported by the two programs in the period 2000-2007 in order to answer the following question: What are the experienced determinants of success and failure of academic life sciences spin-offs within these two programs?

His main conclusion was that various factors determine success and failure. Attracting an external CEO, preferably with experience in the industry and as an entrepreneur, was the most decisive factor for successful spin-off creation. Two other very distinctive factors were commercial quality and focus on business development of the spin-off team.

Explaining these significant findings, Tolsma pointed to several potential benefits of an external CEO compared to the inventor/scientist as CEO. First, the external CEO will bring the needed business focus. Second, he or she brings valuable entrepreneurial skills into the team and, as a consequence, this may increase the value of the firm, which in turn increases the chances of attracting investor capital. Finally, the CEO brings in dedication and commitment to commercialize the scientific invention. Compared to hiring a consultant to write the business plan, or as an interim manager, a CEO with shares in the firm has a strong incentive to make the firm economically successful.

Source: A. D. Tolsma, Success and failure factors of academic life sciences spin-off creation, MSc Research Graduation Report, TU Delft (2009)

Table 1: Instruments for creating knowledge and valorization

Stage of valorization	Instrument examples	Approximate budgets per year (2009)
Awareness	Master class Biobusiness Entrepreneurial Skills Business Course Technopartner SKE** Centers of Entrepreneurship**	EUR 200 k EUR 50 k EUR 1.75 m EUR 1.25 m Total: EUR 3.25 m
Scientific creation*	PPPs in LS	Total EUR 400 m***
Feasibility	NGI Venture challenge NGI Valorisation Award Valorization in NGI Centres Technopartner SKE**	EUR 300 k EUR 1 m EUR 3 m EUR 2 m Total: EUR 6.3 m
Validation & Valorization studies	Pre-seed grant (NGI, ZonMw, LSH) STW Valorisation Grant** ZonMW translational programs	EUR 2 m EUR 0.5 m EUR 2.5 m Total: EUR 5 m
Commercialization I	BioGeneration Ventures Technopartner LS seed funds	EUR 1.5 m EUR 5 m Total: EUR 6.5 m

* Valorization is a small aspect in most PPPs; the main activity financed is research
** These instruments are not life sciences specific; estimation is made of the life sciences contribution
*** The number is estimated using data from PPP websites and the Ministry of Economic Affairs, and includes government, academia and industry contribution

In addition, these budgets are temporary; for instance, the NGI budget for valorization (EUR 32.5 m) is currently one-third of the total available for valorization, and will only be available until 2012.

Overall, we can conclude that valorization of the life sciences in the Netherlands comes against a number of serious barriers. Although the awareness of the importance of valorization issues of policy makers within public research organizations and at the national level has increased in recent years, considerable actions have to be developed in order to overcome the innovation paradox (good in science, not good in valorization). We have excellent research in the life sciences; the next step is to have successful business in this field.

NGI Valorisation: an integrated approach to valorization in the life sciences

NGI is striving to implement the necessary measures to ensure successful valorization of the research results obtained in its 16 research centers, and to boost the valorization in the life sciences sector in general. The NGI Valorisation strategy is implemented along three major action lines:

NGI Genomics Centres

Each of the NGI Genomics Centres has its own budget for valorization accompanied by a set of valorization targets. To further stimulate the NGI Genomics Centres, NGI annually awards a EUR 1 m Valorisation Award to the NGI Genomics Centre that has performed best in terms of valorization.

NGI Valorisation Network

Strong and effective TTOs lie at the heart of successful valorization. NGI therefore brought all life sciences TTOs together in the NGI Valorisation Network to exchange "best practices" and strengthen the profession. NGI also supports the TTOs by offering low-cost access to valorization/licensing and business development courses/trainings and workshops, and organizing visits to foreign TTOs and valorization events.

NGI Start-up Support

NGI has set up a coherent set of activities to support the successful start-up of life sciences companies. The NGI Start-up Support includes the NGI Venture Challenge (a coaching program to help potential entrepreneurs build their business case) and the NGI Pre-seed Grant (a grant for technological and commercial development resulting in a solid business plan). NGI also provides seed funding to early stage life sciences companies through BioGeneration Ventures, sponsors the Masterclass BioBusiness, and supports network activities for young entrepreneurs through partnerships with Yels.Net and New Venture.

A prestigious international Valorisation Advisory Board has been installed to provide NGI with the necessary advice and steering and to act as the jury for the annual NGI Valorisation Award.

E. Valorization 2020: What needs to be done

A starting point for formulating our recommendations was the "Nederlandse Valorisatie Agenda" of the Innovation Platform, published in May 2009 by the Committee of Marco Waas. Our recommendations are mostly in line with those of this committee, but of course more specifically directed towards the life sciences.

The first part of our recommendations relates to valorization at universities (phases 1, 2 and 3 of the eight stages of valorization) and the validation and valorization studies leading to proof of concept (phases 3 and 4 of the eight stages of valorization) following the spinning-out of a new venture.

In addition, we present recommendations on how to strengthen the relationship between universities with established firms in valorization (e.g. within the context of a PPP). Finally, recommendations are presented on how additional national policies can help realize the vision set out in this chapter.

Professional valorization support at universities and university medical centers

In order to increase both the quality and the size of valorization activities at universities, the following actions need to be taken on the level of organizational strategy, culture and financial and human resources.

1. **In addition to research and teaching, valorization should be recognized as the third mission, and consequently, as an unambiguous commitment of universities.**
   More specifically, an integrated policy approach by each university and UMC should be developed that includes all university actors involved in valorization, varying from the executive board to the individual research groups, working towards a mutual goal with commitment from people at all relevant levels.
   We recommend implementation by:
   - Developing a valorization perspective for the long term and commitment at all levels, which means thinking in terms of ten years ahead and even further;
   - Defining strategic goals at each level, documenting them in contracts between the board and faculties (in performance target agreements), and communicating these in valorization plans for university, faculty departments and research groups;
   - Implementing this strategy at an operational level in quality assurance plans and the planning and control cycle as well, and using a set of indicators for monitoring purposes.

2. **Valorization should be adequately funded through new money, not requiring matching support from the university.**

" In the end I would like to move towards the Scottish model; universities there have reserved 2.5% of the budget received from the government for the execution of valorization activities. And they are also judged on their results. "

Marco Waas, Dean at TU Delft, Project Leader Valorization Innovation Platform

(Quote from interview on June 26, 2009)

In line with the recommendations of the Committee Waas (and the FIGON recommendation based on a best practice realized in Scotland, see page 222), the investments in a valorization infrastructure in universities over the next five years should constitute 2.5% of the public funding of the universities ("eerste en tweede geldstroom"). This budget is additional and structural and should thus not be competitive with existing budgets for research and education (this budget is estimated to be around EUR 100-150 m annually) Of course, it should be clear that this budget should be available for all valorization activities, not only for the life sciences.

- These extra funds are needed for:
  - Professionalizing the Technology Transfer Offices;
  - Implementation of stimulating measures such as the NGI Venture Challenges and Valorisation Awards;
  - Funding of feasibility studies and other activities needed to establish viability of project or business model.
- After several years, the amount of funding for each university will be based on metrics related to performance reported on an annual basis (e.g. disclosure interviews, patents applied or filed, technologies licensed, royalties generated, collaborations started, companies formed).

3. Universities should reinforce their TTOs by investing in skilful valorization professionals, seasoned in business development, IP and other legal affairs.

Our concrete recommendations are to:

- Attract and train people who have knowledge of R&D and business experience. They need to be bilingual (i.e. understand both the market and academia);
- Create appropriate compensation for highly skilled people in the TTO: adjustment of the salary scales is needed to ensure that wages are competitive with those in the business world;
- Invest in people who have market intelligence, and dedicate a budget for market research;
- Involve scouts at the research group level and other more generic support services at a central university level;
- Invest in people with management skills for establishment and growth of start-ups (professional managers);
- Invest in specialized support staff (IP, licensing, financial-administrative support);
- Coordinate all of these among universities to ensure exchange of best practices, strengthen the profession and create a nationwide valorization network.

4. Universities should develop an entrepreneurial culture with a high level of awareness of utilization of research.

Measures to be taken are:

- Employment of financial incentives for researchers, for instance by rewarding their valorization activities in terms of added funding. Additionally: create incentives that reward them professionally;
- Embedding entrepreneurship in the education system by including it as a permanent part of the curriculum;
- Marketing good examples of valorization (brochures for the broad public) and invite good role models to the university.

