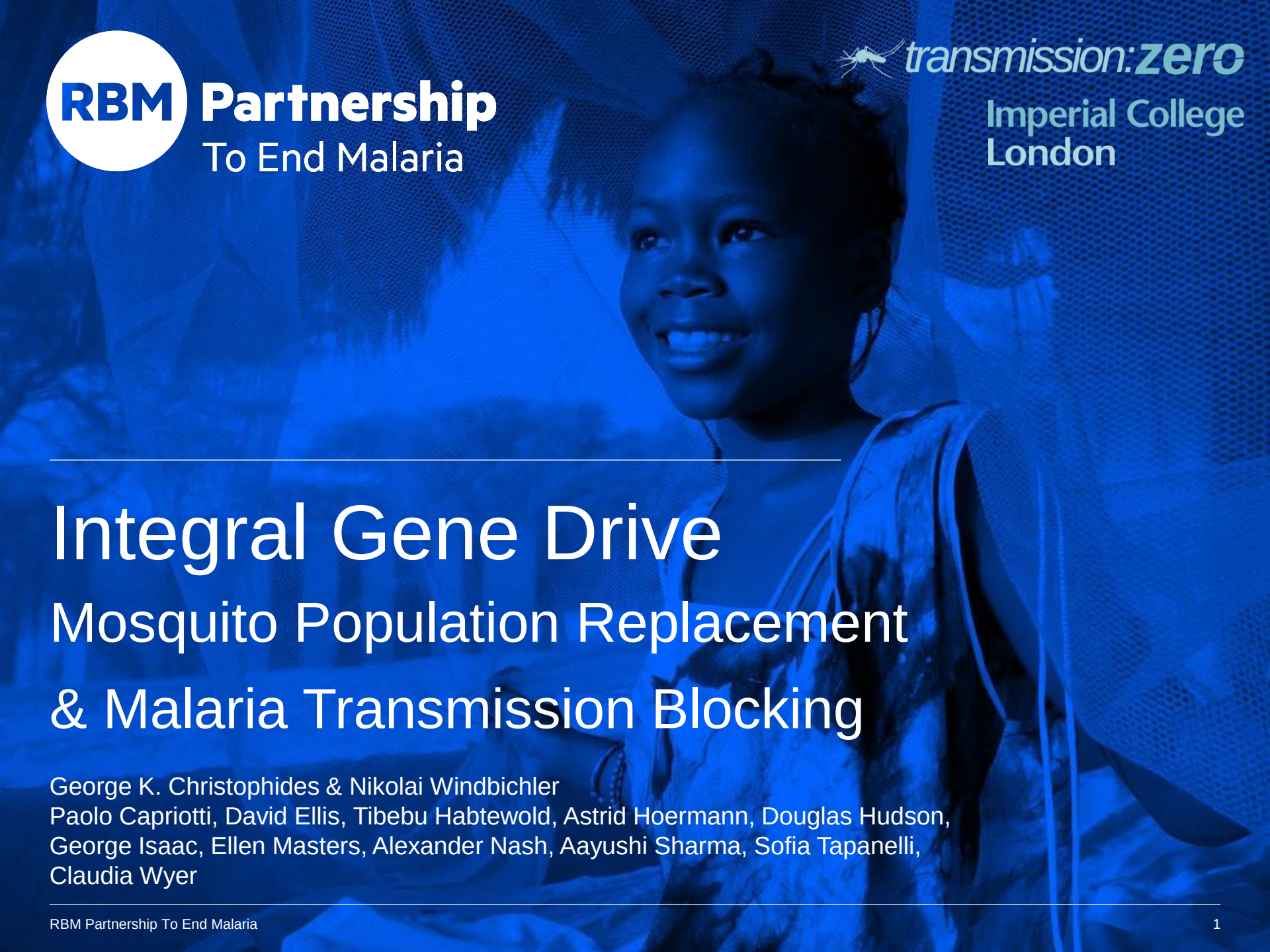


RBM Partnership To End Malaria

transmission:zero

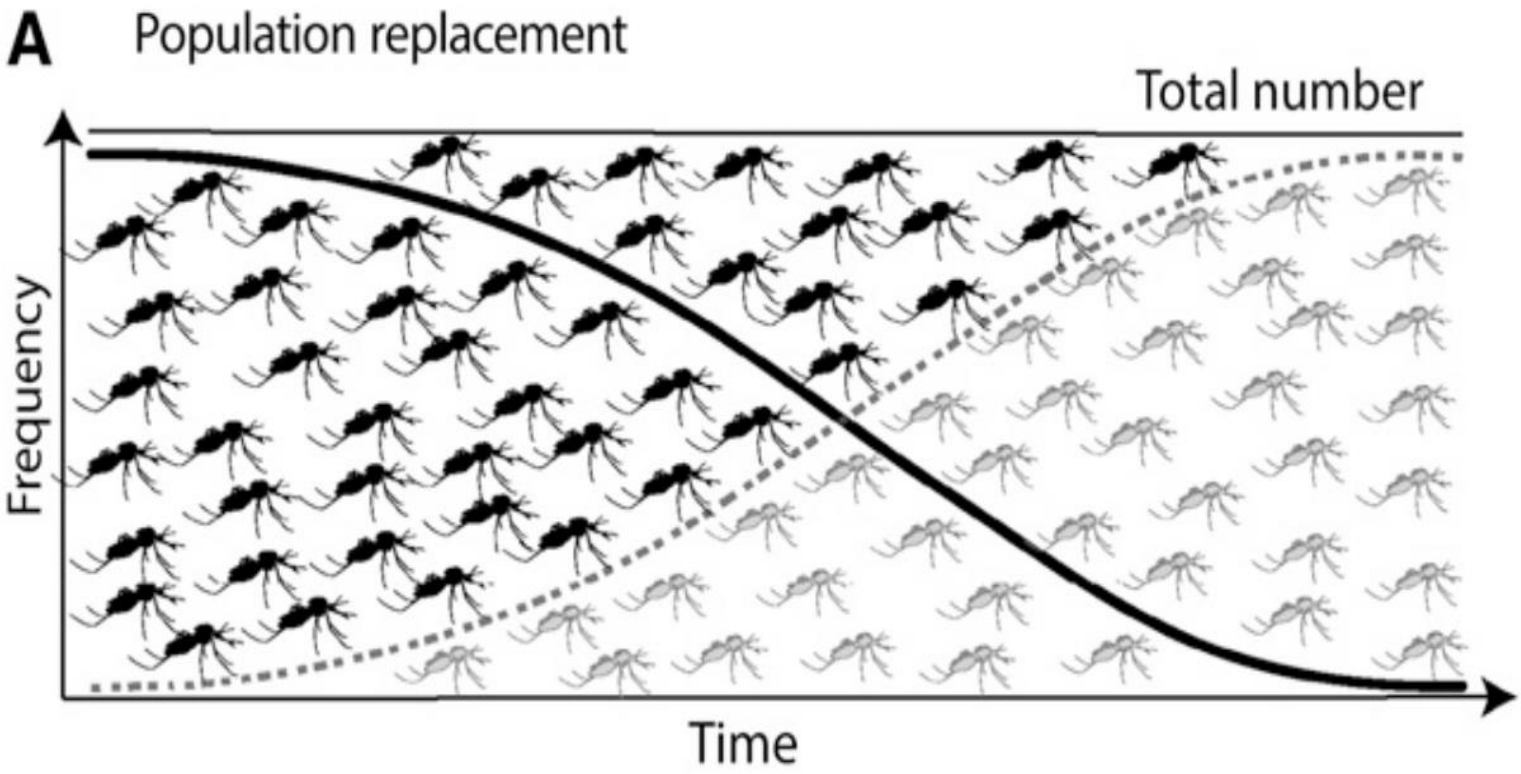
Imperial College London

Integral Gene Drive

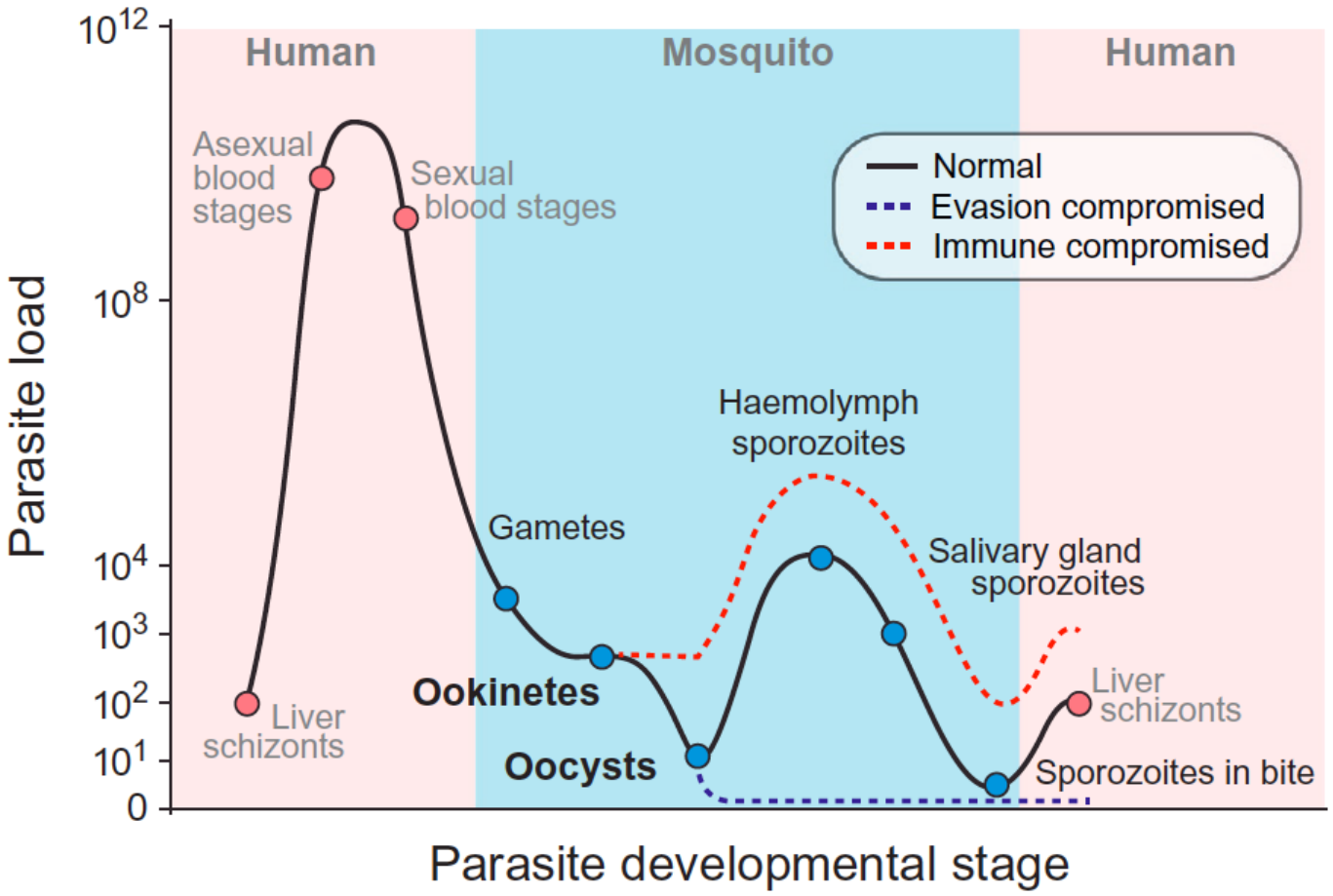
Mosquito Population Replacement & Malaria Transmission Blocking

George K. Christophides & Nikolai Windbichler
