Department of Biological Sciences

Pathways

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COLLEGE OF SCIENCE UNIVERSITY OF NOTRE DAME

Department of Biological Sciences

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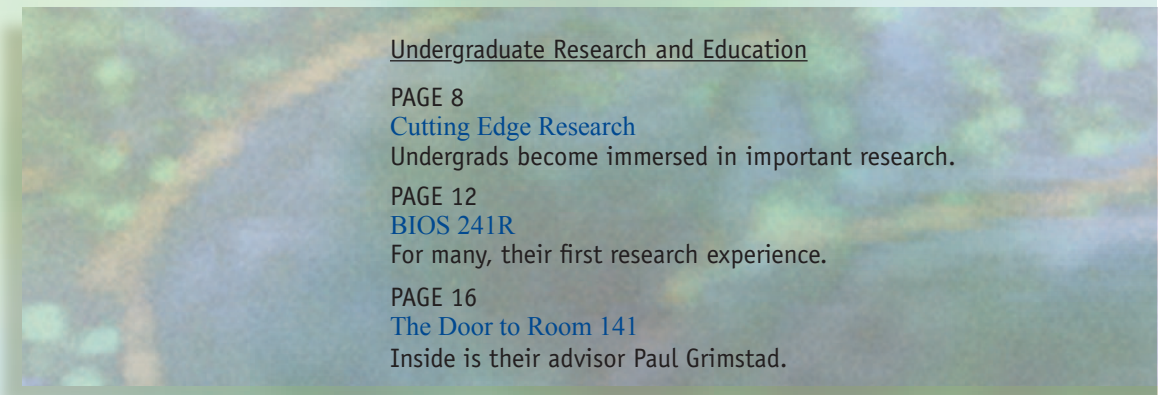

genetically engineered mosquito may be best defense AGAINST Dengue

David W. Severson

Dengue has largely remained in the shadow of the world's most dreaded tropical mosquito-borne disease, malaria.

But sometime late this year, David W. Severson says, the world will hear much more about dengue when he and an international team of scientists announce that they have completed sequencing the genome of the mosquito, *Aedes aegypti*, the principle carrier of both dengue and yellow fever.

A Notre Dame biology professor, Severson is coordinating a multi-country effort to map the entire genetic structure of this tropical mosquito just as his Notre Dame colleague Professor Frank Collins assumed a similar role in an earlier program that successfully determined the complete genomic sequence of the African malaria disease vector, *Anopheles gambiae.* This effort complemented a simultaneous effort to obtain the genome sequence of the malaria disease-causing pathogen, *Plasmodium falciparum*.

That announcement in 2002 was hailed throughout the world as a huge step towards the eventual long-term goal of discovering an effective way to genetically alter these disease-spreading mosquitoes in such a way that the mosquito does not have the ability to transmit the pathogen to humans and does not have unintended ecological consequences. The same applies to dengue.

"Dengue is a disease of global importance, with active transmission throughout much of the subtropics and tropics" said David Severson, Notre Dame Biologist who is coordinating a multi-country effort to determine the complete genome sequence of *Aedes aegypti*. "Dengue is an insidious disease. A person can experience symptoms ranging from a mild cold to a debilitating bout in which the victim is bedridden for weeks. The regular form of dengue is not fatal, but the World Health Organization estimates there may be upwards of 50 to 100 million cases of dengue infections worldwide every year. So it has huge costs in terms of morbidity."

"Sometime late this year we will have the whole genome sequence finished," Severson predicted. "It is a big project involving the sequencing of over 800 million base pairs. So it's about 2.5 times the size of the *Anopheles gambiae* genome."

Unlike malaria, dengue is a viral disease of which there are four related but distinct serotypes.

"In the past few decades a hemorrhagic form of dengue has emerged. Without treatment, the mortality rate is high. Probably 25,000 to 50,000 people a year die from it," Severson said.

There is no cure for dengue. The illness must run its course. However, those stricken with dengue will develop immunity to it. "But because there are four different serotypes, an epidemic will move through a population and

will die down and then at some point another one will cycle through," he noted.

Afterwards, victims appear to be at higher risk for the hemorrhagic form of dengue.

With the eventual completion of the *A. aegypti* genome project around the corner, Severson can turn more of his attention towards the interaction of the dengue virus and the mosquito with expectations that before this decade is complete the most promising genetic countermeasures may be ready for highly controlled and limited testing.

That effort began in the 1990s and has advanced much farther than most people realize.

"We can now experimentally test our theories," Severson said. "Many talented people have and continue to put a lot of work into identifying important genes - that if introduced into the mosquito genome can prevent pathogens from being transmitted."

But scientists are a long way from settling on the right strategy or combination of strategies.

No one can tell at this point if a genetically engineered mosquito will be competitive and survive in the wild. Their experience with sterilized males as a method for population suppression, for instance, gives them reason to pause. Sterilized, laboratory-reared males are often weaker and disadvantaged. They have a hard time competing with indigenous males for mates.

