Medical Xpress

Launch of semi-synthetic artemisinin a milestone for malaria, synthetic biology

April 11 2013

This Kenyan child is in the under-five age group most affected by malaria. According to a 2010 report, about 660,000 people died from malaria around the world, primarily in Asia and Africa. A new semi-synthetic version of the front-line treatment, artemisinin combination therapy, will provide a stable and low-cost supply for these countries. Credit: Courtesy of Zagaya.

Twelve years after a breakthrough discovery in his University of California, Berkeley, laboratory, professor of chemical engineering Jay Keasling is seeing his dream come true.

On April 11, the pharmaceutical company Sanofi will launch the large-scale production of a partially synthetic version of artemisinin, a chemical critical to making today's front-line antimalaria drug, based on Keasling's discovery.

The drug is the first triumph of the nascent field of synthetic biology and will be, Keasling hopes, a lifesaver for the hundreds of millions of people in developing countries who each year contract malaria and more than 650,000, most of them children, who die of the disease. Synthetic biology involves inserting a dozen or more genes into microbes to make them produce drugs, chemicals or biofuels that they normally would not.

Keasling and colleagues at Amyris, a company he cofounded in 2003 to bring the lab-bench discovery to the marketplace, will publish in the April 25 issue of *Nature* the sequence of genes they introduced into yeast that allowed Sanofi to make the chemical precursor of artemisinin. The paper will be available online April 10.

"It is incredible," said Keasling, who also serves as associate director for biosciences at Lawrence Berkeley National Laboratory and as CEO of the Joint Bioenergy Institute in Emeryville, Calif. "The time scale hasn't been that long, it just seems like a long time. There were many places along the way where it could have failed."

The yeast strain developed by Amyris based on Keasling's initial research and now used by Sanofi produces a chemical precursor of artemisinin, a compound that until now has been extracted from the sweet wormwood plant, *Artemsia annua*. Artemisinin from either sweet wormwood or the engineered yeast is then turned into the active antimalarial drug artesunate, and typically mixed with another antimalarial drug in what is called arteminsinin combination therapy, or ACT.

Global demand for artemisinin has increased since 2005, when the World Health Organization identified ACTs as the most effective malaria treatment available. Sanofi said that it is committed to producing semisynthetic artemisinin using a no-profit, no-loss production model, which will help to maintain a low price for developing countries. Though the price of ACTs will vary from product to product, the new source for its key ingredient, in addition to the plant-derived supply, should lead to a stable cost and steady supply, Keasling said.

Key campus support

"This wouldn't have happened without lots of incredible support from the UC Berkeley campus," Keasling added, noting that the university pushed for royalty-free licensing of the process to Sanofi, which in turn will sell artemisinin at cost. "Some really dedicated people put their careers on the line for it, both at UC Berkeley and at Amyris."

The success is due in large part to two grants totaling $53.3 million from the Bill & Melinda Gates Foundation to OneWorld Health, the drug development program for PATH, an international nonprofit organization aiming to transform global health through innovation. OneWorld Health shepherded the drug's development out of Keasling's UC Berkeley lab to Amyris for scale-up and then to pharmaceutical firm Sanofi, based in France, for production.

"With commercial production of semi-synthetic artemisinin underway, we are poised to enable a more stable flow of key antimalarial treatments to those who need them most," said Ponni Subbiah, global program leader for drug development at PATH. "The success of this cross-sector collaboration demonstrates that, with a shared humanitarian goal and the dedication and perseverance of all partners, we can advance science to make a real impact in global health."

"Those three partners working together under a OneWorld Health umbrella has been an amazing collaboration," said Jack Newman, chief science officer of Amyris and a former post-doctoral fellow in Keasling's UC Berkeley lab. "Only through a partnership like that a research lab, a biotech focused on taking the discovery and turning it into something that's industrializable, and a commercial partner to take it to market are these types of results possible."

Keasling encourages other companies to license for free their synthetic processes to make artemisinin in order to ensure that needed doses are available worldwide. The yeast strain described in the *Nature* paper is licensed exclusively to Sanofi.

Ancient Chinese therapy

Sweet wormwood was used in ancient Chinese therapy to treat various illnesses, including fevers typical of malaria. In the 1970s, Chinese scientists rediscovered it and identified its active ingredient, artemisinin, and artemisinin is now extracted from sweet wormwood grown commercially in China, Southeast Asia and Africa. The quality, supply and cost have been unpredictable and inconsistent, however. Keasling's goal was to create a synthetic version with a stable and ideally lower price that could be produced in sufficient quantity to treat the 300-500 million cases of malaria that arise each year.

"The production of semisynthetic artemisinin will help secure part of the world's supply and maintain the cost of this raw material at acceptable levels for public health authorities around the world and ultimately benefit patients," said Dr. Robert Sebbag, vice-president of Access to Medicines at Sanofi. "This is a pivotal milestone in the fight against malaria."

The "semi-synthetic" artemisinin is chemically modified to an active

drug, such as artesunate, and combined in ACT with another antimalarial drug to lessen the chance that the malaria parasite will develop resistance to artemisinin. Sanofi plans to produce 35 tons of artemisinin in 2013 and, on average, 50 to 60 tons a year by 2014, which will translate to between 80 and 150 million ACT treatments. Following regulatory approval expected later this year, semisynthetic artemisinin will be ready for rapid integration into the supply chain for antimalarial therapies, according to the company.

"This artemisinin produced by this semisynthetic process will substitute directly for the artemisnin from the plant, so there will be no difference in the final ACT product," Keasling said.

The 12-year tale started in Keasling's UC Berkeley lab with the discovery that implanting a combination of wormwood and yeast genes into bacteria made the bacteria produce a chemical that could be chemically converted to artemisinin. Further research turned up another gene in 2006 that, when inserted into yeast with the earlier genes, allowed Keasling and his team to synthesize small amounts of artemisinic acid, which is closer chemically to the actual drug. Using synthetic biology techniques from Keasling's lab, Amyris added that gene to yeast along with other plant genes to boost artemisinic acid production by a factor of 15, good enough to interest Sanofi.

The drug company developed its own proprietary photochemical process to convert artemisinic acid to artemisinin, hence the term semi-synthetic. In the *Nature* paper, the Amyris researchers describe an alternative, nonproprietary process for achieving the same result.

More information: dx.doi.org/10.1038/nature12051