GENECONVENE GLOBAL COLLABORATIVE
Advancing Best Practices in Genetic Biocontrol Technology

FNIH
Foundation for the National Institutes of Health

Update on the Development of Gene Drive Mosquitoes for Malaria Control

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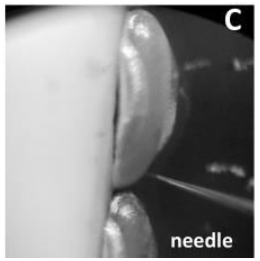
Genetic biocontrol is an umbrella term for a set of approaches

Make a genetic change to cause a desired effect…



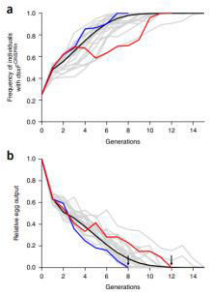
Inject mosquito egg with plasmid DNA

Modified mosquito

…then release into a wild population to mate

Release of modified

Mating between modified and wildtype



Impact based on modification

Genetic biocontrol

Engineered gene drive

- Self-sustaining / autonomous
- Self-limiting drive, e.g., split drive
- …

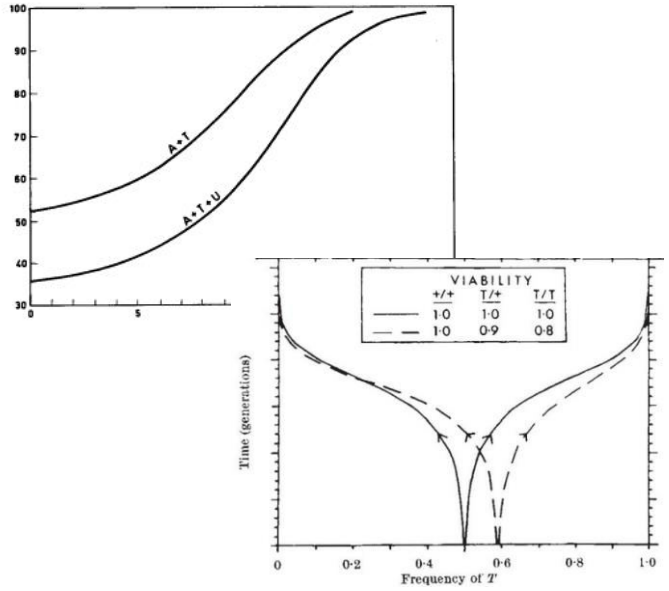
- Self-limiting, e.g., sterile (SIT), male selecting
- …

Genetic biocontrol of insects is an 80-year-old concept

Observations of natural gene drive stretch back ~100 years

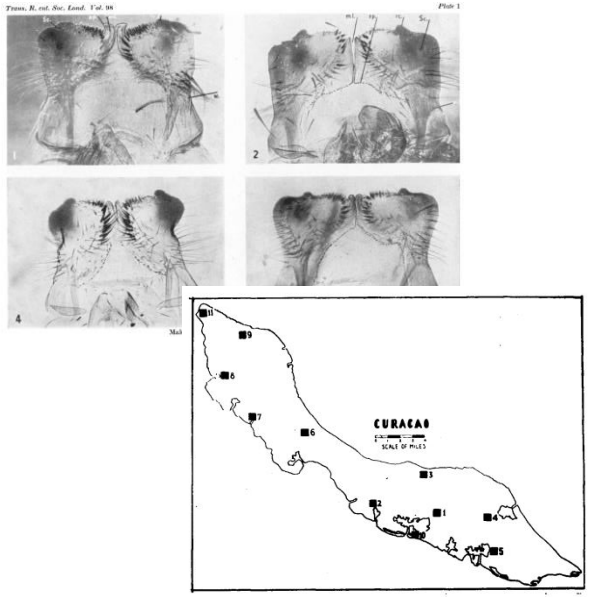
Barbara McClintock

The concept of its use for vector control is over 80 years old



Serebrovsky (1940)
Curtis (1968)

Genetically sterile biocontrol also dates to the 1940s



Vanderplank (1947)
Baumhover et al. (1955)

Detailed genetic biocontrol timeline: www.geneconvenevi.org/gene-drive-timeline

Genetic biocontrol is a persistently attractive approach because of a unique combination of potential benefits