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The WHO has long abandoned the idea of wiping out whole mosquito populations with insecticides. Mosquitoes proved to be too hardy. They evolved. They became resistant to the chemicals. They became tougher.

Replacing the mosquito population with a genetically engineered version that is incapable of transmitting disease has gained considerable support as a promising alternative.

But for this strategy to move forward scientists need to settle on several key points, not the least of which is a genetic driver system that will assist in moving genes into mosquito populations.

One possibility is to use transposable elements or so-called "jumping genes". These elements have the ability to move within a cell's genome, including into gamete cells. One such transposable element called *"piggyBac"* has been developed by Notre Dame professor Malcolm J. Fraser as a means of genetically altering insects. "The idea is to alter an element like *piggyBac* so that it also carries a gene with anti-pathogen effects yet will still incorporate in a state that allows it to actively move and thereby sweep through a population," Severson said. "But you have to also consider the potential for horizontal transfer of these engineered elements and the likelihood they would jump from the mosquito into some other species and have unintended consequences."

Another strategy that holds much promise is a symbiotic bacterial organism called *Wolbachia* that has also had its genome sequenced. The bacteria are maternally inherited and can result in incompatible crosses. For example, infected females can mate successfully with infected or uninfected males, while uninfected females can only mate successfully with uninfected males. - *continued*

Graduate student Jennifer Schneider with Stephen Deonarine, one of the field workers from the Ministry of Health in Trinidad.

Akio Mori

Countries/areas where there is a risk of transmisison. source WHO 2003

"There are researchers who are looking at using that mechanism as a driver, either by introducing genes into the bacteria or looking at identifying genes that are involved in the incompatibility process," Severson said.

There are also endogenous sex linked genes in the genome of some mosquitoes that naturally result in meiotic-drive. "Matings between sensitive females and males carrying the drive gene result in nearly all male progeny. My laboratory is investigating the molecular basis for this effect and its potential for driving genes into populations," Severson said.

All of these strategies are at the beginning stages. But before scientists can even think about engaging in field trials they must overcome a whole range of issues, not the least of which involve ethics and public awareness.

Severson said Notre Dame and many other institutions are hoping that the pending infusion of $40 million in funding from the Bill and Melinda Gates Foundation will greatly accelerate progress in developing a viable genetic control-strategy.

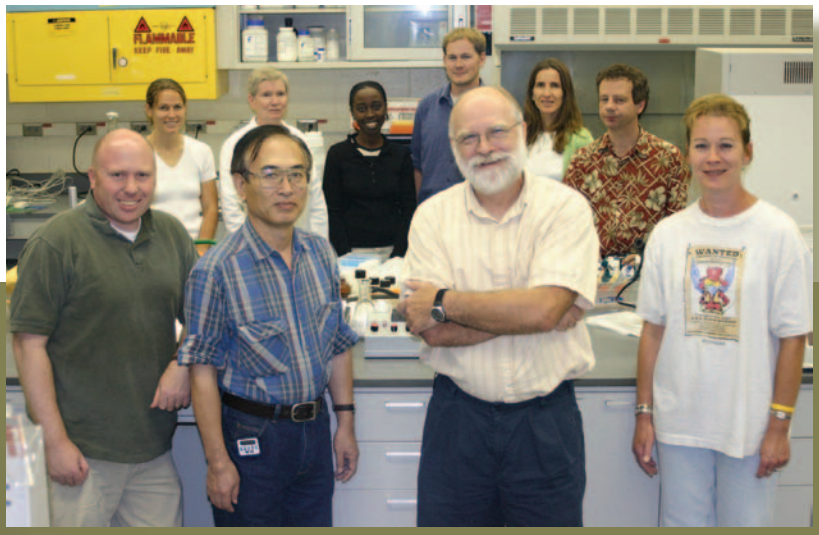
But he is quick to point out that no one should expect immediate results.

"We're not proposing to go to the field with any kind of field release any time soon," he said. "I would guess we're looking at a 10-year minimum of having something ready to be tested in some form of limited field application."

The site might be an island in which scientists would have control over the environment. It could be a village that is surrounded by mountains. Or it could be an arid area "where the mosquito has limited ability to disperse," he said.

"One thing most people agree on is that we are not going into the field with transgenic mosquitoes unless we are ready to use the strategy," he said. "We will not conduct any releases as simple tests of general principles. Everything we do will be done with an intent to directly control disease transmission and will be as safe as possible in terms of risk assessment."

Severson Lab



Notre Dame Professor David W. Severson has been awarded the distinction of Fellow by the American Association for the Advancement of Science.

The AAAS cited Severson for "international leadership in integrating molecular and recombinational genetics in mosquito research and for leadership in directing the NIAID-funded Aedes aegypti genome project." He is among 308 scientists chosen by his peers.

Founded in 1848, the AAAS is the world's largest general scientific society and publisher of the journal, Science.