Little Chemical Factories Pave The Way For Low-Cost Antimalarial Drugs

Berkeley (UC Berkeley)
Office of IP

The genetically engineered microbes in Jay Keasling's laboratory at the University of California, Berkeley (UC Berkeley) are tiny but powerful.

The 'little chemical factories,' as Keasling calls them, have attracted $53.3 million in funding from the Bill & Melinda Gates Foundation, launched a successful startup company and paved the way for low-cost supplies of a semisynthetic antimalarial drugs for those who need it most.

The journey from custom-made microbe to the antimalarial drug took some 10 years, innovative science — specifically, the emerging field of synthetic biology — humanitarian licensing agreements and a unique public-private partnership. As a result of the partnership's efforts, antimalarial treatments with semisynthetic derivatives produced by the healthcare company Sanofi are saving hundreds of thousands of lives.

"Only through cross-sector collaboration between an [academic] research lab, biotech company and commercial partner

could results like these be attainable," says Jack Newman, a former post-doctoral student in Keasling's laboratory and co-founder of the startup Amyris.

Malaria

Long vanquished from the United States and Europe, malaria remains a major health and economic problem in Africa, India and Southeast Asia. The parasitic disease, which is passed from one person to another through the bite of an infected mosquito, causes high fevers, flu-like symptoms and anemia. Without effective treatment, it can result in life-long learning disabilities and death.

"Malaria exists in the tropics in low- and middle-income countries, [places] pharmaceutical companies don't focus on," says Carol Mimura, Ph.D., Assistant Vice Chancellor, IP & Industry Research Alliances at UC Berkeley. "The pharmaceutical industry is not motivated to invest in high-risk projects unless there is a prospect of high reward in terms of recouping the investment."

According to the World Health Organization (WHO), more than 500,000 people — mostly children — die from malaria every year, despite the fact that the disease is curable and preventable.

A Cure

A botanical compound found in the leaves of the Artemisia annua (or sweet wormwood plant) called artemisinin is 100 percent effective against malaria. Artemisinin-based combination therapies, or ACTs, have been recommended as the treatment-of-choice for the most common form of malaria by the WHO since 2005. But due to a number of factors — including drought, seasonality and crop failure — the supply of plant-derived artemisinin is inconsistent and unpredictable.

Keasling's Engineered Microbes

"Jay is a pioneer in synthetic biology and producing [semisynthetic artemisinic acid] was his first high-profile project," says Mimura.

With training and degrees in chemical engineering and biology, Keasling arrived at the University of California-Berkeley in 1992 as an assistant professor and stayed, becoming a professor in of biochemical engineering and Associate Laboratory Director for Biosciences at the Lawrence Berkeley National Laboratory.

"I've been working for about 20 years in the lab engineering the chemistry inside microbes to produce interesting chemicals from simple sugar," says Keasling, the director of UC Berkeley's Synthetic Biology Engineering Research Center.

In 2000, he began working on a platform to build a class of molecule called an isoprenoid, which includes cholesterol, flavors, fragrances and artemisinin.

"The most interesting isoprenoids come from plants," explains Keasling. "Rather than harvest them, [why not] make derivatives that do the same thing?"

Using his synthetic biology platform, Keasling is able to take a metabolic pathway found in nature and graft it into the genetic code of a yeast or bacterium, which then converts sugar into the desired chemical.

"The magic of biotechnology is being able to make unlimited quantities of a compound of interest without having to rely on Mother Nature," says Mimura.

Producing Artemisinic Acid

Keasling's research team found a paper reporting that the first gene in the pathway for the production of artemisinin had been cloned. When the team discovered that there was a dire need for synthetic artemisinin, they knew they had a worthy target for their newly built platform.

> *The team began by discovering and cloning the sweet wormwood genes and grafting them into the genetic code of a bacterium. In 2003, the group published a paper reporting their methods for re-tooling the Escherichia bacterium to produce amorphadiene, a precursor to artemisinin.*

"That paper got a lot of press and pharmaceutical companies that make artemisinin-based therapies called saying 'We'd love to have that microbe,'" says Keasling. "We said 'We're a long way from artemisinin and it will require additional funding."

