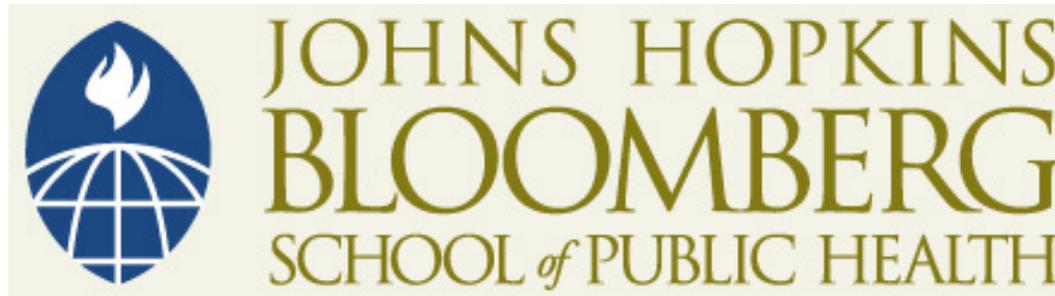


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Genetic Approaches for Malaria Control

Marcelo Jacobs-Lorena, PhD

The Malaria Problem

At risk: >2,000,000,000 in 102 countries

Infected: >270,000,000

Clinically ill: >110,000,000 cases each year

Deaths: >2,000,000 each year

- 90% in Africa
- Mainly children 5-yr-old or younger

Possible Weapons to Fight Malaria

- 1. Drugs that kill the parasite in humans**
- 2. Insecticides that kill the mosquito vector**
- 3. Vaccines**

1. Drugs

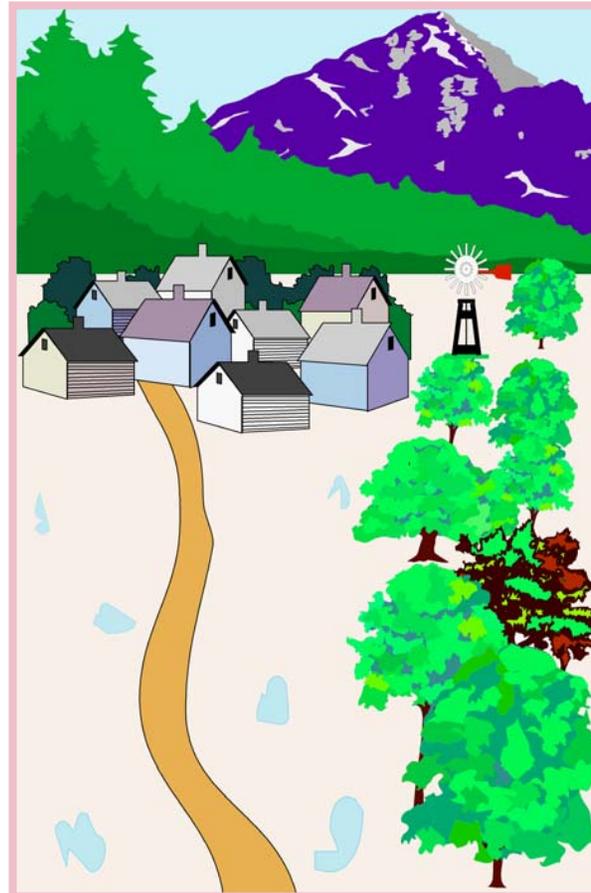
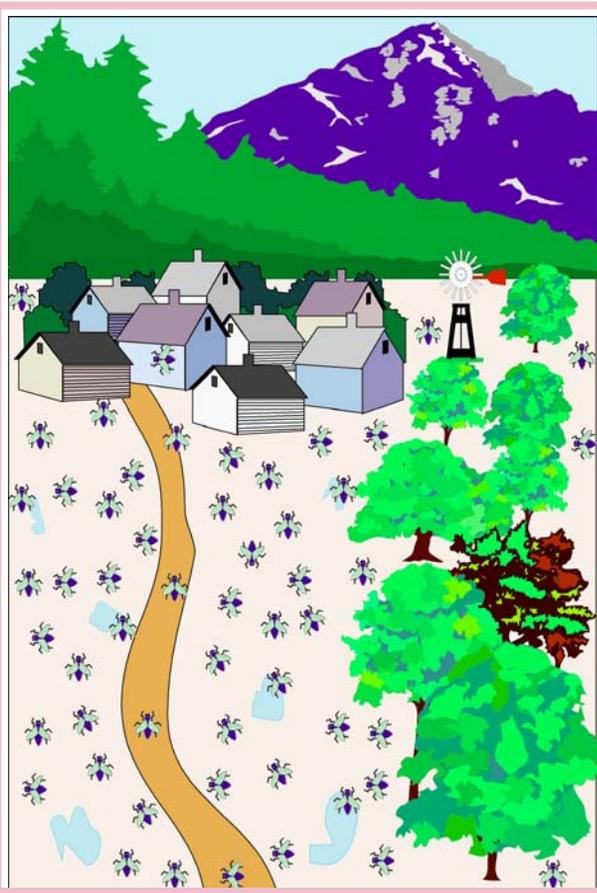
Plasmodium falciparum is now largely resistant to chloroquine, which used to be the most effective drug.