Paolo Capriotti, David Ellis, Tibebu Habtewold, Astrid Hoermann, Douglas Hudson, George Isaac, Ellen Masters, Alexander Nash, Aayushi Sharma, Sofia Tapanelli, Claudia Wyer

Mosquito population replacement



Targeting parasite population bottlenecks

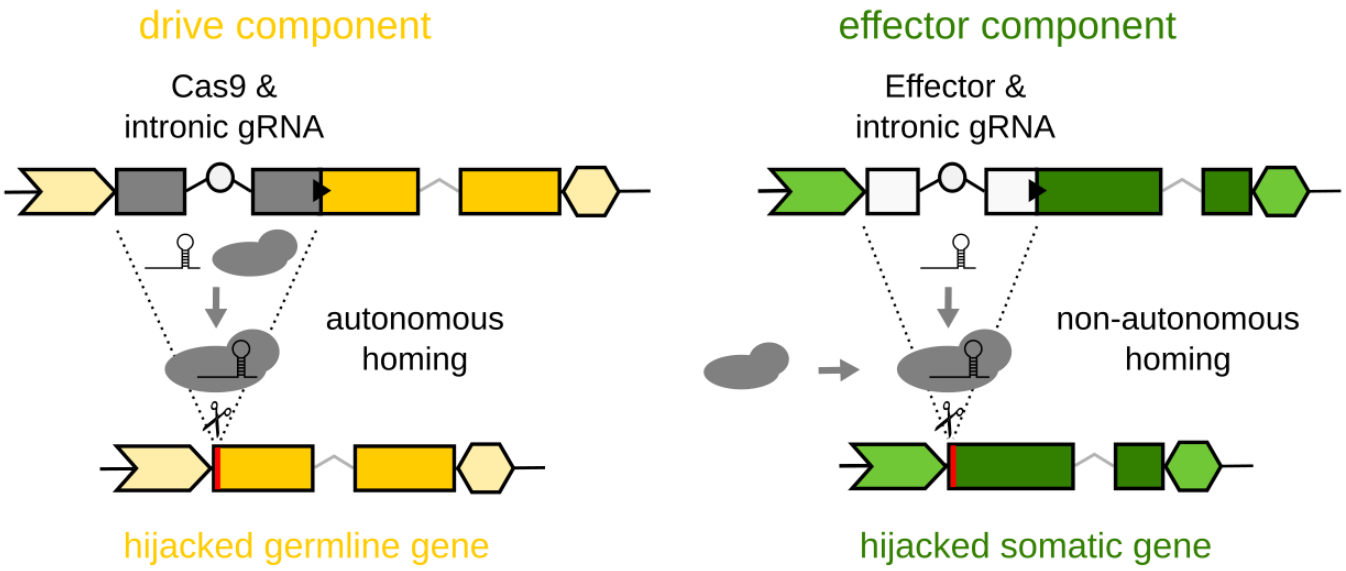


- Mosquito midgut traversal is the most critical phase
- Most parasites are eliminated by mosquito immune responses