Potential benefits of genetic biocontrol

- **Efficacy:** Genetic biocontrol approaches have locally eliminated species
- **Mechanism of action:** Generally independent from other control MOAs
- **Specificity:** Primary impact is on the target organism
- **Area-wide effect:** No individual-level behavior is required for benefits

African Union and WHO recognize potential

African Union

WHO

1990

2021

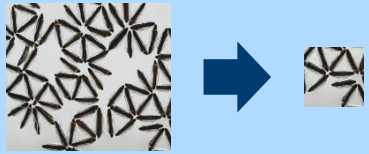
Background figure: PubMed records for "gene drive" from 1990 (1) to 2021 (100)

Key parameters: target outcome of the modification, and how long the modification persists after a release

Target outcome

Population suppression

Fertility reduction/lethality

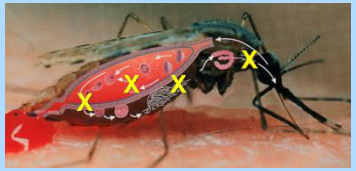


Sex ratio distortion

♀ ♂ ➡ ♂ ♂

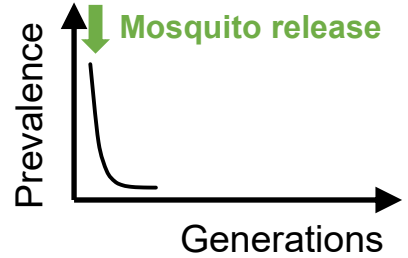
Population modification

Pathogen transmission blocking

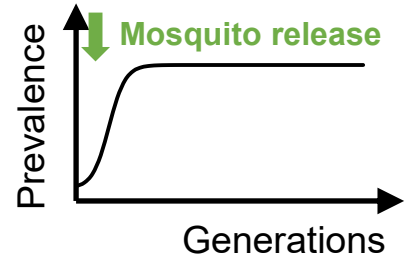


Persistence

None or rapid decline (no drive)



Indefinite (drive)



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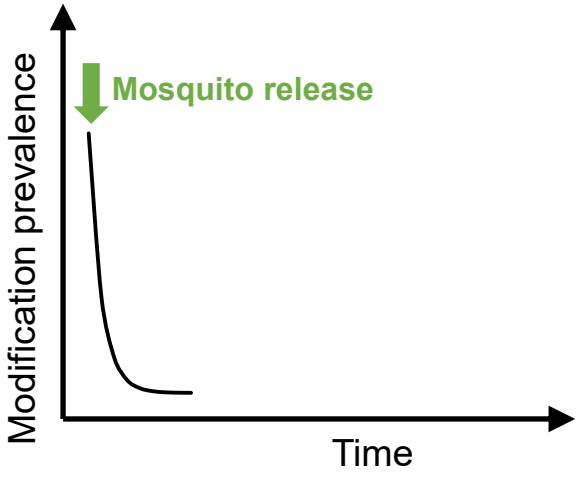
Non-drive approaches like SIT and Oxitec typically require large, sustained releases and have impact localized to the release area

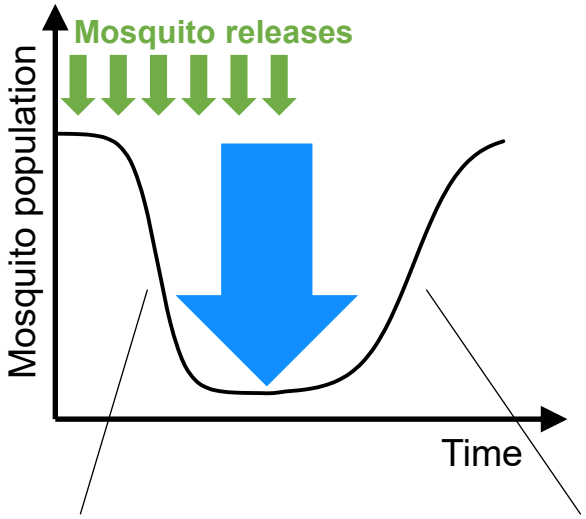
Persistence

When the modification doesn't drive…



Release approach

…it is maintained in the population through sustained releases

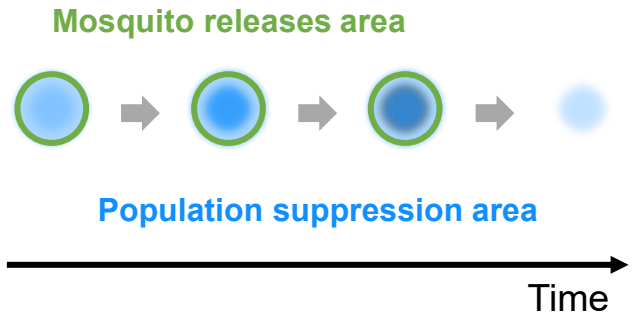


Population suppression with sustained releases

Population recovers after releases stop (unless it is eliminated)