2. Insecticides: Mosquitoes Quickly Acquire Resistance

Before

During

After



Biologic niche intact

Mosquitoes return

Mosquito Breeding



Photo: Marcelo Jacobs-Lorena

Mosquito Breeding

Photo: Marcelo Jacobs-Lorena



Mosquito Breeding



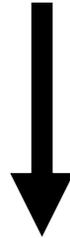
Photo: Marcelo Jacobs-Lorena

3. Vaccine...

... does not exist (yet).

The mosquito is an obligatory vector

(transmission by transfusion has no epidemiological significance)



**Interference with parasite development
will result in decreased transmission**

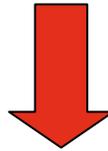
Anopheles gambiae



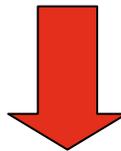
CDC

NEW APPROACH: GENETIC MODIFICATION OF MOSQUITOES

**1) GENETICALLY ENGINEER MOSQUITOES
TO MAKE THEM RESISTANT TO *PLASMODIUM***



**2) INTRODUCE THE REFRACTORY GENE(S)
INTO MOSQUITO POPULATIONS**

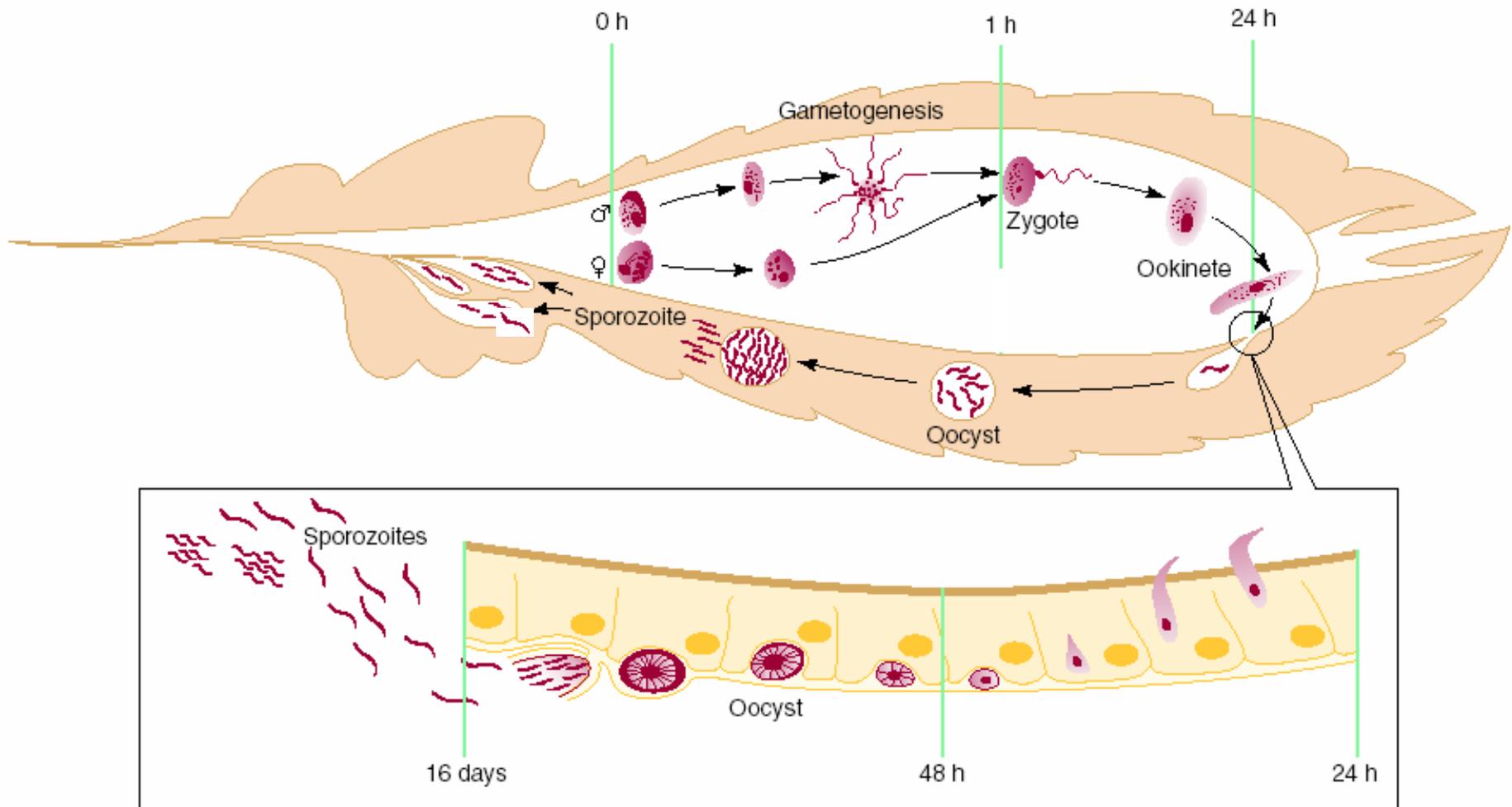


LESS TRANSMISSION



LESS MALARIA

Plasmodium development in the mosquito

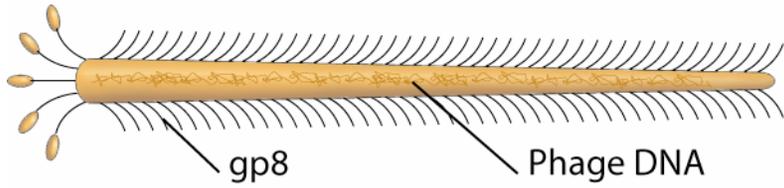


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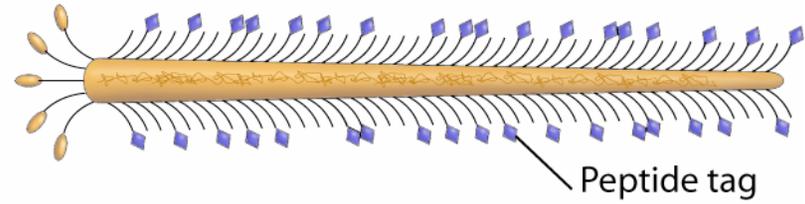
PHAGE DISPLAY LIBRARY

to search for peptides with affinity to mosquito
salivary gland and midgut epithelia

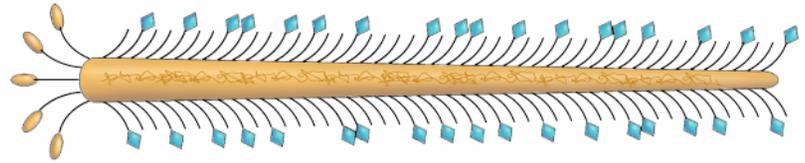
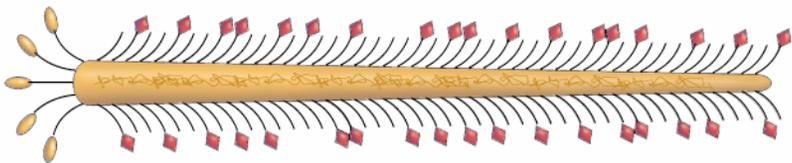
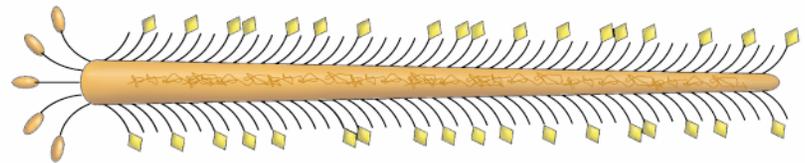
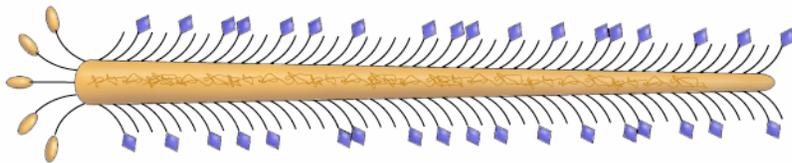
Wild Type Phage