Challenges

- Molecular design and operational complexity
  - Large and complex synthetic constructs
  - Detail spatiotemporal characterisation of promoters
  - Random integration or very little choice of loci
  - Cannot separate drive and effector for testing
- Long-term efficacy and stability of effector/drive module
  - Resistant driver (mutations or non-homologous recombination)
  - Loss of effector
  - Fitness cost of each and all components
- Identification of appropriate effector
  - No ideal effector available
  - Laboratory tests lack sensitivity and robustness
  - Proposed effectors only tested against laboratory parasites
- Regulatory hurdle
  - Driving mosquitoes cannot be easily tested in the field

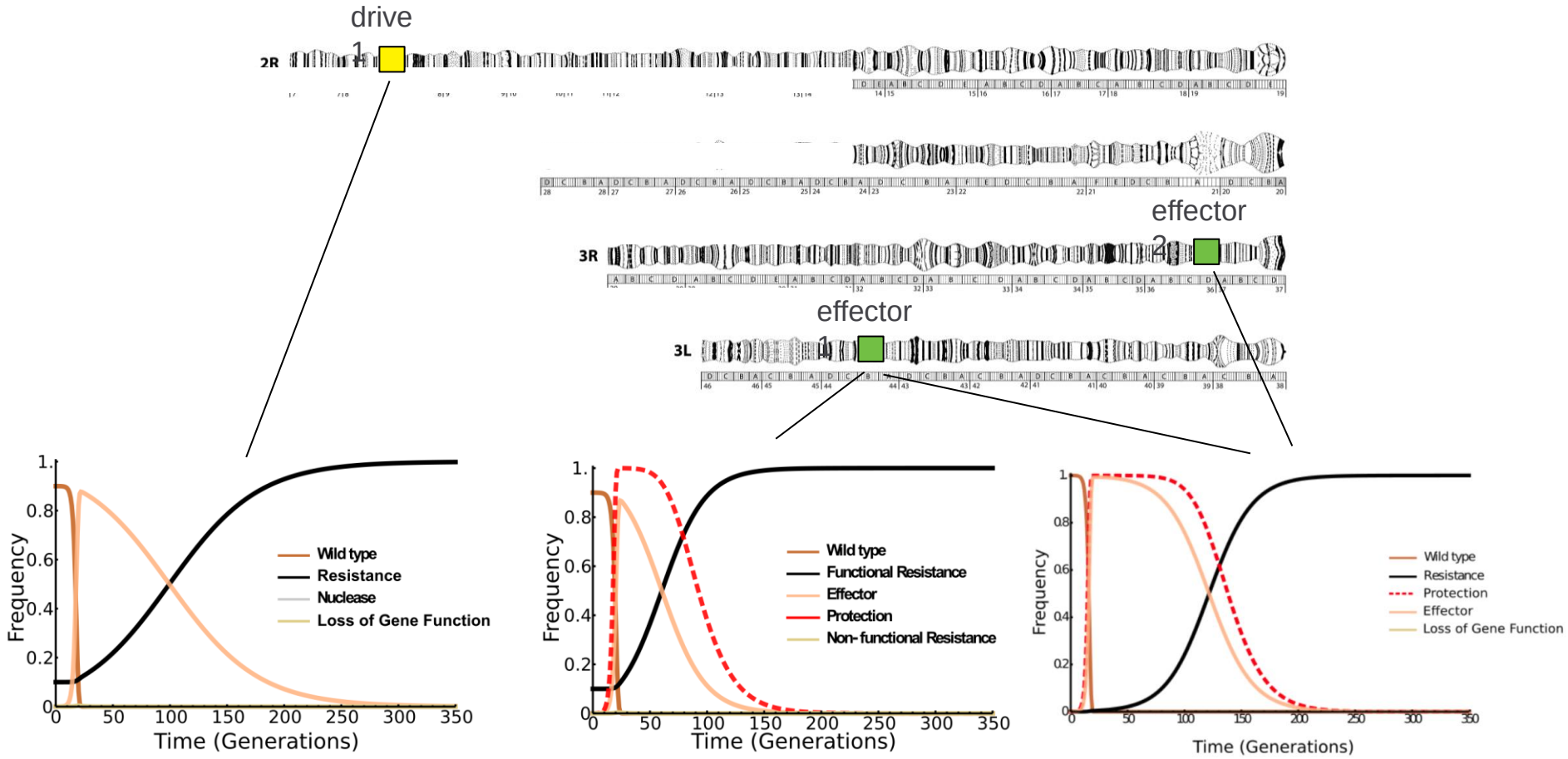
Integral Gene Drive (IGD)



- Disassociate effector and driver
- Effector can drive only in the presence of driver
- Minimal genetic modifications
- Integration within any host gene of choice
- Resistance is linked to loss of host gene
- Combination of multiple drivers and effectors

Nash et al., Open Biology (2018)