5. Additional breeding ground for (open) innovation and facilitating the start-up of new companies should be realized.

Our concrete recommendations are to:

- Stimulate and expand initiatives such as Health Valley Nijmegen/Wageningen/Twente, and life sciences parks/campuses as breeding grounds and drivers of open innovation by creating investment funds initiated by universities and local and regional government;
- Develop a dedicated policy for marketing of life sciences parks/campuses with the aim to attract new (R&D) companies to the site;

- Attract professional management for establishment and expansion of life sciences parks. This should ensure the attractiveness of the life sciences parks in terms of facilities and sufficient support (in ICT, management, etc.);
- Provide a meeting place for those located at the life sciences park for exchange of experience and best practices in valorization, organization of mutual activities, and for training;
- Ensure integration of these local hot spots of valorization activities into the Dutch bioregion concept.

From university to proof of concept

Sufficient professional and financial support should be available to ensure that following its exit from university, the start-up will be able to successfully bridge the "equity gap" and develop into a venture that is sufficiently robust and attractive to private money, either from venture funds or through collaboration with existing companies.

We recommend:

- Continuation and reinforcement of sufficient pre-seed funding, in line with the successful examples of the previous BioPartner Program and the current NGI/LSH Pre-seed Fund and Technopartner Seed fund;
- Continuation of early stage seed funds such as BioGeneration Ventures;
- Continuation of credit facilities as initiated by the LSH program;
- Establishment of a network of experienced entrepreneurs able and willing to assist or strengthen management teams in terms of business development, financial/fiscal aspects or commercialization.

Development of long-term strategic relationships between universities and industry

These recommendations address the development of strategic relationships of universities with companies and stakeholders in society (including government departments).

Recommendations are:

1. **Development of a strategic research agenda by each university together with large companies and relevant public authorities.**
   Our concrete recommendations are to:
   - Ensure that in the selection of themes, priority setting is based on excellent research quality and valorization opportunities (focusing on "user-inspired fundamental research"). These themes should be specifically aimed at social and economic benefits;

"In the Netherlands, government subsidies are uncoordinated and complex. My biggest criticism of Dutch (valorization) instruments is that every arrangement has a short lifespan. STIPt, BTS, Biopartner, everything that once was has already disappeared. For 16 years, Flanders has had an instrument to help companies get through the first phase, which is linked to the growth of employment in Flanders. If you do not grow, it becomes increasingly harder to get subsidies as a company."

Onno van de Stolpe, CEO Galapagos

(Quote from interview on June 11, 2009)

Instrument of the Institute for the Promotion of Innovation by Science and Technology in Flanders (IWT)

Like in many regions, Flanders has a government policy to stimulate innovation. The central organization for implementing this policy is the Institute for the Promotion of Innovation by Science and Technology in Flanders (IWT).

IWT supports (among others) RTD projects for industrial research activities, projects for industrial development activities, and projects for strategic basic research of industrial relevance.

The RTD projects for industrial research or for industrial development are submitted by industrial enterprises. These are the so-called "bottom-up" projects, with no limits on scientific or technological discipline. This bottom-up approach has significant advantages. The most important one is that the program is open to all sectors and is not dominated by "top-down" choices. Another important feature determining its success is the continuity of the IWT instruments. Because the instruments for RTD projects exist for a very long time, and the conditions have hardly changed, the companies know what instruments are available, are familiar with the conditions and the procedures, and are able to incorporate it in their strategic planning.

With respect to start-up companies and small SMEs, IWT has a sharp eye for the potential for economic growth of companies. A requirement for continued funding is that starters and small SMEs do grow. In this way IWT, is favorable for successful companies and not for those with an "arrested development".

Source: www.iwt.be

Valorization in the university medical centers of the Netherlands: Conditions and regulations for transparency in conflict of interests

All commercial development by definition carries the risk of conflict of interest between the public and the commercial stakes. The Dutch Federation of University Medical Centers (NFU) has agreed on a framework for valorization and commercialization of research findings. In the brochure *Naar een goede waarde*, UMCs generally agree that valorization is a social need because knowledge and expertise need to be used, and not stay "on a shelf". In the brochure, the NFU describes the conditions and agreements for commercial valorization. Since the UMCs endorse the stimulation of the use and application of knowledge, they acknowledge potential conflicts of interest that may arise when exchanging public-private researchers. In order to enhance transparency on this issue, they present essential conditions for UMCs such as:

- A clear structure of responsibility (signaling, judgment and decision taking) in the UMCs to deal with conflicts of interest (conflict of interest code);
- An up-to-date code of scientific integrity;
- An independent system of examination/qualifying research projects to be carried out with commercial parties;
- Control of financial incentives such that integrity and public interest are not overruled by commercial interests;
- Additional supervision where normal procedures do not apply;
- Transparency on all commercial activities and choices in publications or public statements.

Source: NFU, Naar een goede waarde, July 2009

- Include stakeholders from society and the business world structurally in the theme selection and development process. Organize platform activities for stakeholder discussions.

2. **In order for large companies to utilize the new research findings of universities, their "absorptive capacity" needs to be up to date.**
   Our concrete recommendations are to:
   - Invest in post-academic education and decide on the specific themes in agreement with stakeholders;
   - Extend the mobility programs for public-private exchange of researchers (Casimir, academic practice ateliers, etc.). With this exchange, university researchers can obtain a better knowledge of the type of problems companies or specific public authorities have and vice versa: researchers from industry get the opportunity to stay up-to-date on developments at the forefront of scientific developments. At the same time one should acknowledge potential conflicts of interest.

3. **The contact between universities and SMEs should be intensified, in order to stimulate technology transfer to SMEs and realize valorization of research findings by companies other than those involved in PPP and existing bilateral contacts.**
   We recommend:
   - One information desk at each university should be installed for SMEs so they are able to easily (find and) approach the university with their knowledge requests;
   - Application projects should be initiated together and in agreement with regional innovation centers (with budgets from these centers) to translate knowledge to application for SMEs.

Additional policies to be implemented by government and research councils

The national government and research councils can play an important role in the realization of the valorization goals set out for 2020. This can be accomplished by using a combination of the following types of innovation policy instruments.

1. **Public policies and governance.**
   Clear agreements between the national government and universities about their "third mission". by means of contracts and accountability (evaluations and indicators).

2. **Investments: strengthening investments in excellent public research and valorization.**
   - An excellent science base is a crucial breeding ground for new economic activity, and improvement and realization of public needs. It is recommended to

> "The continuity of the PPP set-up should be better safeguarded by the government. In the Hague, people must realize that investments in a serious research program must be made for at least 10 years (to have it take the lead) and once it is in the lead, to invest again (to keep it in the lead)."
>
> **Anne Flierman, Chair of the Board of Governors, University of Twente**
>
> (Quote from interview on July 13, 2009)

increase the investments in research in accordance with the Lisbon goals;
- As the FES funds provide impulse support, these resources should be spent on the basis of a long-term national strategic agenda for the life sciences (10-12 years with firm midterm review);
- Sufficient funding for valorization is needed in order to allow universities to implement their mission of knowledge transfer: the budget each university received from the government should be raised by up to 2.5%. After several years, the amount of funding will be monitored and adjusted on the basis of valorization output;
- Sufficient financial support should be given to pre-seed and seed capital initiatives needed to bridge the equity gap that a company faces between exiting the university and being able to attract private funding.

3. A long-term commitment to and consistent policy for valorization.

A set of integral valorization instruments according to the IWT (see box on page 240) should be installed that cover each stage in the valorization chain. They are related to the long-term research programs.

4. Proper legislation for company creation, company growth and attracting foreign companies.

- Tax benefits for companies such as expansion of the WBSO, exemption of royalties for companies (like in Belgium) and reduction of the corporate tax to develop business will stimulate company investments in R&D and attract foreign companies to the Netherlands, thus improving the national industrial base;
- A rapid introduction of the Green Card for Europe, and more simple regulation for attracting scientists from abroad is instrumental for success.

5. Finally, governments can boost innovation in the life sciences by means of public procurement and acting as launching customers, for instance in the field of biomass-based products.

To conclude, only through a structural and long-term valorization national policy that integrates the elements presented above, can our vision for 2020 of valorization in the life sciences become a reality!