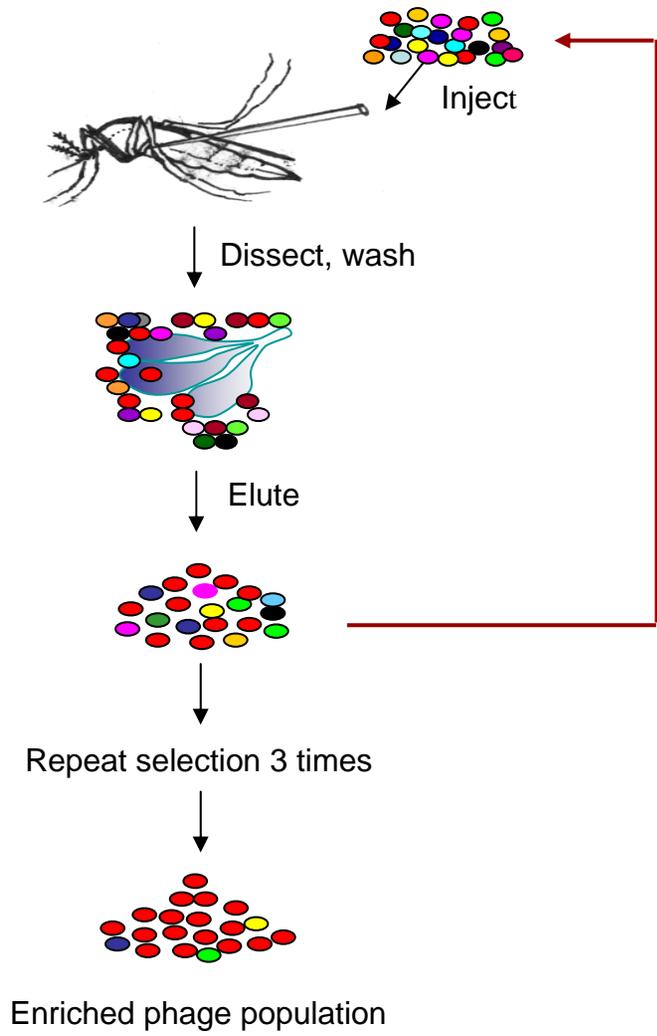
Recombinant Phage



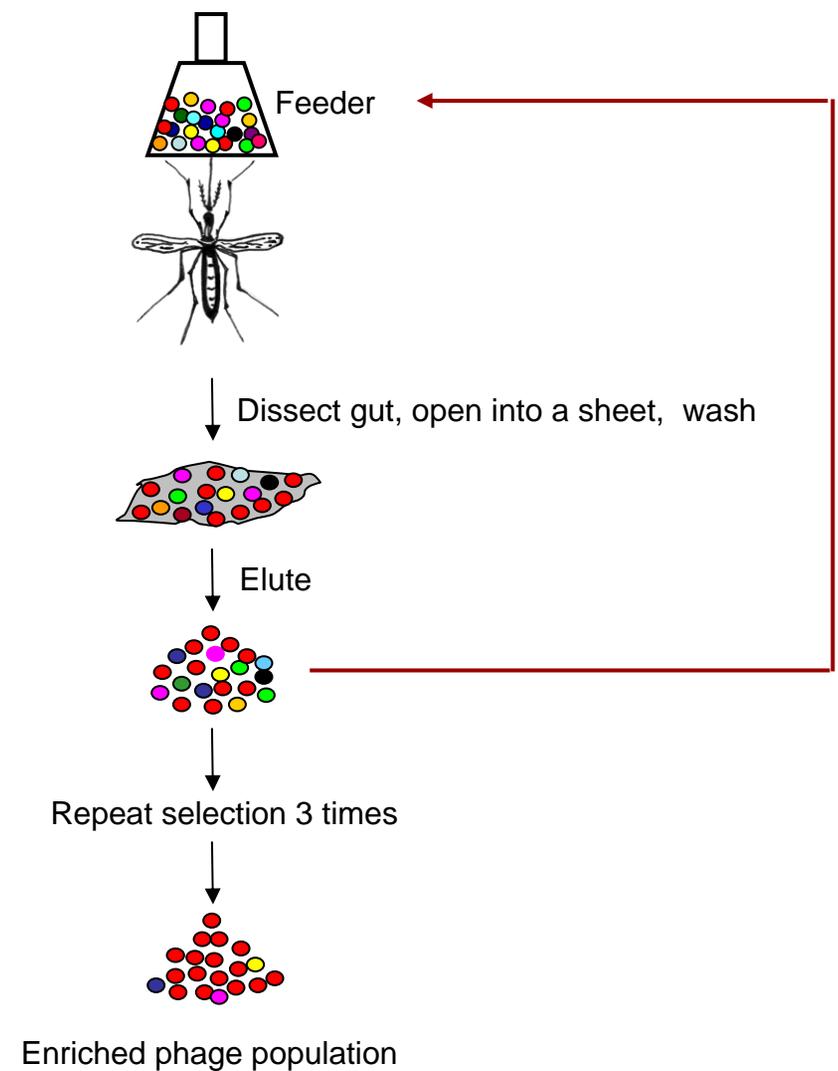
Phage Library



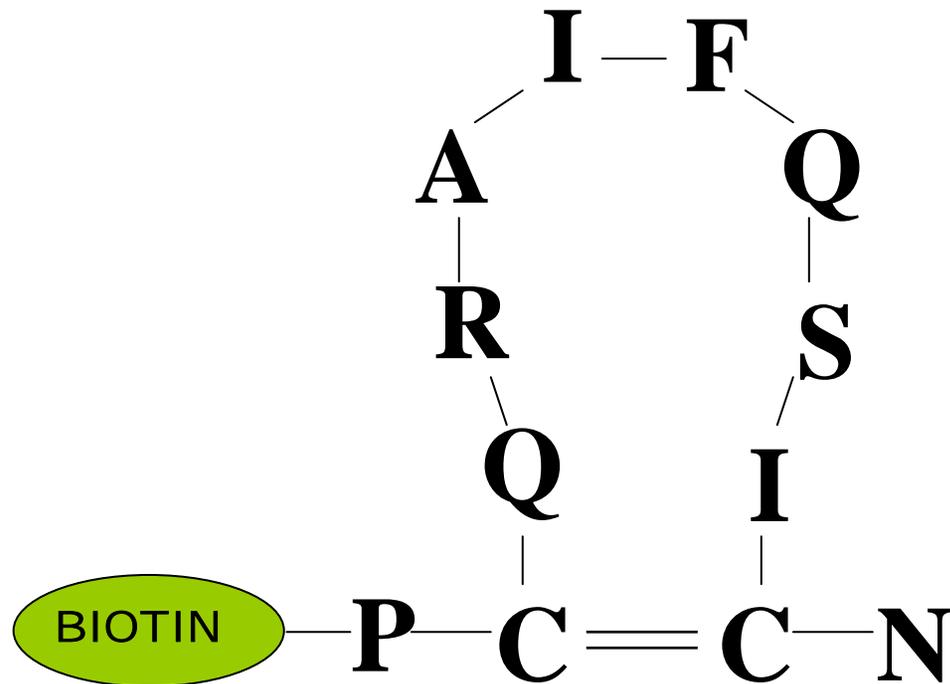