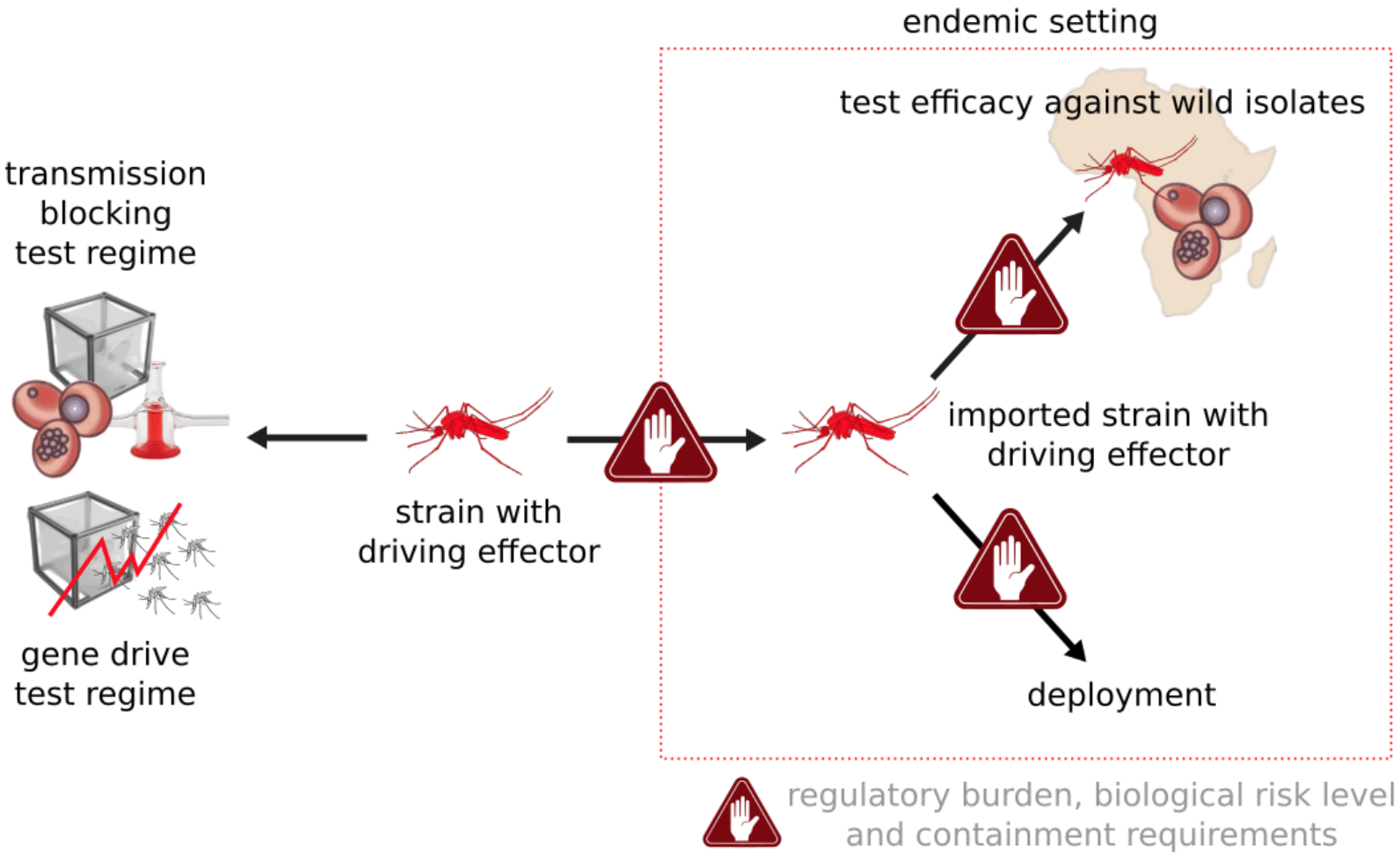
Modelling efficacy of IGDs



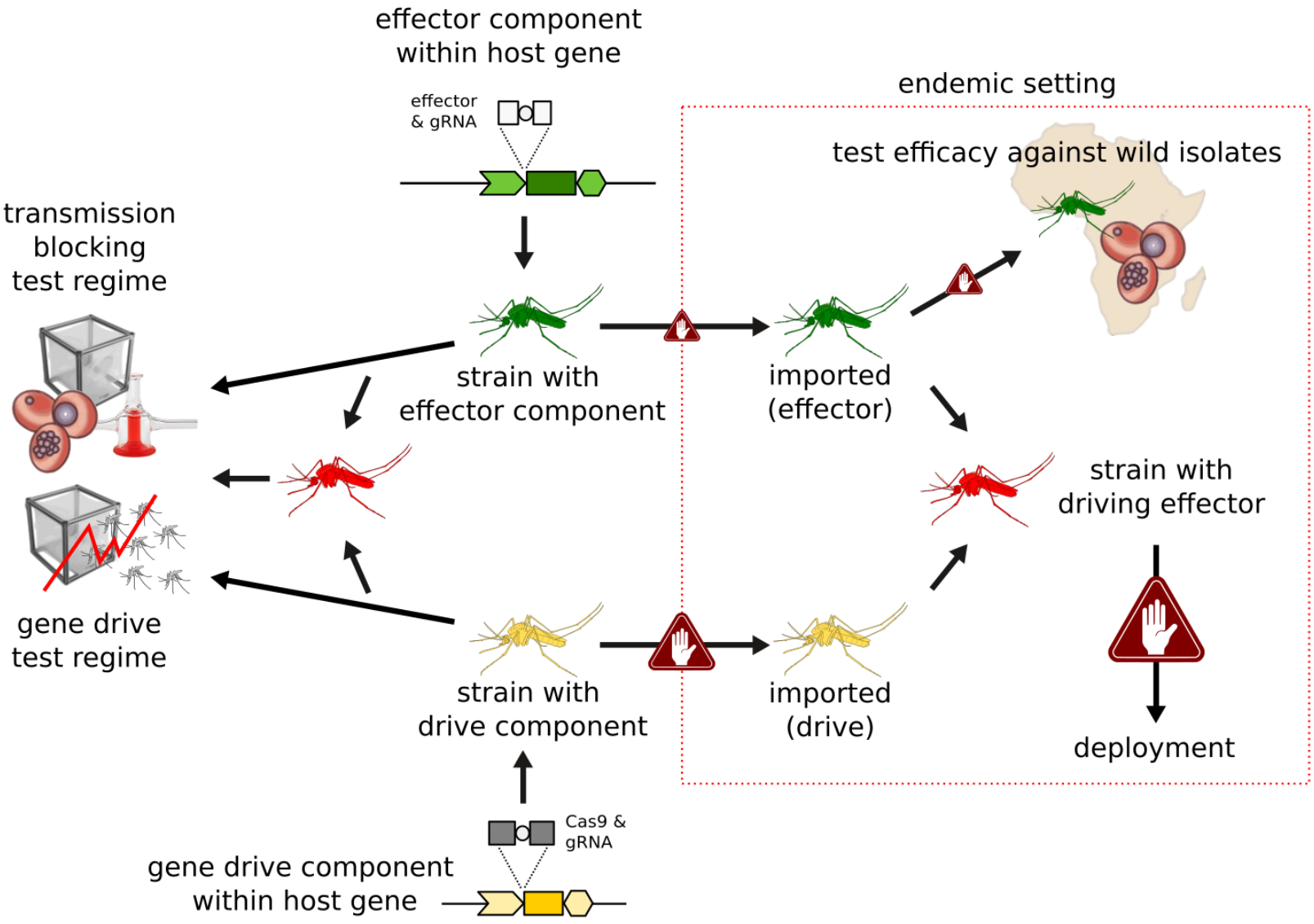
- Substantially increased protection even in case of pre-existing resistance
- Duration of 95% protection: 81 / 15 generations (no / 10% pre-existing resistance; i.e. 5-7 / 1-2 years) and 103 / 38 generations (no / 10% pre-existing resistance; i.e. 6-9 / 2-4 years) for 1 and 2 effectors, respectively

Nash et al., Open Biology (2018)