But R&D funding for a drug for a developing country is hard to come by.

"Companies won't invest because they can't recoup their costs and make a profit," says Mimura.

Gates Foundation

In 2003, a proposal to fund Keasling's research was submitted to the Bill & Melinda Gates Foundation, which has made malaria a top priority. At the time, the going rate for a course of ACT was $2.40 a dose. Mimura, Keasling and the Institute for One World Health (iOWH), which is now PATH —an international nonprofit organization that works to improve health and save lives in Africa and Asia — embraced a challenge issued by the Gates Foundation to reduce the current price of a course of ACT therapy from $2.40 to just 24 cents. To accomplish their goal, PATH and UC Berkeley formed a public-private partnership with Amyris, founded by Keasling and four post-doctoral students, Newman, Vince Martin, Neil Renninger and Kinkead Reiling.

The Gates Foundation responded in 2004 by awarding the partnership with $42.6 million (followed by $10.7 million in Phase 2 funding). Additional funding came from Akibene Foundation, the U.S. Department of Agriculture, the UC Discovery Grant Program, the National Science Foundation and the Diversa Corporation.

"In one day we signed two license agreements and a three-way collaborative agreement that worked together to implement our mutual goals," says Mimura.

De-Risking R&D

UC Berkeley issued royalty-free and 'no profit, no loss' licenses to both PATH (in developing countries, limited to the field-of-use of malaria treatment) and Amyris (in developed countries, all fields of use) — that were ultimately sub-licensed to Sanofi (in the malaria field of use)— covering methods to produce engineered yeast strains that manufacture artemisinic acid. The licenses (and corresponding collaboration agreements) include humanitarian-use clauses addressing access and affordability of the malaria treatment for patients in 88 named developing countries.

"The public-private partnership de-risked the translational research stage with vital funding from the Gates Foundation," says Mimura. "This is the stage of drug development that pharmaceutical companies cannot afford to engage in if the outcome is uncertain or if the prospect of returning a profit on sales is low. Shifting the funding and R&D burden upstream from pharma to the public-private partners enabled a critical gap to be traversed and ultimately created an acceptable value proposition to Sanofi."

For three years, Keasling's lab worked to discover the genes required to make artemisinic acid and construct the first yeast cells to produce artemisinic acid.

Amyris used those genes and others discovered by Pat Covello, a senior research officer at the University of Saskatchewan, to create a significantly modified yeast strain that could produce at industrial levels. PATH shepherded the drug's development from the lab to Amyris and in 2008, to Sanofi for production.

Sanofi began manufacturing its ACT therapy, ArteSunate AmodiaQuine Winthrop, with semisynthetic artemisinin in 2013 using the required no-profit, no-loss production model. The company also began supplying other drug manufacturers with the manmade active ingredient.

Saving Lives

To date, Sanofi has delivered some 16 million antimalarial treatments with semisynthetic derivatives to Africa. The company plans to produce an average of 50-60 tons of semisynthetic artemisinin per year for its own ACT therapy and to sell to other manufacturers, ensuring an annual production of up to 150 million ACT treatments.

"250 million people have malaria at any one time so Sanofi will be [directly or indirectly] supplying half of world's needs," says Keasling. "That equates to saving several hundred thousand lives a year."

For their commitment to increasing access to antimalarial therapies in underserved communities, both UC Berkeley and Sanofi have been awarded the prestigious Patent for Humanity Award from the U.S. Patent and Trademark Office.

"Carol [Mimura] was fantastic to work with and so proactive," says Keasling. "The Gates Foundation was so generous, they allowed us to put the pedal to the metal and get the drug quickly. The whole process keeps giving back."

Indeed, with work on the semsynthetic artemisinin complete, Amyris is now using the synthetic biology platform to convert plant sugars into other useful hydrocarbon molecules.

"We now use this amazing platform to make all sorts of products," says Newman. "Emollients, fragrances, biofuels . . . we make thousands of tons of these at our 1.2 million liter fermentation facility today."

To see available technologies from research institutions, click here to visit the AUTM Innovation Marketplace.