“ My biggest worry is that Boards of Governors now, with second generation Technology Transfer Offices, make the same mistake that they did in the 90s, that is, that they come to expect that knowledge transfer is a sport where you can earn money as a university. Knowledge transfer into society is a core activity of a university and you must accept that it costs money. Valorization is not a cash cow. ”

Eppo Bruins, Director of Technologiestichting STW

(Quote from telephone interview on June 10, 2009)

“Considering the wish for more structural interaction between industry and academia, the government must – via an attractive business climate – ensure that the knowledge that is generated in the Netherlands is also actually further developed and applied here. This also means that the government must make our country (more) attractive for foreign knowledge workers and students: the Netherlands teeming with knowledge! ”

Douwe Breimer, Pharmacologist, former Rector and Board Chairman of the Leiden University

(Quote from telephone interview on June 25, 2009)

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Authors

Wiebe Bijker, Professor of Technology & Society at the Maastricht University
Frans Brom, Head of the Department of Technology Assessment at the Rathenau institute in The Hague
Rob Hoppe, Professor of Policy and Knowledge at the University of Twente
Atie Schipaanboord, Director of Policy and Innovation of the Federation of Patients and Consumer Organisations (NPCF)
Erica Terpstra, Chair of the Dutch Olympic Committee (NOC*NSF)
Annemiek Nelis, General Director of the Centre for Society and Genomics, Radboud University Nijmegen

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Social aspects

The social aspects of the life sciences in 2020

IX Social aspects

A. Introduction

In recent decades, science and technology have had an increasing impact on society. This impact is beneficial when you think of increased health, increased mobility, increased safety (from natural disasters, for example). However, science and technology also produce new risks and vulnerabilities; examples include the toxicity of new chemicals, risks of large technical system failure or ecological damage. New scientific and technological developments therefore often cause public reactions: positive hype, negative fear or debate. Examples range from food additives to GM food and the radiation risks of mobile phones.

Scientific and technical developments are increasingly (though not always) accompanied by public reaction or debate. The virtual ban on GM foods is often cited to illustrate the damage that can be done by not taking public worries seriously enough. Current investments in public dialogue on nanotechnologies show how the Dutch government is trying to do better. The case of the radiation risks of mobile phone masts is an example of a technological development that initially seemed good to society, but which later became cause for debate and even worries among public and experts. In these cases we see a clash between our evolving *knowledge society*, marked by exploiting the benefits of science and technology, and our *risk society*, marked by coping with the risks and side-effects of science and technology.[1]

Social science research is needed to better understand the interactions between science, technology and society; to chart the shifts in depicting our society positively as a knowledge society or negatively as a risk society; and to better deal with sudden changes in public appreciation from hype into fear or *vice versa*. Such social science research also helps design better interactions between a broad range of stakeholders, experts and members of the general public.

The key message of this chapter is that there can be no viable innovation without its acceptance in society: science and technology only function when they are well entrenched in society. And for such adequate embedding of innovations in society, research into the social aspects of specific scientific and technical developments is necessary. With the insights of that research, we then can proactively design adequate forms of dialogue, public debate and interactive forms of development. All these elements should be part of the core business of PPPs that try to move the life sciences into the 2020s.

This chapter thus presents three closely related messages:

1. **Research** into the social aspects of life sciences, also in 2020, is indispensable for a strong life sciences sector;
2. **Organized interactions** – participation, engagement, dialogue and education – with and between different stakeholders and civil society are necessary for a democratic and thereby sustainable development of the life sciences and technologies;
3. **Good governance** of social issues surrounding life sciences innovation requires the facilitation of checks and balances between different types of knowledge, discourses and views.

Together, these activities – research, interactions and good governance – are indispensable for the social entrenchment of life sciences innovations. Without such, innovations cannot be sustained.

“ **We need solid information and good education**

To me, it is beyond a doubt that public acceptance of life sciences innovations is crucial to whether such innovations will actually be used and produced. What we should avoid at all times are unrealistic promises and expectations and we should use solid information to rigorously refute Frankenstein stories that in no way relate to what is really happening in the life sciences. The benefits of life sciences innovations can be high, alleviating pain and suffering, for example, in seriously ill populations. But one mouse with an ear on its back seems to have more impact than 100 serious articles.

It cannot be repeated enough that scientists need to pay due attention to their communication with society. This includes communication with media, politicians and future teachers as these actively shape the different forms of knowledge and images that we find in society. And don’t forget the young generation!

Communication thus is not an additional task for the life sciences but should be an intrinsic part of it. Scientists have a responsibility to provide good information and to reflect on the social aspects of their work, even if this is complex and if it is uncertain what future results may yield.

The social sciences and humanities, in turn, should critically assess what are the issues at stake in life sciences innovations. They should enable good communication about these issues and allow for well-informed and inclusive discussions and debates. Innovations only are viable when they become embedded in society. In that sense, there is still an entire world to win over. ”

Erica Terpstra, Chair of the Dutch Olympic Committee (NOC*NSF) and former Chair of the Standing Committee on genomics in the Dutch Parliament

Photographer: Julia de Boer

Quote from Erica Terpstra

B. Social aspects of the life sciences

What are social aspects?

Over the past decades, attention for the *social aspects* of newly emerging and converging sciences and technologies – such as genomics, nanotechnology, biotechnology, bio-nanotechnology and other innovative technologies – has become an almost natural component of science and technology development.

What do we mean when we speak of *social aspects* of the life sciences? Asking this question to a random group of (life) scientists will generate an array of answers. Where one scientist will define it as a matter of public communication *(the public does not completely understand what we do)*, another will mainly refer to ethical concerns *(how far are we allowed to go in intervening in life?)*, or rather to legal, practical and/or organizational problems *(do participants in biobanks also have the right to obtain research results, and how can this be arranged?)*. These answers are all relevant, to be sure, but they also reveal that the social aspects of the life sciences are diverse and multifaceted.

Background of ELSI/ELSA research

The introduction of the term ELSI is historically tied to the Human Genome Project (HUGO). During his installation as director of HUGO, James Watson, who in 1953 together with Francis Crick elucidated the structure of DNA, rather unexpectedly announced that the ethical and social aspects of this research required special attention and that 3-5% of the National Institutes of Health budget would be spent on social issues involved.[2] Others followed the example of Watson, and the Human Genome Project invested generously in academic research into the social aspects of genetics and into educational projects that familiarized citizens with the pervasive presence of genetics in tomorrow's world.

Interestingly, as a concept ELSI (or ELSA, as is more common in Europe) is used more and more to refer to social study of innovative technology in general, rather than being limited exclusively to genetics or genomics research.[1,3,4]

Research into the social aspects of the life sciences is often called ELSA or ELSI research, which refers, respectively, to innovative technology's Ethical, Legal and Social Aspects or its Ethical, Legal and Social Impact. ELSA research is performed by social scientists (technology scholars, sociologists, psychologists, communication experts, etc.), philosophers (ethicists, theologians), political scientists and legal experts.

In this chapter, we will systematically use "ELSA" as shorthand for scientific study into the ethical, legal *and* social issues and the interrelated activities aimed at education, public debate and dialogue, and interactions between stakeholders and life scientists. ELSA thus includes both analyses and critical reflection (what is the issue, what is at stake) and activities to discuss and interact about issues with different parties.

ELSA typically includes:

- The identification of (ethical, legal and social) issues;
- Interpretation and analyses of these issues;
- Organized interaction and dialogue with stakeholders (including publics);
- Interaction between policy, politics and professional practices;
- Development of new forms to organize the governance of ELSA issues;
- Evaluation of the design and development of the governance of ELSA issues.

While this list may suggest there is a certain order to the activities, this is not necessarily always the case. Interactions may lead to new research questions concerning a particular ethical, legal or social issue and vice versa.

In the next section we will further explore the aim, task and use of ELSA research. This section will continue with discussing what are the social issues concerning the life sciences.

The interrelationships of science, technology and society

The application of new knowledge and technology has not only made our life more enjoyable, efficient, healthy or prosperous; it has also changed our habits and lifestyle, as well as our views and normative frames for judging the world. For instance, the development of the contraceptive pill has contributed to a new sexual morality; large-scale application of prenatal diagnostics has contributed to acceptance of abortion among certain groups; and the development of alternative sources of energy has raised our collective awareness of changes in climate and the environment.

Does technology automatically steer our society in particular directions, including the individuals who are part of it? Things are slightly more complicated than that, because society has a major influence on technology development as well. Research priorities are partly triggered by questions about social issues and are realized in a process in which various parties – such as governments, social organizations and advisory bodies – act as representative of particular public interests. In the public domain, debate and dialogue take place that in part shape science and technology development. In many cases, public debate even functions as a major catalyst: it causes particular developments in research either to *accelerate* or to *decelerate*. While examples of deceleration – such as nuclear energy, GMOs and the sinking of the Brent Spar for example – are mostly well known, acceleration is also common. Developments in forensics research are a case in point, as will be shown in the next paragraph. Importantly, a catalyst itself does not change in the chemical process; it remains unaltered. The metaphor, then, does not apply fully: the nature of a public debate is altered of course as soon as its content changes.

