Institution: Keele University

Unit of Assessment: UoA5 Biological Sciences

Title of case study: Building capacity and infrastructure for controlling malaria transmitting mosquitoes in West Africa

Period when the underpinning research was undertaken: 2000-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Frederic Tripet	Professor in Medical and Molecular Entomology/ Director Centre for Applied Entomology and Parasitology	2006 - present
Professor Paul Eggleston	Professor of Molecular Entomology (now Emeritus)	1999 - 2016

Period when the claimed impact occurred: August 2013-2020

Is this case study continued from a case study submitted in 2014? Y

1. Summary of the impact (indicative maximum 100 words)

The main impacts relate to the globally destructive malaria disease: (i) engagement with key stakeholders (the UN, severely affected countries) has dramatically improved perceptions of genetic vector control approaches to malaria, resulting in policy changes across Africa. (ii) Regulatory and policy development in West Africa that enabled the first small-scale release of genetically modified (GM) malaria mosquitoes in Burkina Faso to demonstrate the feasibility of such approaches. (iii) The development of infrastructure and strengthening capacity for integrated vector management in Africa, notably construction of facilities for GM mosquito containment and/or supporting mosquito ecology research in Mali, Burkina Faso, and Ghana.

2. Underpinning research (indicative maximum 500 words)

Malaria remains a huge global health challenge, with 219 million cases reported to the World Health Organisation (WHO) in 2017 and approximately 400,000 deaths, mostly in children aged under 5. Radical measures are needed to control the mosquito vector, thus breaking the cycle of transmission of this devastating disease. Since the early 1990s, the Centre for Applied Entomology and Parasitology (CAEP) based at Keele University has been conducting highly innovative translational research on vector-borne diseases. The vector control group within CAEP, led by Professor Tripet, focuses on the population structure, ecology and behaviour of the malaria mosquito *Anopheles gambiae* sensu lato. This builds on previous pioneering work at Keele to develop genetic engineering of mosquito vectors (Professor Eggleston) and interactions between mosquitoes and the malarial parasite (Professor Hurd), with the ultimate goal of blocking disease transmission. In 2016, the group became partners in Target Malaria (TM), a not-for-profit consortium aiming to develop novel genetic vector control technologies to tackle malaria.

Gene-drive technologies enable precise genetic modifications, for example, affecting mosquito fertility or permissiveness to the malaria parasite, to be passed onto all offspring so that these traits can spread through populations and decrease malaria transmission. Work at Keele by Tripet, Eggleston and by other researchers from the Target Malaria (TM) consortium has contributed to creating sterile and male-biasing GM mosquitoes as part of a stepwise approach towards future gene-drive releases. Research produced by Keele's vector biology group has highlighted how colonization and laboratory rearing can potentially affect mating behaviour of released male mosquitoes **(3.1)** and the genomic structure of assortative mating (**3.2**). The group developed

cage-invasion studies to assess potential fitness costs associated with the targeted integration of anti-malarial effector genes into the mosquito genome (**3.3**). The group is constantly improving insectary rearing practices **(e.g., 3.4)** and have also developed molecular assays for the monitoring component of mosquito releases, including GM transgene detection methodologies, *Plasmodium* detection and species identification.

Another strand of the group's research is understanding local malaria mosquito population structure through field studies in West Africa to determine the seasonal variation in population size, survival and their dispersal (e.g., **3.5**). This is critical for designing disease control interventions. Within the TM project, the Keele group has ensured that there is an in-depth understanding of local mosquito populations and malaria mosquito demographics in Burkina Faso, Mali and Uganda (e.g., **3.6**). Based on this information and studies conducted in small cage mosquito populations, important models have been developed by the Oxford Target Malaria modelling group to predict the impact of malaria mosquito releases carrying a male-bias construct with or without gene-drive in west African communities. These models have confirmed the high potential effectiveness of such genetic population suppression approaches towards interrupting malaria transmission (for more information visit https://targetmalaria.org/resources/).

