Gene drive-modified mosquitoes for public health

Research and development of gene drive-modified organisms is most advanced in the public health space, and it is likely that the first gene drive-modified organisms to be tested in field environments will be mosquitoes aimed at reducing the burden of malaria on the African continent. The African Union and the World Health Organization (WHO) have both stated that additional new tools are needed to stimulate the next wave of significant reduction in the malaria burden, moving towards elimination.

Forum meeting participants were presented with a review of the 2018 High-Level African Panel on Emerging Technologies report, *Gene Drives for Malaria Control and Elimination in Africa*, that, while acknowledging the contributions of current vector control measures to reductions in the malaria burden, recognized the need for new interventions and recommended that Africa invest in the development and regulation of gene drive technology for the purpose of malaria control and elimination. Toward that end, the African Union Development Agency (AUDA-NEPAD) presented on its capacity strengthening activities with various stakeholder groups. The African Union Development Agency (AUDA-NEPAD) is supporting regulatory capacity strengthening to facilitate informed development of regulatory processes; to apprise decision makers about gene drive technologies to facilitate informed decision making; and to share important information among other stakeholder groups to raise awareness, for example through the newly formed Calestous Juma Executive Dialogue on Innovation and Emerging Technologies.

The WHO is expected to play a critical role in the testing and deployment phases of gene drive mosquito products. Meeting participants heard details about the WHO prequalification (PQ) process for vector control products. The PQ team is focused on ensuring that quality vector control products are available through “evaluation and inspection activities, and by building national capacity for the sustainable manufacture and monitoring of quality vector control products”.

Three research teams evaluating gene drive tools to reduce the burden of malaria by modifying mosquito vector species to reduce their ability to reproduce or to transmit malaria parasites presented to meeting participants.

- **Transmission Zero** is exploring population modification strategies for blocking malaria transmission by *Anopheles* mosquito species. In the laboratory, the team is evaluating several ways in which gene drive technology might be used to disrupt growth of the malaria parasite within mosquito populations.
- The **University of California Malaria Initiative** also is developing population modification strategies for *Anopheles* mosquito species that will block malaria parasite transmission. Although the
research is still in the laboratory phase, the Initiative researchers are working to identify partners on the African continent to join the development process; they plan to work with these partners to identify potential island settings for future field trials.

- **Target Malaria** is developing suppression strategies to reduce populations of malaria transmitting mosquitoes. Product development partners on the African continent include institutions in Burkina Faso, Ghana, Mali, and Uganda, where teams are developing methods to explain the technology to local communities. Although development of gene drive-modified *Anopheles* mosquitoes is still in the laboratory phase, the consortium plans to freely license any resulting products or use by authorities in countries where it has been approved.

**Gene drive-modified agricultural pests**

Agricultural pests can have a devastatingly negative effect on food resources and the overuse of pesticides is creating issues for the environment. Forum meeting participants heard about research to combat pests such as *Drosophila suzukii*, a fruit crop pest. Meeting participants heard about genetic approaches being evaluated in laboratories at the University of California, San Diego as potential new tools to combat agricultural pests.

**Gene drive-modified rodents for biodiversity conservation**

Islands tend to have high levels of biodiversity and to be epicenters of extinctions largely because of invasive species. The **Genetic Biocontrol of Invasive Rodents** partnership is investigating the feasibility and suitability of using gene drive technologies to protect island ecosystems and species extinctions due to invasive rodent populations, which, when left unchecked, decimate the local, often unique, flora and fauna. The international team is working in the laboratory to evaluate potential gene drive approaches designed to suppress local invasive mouse populations.

**Convention on Biological Diversity – activities update**

It will be important for gene drive stakeholders to understand and remain current on activities of the **Convention on Biological Diversity** (CBD), which plays a major international role in issues related to biodiversity and sustainable development. During a presentation, meeting participants heard about an apparent shift since 2016 in the manner in which gene drive technologies are represented in the discussions, with a trend towards less emphasis on generalized negative speculation. Forum meeting participants were informed that at the next CBD COP meeting (2020) there will be a debate on whether appropriate guidelines exist for risk assessments of gene drive-modified organisms. All Forum meeting participants were encouraged to share their expertise through various available platforms.