In recent years, calls for *tough policies* against crime and delinquency have increasingly become common in public debates. In this context, DNA study is often presented as irrevocable proof (even if this is not always true). Cases that receive a lot of public attention and about which there is great public outcry and concern – such as the murder of Marianne Vaatstra in a village in the province of Groningen, in which the initial suspect, an asylum seeker from a nearby refugee center, proved to be innocent – have contributed to social support for expansion of criminal investigation methods. As a result of this case, the Netherlands became the first country where it was *legally* possible to determine the appearance of perpetrators – hair color, eye color, origin – on the basis of DNA material.[5] Although the options for applying this method are *technically* still quite limited, its legal adoption has already stimulated more study of forensic techniques. Another example of accelerated development is given by Steve Epstein in Impure Science.[6] Epstein shows how in the 1990s, AIDS activists pushed for accelerated admission of AIDS medication in clinical trials, thus bringing about a change of regulation.

The abovementioned examples show how science and society mutually influence each other, or, as social scientists call it, *co-construct* each other: developments in science coincide with developments in society. This may imply that knowledge and technologies are developed less rapidly, for instance because their social consequences are unclear or because major parties in society reject a certain development (for the time being). But the reverse is also possible: in some cases, social parties and social developments in fact call for accelerated deployment of knowledge or technology. Both the pace and direction of innovation may need to be *fine tuned* in order to be in line with the social conditions, expectations and opportunities involved.

The concept of co-construction does not only provide an angle for *understanding* the dynamic relationship between science and society; co-construction of science and society may also be actively shaped to enable a better handling of knowledge and innovation. This process of *coordination* between science and society is geared not so much towards creating a social base or public support; rather, it is aimed primarily at creating alignment between specific social institutions, conditions and expectations, on the one hand, and new technological possibilities and promises on the other.

Social issues in 2020

How will the life sciences affect us in 2020? Science and technology increasingly are complex processes, incorporating both scientific and social trends. The transition towards a bio-based economy or poultry farming organized by genetic selection – to use two examples from this volume – requires a transformation of habits and lifestyle, the chain of production, and our attitudes towards energy, mobility and meat consumption. This raises a whole series of questions and it is unclear what will emerge as the main social issues. This has become less and less easy to foresee:

- It is characteristic of recent discussions that topics are complex in a scientific-technical sense. **Example:** *the convergence between biotechnology, nanotechnology, information technology and new technology based in cognitive sciences. This brings together expertise and knowledge from different paradigms and leads to new approaches and bodies of knowledge*
- Social issues increasingly are (connected to) technical and scientific issues. **Example:** *the issue of "ownership". This is connected to questions of open-source and intellectual property rights, biobanks and the use of bodily material, indigenous species and bio-piracy, the use of DNA in court cases and scientific publishing*
- In public discussions, one increasingly is looking for methods that avoid black-and-white contradictions and possible deadlocks. Undoubtedly this also leads to the clouding of political discussion and to results and choices that are not very transparent. **Example:** *the discussions on the widening of PIGD and the freezing of egg cells. These discussions are not just geared towards either an outspoken "pro" or "con", but rather towards the (prior) conditions and circumstances under which these developments would be acceptable*
- In a normative sense, there are multiple voices. It is hard to predict in advance which positions parties will take. On top of this, it is unclear what role religion will play in future issues and debates
- Social issues do not necessarily always affect the public directly. **Example:** *the discussion on breeders' rights and patent rights. This discussion is about access to genetic material and whether it impedes innovation, and this pertains to the business sector, government and universities alike*
- Scientific expertise does not always equal authority, since social issues cannot be reduced to techno-science. For one, scientists do not always agree with each other; nor do we expect them to agree with each other at all times. **Example:** *discussions on climate change or biofuels and the question of whether these are an effective source of alternative energy*. Differences in scientific insights increasingly have become publicly visible and as such have enriched many a debate. However, this trend also shows the uncertainty and diverse character associated with science and technology development

While it is difficult – if not impossible – to predict what the social issues will be in 2020, it is possible to say something about the *nature* of these issues. They will be complex, include multiple questions, address not just the general public (but also industry, scientists and governments), resist simple solutions and mobilize ad-hoc coalitions and spokespersons. As the example of ownership illustrates, issues are not necessary life sciences topics, but are typically issues that require knowledge and understanding of the life sciences. This is exactly what ELSA has to offer.

Dealing with social issues in a sensible way is crucial for the social entrenchment of life sciences technologies. ELSA thus does not aim to avoid issues or prevent them from emerging, but rather aims to allow the *right* issues to emerge, and to use this to improve the quality of innovations and their embedding in society.

C. The contribution of ELSA

ELSA research

The task of ELSA research is twofold. First, it aims to contribute to the theoretical development and understanding of the relationship between (life) sciences and society by asking fundamental questions about this relationship. Second, ELSA research aims to shape and facilitate the relationship between (life) science and society by organizing different forms of interactions and interventions in order to anticipate (emerging) social issues connected to scientific developments. These tasks relate to one another in a productive tension (between critical analyses and interactive design). ELSA research thus can be said to uncover the different and multiple meanings, expectations, forms of knowledge, discourses, opinions and interests related to science and technology development, and, if possible, to confront them with each other. The first part of this task focuses mainly on (fundamental) research; the second requires interaction and intervention with different parties. In the following, we will first explore what we mean by different and multifaceted expectations, framings and discourses and how to anticipate future impacts or effects of science and technology. In the paragraph that follows, we will discuss the interactive design of ELSA research.

Multifaceted developments considered more closely

The starting point of ELSA research is the multifaceted character of developments in the life sciences and how they are addressed. As we will show, the issues we are faced with, as well as the solutions offered by the life sciences, are more ambiguous than commonly represented – also by the authors of this book. This is hardly surprising. The life sciences and social sciences or humanities are different disciplines that have different tasks. We will return to this point later in this chapter, when we discuss the organization and governance of ELSA.

Developments in the life sciences, as described in this volume, will influence our life more and more. In 2020, the life sciences will provide a substantial contribution to major and urgent questions, problems and opportunities in the fields of health, the climate, energy, food distribution and the environment. This book sketches the contours of a world in which energy is no longer derived from fossil fuels, our food pattern will come with fewer animal proteins and be more tailored to our body's specific needs, and the health of an ageing population is monitored at regular intervals. In other contexts – advisory reports, corporate websites, brochures, presentations, documentaries, articles newspapers and weeklies – we find the same promises and we are told that the life sciences address the most pressing and urgent social issues.

There are few people who will deny that the climate, energy, food issues and health pose important future challenges and are therefore worthy of our attention. However, the issue of how these subjects ought to be addressed and which solutions or contributions are needed is much harder to answer. In many of these cases there is no consensus. Urgent social problems are linked to quite diverse solutions. Moreover, in this discussion, different figures, facts and data tend to be used as evidence. We illustrate this point with the example of the global food problem in the box: "The global food problem as an example of shared goals & multiple evidence and solutions".

The parties that we describe in the box – the Minister of Agriculture, Monsanto, plant researchers and NGOs such as Greenpeace – agree that the development of new agricultural knowledge and technologies cannot and should not be limited to national borders. The Netherlands is co-responsible for world food distribution. How this should be arranged by government, science, industry and social organizations is less evident, however.

For example, parties are fighting over whether GMOs offer the right solution and which risks or socio-economic effects

The global food problem as an example of shared goals & multiple evidence and solutions
In discussions about the global food problem it is usually assumed that in 2050 the world population will have climbed from 6.8 to 9 billion people. This growth perspective can be heard in many discussions about the life sciences, often represented by the same figures yet from a different angle.