Salivary gland



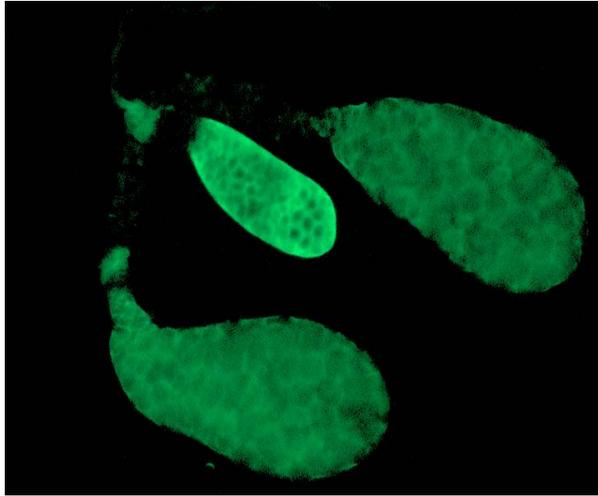
Midgut lumen



SM1 PEPTIDE



SALIVARY GLANDS INCUBATED WITH BIOTINYLATED PEPTIDES

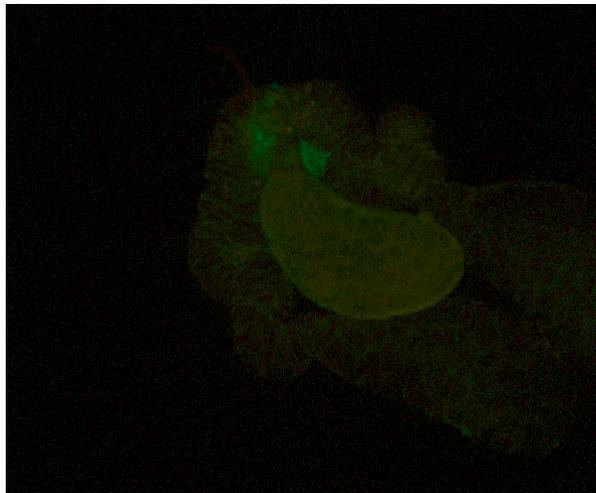