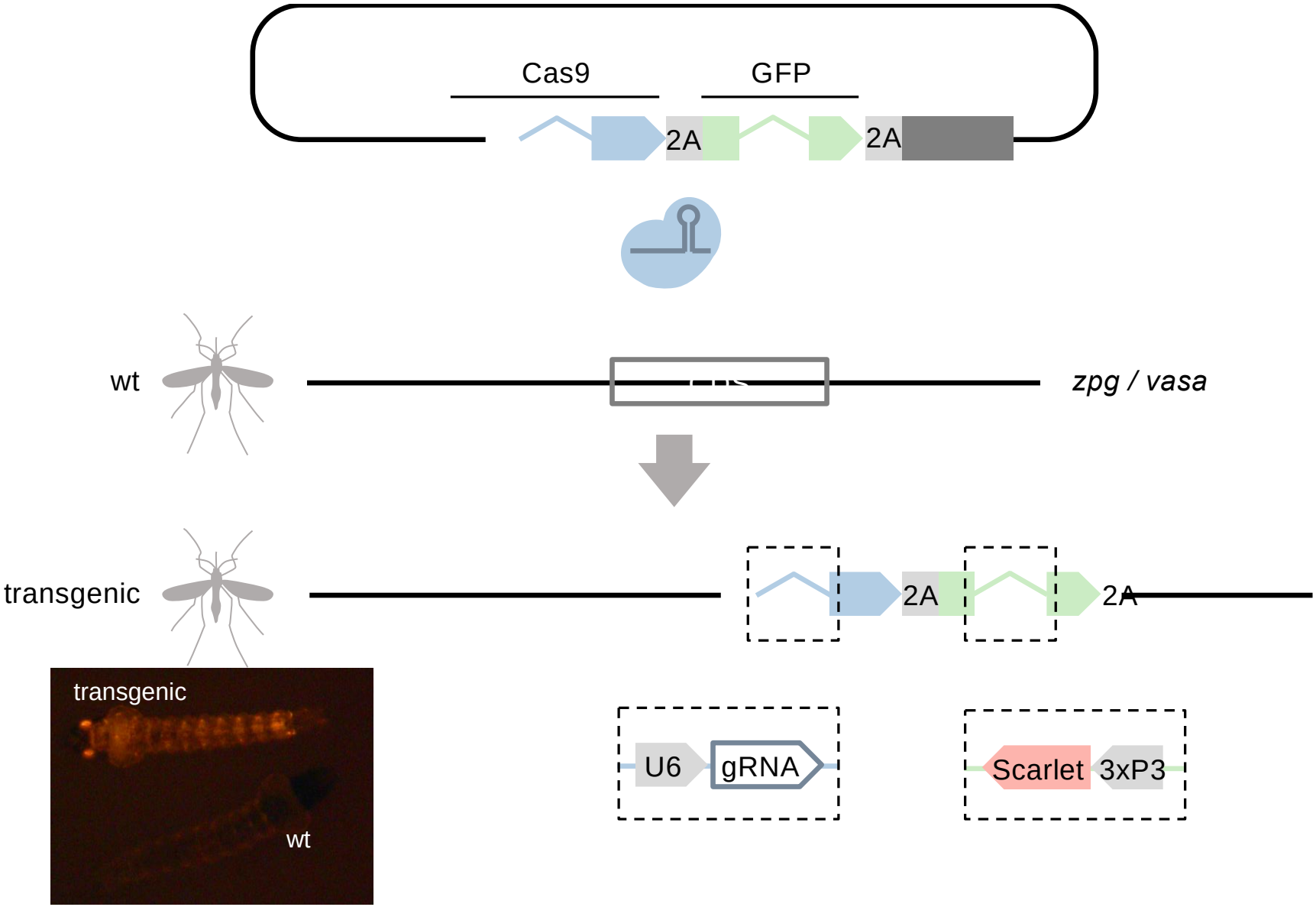
Traditional operational design



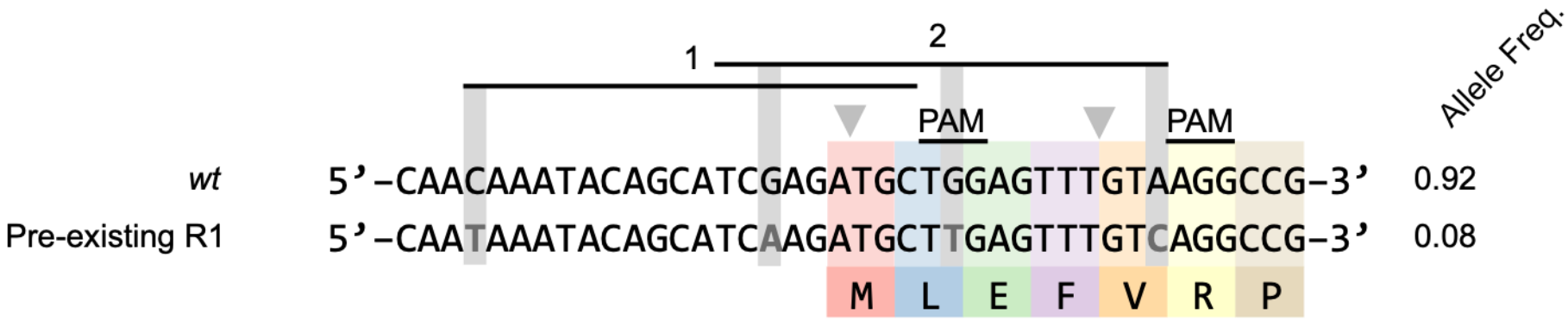
IGD operational design

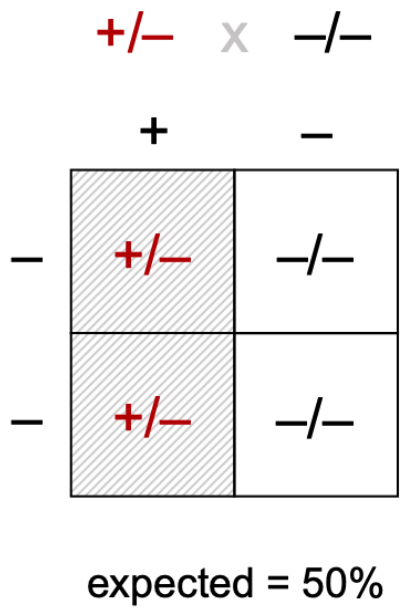


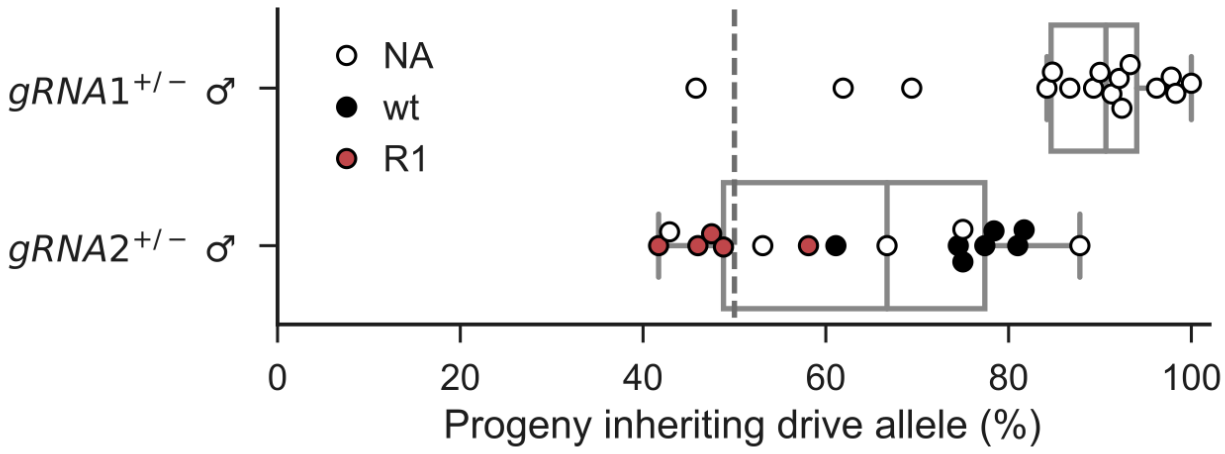