3. References to the research (indicative maximum of six references)

3.1 Ekechukwu N.E, Baeshen R. Traorè S.F., Coulibaly M., Diabate A., Catteruccia F., Tripet, F. (2015) Heterosis increases fertility, fecundity and survival in laboratory-produced hybrid males of the malaria mosquito *Anopheles coluzzii. Genes, Genomes, Genetics* 5:2693-709

3.2 Aboagye-Antwi F., Alhafez N., Weedall G.D., Brothwood J., Kandola S., Paton D., Fofana A., Olohan L., Pazmiño Betancourth M., Ekechukwu N.E., Baeshen R., Traorè S.F., Diabate A., and Tripet, F. (2015) Experimental swap of *Anopheles gambiae's* assortative mating preferences demonstrates key role of X-chromosome divergence Island in incipient sympatric speciation. *PLoS Genetics* 11(4): e1005141

3.3 Paton D., Underhill A., Meredith J., Eggleston P, Tripet F. (2013) Contrasted fitness costs of docking and antibacterial constructs in the EE and EVida3 strains validates two-phase *Anopheles gambiae* genetic transformation system. *PLos One* 8(6): e0067364

3.4 Akpodiete, N.O., Diabate, A. and Tripet, F. (2019) Effect of water source and feed regime on development and phenotypic quality in Anopheles gambiae (sl): prospects for improved mass-rearing techniques towards release programmes. *Parasites & vectors*, *12*(1), 210-221

3.5 Epopa P.S., Millogo A.A., Collins C.M., North A., Tripet F., MQ Benedict M.Q, A. Diabate (2017) The use of sequential Mark-Release-Recapture experiments to estimate population size, survival and dispersal of male *Anopheles gambiae* complex mosquitoes in Bana, a West African humid savannah village. *Parasite and Vectors* 10:376

3.6 Epopa P.S., Collins C.M., North A., Millogo A.A., Benedict M.Q., Tripet F., A. Diabate (2019) Seasonal malaria vector and transmission dynamics in western Burkina Faso. *Malaria Journal* 18:113.

Funding that has come to Keele

- 'Genetic engineering of refractory mosquito vectors for the control of malaria transmission', Wellcome Trust, 2008-2011, £950,000 (Tripet, Eggleston and Hurd)
- 'Targeting male mosquito behaviour for malaria control', British Medical Research Council-African Research Leader Scheme, 2011-2016, £1,000,000 (Tripet, Diabate)
- 'Target Malaria consortium: Vector-Based Control of Transmission', National Institutes of Health & Bill and Melinda Gates Foundations, 2016-2020, (total £35M), ~£700,000 to Keele (Tripet et al)
- 'Towards ecologically-realistic genetic mosquito population control strategies for disease elimination', Royal Society, 2016, undisclosed. (Tripet, Powell, Torre)

- 'Improving Male Mating Competitiveness for Mosquito Releases, Open Philanthropy, 2018-2023, £1,800,000. (Tripet, Burt, Aboagye-Antwi)
- 'Knowledge co-production across disciplines and borders: The case of gene drive mosquitoes in the UK and Mali', British Academy, 2018-2019, £46,603. (Tripet et al)
- 'Target Malaria consortium: Vector-Based Control of Transmission consortium', Bill and Melinda Gates Foundations, 2020-2025 - £85M, ~£1,700,000 to Keele (Tripet et al).

4. Details of the impact (indicative maximum 750 words)

Keele has contributed to tackling malaria through: research supporting GM mosquito-vector releases; efforts to change perceptions, strengthen networks; and establishment of infrastructure and governance processes in critical low-to-middle income countries (LMICs). This was recognised by the former Chair of the All-Party Parliamentary Group on Malaria and Neglected Tropical Diseases (APPMG) (**5.1**). Through the TM project, Keele researchers have used genetic engineering technologies to create sterile male mosquitoes, leading to the first ever GM mosquito releases, acquisition of data about their fitness and behaviour, and changing perceptions on novel integrated mosquito population control strategies (https://targetmalaria.org/resources/). **Tripet** is the Field Entomology Technical Coordinator for TM, playing a leading role in preparing for the first modified mosquito release in Africa (**5.2**, **5.4**).

The work has three main impacts:

1. Engaging with stakeholders on GM technologies

Keele researchers played a key role in informing stakeholders on GM technologies, including the leadership of TM (**5.2, 5.4**), Foundation for the National Institutes of Health (FNIH) (**5.3**), GM insect engineering experts (**5.4**) and the UK government (**5.1**, **5.5**). In 2015, **Eggleston** gave expert testimony to the Advisory Committee on Releases to the Environment (ACRE) on the benefits and safety of GM insect release. This contributed to the report of the House of Lords Science and Technology committee on 'Genetically Modified Insects' that recommended the launch of field trials of GM insects to assess their potential for control of malaria and other vector-borne diseases (**5.5**).