Recently the Dutch Minister of Agriculture argued for a new evaluative frame for GMOs during a meeting in The Hague. It should focus not so much on the safety of GMOs, but on the question of whether and how GMOs may contribute to sustainable agriculture. A major element of sustainable agriculture, the Minister claimed, is its contribution to solving the global food problem. By making use of GMOs, acreage can be used more efficiently, the certainty of harvests can be raised and it becomes possible to use land – such as with saline or dry soils – where before crops did not grow. **To be able to feed all 9 billion mouths in the future, the Minister argued, a new evaluative frame for GMOs is necessary.**

Science and technology, including possibly GMOs, play a major role in the chapter on agricultural life sciences in this book. Here too arguments around efficient use, harvest certainty and new acreage come into play. However, its authors underscore the significance of investments in research, rather than a new evaluative frame. **To feed all 9 billion mouths in the future, according to the authors of the agricultural life sciences vision of this book, research is inevitable.**

In 1997, Monsanto decided to sell its chemical division and focus exclusively on the life sciences. The then director Shapiro explained this step as follows: "We create a new kind of company that concentrates on meeting the worldwide need for food and health" (cited from de Vriend and Schenkelaar, p. 25).[7] In recent discussions on the question of whether patent law would annul breeders' rights through a backdoor, a situation from which large companies seem to benefit for the time being, Monsanto stresses that it has to earn back returns on its investments through patents. **Only in this way, according to the spokespersons of Monsanto and other large companies, it will be possible in 2050 to feed 9 billion mouths.**

NGOs such as Greenpeace and Solidaridad are probably no less concerned about the world food problem than Verburg or the scientists at Monsanto. However, in their plea GMOs are not automatically the solution to the global food problem. "Food security will not be achieved by technical fixes, like genetic engineering (GE). People who need to eat need access to land on which to grow food or money with which to buy food. Technological 'solutions' like GE mask the real social, political, economic and environmental problems responsible for hunger" (www.greenpeace.nl). Poverty, the lack of acreage for poor farmers, unfair trade regimes and disproportionate attention for industrial agriculture are much more important causes. **Small-scale agriculture and attention for these problems contribute to the possibility in 2050 of feeding 9 billion mouths.**

are involved. Moreover, they use the food distribution issue to argue for other things: a new evaluative frame (the Minister), patent rights (Monsanto), research funds (scientists), biological agriculture and assistance to small farmers in developing countries (NGOs).

When we look at the applications of the life sciences, we also find profound differences in how these are framed and valued. Life sciences innovations may lead to pressing questions about their use and value. Which innovation should be applied for what purpose? It is impossible in our pluralist society to give a single answer to this question. It will be no surprise that here, too, we are dealing with a wide array of opinions, views and perspectives. These partly involve ethical questions. For instance, if one party considers the use of embryos for stem cell research a chance to cure people who suffer from serious, untreatable disorders such as Parkinson's, others will dismiss such a proposal as an outright violation of the "right to life". Next to ethical or moral differences, there are also differences of interpretation that flow from a difference in focus or perspective. For example, biological meat production is regarded by many as an important contribution to sustainable animal husbandry; others stress that biological production requires more feed and is generally less efficient. Whether or not something involves a sustainable solution depends on the comparative basis involved (sustainable as relative to what?).

What should we conclude from all of this? Although the same notions, concepts and goals are frequently used, such as environmental problems, climate change, health benefits and sustainability, it is evident that they do not always have the same meaning. These terms and concepts are *seemingly* clear and unambiguous, but they actually disguise the pluralist meanings and stakes we encounter in everyday practices. Meanings, rather than being objective or neutral, are always moral and political.

INTERMEDIATE CONCLUSION The seemingly transparent concepts and goals used in discussions about the life sciences disguise the plurality of meanings involved. ELSA research aims to uncover this plurality.

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Anticipating impacts or effects of the life sciences and technologies

Science and technologies are not merely used to solve or address social issues and concerns; they contribute to the emergence of new questions, issues and problems. We are living, according to Ulrich Beck, in a "risk society".[8] The risks that pose a challenge to modern societies are no longer determined by fate – such as natural disasters like storms, droughts and floods – but rather originate in the application of manmade science and technologies. The paradox of today's world is that it is faced with "mega-dangers or hazards that are on the one hand created by society itself, but on the other are neither attributable nor accountable nor even manageable within society" (cited from Strydom, p. 59).[9] It is also true for the life sciences that the knowledge and techniques we deploy in the next ten or twenty years to solve social issues and problems also result in a number of unknown and unplanned consequences.

There is much speculation as to the future social, ethical and legal effects and impact of developments in the life sciences. At an *early* stage, ELSA researchers, but also novelists and the media, try to anticipate the unknown and unplanned consequences of science and technology development: who is affected by new developments, who benefits from them, but also who or what will suffer possible adverse effects or even harm? The objective of early anticipation of social consequences of developments that have not yet crystallized is to push developments in a socially desirable direction.[10,11,12] ELSA research, we may say, functions as an early warning, indicating what social issues may become relevant or contested in the future.

One way to address future consequences of life sciences developments is through "future images". Through scenario studies, foresight exercises, risk analyses, Delphi-methods and real-time technology assessment, scientists – often together with stakeholders – try to reflect on technological futures. This goes beyond extrapolation of current developments and is actively aimed at desirable futures. Interesting examples can be found in the field of nanoscience. Also in the life sciences, as developments will become more complex and uncertain in terms of applications and effects, such exercises will be increasingly needed.

Promises and expectations, if broadly accepted and subscribed to, push the process of science and technology development into specific directions.[13] This is true both for the promises of life scientists as for the future images created by ELSA researchers. Promises and expectations thus guide future actions and therefore need to be relevant and somewhat realistic. However, sometimes promises are not realistic at all and this too may serve a purpose. This may be a warning, an attempt to frighten people, or an intervention to make developments go into a different direction. A critical analysis of promises, projections and expectations is part of the ELSA agenda. What do promises do? Can we assess the quality of a particular promise? Which promises does ELSA research produce? How do scientists themselves relate to specific promises?

Setting the agenda

Through the anticipation of unknown social consequences, ELSA aims to identify issues and problems that need to be addressed to improve the social entrenchment of the life sciences and technologies. ELSA scholars, from time to time, put issues on the agenda before others have done so and before these have become an issue in the public domain. But, unlike what life scientists sometimes suggest, ELSA is not capable of making an issue public if this is not supported or picked up by others. ELSA can only help put issues on the agenda.

When ELSA identifies problems that should be addressed – as in the case of nanotechnology[14,15,16,17] – this is something to heed. What are the risks associated with new technologies? Which social sensitivities, concerns and worries perhaps play a role at a later stage? Who is concerned about what issue? Where may we expect resistance or support? In short, the work of ELSA researchers establishes which problems, issues and questions may come into play in the future. Naming them provides *insight* into future issues and possible problems and enables their anticipation.

ELSA activities

We have shown that promises and statements around the developments of the life sciences are hardly neutral or unambiguous; rather, they imply a large number of assumptions, choices and perspectives. We have argued that one of the tasks of ELSA researchers is to reveal these differences and to confront, contrast or bring them into line with each other through interactions and interventions. The aim of these interactions is to help shape the social entrenchment of the life sciences. This, then, is done by organizing a confrontation between the different types of knowledge and discourses that are brought to bear on the risks and uncertainties concerning the life sciences. ELSA research, we might say, aims to facilitate the right "checks and balances".

Facilitation of checks and balances

The concept of "checks and balances" originated in 18^{th} century political theory and practice. Applied to political governance in constitutions of all democratic regimes the world over, it is still a vital method to keep single individuals or (interest) groups from becoming too powerful.

Organizing checks and balances is based on a combination of functional separation and sharing of powers. Usually, governance *powers are formally divided* between three branches or entities of government: the executive, the legislative and the judiciary. Equally important in this doctrine of *trias politica* are *mechanisms of formal and informal power sharing*. Essentially, each branch of government has some control over the actions of the other two branches. In this way, the separate branches are empowered to prevent actions by the other branches, but induced to share power at the same time.

Thus, the *checks* attribute to each power the right and actual possibility to monitor and evaluate the decisions and actions by the other branches. We encounter this idea in modern governance often as the transparency requirement; or, in legal terms, the right to be informed. The *balances* part confers on each branch or entity the resources, authority and powers to limit the resources, authority and powers of the others. Jointly, these checks and balances define a control mechanism that guards against abuse of power. For example, the executive (government, cabinet) has the right to propose policy or bills and direct their implementation; but the legislative (parliament and other representative bodies) has the right to approve, reject or amend such proposals, the right to give or withhold funding, and to formally evaluate modes and results of policy implementation; the judiciary may declare executive (and sometimes even parliamentary) decisions as unconstitutional or as contravening administrative laws and principles of good governance.

Applied to the field of the life sciences, ELSA research *facilitates* the right checks and balances between other players. ELSA research and other scholarly activities involve not just inquiry into the ethical, legal and social aspects of distinct innovations and technologies. Moreover, and *unique to the ELSA perspective*, it envisages and conceptualizes the entire governance of an innovation system. By critically examining the relative influences on this system of science, business and government and posting early warning signs on certain phenomena, events, trends and developments, the ELSA perspective contributes to and facilitates good governance of life sciences innovation by enabling the other players to achieve a proper set of checks and balances. Of course, as a *method of "empowering"*, ELSA research and scholarship can never achieve this alone; it clearly depends on dissemination and reception of its messages through fruitful boundary arrangements with the other more powerful and resource-rich players in the field – especially business and government. Yet, good governance is not just about powering and preventing abuse of power. It is also a matter of *creative puzzling*.