**Gene drive nomenclature**

Definitions and terms of use for ‘gene drive’ and related concepts vary within and between the scientific literature, media, and other publications. Two projects reported at this Forum meeting are looking into these terms and their use.

- A new University of Exeter project is designed “to identify the language, stories and metaphors that communities, policy makers and other stakeholders prefer to describe the technology and empower them to make important decisions about whether to use it, and if so, how to use it”. This project has only recently commenced, so there were no results to report at the time of this Forum meeting.
• Should ‘gene drive’ and other related concepts have generally accepted definitions? Would this aid national and international debates about the technology, research and development, and/or implementation? The second project reported at this Forum meeting is designed to: review the current published gene drive technical definitions; work with an international panel of scientific stakeholders towards developing consensus definitions for scientific use of terms; and, make the definitions publicly available. Participants at the Forum meeting provided useful feedback indicating that the definition(s) should be simple and short (for both scientific or non-scientific use). In addition, participants suggested that multiple definitions would be acceptable. Like many scientific terms, definitions of ‘gene drive’ and related terms could vary according to use (e.g. gene drive as a phenomenon or molecular element).

Sharing gene drive project data and information

A presentation about transparency and data sharing preceded discussions about knowledge, where knowledge was defined as facts, information, and skills acquired by a person through experience or education. The presenter started with the following quote about a principle of transparency for gene drive research:

“Knowledge sharing is not only essential for the advancement of science, but for transparency to foster public trust in emergent technologies. The timely reporting of results and broad sharing of data shall be the norm in gene drive research, consistent with the tradition of openness established in its parent communities of genetic and genomic science. Measures of transparency and accountability that contribute to building public trust and a cohesive community of practice will be supported.”1

Given that transparency was defined at this meeting as the condition of being clear and lucid, meeting participants were asked whether the gene drive research community should have a transparency statement. The vast majority of respondents (81%) replied affirmatively, i.e. “yes” (options were ‘yes’, ‘no’, ‘not sure’). And, when asked where such a statement should reside, a large proportion of participants felt that such a statement should reside on each individual research project’s website.

Information and data are different but related terms, and were defined respectively as 1) facts provided or learned about something for someone (information), and 2) facts and statistics collected together for reference or analysis (data). Providing information about a project and/or data might contribute to increased transparency. However, an important question to be considered by gene drive research stakeholders is what is most useful to share and with whom.

Importantly, ‘transparency’ and ‘open access’ are distinct terms that should not be used interchangeably – these two terms are not interchangeable.

Data sharing is one of a number of weighty topics underlying broader science-related (not just gene drive) debates taking place in the public arena. To facilitate a conversation about gene drive project data sharing at the Forum meeting that could inform development of data sharing norms for the field, meeting participants were given five high-level questions – Why should we share? Whom should we share with? What should we share? Where should we share? When should we share? There also was important discussion of the “we” in the data sharing questions: who has the legitimate authority to share which data? This complex topic – involving individual researchers, institutions at which they work,

countries where data are generated, research funders, and other stakeholders – is without a simple answer.

- Why should we share? Whom should we share with?
  An analysis of the data sharing policies of nine funding organizations that had been conducted by a Forum working group was reviewed at this meeting. Results demonstrated broad support for data sharing with some differences in management expectations.
    - Theory vs. practicality: These questions of why data should be shared and with whom facilitated much thoughtful discussion among Forum meeting participants. From a philosophical perspective, participants viewed data sharing as a positive activity that could enhance scientific activities (e.g., better field site modeling, improved study designs) but participants identified practical issues related to what, when and where to share that require further consideration.
    - Data and information audiences: Multiple different audiences for project data and information sharing were identified, including other researchers, funders, regulators, and other publics. It was acknowledged that different audiences might find different types or presentations of information and data most useful.

