MARTIEN GROENEN ON 20 YEARS OF PIG GENES

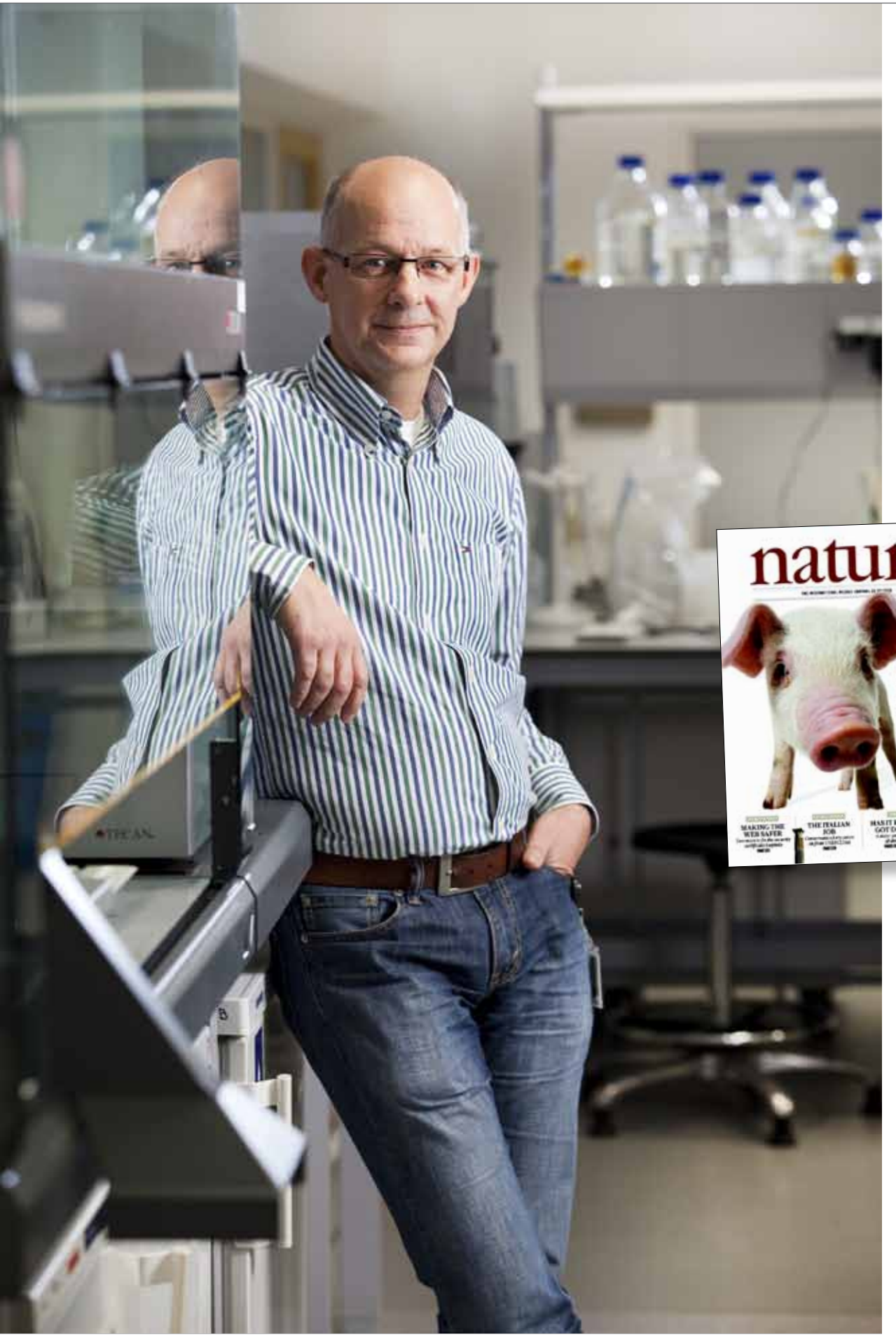
‘I never despaired but there were some sleepless nights’