INTERMEDIATE CONCLUSION The unique contribution of ELSA research and scholarship is in the uncertain part of the good governance of innovation: its (early) warning signs provide creative confrontations between valuable perspectives on life sciences innovation that will increase these innovations' sustainability. !

The role of ELSA within the life sciences is facilitation of the proper *checks and balances*. Parties are thus actively involved in various ways. They are

- **informed** of developments in the life sciences;
- **consulted** on knowledge, views, fears and expectations;
- **mobilized** to participate in discussion, dialogue and decision-making on the application of new knowledge and technology.

Facilitation of the proper checks and balances offers no guarantee for the solution of problems or an effective tackling of issues. ELSA research stimulates the creative confrontation of different perspectives, for example in debate and dialogue, but it can only do so when others join in as well. Creative confrontations may concern particular segments of the public (such as patients, consumers, parents, citizens or students), stakeholders (industry, NGOs, citizens, professionals, retail), scientists (the life sciences as well as social sciences and humanities) as well as those from policy and politics (administrators, finance experts, legislators, decision makers or members of parliament). Diverse groups contribute variously to the articulation of a multiplicity of ideas, expectations, notions and goals around the life sciences. While we often make use of simplified distinctions, such as that of experts, policymakers and citizens, these categories in fact refer to a wide diversity of groups and individuals. In the following, we focus in particular on interactions with the public and with policy/politics.

Interactions with the public

The general public, ranging from citizens to workers in laboratories, plays a major role in the development of science and technology. People are confronted with the applications, and hence the risks, unplanned effects and benefits of life sciences developments. Furthermore, the general public in democratic societies is entitled to join in decisions on public matters. In the context of the life sciences, this means that citizens have indirect decision power (through elections) or direct decision power (as consumer, patient or citizen). The public forms an important check or counterbalance: “Expertise is constituted within institutions, and powerful institutions can perpetuate unjust and unfounded ways of looking at the world unless they are continually put before the gaze of laypersons who will declare when the emperor has no clothes” (cited from Jasanoff, p. 397-98).[18]

It is often argued that, to be able to join decisions on public matters, it is essential that citizens have access to information, (various forms of) knowledge and expertise. Both ELSA researchers and life scientists have an obligation to provide such information and, related to this, education and communication. Various different examples are available to achieve this, such as:

- Education at schools (competitions, websites, workshops, internships and site-visits);
- Training (young) scientists to communicate (even better) with various public about their field;
- Public meetings and discussions with scientific experts and other stakeholders;
- Entertainment, festivals and exhibitions;
- Films, books and documentaries.

The availability of information and education is a prerequisite for the public to understand and evaluate developments in the life sciences. However, providing information and education about life sciences developments is not a goal in itself. It aims to empower citizens to assess and counterbalance different forms of expertise. Experts and the knowledge and information that they provide – life scientists and ELSA researchers alike – have their own biases. “Public engagement is needed in order to test and contest the framing of the issues that experts are asked to resolve. Without such critical supervision, experts have often found themselves offering irrelevant advice on wrong or misguided questions” (cited from Jasanoff, p. 397-98).[18]

Public engagement or public participation exercises may take different forms at various levels. The key to public engagement is that the public is actively involved in some issue. This applies to more than just an exchange of ideas and points of view. In many cases it calls for the organization of genuine dialogue. The results may vary: organized interactions may contribute to the exploration of difference and the formulation of possible directions for solutions. Interactions may be aimed at a) shared study of issues; b) exploring differences in views and/or perspectives; or c) formulation of shared frames, rules, solutions or visions. In some cases (consensus conferences, stakeholder meetings) participants are explicitly asked to develop a shared point of view. In other cases the conclusions may well reflect the various input, but a single conclusion or consensus is not pursued.

More important than the actual organization of public engagement activities is the framing or the context of engagement activities. The facilitation of the right checks and balances primarily asks for an analysis of *who* participates, who determines the *agenda* and what is the *aim* of the event.

Framing the debate

Social issues concerning the life sciences may affect the public, industry, scientific experts or government regulators, to name just a few parties. How these issues are addressed and who is allowed to join the debate cannot be derived automatically from an issue itself. Who may join a debate about some issue and – perhaps even more importantly – who decides on its topics are part of the dynamic and debate around technological innovation. A case in point is the debate on Food and Genes *(Eten en Genen)* that took place in 2002. This debate, organized by the Terlouw Commission, was criticized by a coalition of the Dutch branch of Greenpeace and 14 other Dutch NGOs. In a press release they claimed that they very much welcomed public debate, but that it should be based on an open agenda. The debate's main goal was to clarify under which conditions the application of modern gene technology in food production would be acceptable to society. According to Greenpeace and the other NGOs, this was too limited a question: "The fundamental question of **whether** gene technology is desirable and necessary at all does not seem at issue. We are only allowed to talk about **how** it is to be applied" (cited from de Wilde et al, p. 66).[19] At a recent meeting in The Hague, organized by the Dutch Minister of Agriculture, a discussion erupted on the 2002 debate's agenda. In her opening speech, the Minister indicated that as far as she was concerned the question "do we want GMOs?" was no longer relevant. In feed, cotton and other products, she argued, so many GMOs are used already that there is simply no way back anymore (NRC Handelsblad, June 10, 2009). Reactions from the audience and also in the various workshops revealed that many people disagreed. Attempts to put this on the political agenda were to no avail, however.

The question of who or what sets the agenda for public debate is not just limited to the debate's topic. Part of this question is also which arguments in the debate are considered valid. Emotions, for example, tend to be pushed aside as unfounded, not objective (hence, subjective) and therefore "invalid".[20] Thus it is ignored that precisely emotions may have a major effect. The British minister who during the BSE crisis offered his daughter a hamburger in front of the TV cameras to prove that eating beef was not a risk has become legendary. It led to major public and even media distrust. What this incidence showed is that the public, in these cases, is always right. The public uses different forms of evidence to establish whether British beef is safe or not. It is the *effect* of this process that matters (to British industry and farmers for example). Emotions have a large influence on social perception, acceptance and therefore also the uptake of new developments.

Finally, the stakes of the debate are important as well: what, exactly, is the purpose of articulating views in the context of a debate? It should be clear from the start which interests are at issue. An example is the assignment of the recently established *Public Dialogue Nanotechnology Commission*. In its assignment letter to the Commission, the Dutch Minister of Economic Affairs writes that the Commission should make clear to the participants that they ought not to expect the government to "follow up on all outcomes". The Cabinet, the Minister points out, has the responsibility to weigh the issues on its own, even if it will also "deal very carefully with the outcomes of the public dialogue".[21] That the government does not follow up on all suggestions from citizens seems obvious. Conversely, the meaning of "dealing very carefully with" leaves ample room for interpretation or implementation.

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INTERMEDIATE CONCLUSION To allow for the richest possible review of the risks, benefits and implications of new technologies, the following questions are important:

- Who has the opportunity to join the discussion?
- Who has a say about the concerns addressed?
- Which arguments are considered to be valid? Which arguments are kept outside of the discussion (or should have to be kept outside of it)?
- What is the purpose of the discussion and thus what is at stake?

Policy interactions

A major critique of the American ELSI program of the 1990s is that it mainly generated academic output, but that the program has had little influence on policies. According to Michael Yesley, who for years was responsible for part of the ELSI program, it was used from the start "to avoid establishing an independent advisory commission, selecting topics of ethics research that will facilitate rather than challenge the advance of genetic technology, and spending ELSI funds on promotion in the guise of education" (cited from Yesley, p. 4).[22] The ELSI program, Yesley argues, was *uncommissioned* and it was also unclear who specifically was awaiting its results. It served as a pretext to be able to say that attention was given to the social aspects involved.

Others agree with Yesley that the ELSI program has had little impact.[2,18] However, the question is whether Yesley is right when he points to the "uncommissioned nature" as the main cause for the lack of impact of the ELSI research. Another possible cause for this shortcoming is that ELSA researchers have poorly succeeded, if at all, in linking up with decision makers.

Scientists and decision makers, according to Lomas,[23] often have a distorted image of each other and insufficiently recognize that both are part of an intricate but shared context. Implicitly, they confirm the image they have of each other: scientists deal with facts and truth, policymakers with values and power.[24,25] Scientists expect that decision making takes place in a specific setting and at a certain point in time. Likewise, decision makers expect from scientists that their results are ready available when they need them: "it is like two people completing a jig-saw puzzle, each with half the pieces but each working in a separate room" (cited from Lomas).[23] In practice, policy as well as research are pragmatic and context-bound. Both research and decision making are heterogeneous, complex and often take up much time.