Spatial extent

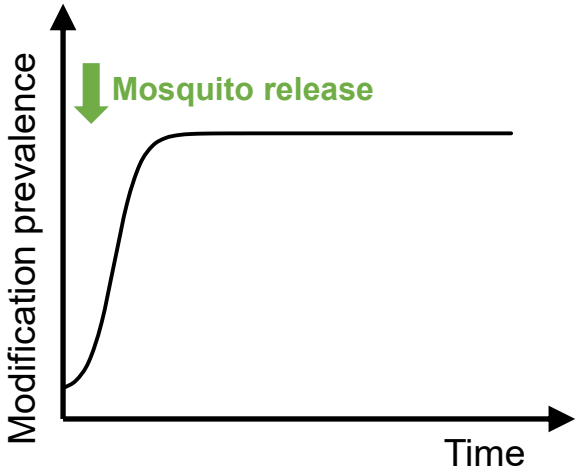
Impact is localized to the release area



Self-sustaining gene drive approaches like Target Malaria typically require small, sparse releases to have wide, sustained impact

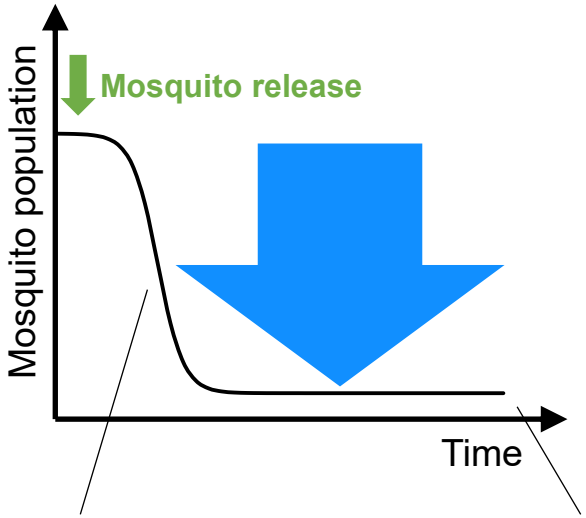
Persistence

When the modification drives…



Release approach

…small releases are sufficient to achieve impact over time

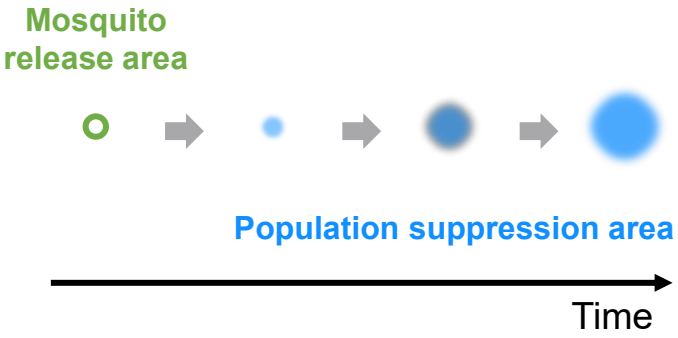


Population suppression after modification reaches high prevalence

Suppression is sustained until elimination or resistance

Spatial extent

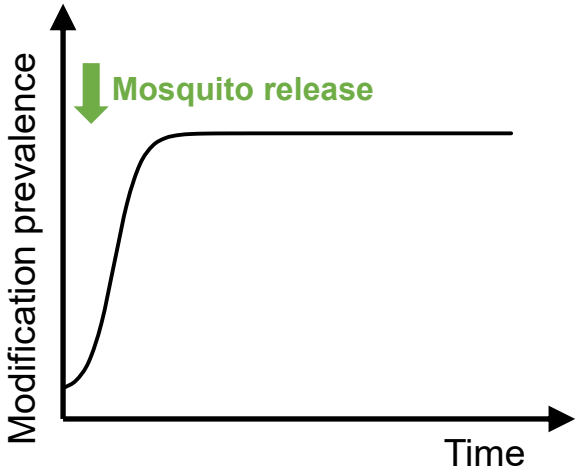
Impact area grows as drive spreads from release area



