

2 June 2011

GM MOSQUITOES

May 2011 Gene-drive mosquito – view from Mark Benedict

<http://www.malariaworld.org/blog/hot-or-hot-air-media-acclaim-gene-drive-mosquito>

May 2011 Engineered resistance to Plasmodium falciparum in Anopheles stephensi

<http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1002017>

May 2011 Should GM mosquitoes be released ?

<http://www.dailymail.co.uk/sciencetech/article-1387191/Should-let-scientists-release-mutant-mosquitoes-wild-try-wipe-malaria.html?ito=feeds-newsxml>

May 2011 BBC World service - RIDL mosquitoes in Brazil

<http://www.bbc.co.uk/programmes/p002w557>

DENGUE

6 May 2011 WHO and ASEAN initiate region wide dengue initiatives

http://news.xinhuanet.com/english2010/world/2011-05/06/c_13862561.htm

MALARIA

Nov 2010 Cost and feasibility of malaria elimination

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(10\)61355-4/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)61355-4/abstract)

May 2011 Africa loses \$12bn a year through malaria

<http://www.mmegi.bw/index.php?sid=11&aid=623&dir=2011/May/Friday6>

OTHER

Heat shock proteins found in female mosquitoes taking a blood meal

http://www.linkedin.com/news?viewArticle=&articleID=491496963&gid=147964&type=member&item=51951927&articleURL=http%3A%2F%2Fwww%2Esciencedaily%2Ecom%2Fnews%2F2011%2F04%2F110425153635%2Ehtm&urlhash=vURk&goback=%2Egde_147964_member_51951927

GM Mosquitoes

Hot or hot air? Media acclaim of gene drive in a mosquito

Submitted by mqbenedict on April 29, 2011 - 16:36

You've probably noticed that the number of pages in newspapers and science journals does not expand and contract much while the importance of underlying news stories varies wildly. So is the hoopla surrounding the recent report of a demonstration of gene drive in mosquitoes about something hot or just a bunch of hot air? I'll tell you what I think.

Arguably, I'm not an unbiased observer. I am tangentially related to testing the technology coming from the labs developing mosquito gene-drive technology. However, my children will attest to the fact that I'm an unflinching critic regardless of relationships. (Just ask my son whose novella I edited!) I simply have little capacity to change my opinion based on relational attachment.

With that disclaimer, I'll weigh in on whether I think the [recent report \("A synthetic homing endonuclease-based gene drive system in the human malaria mosquito"\)](#) of a gene drive system demonstration in *Anopheles gambiae* is hot, or does the wide reporting of this publication simply reflect the fact that there are hundreds of media outlets hungry for content, no matter how humble.

It's hot.

Background: Those developing genetic modification technology for mosquitoes have faced a daunting reality: In spite of the fact that many of these scientists have spent little time in the field, they still recognize that there are lots and lots and lots of mosquitoes out there! Raising the frequency of genes among such large numbers of mosquitoes so that malaria transmission is affected enough to make any difference is impossible. Impossible, that is, unless there were some way to cause the gene introduced into populations to increase in frequency by using a natural process such as genetic invasion (as observed with transposable elements), selection or something analogous to cytoplasmic incompatibility (as is being used against dengue in *Aedes aegypti*).

Enter the polyglot mosquito research group at Imperial College London and their whiz-bang protein-engineering colleagues at the Univ. of Washington in Seattle, USA. For the first time, they have demonstrated that a mobile genetic element called a homing endonuclease gene (HEG) can invade the genome of cage populations in a site-specific way and increase in frequency at rates consistent with models. (Yep: they got the controls right in spite of my certainty that they wouldn't.)

If you can wade through the molecular biology you'll realize that the targets of the HEGs were easily assayed fluorescent markers. Fluorescent markers. Big deal. How useful is that? Another academic exercise. But wait. It has already been demonstrated that the site specificity of HEGs can be artificially altered, and numerous genes have been identified as containing HEG targets. These facts mean their demonstration is not merely an academic proof-of-principle. As they claim: "...these genetic elements could overcome a major roadblock...genetic manipulation of entire field populations starting from a few laboratory individuals."

Of course, the phrase "could overcome" is loaded with uncertainty about what changes that qualifier to "would." What's solid about the HEG scheme that has been demonstrated is that it not only brings site-specific spread into the equation (which

reduces uncertainty about off-target effects) but it also reduces concerns about another bugaboo: loss of linkage between an effector and the drive mechanisms. Because the target will almost certainly be a genomic target whose disabling IS the effect, drive IS the effect and loss of linkage is irrelevant. (Still relevant is target site or HEG mutation, but that's another issue.)