- What should we share?
  There is a broad spectrum of data and information associated with research, and a number of participants indicated that the term ‘data’ needed to be well-defined in the context of data sharing norms for gene drive research. Data and information may include project plans and funding sources, methods including protocols and software, and results from laboratory experiments, field data collection, and computer simulations.
    - Access across data audiences: Participants discussed various potential data access scenarios. Most at this meeting favorably viewed data sharing scenarios that differentiated data access to meet the varying needs of different audiences. Although many ideas were discussed, the details of gene drive project data sharing will need to be more thoroughly explored among a wider representation of stakeholder groups.
      - Important considerations included the perceived value of the data to the audience and the possible costs and risks that can be associated with sharing data. Potential risks that were discussed at the meeting included violation of individual privacy, stigmatizing impact on communities, risks to the research or program staff, the potential for misinterpretation of data that has been taken out of context, and loss of opportunity for scientists with fewer resources to conduct and publish their own analyses when their data are shared widely with scientists with access to more resources early in the process.
      - Some data that remain unpublished may be valuable to certain audiences but don’t always have platforms suitable for dissemination (e.g., lack of interest from scientific journals).
    - Governance: During discussion, meeting participants also brought up the importance of adhering to individual government positions and laws that may supersede donor policies on sharing certain data and information. For example, for human subjects research, researchers will need to consider any limitations on repurposing data for new analyses, in addition to standard privacy considerations.

- Where should we share?
Current relevant data sharing sites: To give Forum meeting participants an overview of the types of data sharing platforms that might be relevant for gene drive project and field data, three current data sharing sites were described. Each either is created for sharing gene drive project data or has the capacity to expand its activities.

- **CSIRO Data Access Portal (DAP):** The DAP “provides access to research data, software and other digital assets published by CSIRO across a range of disciplines”. And, CSIRO has proposed creating a repository to permanently archive data produced by the international gene drive/genetic control community through this mechanism. The DAP is searchable and provides a unique Digital Object Identifier (or DOI) for referencing data sets; data can be downloaded or streamed directly from the site for further analysis. This site, at present, is intended for pre-filed trial data such as genomic or ecological data.

- **Texas Advanced Computing Center (TACC):** The TACC provides powerful advanced computing technologies and software solutions to researchers in a wide variety of research fields including the DARPA Safe Genes project for which it is used to create synergy between different projects. It allowed for easy sharing of data among collaborators.

- **VEuPathDB:** The VEuPathDB website will combine the EuPathDB and VectorBase resources and is due for completion in the first half of 2020. This database provides geospatial visualization and query capabilities, as well as, some analysis capabilities for data sets. VEuPathDB hosts a variety of data sets including genomic and phenotypic resources to abundance data. The EuPathDB project is a family of databases that includes ClinEpiDB and MicrobiomeDB that has the same underlying infrastructure, allowing for interoperability between databases.

Leveraging resources: Participants emphasized the financial cost of data sharing, in particular for sharing that extends beyond the duration of individual project funding. Strong recommendation was made to consider leveraging existing data sharing platforms. However, when meeting participants were asked whether they thought that current data platforms were suitable for gene drive research data sharing, 30% responded ‘yes’, 10% responded ‘no’, and the majority (60%) responded ‘not sure’. These informal survey results seem to indicate a need for more clarity about the capabilities of existing databases, and perhaps more clarity on how data sharing processes would work.

Legal requirements: In addition, meeting participants discussed the need for data owners to understand the laws by which data sharing is governed. Depending on those laws, an appropriate data sharing site, or mirroring site of the data access site located out of country, may be required. For example, the Pan-African Mosquito Control Association (PAMCA) might provide a platform to share data and/or mirror data sharing sites. It is creating common indicators and a repository for standardized data on vector surveillance in Africa, and expanding its capabilities in data management and sharing.

**When should we share?**

To the question of when data should be shared, 27% of respondents chose ‘post-publication’, 40% chose ‘pre-publication (with agreement)’, 10% responded ‘after the study concludes’, and 23%
had ‘other’ thoughts (not collected). No one at the meeting supported the idea that data should be shared automatically ‘12-18 months after being collected’.