Self-sustaining population modification (transmission-blocking) approaches like UCMI and Transmission Zero are similar

Persistence

When the modification drives…



Release approach

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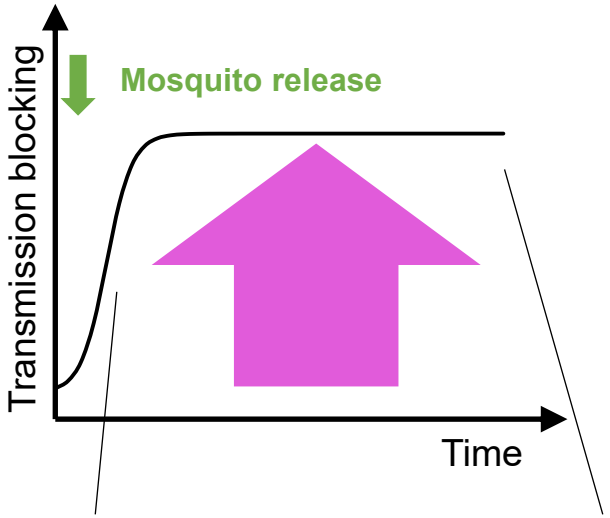
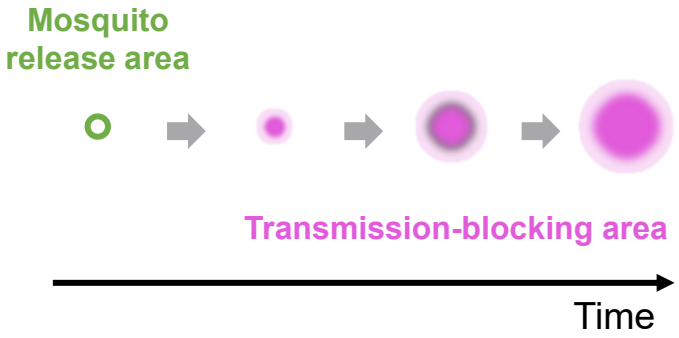


Transmission blocking increases as modification increases in prevalence

Transmission blocking is sustained (until resistance)

Spatial extent

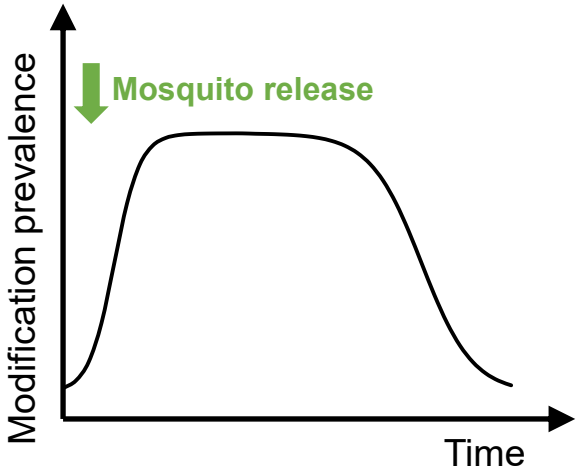
Impact area grows as drive spreads from release area



Split-drive-type approaches are designed to decay after 10s-100s generations of persistence near the release area