So kudos to the team that has made this advance. It's a long road to turn pipe-dreams into toasts. But even given the difference between "could" and "would," I'll hoist a pint to this effort, even if it's a British "hot" one.

Engineered Resistance to *Plasmodium falciparum* Development in Transgenic *Anopheles stephensi*

Alison T. Isaacs^{1#}, Fengwu Li^{2#}, Nijole Jasinskiene³, Xiaoguang Chen⁴, Xavier Nirmala^{5,6}, Osvaldo Marinotti³, Joseph M. Vinetz², Anthony A. James^{1,3*}

1 Department of Microbiology and Molecular Genetics, School of Medicine, University of California, Irvine, California, United States of America, **2** Division of Infectious Diseases, Department of Medicine, University of California-San Diego School of Medicine, La Jolla, California, United States of America, **3** Department of Molecular Biology and Biochemistry, University of California, Irvine, California, United States of America, **4** Department of Parasitology, School of Public Health and Tropical Medicine, Southern Medical University, Guang Zhou, GD, China, **5** Department of Entomology and Nematology, University of Florida, Gainesville, Florida, United States of America, **6** USDA/ARS, Center for Medical, Agricultural and Veterinary Entomology, Gainesville, Florida, United States of America

Abstract [Top](#)

Transposon-mediated transformation was used to produce *Anopheles stephensi* that express single-chain antibodies (scFvs) designed to target the human malaria parasite, *Plasmodium falciparum*. The scFvs, m1C3, m4B7, and m2A10, are derived from mouse monoclonal antibodies that inhibit either ookinete invasion of the midgut or sporozoite invasion of salivary glands. The scFvs that target the parasite surface, m4B7 and m2A10, were fused to an *Anopheles gambiae* antimicrobial peptide, Cecropin A. Previously-characterized *Anopheles cis*-acting DNA regulatory elements were included in the transgenes to coordinate scFv production with parasite development. Gene amplification and immunoblot analyses showed promoter-specific increases in transgene expression in blood-fed females. Transgenic mosquito lines expressing each of the scFv genes had significantly lower infection levels than controls when challenged with *P. falciparum*.

Should we let scientists release mutant mosquitoes into the wild to try to wipe out malaria?

By [FRED PEARCE](#)

Last updated at 10:56 PM on 14th May 2011

I don't know if Cheryl Cole ever glances through the respected science journal Nature. Maybe not. But she might find a recent issue fascinating reading.

For British researchers have just announced in its pages a breakthrough that could eliminate one of the world's most deadly diseases.



Mutant mosquitoes: Scientists say they could eradicate malaria by releasing genetically-modified versions of the insects into the wild

That disease is malaria, which struck Cheryl after her safari holiday in Africa last summer.

Malaria is one of the world's last great scourges. It affects more than 200 million people and kills almost a million African children each year.

With other great killers such as smallpox and measles banished or in full retreat, malaria is surely ripe for elimination.

But malaria is a resourceful enemy, spread by certain types of mosquito that carry a parasite that harbours the disease. The mosquitoes pass on the parasite in their bite.

Pesticides haven't killed off malaria and the drugs we are told to take when we fly to malarial zones don't always work.

Now scientists say they have invented a way of stopping malarial mosquitoes in their tracks. They say it could rid the world of the disease in just a few years.



Victim: Cheryl Cole suffered greatly in her recent battle with malaria

'That's why it's so exciting,' says the biologist behind the breakthrough, Andrea Crisanti of Imperial College London.

The trick is a nifty bit of genetic engineering that might cause those opposed to 'Frankenstein' technology to think again – or maybe not.

It is ten years since scientists announced that they could change the genes of mosquitoes so that they did not pass on the malaria parasite. But that was in the lab.

The problem is you can't bring all the world's mosquitoes into the lab for a genetic refit.

And however many of the mutants you release into the wild, their new genetic trait will most likely die out within a few generations.

So the scientists decided they needed to up the odds that the offspring of the mutant mosquitoes would inherit and pass on the genetic modification. This is what they think they have now achieved.

They have done it by adding a second 'super-gene' that dramatically increases the male mosquito's ability to spread the anti-malarial gene.

They found the super-gene in fungi and successfully transplanted it into *Anopheles gambiae*, the set of species of mosquito that causes three-quarters of all malaria deaths.

The super-gene is sometimes called a selfish gene because it ensures that all the sperm produced by genetically modified mosquitoes carry the same trait. And that is enough to give this genetic trait a huge advantage when it comes to the survival of the fittest.

