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Malaria, Science, and Social Responsibility

Nonprofit drug-development partnership seeks to cure the ills of developing nations

| By Bennett Daviss

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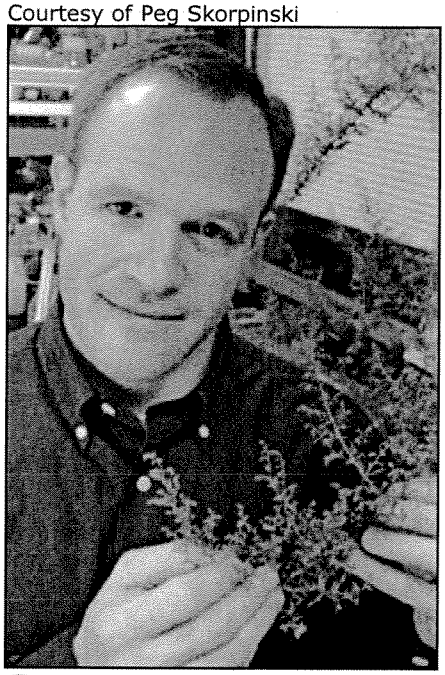
Courtesy of Peg Skorpinski



Jay Keasling

A problem that has seemed intractable for decades may finally be cracking: How to create affordable drug therapies for people who don't offer pharmaceutical companies a commercial market?

Jay Keasling, at the University of California, Berkeley; Amyris Biotechnologies, in Emeryville, Calif.; the Institute for OneWorld Health in San Francisco; and the Bill and Melinda Gates Foundation have formed a public-private partnership to produce a genetically engineered version of one of the world's most effective malaria drugs.

Such partnerships aren't new. The International AIDS Vaccine Initiative in New York and the Geneva-based Global Fund to Fight AIDS, Tuberculosis, and Malaria work in a similar way. But the latest collaboration puts a new twist on the idea. A multimillion-dollar grant will be used to pursue an unproven technology that, if it works, will not only be useful against malaria and other ailments, but also will be given to the world for free.

A $42.6 million Gates gift will fund a four-step process. First, Keasling will perfect a method that uses bacteria to synthesize a dirt-cheap version of a plant-based medicine. Second, Amyris will engineer a commercial process to grow the bacteria and harvest the targeted compound. Third, OneWorld will shepherd the drug through equivalency trials and regulatory and FDA-approval channels, and then, fourth, make the product available to drug makers at vastly lower costs than is currently possible.

In fashioning a new collaboration to tackle a persistent problem, the four players may also have created a new kind of health initiative. William Haseltine, founder of Human Genome Sciences and now an international consultant in Washington, DC, calls the partnership "the beginning of a new paradigm that could be transformational" in making affordable treatments available for infectious diseases that plague the developing world.

"It was an easy decision for us," Keasling says. "A university can't produce a drug, and producing a drug with a knowledge it won't make a profit is something that a traditional company can't do. This kind of combination is the way to go."

FIRST TARGET: MALARIA Each year, between 300 million and 500 million people in Asia and Africa contract malaria and 1.5 million die, most of them children. In 2004 the Copenhagen Consensus, a panel of globally renowned economists, estimated that less than $1 billion spent on preventing and treating malaria would return an estimated $14 billion in overall economic gains. But, like tuberculosis, malaria has become steadily more resistant to conventional drugs.

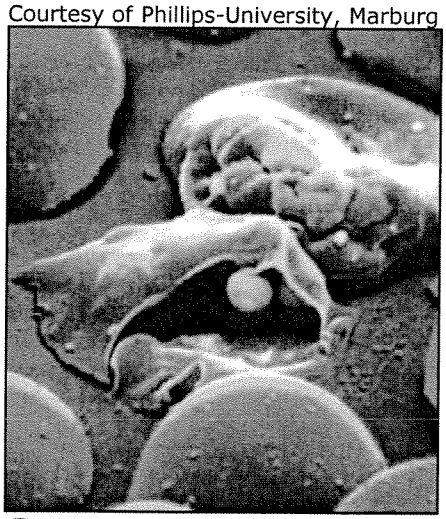
The good news is that combination therapies based on artemisinin (derived from the sweet wormwood plant) and given over three days are more than 95% effective in curing malaria. Novartis developed artemisinin as the basis for artemetherlume-fantrine (Coartem), a drug combination that kills the plasmodium parasite and is effective against resistant strains. The therapy works so well that the World Health Organization included Coartem on its list of essential malaria medicines in 2002, which led many developing nations to declare the drug as the chief treatment for malaria.

But that's the bad news, too. The annual demand for artemisinin jumped from 100,000 doses in 2001 to an estimated 60 million doses for 2005, according to Paul Herrling, head of corporate research at Novartis. "It happened pretty fast," says Herrling, who is also chair of the nonprofit Novartis Institute for Tropical Diseases, a new facility in Singapore. "The results were so spectacular ... that everybody wanted to switch to this drug, and that caused a bottleneck in producing the plant."

Suppliers of the plant, grown mostly in China and Africa, were unable to keep up with demand. "You plant this plant and you harvest it and you extract the active component, and of course you are depending on plantations, and where this plant is growing," Herrling says. Novartis makes the drug available at cost to developing nations, but a course of treatment still costs about $2.40 – cheap by western standards but still prohibitive to nations that need it most.