More attention for what in the Netherlands we awkwardly refer to as "knowledge valorization" might increase the impact of ELSA research. An important aspect of the valorization of knowledge is early involvement of decision makers in both the overall process and the results of the research.[23,26] Experience with technology assessment (TA) underscores that this is no simple task. This experience "show(s) that just publishing the results of these quantitative and qualitative studies within academic journals will not lead to a big impact in the real world. To achieve that, the results need to be purposefully translated and communicated towards, for example, the policy arena or a wider public. Moreover, one needs to build personal connections with these different worlds to have an impact on these worlds" (cited from van Est).[4]

INTERMEDIATE CONCLUSION The relationship between scientists and policymakers cannot be shaped in an ad-hoc fashion. It requires intensive mutual exposure and interaction between scientists and decision makers. This exposure is needed for the actual use of research results in policy.

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D. Governance of ELSA research

Attention for the social aspects of innovative knowledge and technology is hardly new. This type of research has been performed since the 1970s from various angles, including bioethics, technology assessment (TA) and science and technology studies.[27] From the start of this century, universities, aside from doing fundamental research, have paid increasingly more attention to the *governance* of new, innovative and converging technologies and the question of how the expectations of the market, government, civil society and science can be aligned. This is what, in this chapter, we have called the facilitation of the right checks and balances.

The need for ELSA research and other scholarly activities that contribute to the good governance of new, innovative and converging technologies is not restricted to PPPs. These are only one place or setting where ELSA matters. While it can be argued that there are social issues that are perhaps pecifically relevant for PPPs, such as the analysis of bold promises to solve issues that worldwide are seen as global problems, these social issues, however, are not restricted to PPPs. The questions and issues that we have identified in this chapter are related to life sciences development and innovation in a broad sense. As we have shown, technology and society co-construct one another: technology, by implication, is *socio*-technology.

For technology to become embedded in society, both technical and social expertise are necessary. These are only partly separated domains. ELSA researchers have to be very knowledgeable about the technologies they study while life scientists, either through experience or interest, are knowledgeable about social issues. However, disciplines have different tasks. Scientists consider it their task to *develop* science and technology that contribute to the solutions of concrete social problems or issues. ELSA researchers and scholars also contribute to solving or coping with concrete social problems, but do so by questioning the (anticipated) *effects* of science and technology development. There is, then, a clear distribution of tasks between the life or natural sciences and the social sciences or humanities. Both bring different competencies, but have mutual interests and together their skills are complementary.[28] It is only together that these disciplines are able to improve the embedding of technological innovation.

Today, ELSA research of the life sciences is organized and funded in different ways, via single projects of individual research groups, small programs funded by NWO or the EU or sizable programs that are part of a PPP. ELSA research around genomics is, in a number of respects, the absolute priority. ELSA genomics is well funded, well coordinated, is visible in many contexts and it has led to a consolidated program. Within NGI, the social aspects of genomics are explored by the Centre for Society and Genomics (CSG) and the Genomics Centres of CMSB, Kluyver, CGC and CBSG. In the current round of subsidies for NGI (2008-2013), EUR 25 million have been earmarked for the social aspects of genomics. While other programs, such as the Leading Technology Institutes (TTIs), also pay attention to social aspects, they do so at a much smaller level and in a less coordinated fashion.

ELSA research of the life sciences requires coordination and a substantial investment. This will enable programs that consolidate different questions and approaches, are visible to life scientists, industry, politics and society and have the ability to have a substantial impact on the social entrenchment of the life sciences.

INTERMEDIATE CONCLUSION To make a genuine contribution to the life sciences, substantial research and public communication around the social aspects of the life sciences are necessary. Internationally, 3-5% of the life sciences' total budget is considered standard for ELSA.

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The need for a coordinated effort and a substantial budget does not necessarily imply that ELSA research should be organized in one single project or location. Rather, we advocate a pluralist approach. Characteristic of the way in which present and future societies deal with science and technology development is the existence of different forms of knowledge, norms, values, ideas and expectations. This is no less true for ELSA itself. ELSA research, the scholarly activities of ELSA and the institutions involved in this work are multifaceted: ELSA brings together different disciplines, views, approaches, experiences and interests. This pluralism is enriching and should not be reduced to a single type of organization. Different forms are needed:

1. Open calls

Open calls, such as the recently completed NWO program on "societal aspects of genomics", enable research that poses a range of questions and makes use of a variety of methods, approaches and themes. More importantly, open calls allow researchers to ask both fundamental questions and to use methods or approaches that are innovative, experimental and/or – theoretically or methodologically – "daring".

2. Commissioned programs

Commissioned programs are coordinated efforts characterized by producing focus and mass and providing a context in which specific questions can be addressed or where questions can be addressed in a specific way. With respect to PPPs, commissioned and coordinated programs can be either embedded in a PPP or be realized in independent programs with a critical distance from PPPs:

2.a Embedded programs

PPPs, as defined in this book, are collaborative projects in which partners from industry, government and universities work together on equal footing. The aim of PPPs, as we have seen, is to produce innovations that realize social and economic value. PPPs themselves have a responsibility to deal with the social aspects of their work. This may concern several things, such as the anticipation of and reflection on social issues and communication with the public, but also the public legitimating of PPPs. Since PPPs are set up with a majority of public funds, they are publically accountable for what they do. ELSA research may need to be embedded within PPPs as the place where mutual learning between ELSA research and the life sciences takes place.

2.b Independent programs

It is also important to acknowledge the critical function of ELSA research. Facilitating the proper checks and balances calls for a critical attitude with respect to, for example, the vested interests, the hegemony of scientific knowledge and the parties playing a role in creating innovations. If we take serious the assignment of ELSA research to address and confront the many different types of knowledge, promises and discourses brought to bear on the risks and uncertainties surrounding the introduction of life sciences, research should also be independent of PPPs. This does not eliminate the possibility of collaboration. However, it points to the necessity to have a part of ELSA research that is independently organized and funded. For this type of research, matching with industry is problematic, as the governance of ELSA issues in these settings requires critical and independent analyses of the types of knowledge, discourses, parties and institutions of *all* stakeholders, including those partners of PPPs.

CONCLUSION ELSA research and scholarly activities demand different modes of organization, both embedded in and independent of PPPs. In case of the latter, matching is not a feasible option. !

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Postface

Partners in the Polder is a wide-ranging, ambitious book. I have read it with great interest and am happy to offer some reflections on its subject matter and main ideas.

I regard the life sciences as one of the foundations of the 21st century economy and absolutely essential to building a sustainable society. Sustainability implies improving relationships between people and between people and nature, our ecosystems. Today those relationships are less than healthy. Often, they are destructive and harmful. As we come to better understand life and the processes of life, we must use this knowledge to improve our quality of life, including that of our environment.

We are on the brink of a major transformation: from consuming (and depleting) finite resources to harvesting and renewing the flows of life. We must transcend the fossil phase in the development of our society and make the transition towards a more bio-based economy. Biomass is a tremendous source that can provide for much of what we need. The trick is to harvest it sustainably, use it responsibly and recycle it where possible. A similar transition is taking place in healthcare. There, we will go from cure to prevention. Instead of mainly dealing with disease, we will put more emphasis on optimizing health and vitality, thus enabling everyone to live, enjoy and contribute his or her full potential.

I therefore welcome this initiative. *Partners in the Polder* shows the potential of the life sciences and paints a tantalizing picture of a future where they deliver on their promise. However, it also highlights the challenges to overcome before such a future can become reality. We need to invest time, (creative) energy and money. Not sometime in the far future, but starting today. The financial and economic crisis provides us with an excellent incentive and opportunity to take a major stride towards a sustainable (knowledge) economy. If we miss that train, it will not come by again.

I must confess to a fatherly affection for this public-private partnership that dates back to my role in launching the Netherlands Genomics Initiative in 2002. I have seen the partnership develop from the infant I helped conceive, into the adolescent it is today. Now it must reach maturity and fulfill its social, ecological and economic potential. We have a prominent position in both basic science and PPPs and we cannot afford to let that slip away.

That next step to maturity we should take together, on a nationwide basis. The Netherlands is a small place. Distinctions within it barely show up on the international radar. Together, however, individual "blips" amount to a steady beacon that will draw attention, talent and investment to the Dutch life sciences. But we should look beyond the life sciences too. Fields like informatics, nanotechnology and the life sciences increasingly depend on each other for success.