'In the lab, the mutation spread to more than half the population within 16 generations – less than a year,' says Crisanti.

Now he is thinking big. Re-engineer a few thousand male malarial mosquitoes, release them into the wild and watch them and their sperm take over the mosquito world.

Now that the genetic transport mechanism is sorted out, the big question is exactly what genetic traits the new mutant mosquitoes should pass on. How best to kill off malaria?



Spray the game: Ahead of the Commonwealth Games Delhi in 2010 the organisers worked very hard to try to prevent a mass outbreak of malaria

There are three possible lines of attack, says Crisanti.

The first is to stop the mosquito excreting the parasite when it bites.

The second is to destroy the genes that mosquitoes use to recognise humans to bite.

This seems to be to do with smell (mosquitoes love cheesy feet – I once went to an insect lab in Kenya, one of the world's malarial hotspots, where volunteers with smelly feet camped out in the name of science to see who would be bitten most).



No game: Chelsea striker Didier Drogba suffered illness and a serious loss of form after contracting malaria

Crisanti says he knows how to snip out the gene that allows mosquitoes to sniff us out. After that, he says, they will bite animals instead.

The third option is to screw up their reproductive systems so that they produce only males.

Not surprisingly, if you set that gene rolling, after a few generations the entire population crashes. Again, he says, the gene engineers know how to do that.

So problem solved. Buzz off malaria.

Well, sure. Except that nobody is quite sure what the wider effects of messing with the genes of mozzies might be.

Re-engineering trillions of insects that spend their lives going round biting other members of the animal kingdom might risk spreading genetic mayhem.

Ingeborg van Schayk, director of the Malaria Foundation, whose membership comprises more than 6,000 medics and others fighting malaria, says: 'We do not support the release of GM mosquitoes as long as the long-term effects on people and their environment remain uncertain... We don't know if malaria mosquitoes will adapt to being "modified" and leave us with even bigger problems.'

Janet Hemingway, an insect specialist at the University of Liverpool, says that GM mosquitoes are unlikely to develop Frankenstein tendencies such as spreading other diseases or expanding their terrain to invade the streets of Britain.

'There is no logical reason why they would,' she says.

'And it is almost inconceivable that they would suddenly start to vector other diseases.'

She is concerned that the malaria parasite itself might evolve to find another route to reach us.

'But that is difficult to predict in advance. We will probably only find out when the big eradication push is well under way,' she says.



Hundreds killed: Do we in the malaria-free world have the right to dictate a policy on malaria when it is not our children that are dying

What if the GM mosquitoes passed on their mutant genes to other species, either animals that they bite or animals that eat mosquitoes?

Crisanti believes the chances of that happening are 'near zero'. But to check he is building a mosquito lab in his native Italy, where he will incarcerate thousands of GM mosquitoes for three years in a near-natural environment.

If all goes well, he could be doing big field trials in the African bush within three years.

So is the risk worth taking? Should we be bold, whatever our fears?

Some people say we are still stuck with the malaria problem today only because we were squeamish once before.

Back in the Sixties, it looked as if the world was about to eradicate malaria using a pesticide that was amazingly effective at killing mosquitoes. That pesticide was DDT.



Blood suckers: DDT cut malaria deaths by as much as 95 per cent but it was abandoned on ecological grounds

The U.S. government set aside half-a-billion dollars, and thousands of drums of DDT headed to the developing world for spraying on hut walls, where malarial mosquitoes gather at night after biting their human hosts.

Malaria deaths fell by as much as 95 per cent at the height of the spraying. The end seemed near.

But then came Rachel Carson's famous book *Silent Spring*, which described the horrific damage DDT and other new farm chemicals caused to wildlife.

Carson called for a ban only on spraying DDT in fields, not in houses to kill mosquitoes. Even so, the world got cold feet, DDT was largely withdrawn and malaria made a comeback.

Only in 2006, did the World Health Organisation again back DDT as one of its main weapons against malaria.

Many scientists today fear we may repeat the mistake – by letting our concerns about genetic modification get the better of our desire to banish malaria.

'I am not saying using GM mosquitoes is without any risk,' says Crisanti.

'I am as concerned about environmental safety as anyone. But, meanwhile, a million children continue to die every year from malaria.'

If he gets the go-ahead, Crisanti reckons it may not take much more than a couple of years to wipe out malaria once and for all.

Do we in the malaria-free world have the moral right to try to stop him?

It's not our kids that are dying. Not many of us have direct experience of this dreadful disease.