Through TM, the vector biology group has indirectly but crucially informed debates taking place at the United Nations convention on Biological Diversity (UN) on the technical dimensions of gene-drive mosquitoes. This included organisations opposed to implementation of GM technology and was fundamental to gene-technologies entering the next phase of efficacy trials in Burkina Faso (**5.6**). As a result, at the UN Convention on Biological Diversity in Egypt (29/11/2018) a moratorium forwarded to ban gene drive research was rejected. Instead, UN members signed a treaty declaring that gene drive projects would be evaluated on a case-by-case basis.

Tripet has made significant contributions to discussions and workshops supported by the FNIH Agriculture & Food Systems Institute, which aims to advance knowledge on gene drive technologies and inform policy (**5.3, 5.10**). Recommendations from these activities have been implemented, for example, by informing an update of the WHO's Guidance Framework for testing GM mosquitoes (**5.3**).

Involvement with local stakeholders is exemplified by the field study in Burkina Faso (**3.5)** where the group worked with TM and the community to co-develop the project and empower decisions about whether sterile GM mosquitoes could be released locally (**5.6**). The community advisory group allowed a small-scale release of mosquitoes in the summer of 2019 (**5.6**).

2. Regulatory and policy development

Tripet's group contributed to field entomology guidelines for TM's activities in Burkina Faso, Mali and Uganda (**5.2**, **5.8**). These produced regulatory dossier submissions to the in-country biosecurity agencies that outline protocols and interventions (e.g., GM mosquito release and

monitoring schemes). This led to approval, by the Burkina Faso Biosecurity Agency, for the first small-scale releases of GM sterile malaria mosquitoes in Africa (**5.2, 5.6**).

On a continental level, in 2017, the African Union passed a resolution that "commits to invest in the development and regulation of the gene-drive technology" (**5.7**). Globally, Keele researchers worked with the Organisation for Economic Co-operation and Development (OECD) to assist regulators and risk assessors in developing guidance, including an *Anopheles gambiae* biology consensus document. This has informed risk assessments and approvals for "evaluating these genetically engineered mosquitoes on a case-by-case basis, before their possible approval for release in the environment" (**5.8, 5.10**).

3. Infrastructure and capacity building

The development of infrastructure and capacity for integrated vector management in Africa is a key WHO priority. Tripet has led projects and overseen the construction of facilities for GM mosquito containment (CAT-2) (**5.4)** in Mali, Burkina Faso, and Ghana. In 2009, CAEP built the first specialised CAT-2 facility in West Africa (Mali), followed in 2011 by a large semi-field system for ecological mosquito studies in Burkina Faso. These institutions utilise standard operating procedures developed by Tripet and others (**5.2**, **5.4**). TM described the opening of CAEP's CAT-2 containment facility, in 2019, as "a major contribution to infrastructure capacity development for health research in Uganda" (**5.9**). Tripet has also led the training of early career researchers in entomology research, helping to establish the next generation of African researchers and leaders in disease vector control (**5.2**, **5.4**).

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 House of Commons Debate on Tropical Diseases (27/10/2015, 9:30 am)

5.2 Testimonial from Dr Abdoulaye Diabate (PI for Target Malaria in Burkina Faso), Institute of Research in Health Sciences, Bobo-Diolasso, Burkina. 18th August 2020

5.3 Testimonial for Dr Stephanie James, Senior Vice President, Science, Foundation for the National Institutes of Health (FNIH). 11th September 2020

5.4 Testimonial from Professor Austin Burt (PI for Target Malaria consortium), Imperial College London. 24th August 2020

5.5 House of Lords Science and Technology Select Committee, 1st Report of Session 2015 - 2016, 'Genetically Modified Insects'

5.6 Blog (2019) 'Target Malaria proceeded with a small-scale release of genetically modified sterile male mosquitoes in Bana, a village in Burkina Faso'

5.7 African Union resolution, Assembly of the Union Twenty-Ninth Ordinary Session 3 - 4 July 2017 Addis Ababa, Ethiopia

5.8 Organisation for Economic Co-operation and Development (OCED) Working Group on the Harmonisation of Regulatory Oversight in Biotechnology, 14-15 March 2019

5.9 Invitation to the opening of the Target Malaria Insectary by His Excellence Yoweri Kaguta Museveni, the President of the Republic of Uganda. 29th July 2019

5.10 Testimonial Dr Andrew Roberts, Vice President of Biotechnology at the Agriculture & Food Systems Institute (AFSI). 21st September 2020.