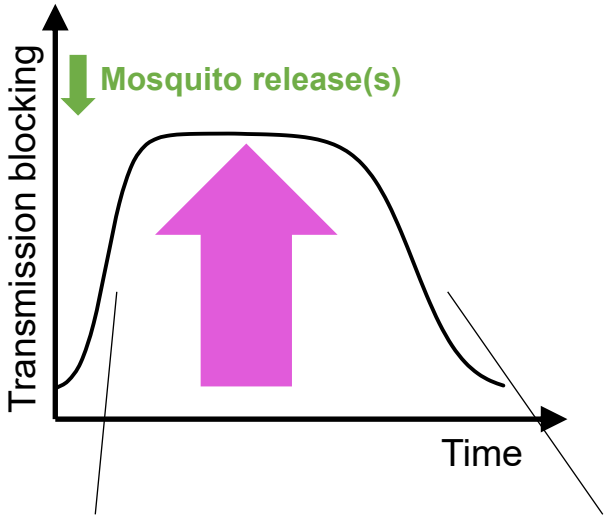
Persistence

Drive ramps up then down over time



Release approach

Increase and decrease of modification depend on releases

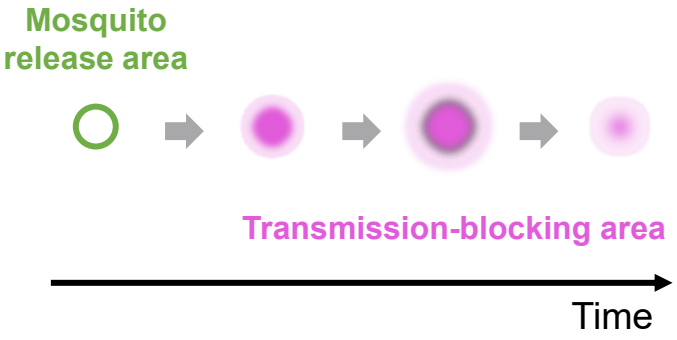


Transmission blocking increases as modification increases in prevalence

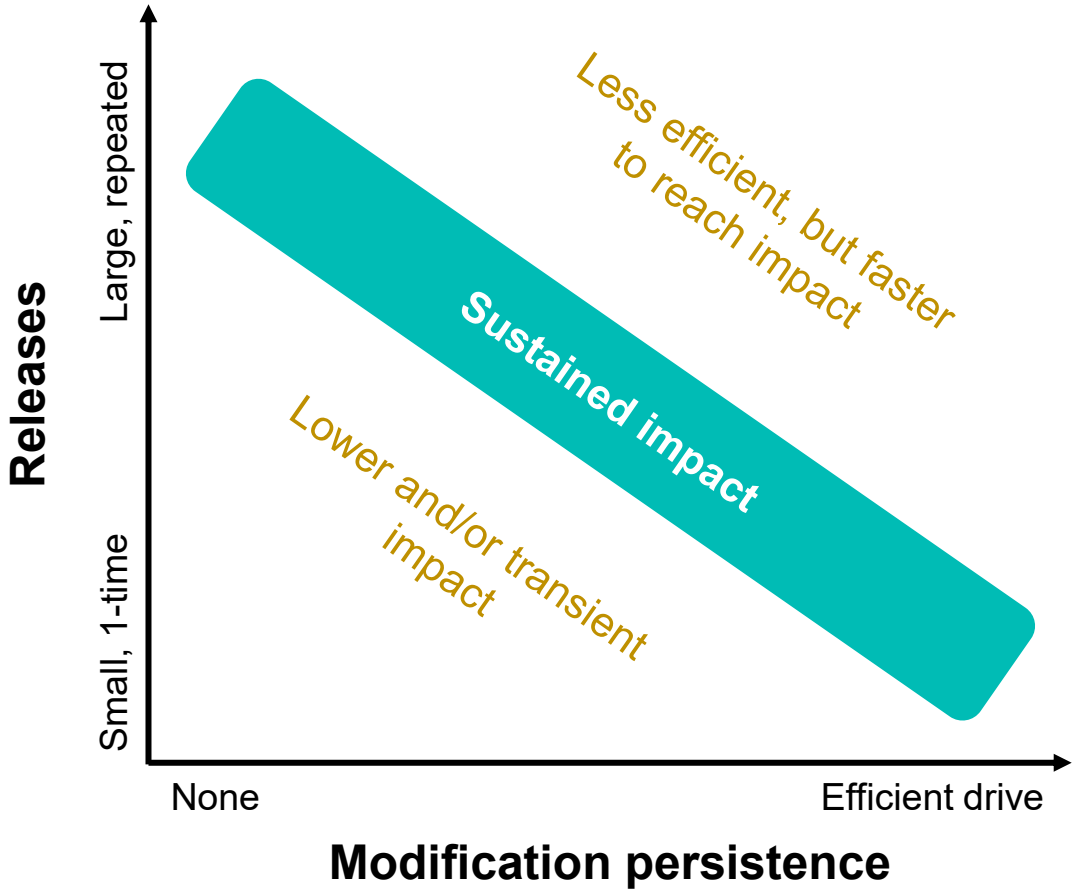
Transmission blocking is sustained until drive fades and modification decays

