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Executive summary

Working-group participants

A scientific working group[1] convened in Nairobi, Kenya, from 14 to16 July 2004, to further discussions[2] on the potential use of genetically modified vectors (GMVs) for the control of vector-borne diseases, particularly malaria and dengue. The meeting was jointly sponsored and organized by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), the National Institute of Allergy and Infectious Diseases/US National Institutes of Health (NIAID/NIH), the International Atomic Energy Agency (IAEA) and Frontis (Wageningen University and Research Centre). The group specifically focused on how to increase involvement of disease-endemic country (DEC) scientists in this endeavour as well as enhance collaboration between field and laboratory researchers.

A comprehensive research agenda and strategic plan to bridge laboratory and field research was presented along four thematic sessions. Historical applications of genetic vector control, population biology and vector genomics were discussed first. These were followed by descriptions of the state-of-the-art and future needs in laboratory and field sciences, with emphasis on how to integrate these two branches of entomology. The third part described the vector-borne-disease situation in different geographical regions with a focus on malaria and dengue vectors, while the final session included twelve key areas for research involving both laboratory and field sciences, structured to a) describe the state-of-the-art of each topic, b) identify salient issues and challenges, c) state research opportunities and d) propose future directions for research and capacity/partnership building.

Seven key points with recommended actions were recognized that would provide a basis for TDR to define its own research programmes, whilst taking into account its comparative advantages in both research and capacity-building activities.

Recommendations

The goal of the meeting was to provide technical and scientific guidance for addressing issues and challenges about genetic control of disease vectors and to develop a strategic plan to bridge laboratory and field research. Particular emphasis was placed on identifying research opportunities that merge interests from both branches of medical entomology and that can significantly advance the GMV approach for disease control.

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[1] List of participants, see elsewhere in this volume.

[2] For previous meeting reports see Alphey, L., Beard, C.B.; Billingsley, P., et al., 2002. Malaria control with genetically manipulated insect vectors. Science, 298 (5591), 119-121; Takken W. and Scott, T.W. (eds.). Ecological aspects for application of genetically modified mosquitoes. Kluwer Academic Publishers, Wageningen UR Frontis Series, Vol. 2.

To this effect, the participants recognized the following seven key points with recommended action:

1. Genetic modification of insects could be used to control vector-borne diseases

Replacement of existing populations with resistant or refractory strains is expected to contribute to the control of disease. Recent successful and stable genetic transformation of important vectors has underlined the need to optimize and standardize transformation technology. The search for systems that incapacitate pathogen development in the vector should be strengthened. Additional endogenous and/or synthetic effector genes, conditional lethals, and novel phenotypes should be searched and characterized. Tissue-specific promoters for such systems need to be identified and adequately engineered to ensure complete refractoriness based, ideally, on multiple effector genes in order to prevent pathogen adaptation. Finally, recent studies are showing promise towards paratransgenic approaches requiring the identification of suitable bacterial strains and the study of subsequent delivery in field populations after genetic engineering.

2. Develop techniques for driving effector genes that interfere with disease transmission into wild insect populations

Proof of principle has been established for implementation of anti-pathogen constructs, but appropriate drive mechanisms are still to be developed. Genetic stability of effector and drive mechanisms and their associated fitness cost must be researched, including genetic phenomena that alter segregation ratios to spread specific genes or alleles through populations. Such systems should first work in the laboratory, subsequently progress to the semi-field, and be subjected to appropriate risk assessment. Systems must then be introgressed into recent field-derived mosquito strains and evaluated for reproductive and competitive abilities in semi-field systems, also assessing potential horizontal transfer among closely related species. DECs are best suited for carrying out this research, and their inclusion in these activities is essential.

3. Studies of vector field populations with respect to potential future release of a GMV

Sufficient data on target vector populations (e.g. population structure, gene flow, and behaviour and ecology) are needed to model and predict the behaviour of introduced genes, providing the required baseline information in terms of vectors and the diseases they transmit.

Selection of field locations should focus on settings with manageable complexity in terms of vectorial system, pathogen transmission, and adequate isolation. A framework for this needs to be developed and its implementation will have to be guided by a coordinating body (see below under 7). The acquisition of additional knowledge on vector populations and disease transmission requires further development of sampling methods and molecular tools.

Correlates between field populations and disease transmission parameters should be based on the use of integrative models and be tailored towards the assessment of both efficacy (e.g. measuring sporozoite rate) and effectiveness (e.g. disease incidence) of GMV introductions. Suitable entomological parameters for measuring dengue transmission are in need of development.

Potential fitness effects of genetic transformation and mating success will directly influence the outcome of GMV releases, thus standardized procedures that enable comparative evaluation of fitness effects are needed. Whether fitness costs can be

compensated for by a highly efficient transgene drive mechanism remains unknown. Pertinent laboratory research is still preliminary and further investigations in more realistic environments are required.

Mosquito mating behaviour remains understudied, and application of new approaches (e.g. genomics) is yet to commence. Research should primarily assist in assessing whether or not released transgenic males can effectively compete for females of the wild vector populations.

Key issues underpinning the success of GMVs, such as recombination and subsequent impact on transgene drive, may only be studied through modelling. Models should focus on defining threshold levels in terms of system efficacy in order to attain maximum epidemiological impact in both spatial and temporal dimensions.

DEC activities should include efforts to comprehensively identify and characterize potential field sites and research to assimilate better knowledge on the relationship between transmission intensity and disease outcome.

4. Development of processes dealing with the ethical, legal and social issues (ELSI) of the use of GMVs

Various biotechnological and implementation challenges remain to be addressed in order to make GMVs a control approach applicable in the public-health arena. There is consensus that the introduction of GMVs must result in a predictable and positive public-health outcome. The process of mobilizing active support and involvement at all levels in society needs to be put in place to provide a proof of efficacy and safety (i.e. minimizing risk) of the use of GMVs for disease control, required to initiate the process of formalizing ethical, legal and social issues.

Effective strategies to communicate with the media and policymakers are crucial. A long-term effort to clarify the scientific uncertainties under different experimental conditions and with the involvement of DEC investigators is mandatory, as is the development of guidelines and principles for minimum-risk field research that includes environmental risk management.

5. Enhanced involvement of scientists and institutes in DECs

Closer involvement and participation of DEC scientists in the GMV endeavour is essential. The challenge of fighting vector-borne diseases is international in nature and needs an inclusive, open research community that exploits the expertise of all scientists. DEC scientists are frontline stakeholders and their laboratories should be engaged in equitable partnership in the pertinent research including research areas such as post-genomics and bioinformatics. Frequent courses, workshops and meetings could strengthen partnership and collaborative efforts. The inter-relationship between academic and implementation communities in DECs should be reinforced

6. Inclusion of GMVs in disease control programmes

GMVs have to be aligned with existing control strategies already adopted and implemented by health authorities in DECs. Appropriate mechanisms for evaluating the impact and cost–benefit relation of GMVs against a background of ongoing control strategies (e.g. insecticide-treated bednets) will have to be developed. Integration of GMVs into Integrated Vector Management (IVM) policy frameworks is foreseen and deserves consideration.

7. Coordinating and follow-up mechanism for GMV research and implementation

The complexity of issues related to GMV development and implementation requires a multi-disciplinary effort and a coordinating board should be put in place. This will focus on the broader dissemination of scientific progress to stakeholders and the facilitation of collaborative efforts and partnership strengthening within and beyond the scientific community.