- **Project data:** In addition to the understanding that journals typically require the public release of data once analyses, results, and conclusions are published, many at the Forum meeting felt that determining the timing of data sharing for each project should be a collective, coordinated effort among project researchers and funders, appropriate government officials, and other relevant project stakeholders. Meeting participants suggested that data types, pros/cons of sharing specific data, country laws and regional guidelines, approvals needed, etc. should be considered.

- **Accessibility:** It was widely understood that sharing data may require granting permissions to access data, but laws and regulations may also govern the timing of data release. In addition, the issue of transparency from those requesting data generated some discussion about whether those generating data have the right to ask those requesting it what they want it for, and what the process or recourse might be if the data are used for some purpose other than the one provided at the time of the request.

**Gene drive project registry**

Debate about the utility of a gene drive research registry was preceded by a WHO presentation on its proposed [global registry on human genome editing](#) intended to track clinical trials on human genome editing projects. The scope of this WHO registry is 1) clinical trials involving genome editing tools on human somatic cells; and, 2) any proposed clinical trials involving genome editing tools on human embryos and germline cells that will be used to initiate pregnancies; and 3) research using genome editing technologies on (i) human embryos and (ii) germline cells or their progenitors when gametes derived from these will be used to create embryos, even when there is no attempt to initiate/establish a pregnancy. The WHO speaker emphasized that creation of such a registry “does not mean that WHO advocates and endorses such activities”.

Forum meeting participants debated whether registries are important for transparency in gene drive research. When presented with the statement “a registry of projects would help with transparency”, 68% of participants agreed with the statement, with 29% neither agreeing nor disagreeing.

In general, meeting participants felt that information contained in a registry likely would be useful for project transparency purposes. Participants familiar with the complexities of maintain trial registries cautioned that a scoping exercise is needed to determine the value to stakeholders, to identify information and project details to be included, to explore potential registry host organizations, and to consider potential funding sources. In addition, such a scoping project should look into: authentication of projects and curation of project entries; how to address applicable country laws; resources needed for set-up and maintenance of the platform; registry access options; registry site mirroring needs and requirements; motivating (and demotivating) factors for researchers to upload project information; and other registry-related details.

When asked where such a registry should be hosted, the majority of ideas centered on international organizations.

**Recommendations**
• Data sharing: Different cross-sections of stakeholders need to be engaged to make recommendations regarding the many and diverse questions brought forward during discussions at this Forum meeting and summarized in this report.
• Registry: A wide diversity of stakeholder groups need to be engaged to develop recommendations for the appropriate scale of a gene drive registry scoping project and to potential funding sources.

Organizations represented at this meeting (in alphabetical order):

- African Union Commission
- African Union Development Agency (AUDA-NEPAD)
- Bill & Melinda Gates Foundation
- CAB International, Kenya
- Center for Global Development
- Colorado State University
- Commonwealth Scientific and Industrial Research Organisation (CSIRO)
- EHS Consultancy Ltd
- European Food Safety Authority (EFSA)
- Foundation for the National Institutes of Health (FNIH)
- Ifakara Health Institute
- Imperial College London
- Institut de Recherche en Sciences de la Santé/Centre Muraz, Burkina Faso
- Institut Pasteur de Dakar
- ISAAA AfriCenter
- Island Conservation
- Japan AMED, London office
- Jikei University School of Medicine
- Kenya Medical Research Institute (KEMRI)
- Leverage Science LLC
- Liverpool School of Tropical Medicine
- McMaster University, Institute on Ethics & Policy for Innovation
- National Biosafety Authority, Kenya
- Noguchi Memorial Institute for Medical Research, University of Ghana
- North Carolina State University
- Open Philanthropy Project
- Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale (OCEAC)
- Outreach Network for Gene Drive Research
- Pan Africa Mosquito Control Association
- Policy Cures Research
- Uganda Virus Research Institute
- University of California, Davis
- University of California Malaria Initiative
- University of California, Berkeley
- University of California, San Diego
- University of Dar Es Salaam
- University of Exeter Business School
- University of Notre Dame, Eck Institute for Global Health
- University of Toronto
- US National Institutes of Health
- World Health Organization