

A QUICK LOOK AT NEXT GENERATION MOSQUITO CONTROL

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Assistant Director

Chatham County Mosquito Control

WHAT WILL BE COVERED

- **Gene Drive**
- **Chromosomal Translocations**
- **RNA interference (RNAi)**
- **Amino Acid / Protein Regulation**
- **Hormones**
- **New Pesticide Modes of Action**

WHAT WILL NOT BE COVERED

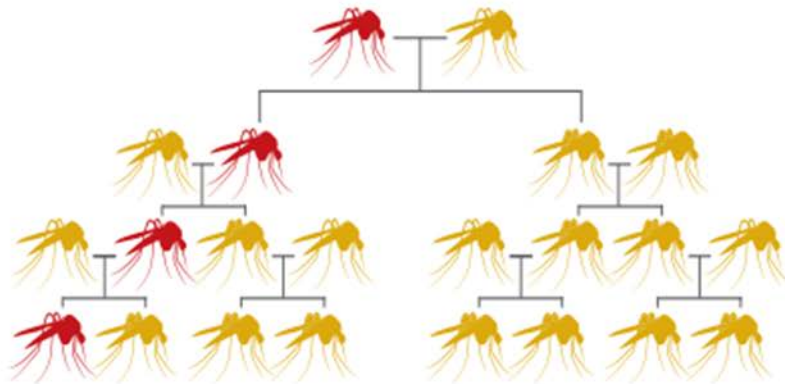
- **Lethal Genes**
- **Wolbachia**
 - **Sterility**
 - **Vector competence**

GENE DRIVE

- **Altered gene from GM parent converts unaltered gene from other parent into the altered gene**
- **Inheritance of the altered gene increases to more than 50%**
- **Altered gene may take over the population in a few generations**

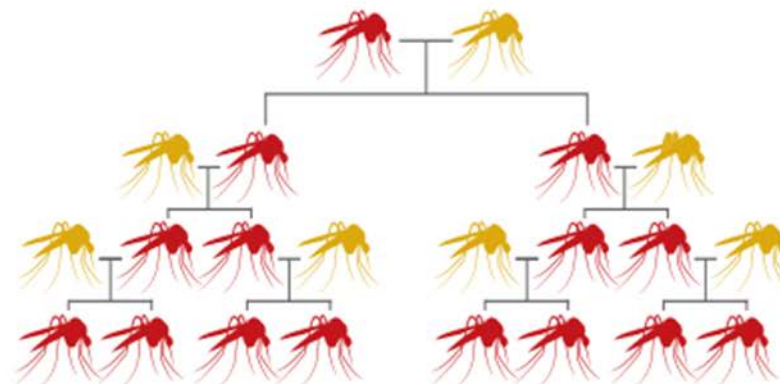
GENE DRIVE

Normal inheritance



Altered gene does
not spread

Gene drive inheritance



Altered gene is almost
always inherited

Saey, T.H



A genetically modified organism could end malaria and save millions of lives — if we decide to use it

The debate over whether to use genetically modified mosquitoes to fight malaria, explained.

By Dylan Matthews | @dylanmatt | dylan@vox.com | Updated Sep 26, 2018, 5:03pm EDT

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Kevin Esvelt wants me to know that if I fuck up this article, 25,000 children could end up dead.

Esvelt is a biologist at MIT and the first person to formulate a technology known as a CRISPR gene drive, a gene editing application that represents humanity's single best chance to eradicate malaria.

Somewhere **between 438,000 and 720,000 people were killed by the parasite** in 2015. Seventy-two percent of those were kids younger than 5, and nearly 90 percent were in sub-Saharan Africa. Many more people infected with malaria don't die but suffer a painful and temporarily disabling infection nonetheless. In 2015, anywhere from **187 million to 222 million** people were infected. That's about 3 percent of all humans on Earth, every year.