FITC

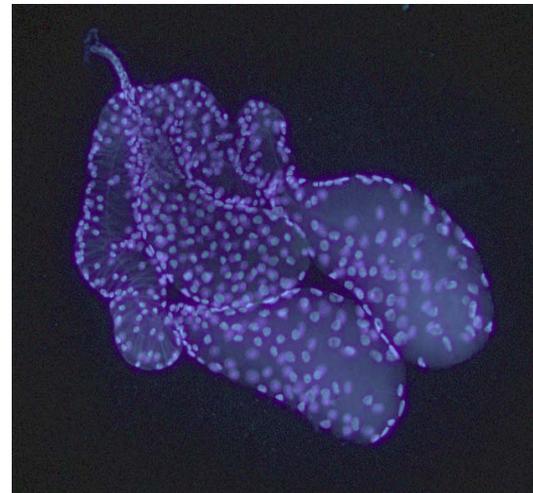
pSM1



DAPI

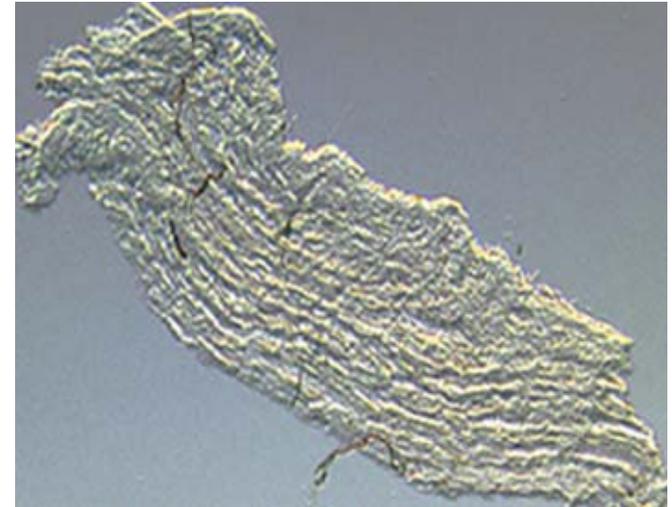
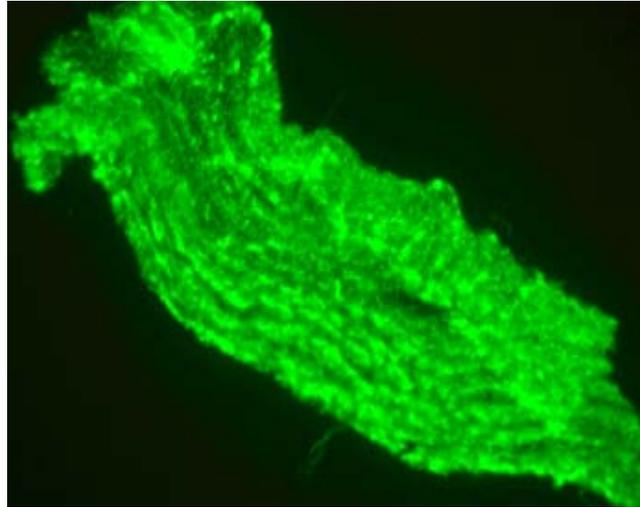