Spatial extent

Little drive outside of the release area



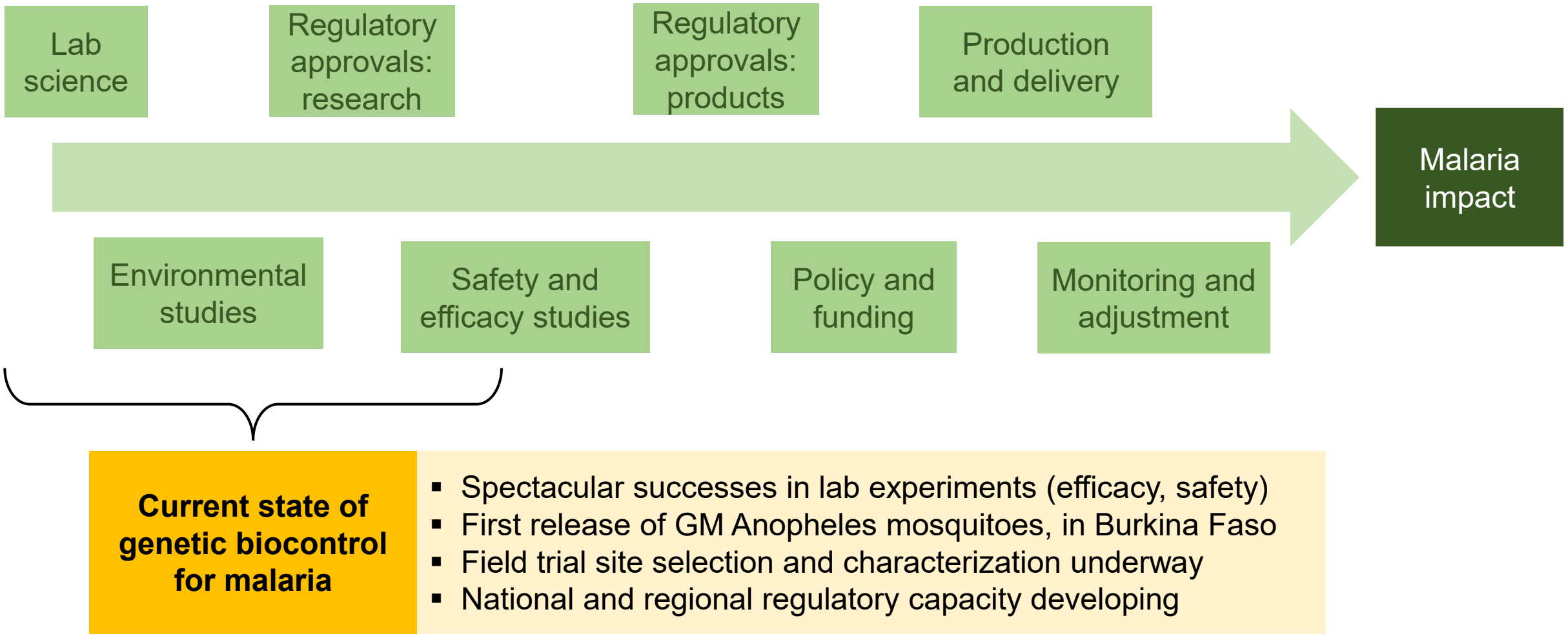
To achieve impact, there is a general balance between persistence and release requirements, with many possible variations



- Wide range of **intended persistence** is possible
  - **Sterile** (no persistence)
  - **Male bias / daughterless** (rapid decay)
  - **Split drive / daisy drive** (drives for 10s-100s of generations, then decays)
  - **Self-sustaining / autonomous** (intended to drive indefinitely)

- Persistence has implications for spatial spread, but other mechanisms **control spread directly**
  - **Threshold drive** (drive only above threshold prevalence)
  - **Private allele / tethered drive** (drive only in specific genetic background)

Recent progress on genetic biocontrol for malaria has been impressive, with important steps ahead to achieve impact