So it would be interesting to know what Cheryl thinks.

Dengue

ASEAN, WHO gear up for region-wide dengue action

English.news.cn 2011-05-06 19:00:21

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JAKARTA, May 6 (Xinhua) -- The Association of Southeast Asian Nations (ASEAN) and the World Health Organization (WHO) have joined forces to assist Asia Pacific countries in identifying priority actions for dengue prevention and control, a statement released by the ASEAN Secretariat said here on Friday.

Dengue is the most rapidly spreading mosquito-borne viral disease in the world and Asia Pacific bears 75 percent of the current global dengue disease burden. The disease has large impact on health, the economy and the entire society.

At a workshop in Manila, Philippines, from May 3 to 5, representatives of ASEAN member states recognized the need to extend advocacy for dengue prevention and control to all sectors of the society.

They also shared their national plans for the forthcoming simultaneous launch of the ASEAN Dengue Day on June 15.

Advocacy plans will center on calls for shared responsibility and the need for everyone to act. "Dengue prevention and control is a shared responsibility," said Ferdinal Fernando, Assistant Director of the Health and Communicable Diseases Division of the ASEAN Secretariat. "Unless everybody plays their role, dengue will not be controlled."



Participants also agreed to move from response-driven activities to long-term prevention and preparedness, strengthening national and regional alert and response capacities, as well as enhancing regional collaboration.

"Dengue will continue to be a problem as the world faces population growth, greater urbanization, increases in population movements and variations in climate," said Takeshi Kasai, Director of the Division of Health Security and Emergencies, WHO- Western Pacific Regional Office. "We have to go beyond reacting to taking action all year round."

Editor: Yang Lina

Malaria

Costs and financial feasibility of malaria elimination

[Oliver Sabot](#) BA ^a  , [Justin M Cohen](#) PhD ^a, [Michelle S Hsiang](#) MD ^c, Prof [James G Kahn](#) MD ^d, [Suprotik Basu](#) MSH ^e, Prof [Linhua Tang](#) PhD ^h, [Bin Zheng](#) PhD ^h, [Qi Gao](#) PhD ⁱ, [Linda Zou](#) BA ^a, [Allison Tatarsky](#) MPH ^a, [Shahina Aboobakar](#) MD ^f, [Jennifer Usas](#) MS ^a, Prof [Scott Barrett](#) PhD ^g, [Jessica L Cohen](#) PhD ^b, Prof [Dean T Jamison](#) PhD ^j, Prof [Richard GA Feachem](#) DSc [Med] ^c

Summary

The marginal costs and benefits of converting malaria programmes from a control to an elimination goal are central to strategic decisions, but empirical evidence is scarce. We present a conceptual framework to assess the economics of elimination and analyse a central component of that framework—potential short-term to medium-term financial savings. After a review that showed a dearth of existing evidence, the net present value of elimination in five sites was calculated and compared with effective control. The probability that elimination would be cost-saving over 50 years ranged from 0% to 42%, with only one site achieving cost-savings in the base case. These findings show that financial savings should not be a primary rationale for elimination, but that elimination might still be a worthy investment if total benefits are sufficient to outweigh marginal costs. Robust research into these elimination benefits is urgently needed.

Africa loses \$12 bn a year to Malaria: Study

SOUTH AFRICA: Malaria costs Africa \$12 billion (eight million euros) a year in lost productivity, an expense that businesses can reduce by investing in prevention schemes, said a study released on Thursday.

"Malaria is bad for business. The disease is responsible for decreased productivity, employee absenteeism and increased health care spending and can negatively impact on a company's reputation," said the report by the Roll Back Malaria campaign. "This heavy burden has serious impacts on businesses and economies, costing the African continent \$12 billion annually in lost productivity," it said.

The report, presented at the World Economic Forum for Africa in Cape Town, analysed economic impact of malaria prevention and programmes at three companies, which cut overall medical spending in company clinics and reduced absenteeism.

"For these companies, investing in malaria prevention and control for workers and their dependants was cost effective, resulting in increasing their bottom line, producing an estimated rate of return of 28 percent under very conservative assumptions," the study said.

Malaria hurts local economies by reducing workers' ability to save, while straining public health budgets and reducing tax revenues. About 90 percent of malaria deaths each year occur in Africa and 92 percent of those are children aged under five. **(Sapa-AFP)**

Other

How Mosquitoes Handle the Heat of a Hot Blood Meal

ScienceDaily (Apr. 27, 2011) — Mosquitoes make proteins to help them handle the stressful spike in body temperature that's prompted by their hot blood meals, a new study has found.