unrelated
peptide



THE SM1 PEPTIDE BINDS TO THE MIDGUT LUMEN BUT NOT TO THE OUTSIDE

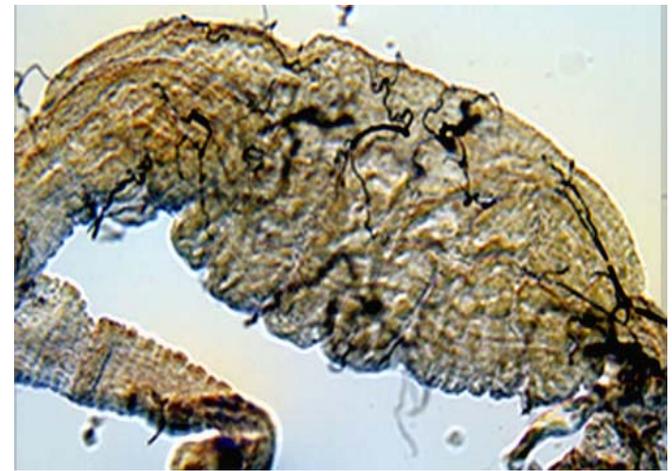
Open midgut
sheet



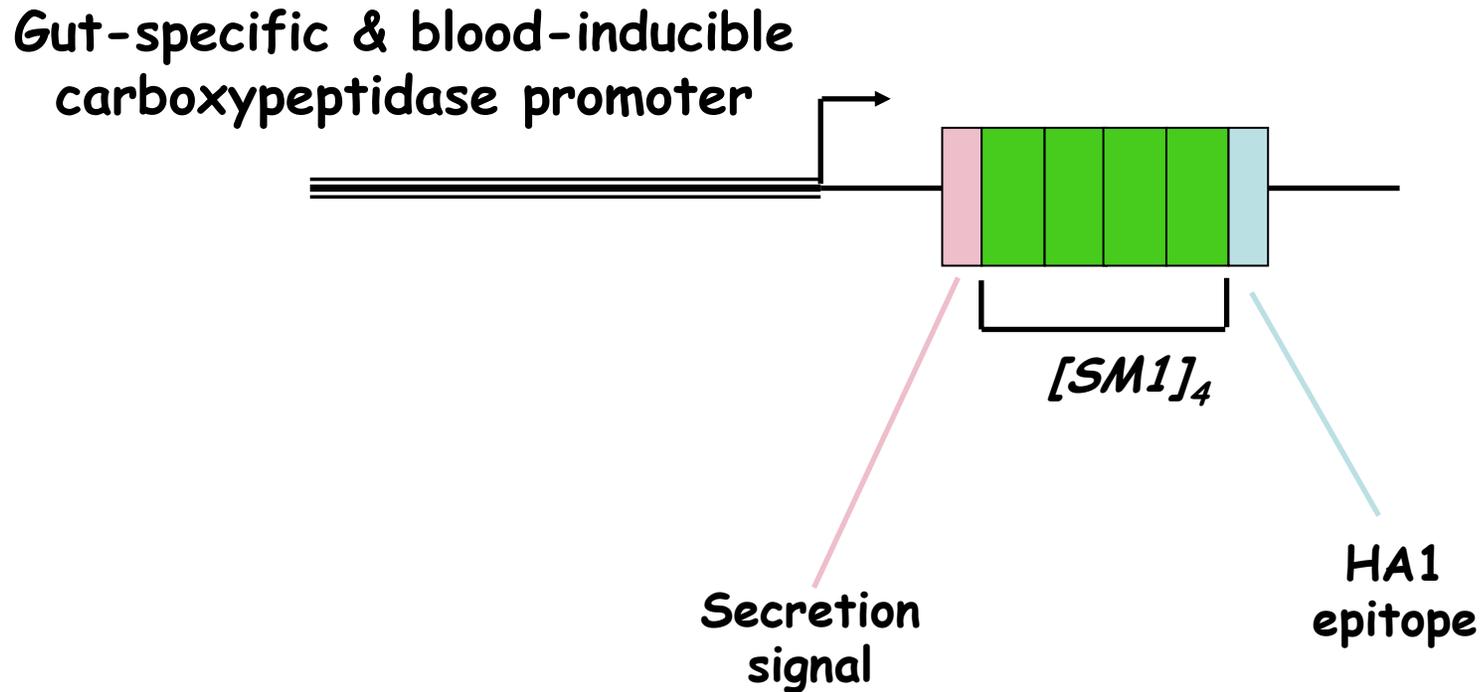
FITC

DIC optics

Closed (intact)
midgut

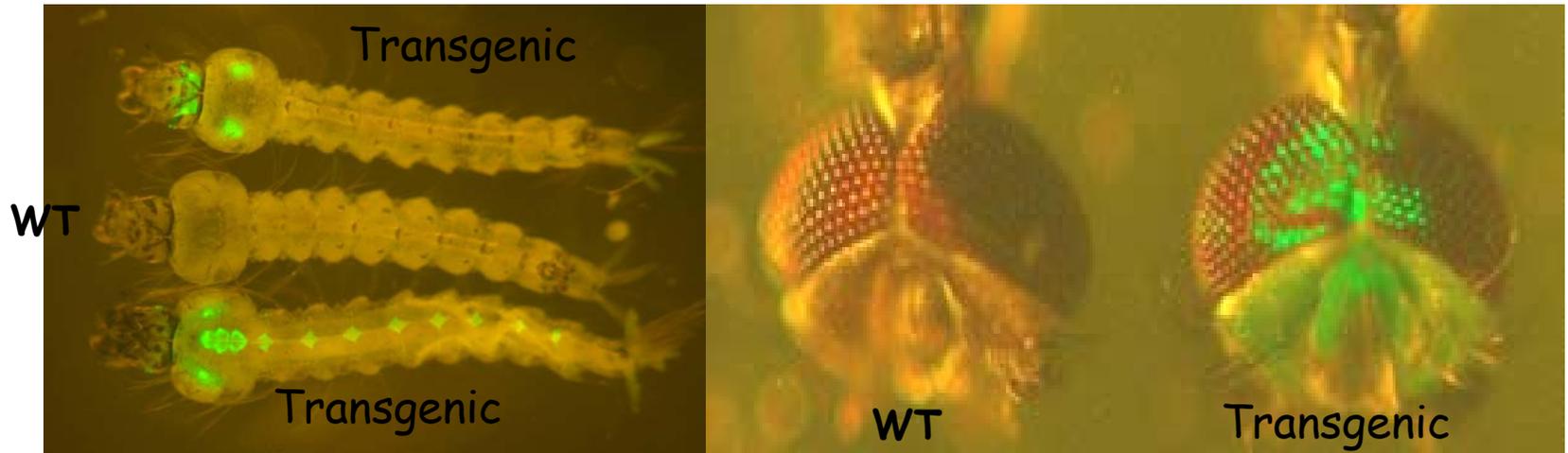


SM1 Construct for Mosquito Germ Line Transformation



An. stephensi - piggyBac (3xP3-eGFP)

eye-specific promoter



Larvae

Adults

Inhibition of oocyst formation in *CP-[SM1]₄* transgenic mosquitoes

Average of 9 experiments:

	Oocysts/ gut	Inhibition