Gene drive – example in zpg locus



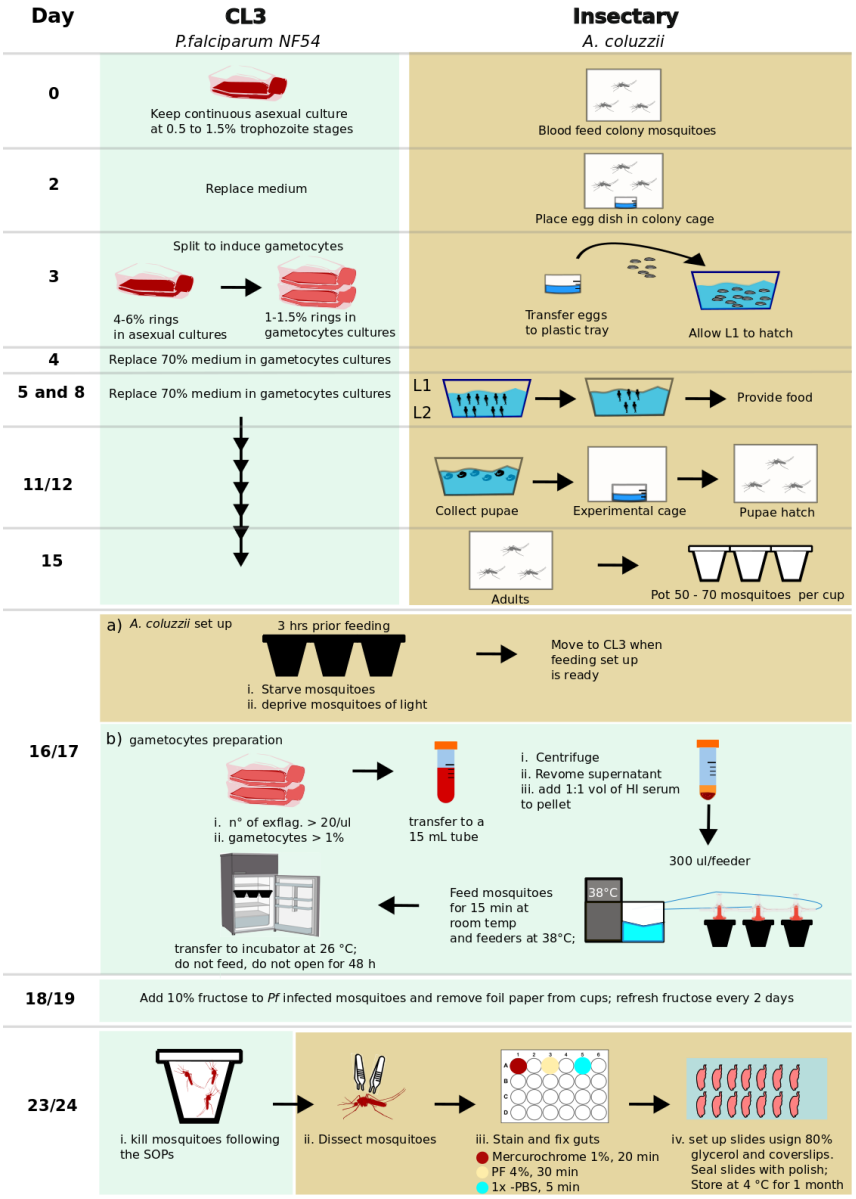
Gene drive and pre-existing resistance

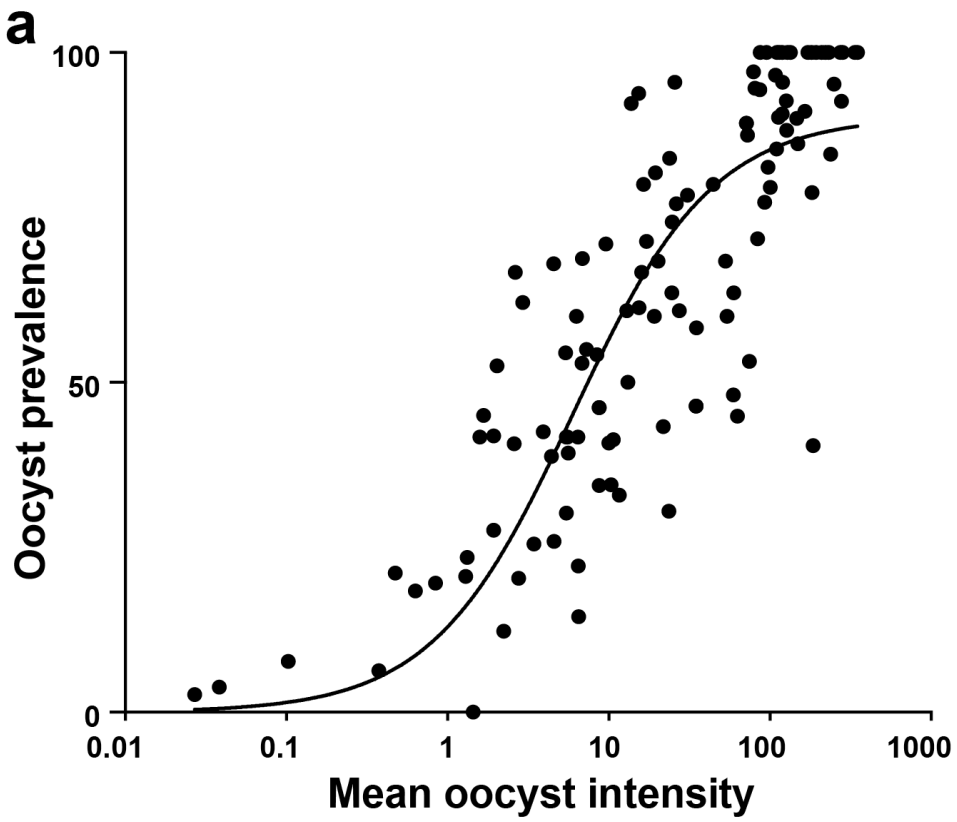






SMFA sensitivity and robustness





Habtewold et al., Malaria J (2019)