Martien Groenen’s name is in *Nature* as first author of an article about the pig genome. Followed by the names of 136 co-authors. This megaproject has taken more than 20 years. How do you coordinate something like that? And what is the aim? The chemist by training gives his down-to-earth view of things. ‘We really had to scrape together the funding for this project.’ **TEXT** RIK NIJLAND **PHOTOGRAPHY** JAN WILLEM SCHOUTEN

After a long search, Martien Groenen manages to locate the memorable photo from 2009 on his PC. It shows the Wageningen professor of Breeding and Genetics posing with his American colleagues Larry Schook and Greger Larson with a pig’s head. It is the head of TJ Tabasco, a pig of the Duroc breed, which hangs in pride of place on the wall of the lab at the University of Illinois, like a trophy.
TJ is the main character in a story told in the scientific journal *Nature* in November, which lifts the veil on the pig genome. The American sow was the cornerstone of the research but the genome of a few dozen other pigs was unraveled as well, mainly thanks to Groenen. That is why he is the first author among the 136 scientists – coming from 54 research groups in 12 different countries – who worked on the publication.

The coordination of this extensive and long-haul study was in the hands of Larry Schook, Alan Archibald of the Roslin Institute in Scotland, and you. How did you arrive at that particular trio?
‘In the early nineteen nineties we in Wageningen were involved in plans for genetic research on pigs, but in the early years we did not play a major role. In a small research group you have to stay focused: our priority was the chicken. In 2004 we were one of the main groups behind the publication of the chicken genome. After that, the pig was the next challenge, given the expertise we had acquired.

So people think: that Groenen would be a good person to have on board?
‘Yes, it does work a bit like that of course. It must click between you. Even on a personal level, I get on very well with the other two. That contact has developed into a friendship. In the summer of 2009 I even did a short sabbatical with Larry in Illinois.
But contents-wise, our experience with the chicken >



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made us very welcome on the Swine Genome Sequencing Consortium which had been established by then. In 2008 Wageningen made its mark again when we came up with a chip that is used a lot both in the business world and by researchers to determine the genetic characteristics of pigs quickly. Our contribution to the consortium went into the fast lane after we obtained a grant from the European Research Council (ERC) at the end of 2009.'

An honour, a prominent role like that. But it must be no sinecure to keep all those researchers with totally different research questions on the right track?
'One works on meat production, the other on veterinary problems, a third on the use of pigs as biomedical experimental subjects, but we all stood to gain by joining forces. So it wasn't that hard. Many of the 136 people mentioned in the publication I don't know personally, but there has always been a positive attitude. Once every couple of weeks fifteen of us, the main project leaders, held a Skype conference.'

> **'The pig is a useful animal, but it doesn't appeal to many people emotionally'**

Martien Groenen (right) with his American colleagues Larry Schook and Greger Larson.

Nevertheless, in the final phase of the project there was quite a delay. Did you never despair?
'I never despaired, though I did have some sleepless nights. The funding, for example, was quite a headache. The pig is a useful animal, but it doesn't appeal to people emotionally. That is why the genome of the horse was completed much earlier. We really had to scrape together the funding for this project. The delay in rounding it off can partly be blamed on a change of policy at the Sanger Institute, where the sequencing was done. That institute has gradually focused more and more on the functioning of the human genome, so our project got neglected. A new institute, The Genome Analysis Centre, offered to continue the work without extra funding, but they underestimated the amount of work in the last phase, when you have to put all the information together. Removing all the errors cost us at least a year. In 2009, the sequencing itself was as good as done, but it took until 2012 before the publication came out.'

Never felt like throwing in the towel?
'Not as such. We were worried that *Nature* and *Science* would have lost interest because by now so many genomes have been published. As a scientist, of course your aim is to be published in the top journals. Along with the genome, there is more and more emphasis nowadays on having a good biological story to tell about it. Luckily we had that. Both journals were interested, but we sensed a bit more commitment from *Nature*. After the publication I got an email from *Science*. Yes, I think they were a bit jealous.'