TARGET MALARIA PROJECT

- **4 step process**
- **Step 1: Contained lab experiments**
 - **Started November 2016 with *Anopheles gambiae***
 - **A wild population eliminated in 7 generations**
 - **A wild population eliminated in 11 generation**

TARGET MALARIA PROJECT

- **Step 2: confined small scale release**
 - Releasing 10,000 *Anopheles coluzzii* and monitor for 1 year
 - Sterile males are genetically modified
 - Sterile males do not contain gene drive
 - Measure genetic flow, and development of adverse mutations

TARGET MALARIA PROJECT

- **Step 3: open small scale release**
 - **Sterile males will contain gene drive**
 - **Measure ecological impacts in an isolated area**
 - **Measure genetic flow and resistance to gene drives**
- **Step 4: large scale field releases**
 - **Measure impact on Malaria transmission**

TARGET MALARIA PROJECT

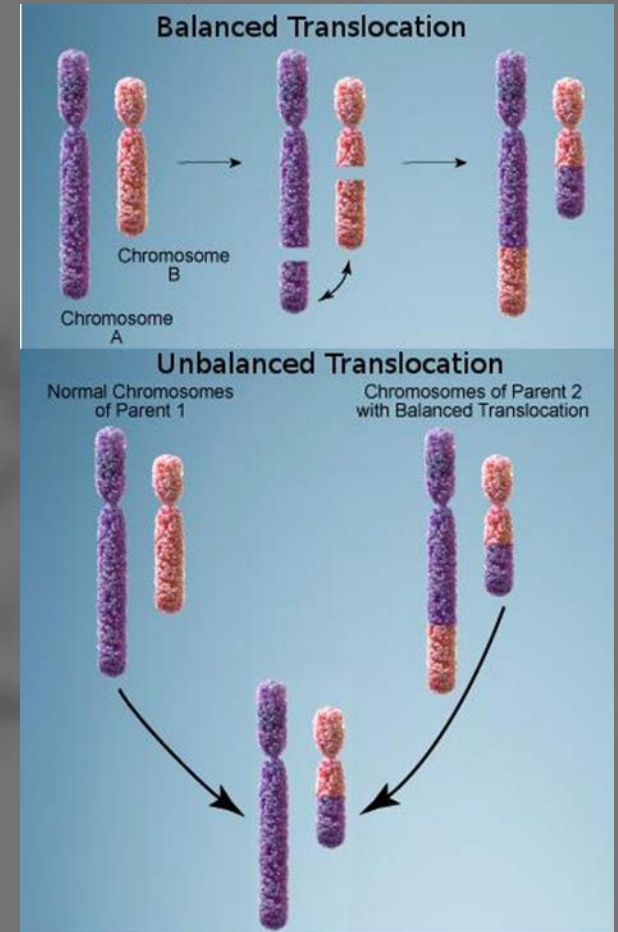
- **Village of Bana in Burkina Faso**
- **Village leaders granted permission May 2018**
- **Federal Government Granted permission August 10, 2018**
- **Gene drive males will produce 95% male offspring**
 - **The gene is on the Y chromosome and it fragments the X chromosome**
- **Also working on an infertile female GMM**

CHROMOSOMAL TRANSLOCATIONS

- **Old idea still being researched**
 - **Called semi-sterility is 1914 by Belling**
 - **Proposed for insect control in 1940 by Serebrovskii**
 - **Cage experiments published in 1972 by Laven**
- **Not much success in wild populations**

CHROMOSOMAL TRANSLOCATIONS

- Unusual arrangement of chromosomes
 - Lower reproductive ability
 - Reduce ability to transmit pathogens
- Research at UC Riverside into disease resistant aegypti using “translocation-mediated gene drives”



RNA INTERFERENCE (RNAi)

- RNAi is used to stop a gene from being expressed
- Also called co-suppression, post-transcriptional gene silencing (PTGS), and quelling
- Gold standard to determine gene function
- 1998 article in Nature by Fire, A. & Mello, C.
 - Awarded 2006 Nobel Prize in Physiology or Medicine

RNA INTERFERENCE (RNAi)

- **University of Indiana / Purdue University**
 - **short hairpin RNAi (shRNAi)**
 - **Using yeast to introduce shRNAi into mosquitoes**
- **University of Texas Medical Branch Galveston**
 - **Also shRNAi**
 - **Using E. Coli to introduce shRNAi into mosquitoes**

AMINO ACID REGULATION



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New Mexico State University
News Center

Headline

\$1.46 million grant to help NMSU professor study mosquito reproduction

Date: 07/25/2018

Writer: **Billy Huntsman**, 575-646-7953, wthv8420@nmsu.edu

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A professor in New Mexico State University's Department of Biology received a \$1.46 million grant to study amino acid transport in mosquitoes in the hopes of finding new ways for controlling their population.