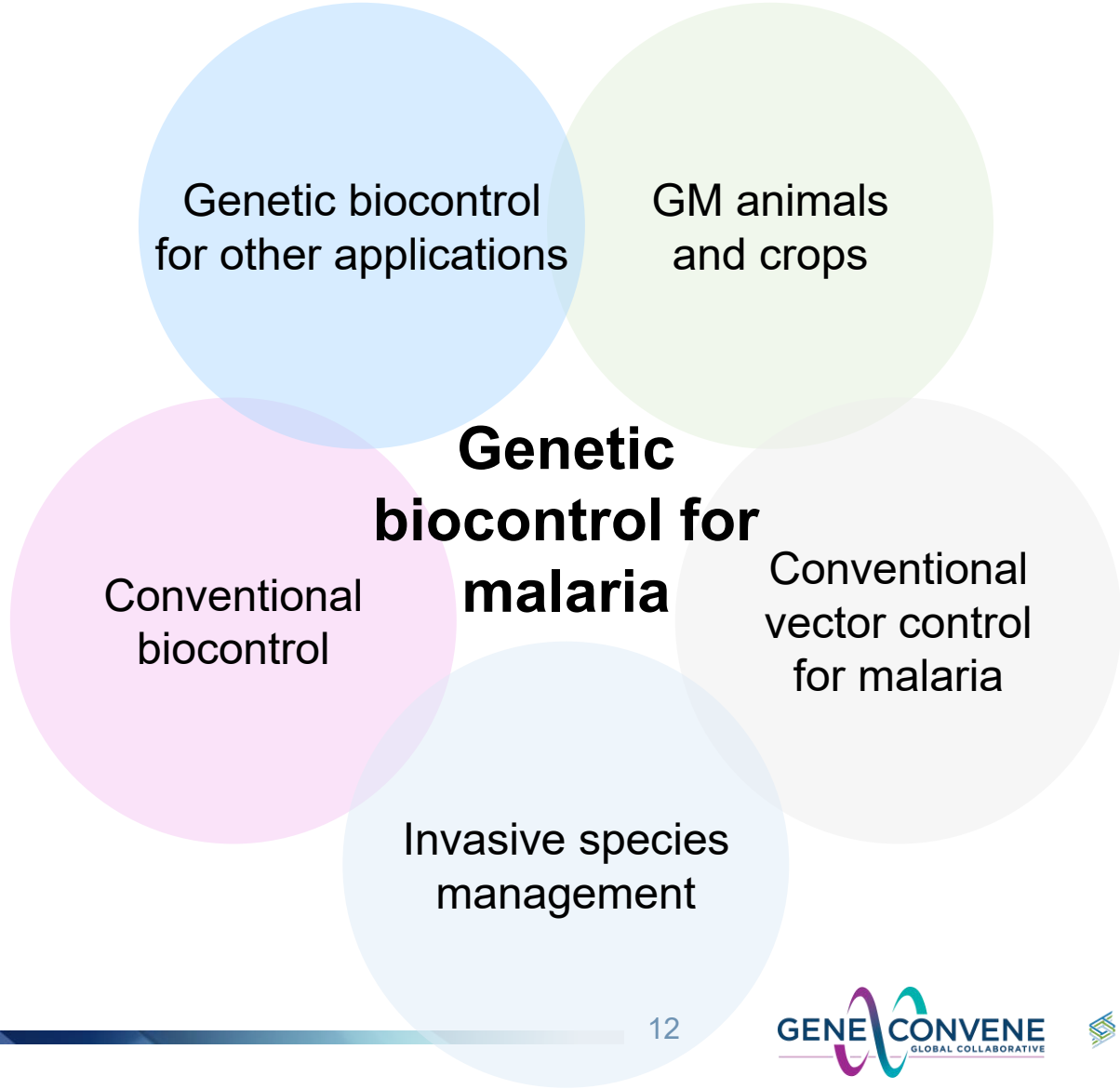


Current state of genetic biocontrol for malaria

- Spectacular successes in lab experiments (efficacy, safety)
- First release of GM Anopheles mosquitoes, in Burkina Faso
- Field trial site selection and characterization underway
- National and regional regulatory capacity developing

Many open questions for consideration, but also many domains to draw on to inform the answers

- **Enabling regulatory and policy environments for approaches that may spread across national borders**
- **Design of field trials and transition to implementation at scale**
- **Role of genetic control and reversal as risk mitigation tools**
- **Cost-effective use cases for localized genetic biocontrol**
- **Priorities for next-generation product development**



Thank you!

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www.GeneConvene.org
www.GeneConveneVI.org

The mission and approach of the GeneConvene Global Collaborative

GENE CONVENE GLOBAL COLLABORATIVE
Advancing Best Practices in Genetic Biocontrol Technology

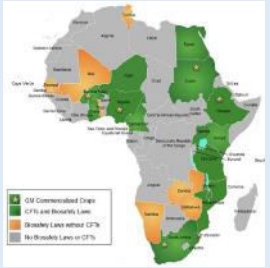
FNIH
Foundation for the National Institutes of Health

Mission

Advance best practices and informed decision making

for the development of genetic biocontrol technologies to improve public health

Identifying and Addressing Key Questions



Providing Technical Advice

Strengthening Capacity and Sharing Information

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