Effectors currently tested

Antimicrobial peptides from other species

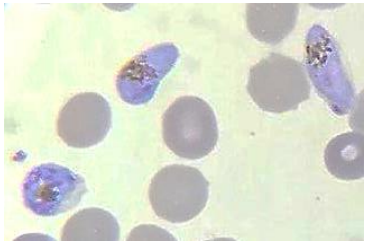
Scorpine

Mellitin

Magainin

Anopheles infection regulators*:*
anti-malarial: REL2
pro-malarial: CLIPA2, CLIPA12
Homeostasis: FN3Ds

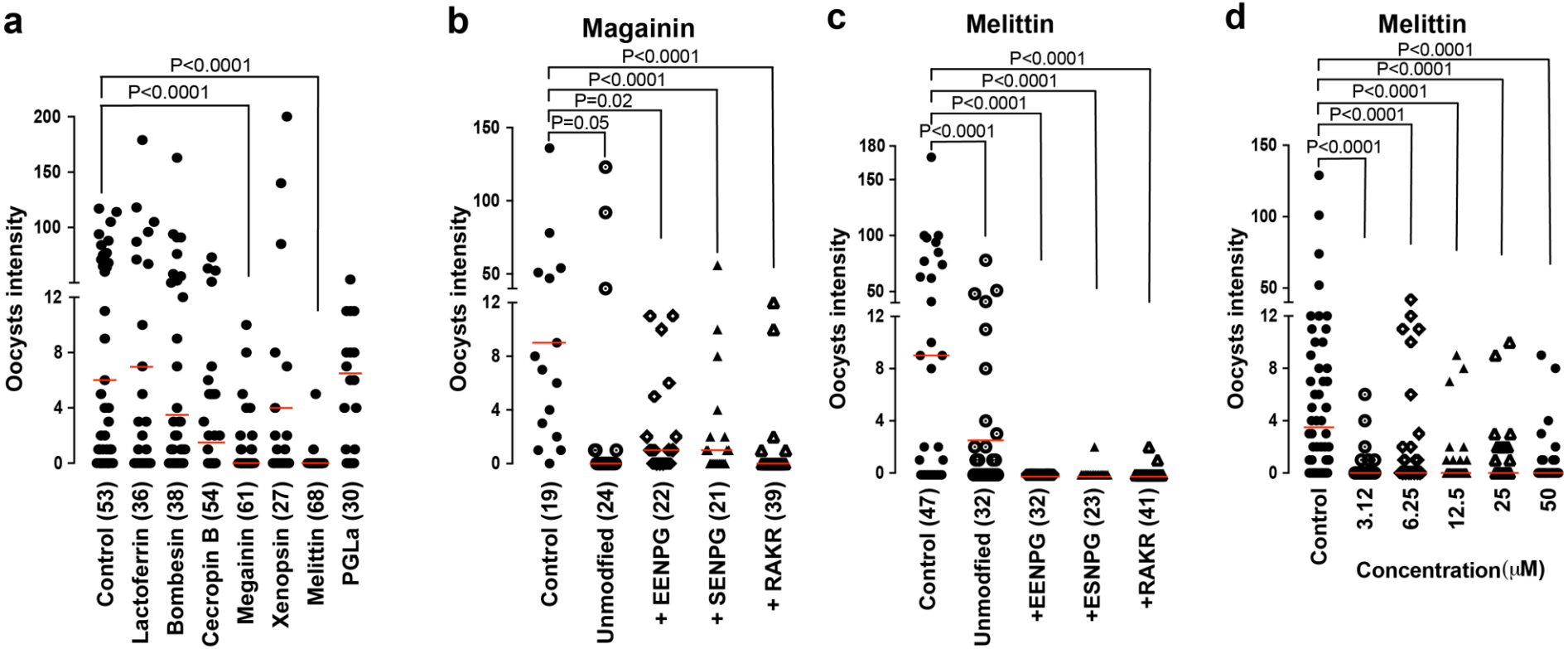
Plasmodium immune evasion: PIMMS43, P47, P230



nanobodies raised

in llamas

Exotic Antimicrobial Peptides



Habtewold et al., Malaria J (2019)

