Background

Malaria is a disease caused by protozoan parasites in the genus *Plasmodium* and is transmitted to humans by the bites of infected Anopheles mosquitoes. The World Health Organization (WHO) estimates that there were ~216 million cases and ~445,000 deaths due to malaria in 2015 (World Malaria Report 2017) and more than 90% of these were in Africa. No effective vaccine exists yet for this disease, and parasite resistance to prophylactic and therapeutic drugs requires the discovery of at least one new chemical every five years.

Mosquito vector control measures have the greatest success in reducing malaria infections and deaths (Effect of malaria control). Insecticide-treated nets can reduce severe disease by 60% and other vector-targeted approaches also contribute significantly. However, these measures alone are not enough to achieve eradication (Reducing Malaria Transmission), and new technologies are needed urgently. Among the more promising are genetic strategies that will control vector mosquitoes and block parasite transmission.

Genetic strategies seek to eliminate vector mosquitoes or reduce their densities below thresholds needed for stable parasite transmission (population suppression), or make them incapable of transmitting parasites (population modification) (Genetic Modification of Vector Populations). Transgenesis technologies can produce mosquito strains that carry genes that contribute to both strategies however, long-term, cost-effective and sustainable malaria elimination requires the development of genetic strategies that are resilient to the immigration of parasite-infected mosquitoes and people, and the lack of such tools represents a significant unmet need in the malaria eradication agenda.

Mosquito population modification strains carrying genes conferring parasite resistance have the appropriate design features for this purpose. Wild, parasite-susceptible mosquitoes invading a region populated by an altered strain acquire the parasite-resistance genes by mating with the local insects, and persons with parasites moving into the same region cannot infect the resident vectors, and therefore are not a source of parasites for infection of other people. Population modification also shares with other genetic control strategies the exploitation of the ability of male mosquitoes to find females, and this is expected to offer access to vector populations that would be unreachable using conventional tools. Release of a population modification strain alone or in conjunction with other tools should make elimination possible in carefully-selected endemic areas. Population modification strategies can be used as early as the control phase of an elimination campaign alongside other measures that reduce disease incidence. As the efforts progress, this strategy takes on a larger role and ultimately is the mainstay of the prevention of reintroduction phase. As this elimination is achieved, the released altered mosquitoes facilitate consolidation of this success by allowing resources to be moved to another region with the confidence that the area just cleared will remain so. Thus, population modification offers a real chance to achieve sustainable elimination and therefore contributes significantly to malaria eradication.

A promising newly-emerging strategy for combating malaria is based on harnessing gene drive systems to spread anti-malarial genes throughout mosquito populations rendering them unable to transmit the parasites. The James laboratory (UC Irvine) developed highly-effective anti-malarial gene cassettes that can result in a 100% block of P. falciparum, the deadliest human malaria parasite, in mosquitoes (Resistance to Plasmodium). Working in collaboration with Ethan Bier and Valentino Gantz (UC San Diego), these effector gene cassettes coupled to a gene-drive system based on CRISPR/Cas9 biology were shown to spread with 99.5% efficiency in An. stephensi, the major malarial vector mosquito in urban India (gene drive). We will adapt this new technology to a major African vector, An. gambiae, and perform a confined field trial in a well-chosen site to demonstrate proof-of-principle for how this system will eliminate malaria locally. If successful, this strategy then could then be incorporated as part of a broader initiative to achieve malaria elimination throughout Africa within the following decade.