Immo Hansen, an associate professor in the College of Arts and Sciences, received the grant from the National Institutes of Health at the beginning of July.

"We're going to study how mosquitoes move amino acids from one tissue to the next," Hansen said. "They get these amino acids from our blood when they bite us. Then, in other tissues, they use these amino acids to make yolk proteins in order to make eggs and reproduce."

The amino acids cross a layer called the mid-gut, then are transported to the fat-body tissue, where they are made into yolk proteins, Hansen said.

"The amino acids move across at least four cell membranes and in order to do that, they need a transporter protein," Hansen. "Mosquitoes have more than 100 different amino acid transporter proteins but we're going to focus on a group of cationic transporters that have been shown to be really important. If you can develop inhibitors that stop these transporters from doing their job, the



Professor Immo Hansen examines a mosquito trap. Photo by Darren Phillips.

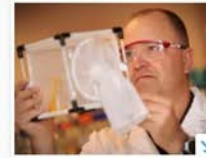


Las Cruces Sun News.

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\$1.46 million grant to help NMSU professor study mosquito reproduction

Billy Huntsman, For the Sun-News Published 12:50 p.m. MT July 29, 2018



(Photo: Courtesy Photo/Darren Phillips)

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More: [New Mexico State University announces search for new provost](#)

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FROM THE USA TODAY NETWORK

AMINO ACID REGULATION

- Mosquitoes take a blood meal to obtain protein
 - Proteins broken down into amino acids
 - An increase in amino acids after a blood meal activates egg development
- Can this process be interrupted?
- 12 amino acids are essential to *Culex pipiens* development

AMINO ACID REGULATION

- Artificial blood meal for rearing mosquitoes
 - SkitoSnak
- Potential to last for up to 80 days



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Researchers to investigate role of hormones in mosquito's ability to use human blood for egg production

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Jul 16 2018

Entomologists at the University of California, Riverside have received a five-year grant of \$2.44 million from the National Institute of Allergy and Infectious Diseases, or NIAID, to investigate the role hormones play in the female mosquito's ability to use human blood for egg production.

Vector mosquitoes need vertebrate blood to develop each batch of their eggs. As a result, reproduction in female mosquitoes is closely linked to blood feeding. The NIAID funding -- a competitive National Institutes of Health grant renewal -- will allow the entomologists to introduce novel research tools for genetic manipulation, such as CRISPR, in their exploration of the genetic basis for the hormonal control of mosquito reproduction.

"A clear understanding of the molecular mechanisms regulating egg development in mosquitoes can play a critical role in our coming up with innovative and novel vector control methods," said Alexander Raikhel, a distinguished professor of entomology who

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Researchers to Target Mosquito Egg Production to Curtail Disease

Five-year grant to UC Riverside entomologists will support the ongoing study

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AUTHOR: **IQBAL PITTALWALA**

July 13, 2018

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- **Looking at hormones to control egg production**
- **Movement of ecdysone in and out of cells**
 - **Ecdysone activates some genes and represses others**
 - **Involved in reproduction, molting, and metamorphosis**

HORMONES

- **Small grant to Kansas St. University**
- **Ecdysis Triggering Hormone Receptor (ETH-R)**
 - **Two types ETH-R-A, ETH-R-B**
- **ETH critical in the molting process**
 - **Molting if not completed properly typically results in death**
- **Being investigated as possible pesticide target sites**

POTENTIAL NEW MODE OF ACTION

- **Purdue University**
- **Looking for mosquito specific allosteric modulators**
 - **Mosquito dopamine receptors**
- **Currently a common group of pharmaceuticals**
 - **Benzodiazepines**
 - **aka – benzos, downers, z-bars**
 - **most well known Valium, Xanax**

POTENTIAL NEW MODE OF ACTION

- **Ohio State University**
- **Inward Rectifier Potassium (Kir) channels**
- **Working on mosquito specific molecules**
 - **Molecule non-lethal to adult bees**
 - **Molecule selective for mosquito over mammalian Kir**
- **Disrupts fluid secretion, impairs flight, reduces fecundity**

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