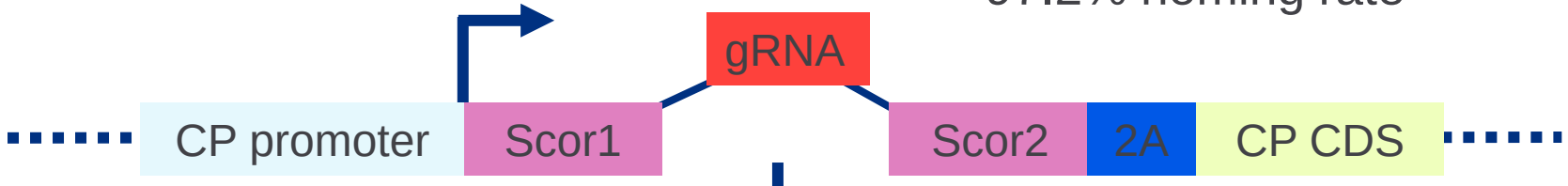
Scorpine – an example in the CP locus

Carboxypeptidase locus

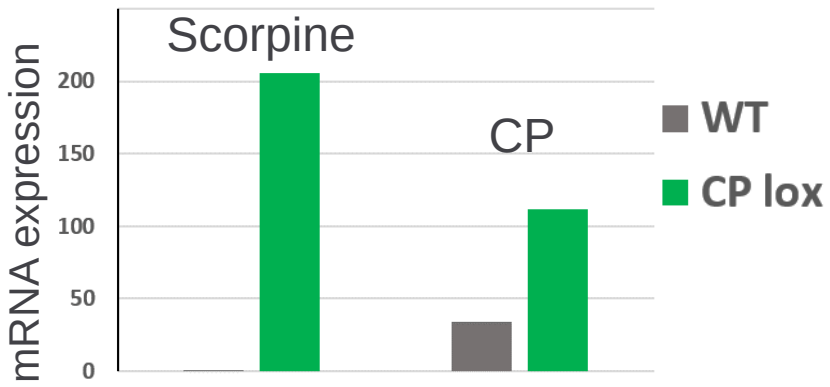
lox-out marker

X Cas9

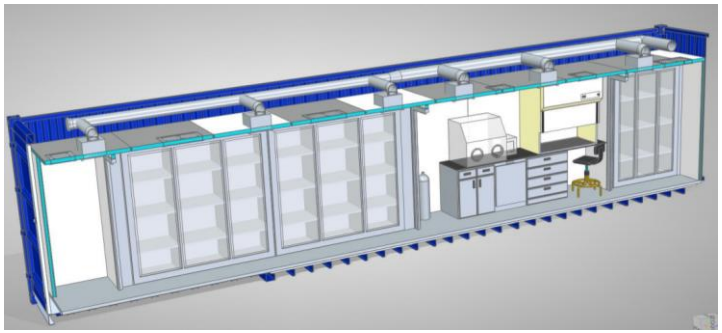
97.2% homing rate

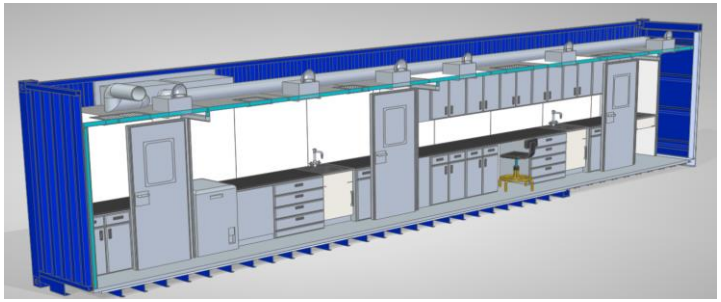


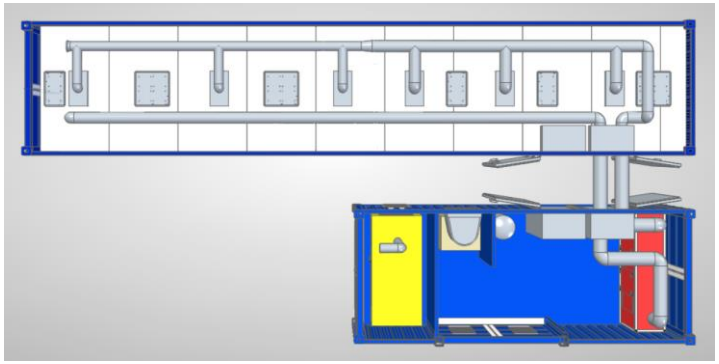
splicing efficiency:



Mobile Portable Laboratory CL3 (MBL CL3)







INGECLIMA (The Albian Group), Bilbao, Spain
Technical plans available via Global Access

IFAKARA HEALTH INSTITUTE
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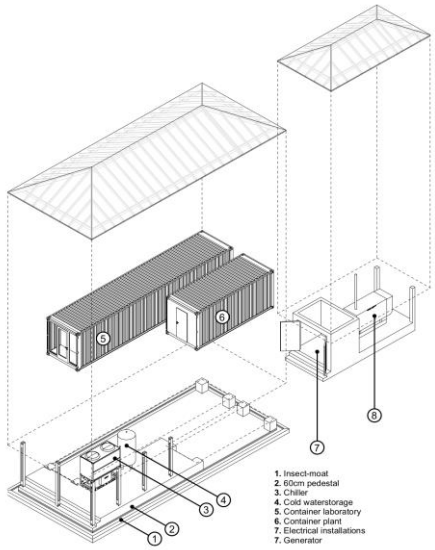


Brian Tarimo, Sarah Moore, Fredros Okumu
Marcelina Finda, Lorenz Hofer, Theresia Nkya

Future plans for field testing

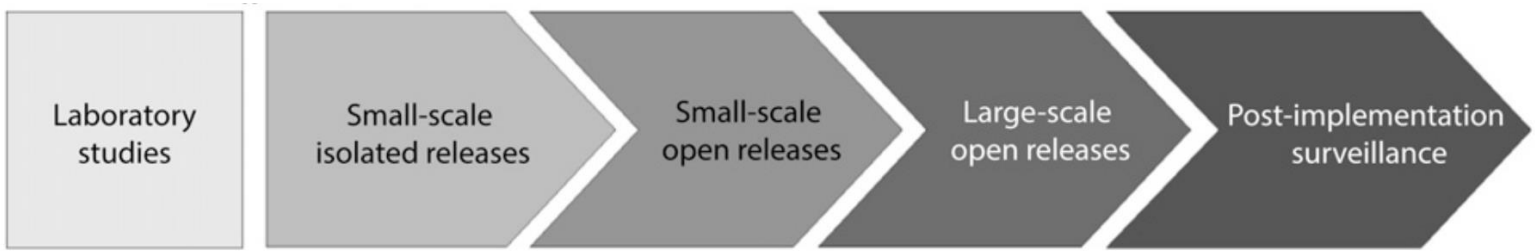
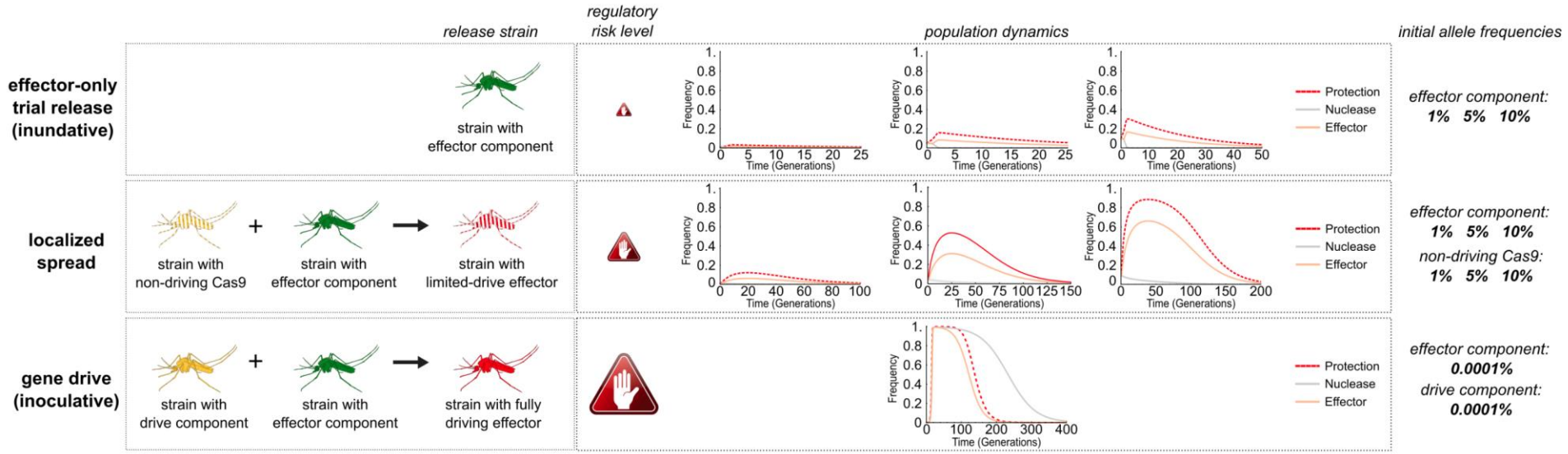


FIGURE 3. Pathway to deployment of gene drive mosquitoes.



Institutions & Funding