The mosquito's eating pattern is inherently risky: Taking a blood meal involves finding warm-blooded hosts, avoiding detection, penetrating tough skin and evading any host immune response, not to mention the slap of a human hand.

Until now, the stress of the hot blood meal itself has been overlooked, researchers say.

Scientists have determined in female mosquitoes that the insects protect themselves from the stress of the change in body temperature during and after a meal by producing heat shock proteins. These proteins protect the integrity of other proteins and enzymes, in turn helping the mosquitoes digest the blood meal and maintain their ability to produce eggs.

Tests in two other types of mosquitoes and in bed bugs showed that these insects undergo a similar response after a blood meal.

"These heat shock proteins are really important in a lot of stress responses. Our own bodies make these proteins when we have a fever," said David Denlinger, professor of evolution, ecology and organismal biology at Ohio State University and senior author of the study. "It's one of those things that, in retrospect, seems obvious -- that blood meals might cause a stress like that. But it hadn't been pursued before."

The research appears this week in the online early edition of the *Proceedings of the National Academy of Sciences*.

Denlinger and colleagues conducted experiments in the *Aedes aegypti* mosquito, which is a carrier of yellow fever.

The researchers placed sensors on female mosquitoes and observed that upon taking in a blood meal on a chicken, the insects' body temperatures increased from 22 to 32 degrees Celsius (71.6 to 89.6 Fahrenheit) within one minute -- among the most rapid body temperature increases ever recorded in a cold-blooded animal. After the feeding, their body temperatures decreased to room temperature within a few minutes.

In response to that blood feeding, the mosquitoes' level of Hsp70 -- heat shock protein 70 -- increased nearly eightfold within one hour and remained at least twice as high as usual for 12 hours. The increase in these proteins was most pronounced in the midgut area.

Denlinger and colleagues tested potential triggers for this protein increase by injecting the mosquitoes with a saline solution at two temperatures: 37 degrees Celsius (98.6 degrees Fahrenheit) and room temperature. Only the warmer saline generated an increase in Hsp70, suggesting that the elevation in temperature associated with the meal, rather than the subsequent increase in body volume, is what causes the generation of those proteins.

Sometimes, mosquitoes feed on cold-blooded amphibians, which should not cause the same amount of stress. To test that theory, the researchers also gave mosquitoes a feeding opportunity on cooler blood, which failed to generate an increase in heat shock proteins.

And what happens if this protein is not produced? The researchers manipulated the mosquitoes' RNA to figure that out.

When the scientists knocked down expression of the gene that encodes the heat shock protein, the amount of Hsp70 production was reduced by 75 percent. Under those circumstances, mosquitoes still ate a normal blood meal. But blood protein levels remained elevated for a longer period of time, suggesting that digestion of those proteins was impaired. In addition, egg production decreased by 25 percent when the heat shock protein was suppressed.

Heat shock proteins help maintain the three-dimensional integrity of enzymes and proteins when temperatures rise suddenly, and can target damaged proteins and enzymes for elimination, Denlinger said. "We think that in this case, they are important to maintaining the integrity of some critical enzymes and proteins involved in digestive processes. When we knock out those proteins, it impairs digestion a bit and as a result the mosquitoes don't lay as many eggs," he said.

The researchers observed similar body temperature increases and elevations in Hsp70 levels in three other insects: *Culex pipiens* and *Anopheles gambiae*, mosquitoes that are carriers of West Nile virus and malaria, respectively, and *Cimex lectularius*, the bed bug. Though new knowledge about the

genetics of these insects, especially the mosquitoes, might someday inform attempts to kill them as a method of disease control, Denlinger said the primary contribution of this research is better understanding of how mosquitoes protect themselves in this novel way.

This work was supported by grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases and the National Science Foundation.

Co-authors include Joshua Benoit, a former Ohio State graduate student who is now a postdoctoral researcher at Yale University, and Giancarlo Lopez-Martinez, Kevin Patrick, Zachary Phillips and Tyler Krause of Ohio State's Departments of Entomology and Evolution, Ecology and Organismal Biology. Lopez-Martinez is now at the University of Florida.

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1. Joshua B. Benoit, Giancarlo Lopez-Martinez, Kevin R. Patrick, Zachary P. Phillips, Tyler B. Krause and David L. Denlinger. **Drinking a hot blood meal elicits a protective heat shock response in mosquitoes.** *PNAS*, April 25, 2011 DOI: [10.1073/pnas.1105195108](https://doi.org/10.1073/pnas.1105195108)

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