Non-transgenic	93	
<i>CP-[SM1]₄</i>	18	82% (range: 69% - 95%)

Challenge: Driving Genes into Mosquito Populations

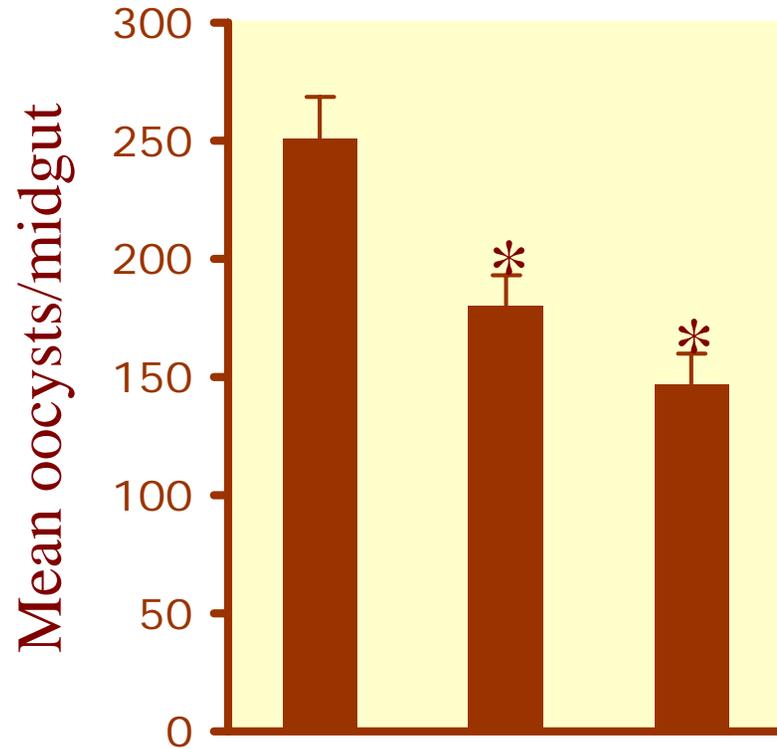
What drive mechanisms are being considered?

1. Transposable elements
2. Wolbachia
3. Meiotic drive

An Alternative

Introduce genes into bacteria of the mosquito midgut, instead of into the mosquito itself

- Feed *E. coli* (●, ● or ●) to *An. stephensi* mosquitoes
- After 24 h feed a *P. berghei*-infected blood meal
- After 15 d count oocysts per gut (n > 100 mosquitoes)



* p < 0.001