I call on everybody, scientists, researchers, business people, policy makers, professionals and citizens, to work together to build a healthy and sustainable future. It may be the most important message to take from this book: that we need each other and should try to understand and help others do their part and be successful. *Partners in the Polder* calls for a long-term approach and policy continuity. Researchers and entrepreneurs in the life sciences operate on timelines of ten to fifteen years and more. Frequent policy changes hamper progress and investment. The sector should recognize, however, that providing continuity and stability over several parliamentary periods would be a formidable achievement and cannot be a one-way street. Politicians and civil servants will rightly want to exert influence and results in the medium and short term, as well. Policy continuity will only be forthcoming if the field understands that and is prepared to be transparent and accountable to the public and its elected representatives. Politicians and civil servants, on the other hand, must realize that without continuity results will be limited, and fall behind what society needs.

No one can do this alone or purely on his or her own terms. The future is a common project that will be shaped by our collective efforts. *Partners in the Polder* has set out a vision for a future enlivened by the life sciences. I would like to see that future come true. I would like to see a truly sustainable society and knowledge economy develop, and I am convinced the life sciences can and must play a major role in bringing it about. I hope researchers, entrepreneurs and all those involved will act to deliver on the promise of the life sciences they have so appealingly described in this book. They deserve our support.

In the preface, the authors quote a proverb: “beginning is easy, continuing hard”. Let me conclude in similar vein: good start, do continue!

Herman Wijffels,
September 2009

Samenvatting van de hoofdaanbevelingen

Dit is het tijdperk van de life sciences. Zij helpen ons maatschappelijke uitdagingen het hoofd te bieden in gezondheidszorg, voedsel- en energievoorziening en milieu. Ook werken zij als een motor voor onze kenniseconomie. Nederland heeft een unieke uitgangspositie in de life sciences. Ons wetenschappelijk onderzoek behoort tot de top drie in de wereld en Nederland heeft in voeding, gezondheid, agricultuur en chemie & energie sterke industriesectoren die de belofte van de life sciences kunnen inlossen.

Desondanks blijkt het moeilijk onze sterke kennisbasis te vertalen naar nieuwe producten, processen en diensten en die te leveren aan de maatschappij. In antwoord op deze uitdaging hebben academici, industrie en de overheid recentelijk op grote schaal de krachten gebundeld in pre-competitieve onderzoeksamenwerking. Nu is het tijd om door te pakken en deze investering te laten renderen.

Vele vertegenwoordigers uit het life sciences veld zijn samengekomen om *Partners in the Polder* te schrijven. Het boek beschrijft de belofte van de life sciences en hoe Nederland deze belofte kan inwilligen, met bijzondere aandacht voor de rol van publiek-private partnerschappen (PPPs). *Partners in the Polder* kijkt naar hoe academici en industrie samenkomen om de kennisbasis te vertalen naar toepassingen: het ontstaan van PPPs, hun bedoeling en vooruitzichten, sterkten en zwakten, successen en mislukkingen.

Partners in the Polder komt tot drie hoofdaanbevelingen die breed gedragen worden door het veld en voortkomen uit de ervaring en deskundigheid van wetenschappers, onderzoekers, zakenlieden en beleidsmakers uit alle hoeken van de life sciences en uit studies en publicaties van industrie-organisaties, de OECD, het Innovatieplatform en vele anderen. De auteurs hopen dat deze samenvatting de interesse van de lezer wekt in het boek zelf. Dat bevat nog veel meer observaties, lessen en aanbevelingen.

I. Voorzie in continuïteit van innovatiebeleid voor 15 jaar of langer (p. 62-66)
Nederland heeft de ambitie een internationaal toonaangevende kenniseconomie te worden en een prominente rol te spelen bij het aanpakken van maatschappelijke uitdagingen als klimaatverandering. Innovatie is daarvoor onontbeerlijk. In de life sciences vergt innovatie 15 jaar of meer: van eerste idee tot het omarmen van een nieuw product, proces of dienst door de maatschappij. Daarbij moet veel tijd, energie en geld worden geïnvesteerd bij onzekere uitkomsten. De Nederlandse overheid heeft goede instrumenten om innovatie te stimuleren, maar het beleid zelf verandert tenminste iedere vier jaar – in prioriteiten, criteria, instrumenten, procedures en aanspreekpunten. Als de regels blijven veranderen tijdens het innovatiespel blijven rendementen op eerdere investeringen uit, nieuwe initiatieven liggen en onze ambities bij woorden.

Om dit te veranderen moet het veld duidelijk uitdragen waar het heen wil en wat daarvoor nodig is. Dat is de bedoeling van *Partners in the Polder*. Hiermee kan de overheid lange termijndoelen (> 15 jaar) definiëren als leidraad voor innovatiebeleid en zo de regels grotendeels constant houden, laten aansluiten bij (inter)nationale “best practices” en op maat snijden voor de life sciences. De juiste (combinaties van) instrumenten kunnen dan in ieder stadium van innovatie worden ingezet en voortgang en resultaten voortdurend bewaakt. Op deze manier wordt publiek geld effectief en legitiem geïnvesteerd.

II. Bouw voort op de sterkten die zijn ontwikkeld (p. 67-75)
Alle belanghebbenden in de life sciences moeten voortbouwen op de sterkten die tot stand zijn gebracht. De eerste prioriteit moet zijn de vruchten te plukken van eerdere investeringen door de beste condities te scheppen voor het gebruik en vermarkten van innovaties. Daartoe horen goede toegankelijkheid van kennis en patenten, ruime beschikbaarheid van (durf)kapitaal, vrijwaring van onnodig restrictieve regelgeving, goed geïnformeerde en kritische burgers en een goed functionerende markt. Het veld en de overheid moeten deze condities samen creëren. *Partners in the Polder* bevat vele tips en ideeën: van valorisatiemechanismen tot certificatiesystemen tot “launching customers”.

Nederland moet haar rijke (nationale) PPP landschap naar het volgende niveau van schaal en bereik tillen. Het veld zou de meer dan 40 Nederlandse PPPs waarin de life sciences een rol spelen moeten consolideren tot tien of minder clusters die deel uitmaken van internationale netwerken. De overheid zou moeten blijven investeren in dergelijke partnerschappen. Ook zou de overheid meer moeten investeren in fundamenteel onderzoek door academici om onze internationaal leidende kennispositie te behouden (juist in economisch moeilijke tijden). Universiteiten hebben de verantwoordelijkheid om onderzoeksresultaten te valoriseren en het makkelijk te maken voor ondernemers om toegang te krijgen tot kennis en patenten en die te gebruiken. Ook onderwijs is een prioriteit. Innovatie in de life sciences vraagt zowel om goedopgeleide onderzoekers, ondernemers en investeerders als om welingelichte burgers die zelf kunnen besluiten een innovatie wel of niet te gebruiken.

III. Positioneer Nederland als één bioregio (p. 75-78)
In de Nederlandse life sciences zijn de afstanden klein. Internationaal leidende academische groepen en sterke industriesectoren (voeding, gezondheid, agricultuur en chemie & energie) zijn verenigd op een klein oppervlak. Door zich te positioneren als één bioregio met lokale zwaartepunten en te profiteren van de Nederlandse tradities van samenwerking en handel, kunnen de Nederlandse life sciences zeer concurrerend zijn en buitengewoon aantrekkelijk voor internationale partners.

Succesvol samenwerken wordt steeds meer een bron van concurrentievoordeel. Het life sciences veld zal de samenwerking na dit boek doorzetten, ervaringen blijven delen en (informele) coördinatie opzetten waar nuttig. De PPPs van vandaag zullen toekomstige PPPs helpen hun voordeel te doen met de lessen die zijn geleerd en de ”back offices” die reeds bestaan. Kortom, de belanghebbenden bij de Nederlandse life sciences zullen steeds meer worden tot *Partners in the Polder*.

Herman Wijffels, Professor of Sustainability and Social Change, Utrecht University

... I would like to see a truly sustainable society and knowledge economy develop, and I am convinced the life sciences can and must play a major role in bringing it about ...

Ab Klink, Minister of Health, Welfare and Sport

... A long-term vision supported by all stakeholders is essential to guiding the innovations that will help us overcome these challenges – together ...

Robert-Jan Smits, Director DG Research, European Commission

... A knowledge economy can only be created by investing in it! ...

Feike Sijbesma, CEO Royal DSM

... The only other ingredient needed for a flourishing life sciences field and bio-based economy is a firm commitment from all stakeholders involved to help make the Netherlands the world's "Life Sciences Polder" ...