Keasling thought he had an answer. He specializes in the chemistry of isoprenoids, a family of about 30,000 chemical compounds that include precursors of plant products used to make medicines, such as the anticancer agent taxol from yew trees. As an alternative to the costly and laborious process of isolating natural elements from harvested plants, he decided to try to turn *Escherichia coli* into an artemisinin factory.

Courtesy of Phillips-University, Marburg



Plasmodium Falciparum

"We didn't set out to produce an anti-malarial drug," Keasling explains. "My lab works on questions of how to redesign and manipulate cells' metabolism." Keasling was creating a process to synthesize iso-prenoids using microbes and was looking for a "killer application" about the time that the genetic pathway of artemisinin formation was described and the first gene in the pathway was cloned. "It all happened in a very timely way," Keasling says.

Others have tried to craft bacteria into pharma production lines, but the engineering typically involves a protracted battle with the bacteria's own chemical pathways governed by control mechanisms that aren't easy to understand, much less to control. Keasling's inspiration was to bypass the organism's own pathways and instead implant in *E. coli* a similar isoprenoid pathway taken from yeast. The yeast's pathway uses acetyl coenzyme A to produce the isoprenoid precursors isopentenyl pyrophosphate and dimethylallyl pyrophosphate. He plans to add genes from wormwood that turn the compounds into amorphadiene, a chemical precursor of artemisinin.

When completed, the process could likely be used generically, to create not only other drug ingredients and synthesized derivatives of plants, but also even such compounds as flavors and fragrances.

DETAILS OF THE DEAL So what does it take to move science from the bench to bedsides in the developing world? Keasling and UC-Berkeley offered to provide a royalty-free license for the artemisinin-producing bacteria to Victoria Hale, founder of OneWorld Health, the first nonprofit drug development company in the United States. It is the fourth such license that Berkeley has granted under its 2-year-old, socially responsible licensing program. When a Berkeley researcher creates a technology that promises exceptional benefit to the developing world, the researcher and executives of the university's office of technology licensing weigh a variety of factors and decide whether to donate it.

"Berkeley has a strong component of social responsibility in its business school and of social justice in its law school," explains Carol Mimura, director of technology licensing. "It's part of our culture and it extends to our intention to ensure access to technology and medicines when licensing intellectual property that could benefit the developing world." Not all schools share that attitude. When a colleague at another university heard about Berkeley's donation to the malaria project, "the person told me, 'that would never fly here,"' Mimura recalls.

Regina Rabinovich, the Gates Foundation's director of infectious disease programs, says Berkeley's commitment not to take royalties is "groundbreaking." She and the foundation usually find themselves working to negotiate down the share of a project's revenues for which a university and its researchers will settle. "In cases where you're talking about people who aren't getting life-saving drugs because $2.40 is too expensive for them, to be talking about royalties is difficult," she says.

Mimura says the partnership is unique because it bundles basic research at a university, translational research in a biotech company, and the preclinical and clinical validation and regulatory work of a pharma company into one grant. "Normally, we'd complete the basic research and then desperately look for a commercial partner," she says. "Even when we were able to put together those relationships, often there would be gaps between the hand-offs. The fact that we can see this through from basic research to product approval in one package is exciting."

Haseltine credits the Gates Foundation for the increase in efforts to tackle thorny problems in developing nations. "Until recently, [many] people seemed loath to engage in this kind of public-private partnership," he says. Melding for-profit and nonprofit players in a single venture seemed "somehow impure" to project funders, he adds. "That concept is no longer sacrosanct. There's been a key change in the intellectual climate of the not-for-profit community, and it's taken the vision of the Gates Foundation to crack that."

"The reason that this new collaboration is good news is that it's another innovative attempt to address a critical question that cannot be addressed by any single entity: How can we make these new compounds available to treat drug-resistant malaria?" says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. "We're seeing that collaborations, coordination, and synergies among the public and private sectors are becoming increasingly essential."

WHAT'S NEXT FOR MALARIA? One prototype is the Medicines for Malaria Venture (MMV), a Geneva-based nonprofit drug development initiative working to get malaria drugs to developing nations. At the University of

Nebraska, researchers created a family of malaria drugs known as "Oz," based on synthetic peroxide derived from wormwood. They gave a royalty-free license to MMV and allowed the nonprofit to file patents on the compounds. Pharma giant Roche donated its help to the school to do preclinical studies, and then stepped aside to allow Ranbaxy Laboratories in India to develop and distribute the drugs, which are now in trials.

It may take some time for a genetically engineered version of artemisinin to make it to market, and it's unlikely to do so before 2009. Keasling's process requires 12 steps. He has now completed nine and is "looking for the last few genes," he reports.

After artemisinin, Keasling plans to use his process to synthesize prostratin, a promising anti-AIDS compound derived from the bark of Samoa's mamala tree. Berkeley's agreement with Samoa acknowledges the country's sovereign rights over prostratin's gene sequence.

That's fine with Keasling: "If you can do fun science and save a million lives a year, that's great."

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