What did you consider the most striking result of the genome study?
'It is funny that you can see so clearly that pigs have a very good sense of smell. They have many active genes for smell recognition. For taste, on the other hand, they have very few, which is why they are not very fussy. We also know that the European and the Asian wild boar

went their separate ways as long as one million years ago. The domestication of the pig happened in Europe and Asia independently of each other. In the 18th and 19th centuries, Asian pigs were used to improve European breeds. They had much more influence than we realized. One third of the genome of our commercial breeds can be traced back to those Asian breeds.'

That biological story largely comes out of your work. It is not only the genome of TJ Tabasco that has been sequenced, but also those of about 50 other domesticated and wild pigs. How was that possible? It took 20 years to map the genome of the first pig, and in no time you've got that of 50 others?
'Once we knew the global base sequence for TJ Tabasco, plus the place of quite a number of other genes, it was relatively easy to use this blueprint to identify the genome of other pigs. We are now at number 170.'

Where does all this interest in the pig genome come from?
'We want to know how the genome of this animal has changed through evolution and by domestication. We are also studying how species are formed. For that we are now also looking at other species of swine in Asia, such as the bearded pig and the Javanese warty pig. We expect to end up with about 400 sequenced animals from places ranging from the Dutch Veluwe district to parts of Asia.
'Apart from those purely biological issues, there is also a commercial side to our research. At TOPIGS, a big pig-breeding organization in the Netherlands, they have two bloodlines which came out of a single population 30 years ago, about 25 generations back. One of them was selected for fertility, the other for meatiness. We sequenced ten animals from each line to see what happens in the genome if you select for such different characteristics, and which genes are involved.'

Do I then end up with a tastier or cheaper pork chop on my plate? Or is the pig more resistant to disease?
'That of course is up to the breeding companies: it depends what they want to concentrate on. But in any case it will take years before we notice anything. First we need to find out more about which characteristics are linked with which genes. Of course there are many more applications besides improving pork chops or immunity to diseases. We are working with TOPIGS on finding out why some boards produce boar taint, a bad smell given off by the meat of a small percentage of the animals, but which is the reason all males are castrated. If we can cut the proportion by half, the castration without anaesthetic that is done in many countries may no longer be necessary.'

After the publication, researchers were emphasizing in press releases and interviews the potential for biomedical research. Will the pig be the new lab rat?
'In the genome that has been described we can see variants of genes that are linked in humans with obesity, diabetes, Alzheimer's and Parkinson's. That offers scope for doing further research on the effect of these genes. Like humans, pigs are omnivores with a similar digestive system and physiology. Certainly, when it comes to the diseases of affluence such as diabetes and cardiovascular disease, the pig is an interesting research model. But in view of the costs of keeping pigs and their longer life cycles, I don't think the use of the pig as a lab animal is likely to take off. But the groups that do use pigs will now be able to go about it much more efficiently.'

What will be your next 'victim'?
'We have already got a long way with the coal tit, together with the Dutch Institute for Ecology, the NIOO here in Wageningen. We are studying differences in the timing of when tits start brooding. And we want to look at behavioural differences between the machos and the more timid animals, which you can trace back to the genome. That is very interesting too.' ■

FROM CHEMIST TO PIG GENES

Martien Groenen (1958) was born in Venray, the district with the biggest pig population in the Netherlands. He studied chemistry at Nijmegen University, got his PhD at Leiden and worked for food ingredients and medicine manufacturer Gist-brocades in Delft. 'The transfer to Wageningen happened by chance, really,' says Groenen. 'At a party in Leiden in 1987 I got chatting to Maruis Giphart, then special professor in the Livestock Breeding department. I was keen to go back to university work and be able to talk and write freely about my research. At that time I was able to contribute my expertise in molecular biology to the Breeding department. I didn't have any experience with farm animals, although as a student I was involved in a study on the genes responsible for bovine eye lens proteins.' Early in 2002 Groenen was appointed personal professor in the Breeding and Genetics chair group.