Improved Production of a Natural Product Treatment for Malaria: OneWorld Health, Amyris, and the University of California at Berkeley

In December 2004 the Bill and Melinda Gates Foundation[1] awarded a five-year product development grant to the Institute for OneWorld Health (iOWH),[2] a nonprofit pharmaceutical company, to create a unique three-way partnership between iOWH, a university (University of California at Berkeley),[3] and a for-profit company (Amyris Biotechnologies, Inc.).[4] The goal of this project[5] is to significantly reduce the cost of artemisinin, a key precursor in the production of Artemisinin Combination Therapies (ACT), through synthetic biology, industrial fermentation, and chemical synthesis. Artemisinin is chemically converted to one of several derivatives and then combined with other drugs to make an ACT for the treatment of malaria.

Malaria is a parasitic blood disease that inflicts as many as 500 million people annually. About 1.5 million people die each year from the infection, primarily children in Africa and Asia. More than half of the deaths occur among the poorest 20 percent of the world's population. Studies in Vietnam have shown that the botanically derived medicine, artemisinin derivatives, can reduce deaths from the illness by 97 percent. However, the current cost of a three-day course of drugs containing artemisinin is US$2.40, which places it out of reach for people in many nations where the disease is most prevalent. Reducing the price would make the treatment more widely accessible.

Artemisinin is currently extracted from the wormwood plant, which is supplied by farmers in Vietnam and China (and more recently, Africa). Seasonality and availability of the plant contribute to the high price of the drug. The Gates-funded project hopes to eliminate the need for plant extraction by utilizing a platform technology of synthetic biology developed by Dr. Jay Keasling at the University of California (UC), Berkeley.[6] The goal is to lower the cost of artemisinin-containing drugs ten-fold by producing a consistent, reliable, high-quality supply of artemisinin in microbes.

The US$42.6 million grant was divided among the three partners: US$8 million to UC Berkeley for continued basic research, US$12 million to Amyris for applied research on the fermentation and chemical processes, and US$22.6 million to iOWH to perform the required regulatory work and lead the implementation of the product development strategy for the developing world. UC Berkeley's role focuses on the engineering of drug-precursor-producing microbe. Amyris' efforts span engineering of the production microbe to optimizing the semisynthesis of the drug through fermentation and novel downstream synthetic chemistry. The role of iOWH includes developing a commercialization strategy based on a thorough understanding of the worldwide regulatory requirements and an analysis of the current ACT manufacturing supply-chain and distribution models. This one grant enables activities in all three areas of development and creates an integrated team, each of the partners applying its expertise to streamline translation from bench to bedside.

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To ensure accessibility and affordability, the partners have committed to reduced returns in the malaria field. UC Berkeley has issued a royalty-free license to iOWH and shall grant royalty free licenses to Amyris for IP that is developed during the collaboration for the treatment of malaria in the developing world with the goal of significantly reducing the price of ACT products, and reducing the use of artemisinin monotherapies per the World Health Organization's recommendations for uncomplicated malaria.

This arrangement has benefits for all the parties. The university benefits from the research funding as well as from any royalties that may be realized on profit earned from sales by Amyris in areas outside of malaria in the developing world. As a for-profit company, Amyris can apply the innovations developed for the artemisinin project to other projects that rely on the same platform technology. As a nonprofit pharmaceutical company, iOWH is able to make malaria treatments more affordable for people in the developing world.

PARTNERS

Partners in this project are:

- from academia, the University of California, Berkeley
- the nonprofit pharmaceutical company Institute for OneWorld Health (iOWH)
- the for-profit pharmaceutical company Amyris Biotechnologies, Inc.

The Bill and Melinda Gates Foundation provided the funding for the project.

THE TECHNOLOGY

The preferred and most effective treatments for malaria today are artemisinin-based combination therapies (ACT). Artemisinin, a complex natural product known as an herbal remedy for thousands of years, is typically derived from the wormwood plant. Plant sources of the chemical are variable and crop shortages contribute to increased cost. Chemical synthesis of the molecule would require 30 to 40 steps and is therefore impractical on a commercial scale.

Dr. Jay Keasling, a UC Berkeley professor of chemical engineering, developed a process of "synthetic biology" to produce an artemisinin precursor through a multistep process in bacteria.[7] The precursor can then be chemically converted to artemisinin through synthetic chemistry developed at Amyris. Producing the drug precursor in microbes would lead to a more consistent and reliable supply and therefore reduce the cost of production.

The synthetic biology platform may also be used to produce other drugs, nutraceuticals, and flavors and fragrances.

PROGRESS, CURRENT STATUS, AND GOALS

During the five-year granting period, which began in 2005, the partners would carry out the following activities shown in Figure 1.

UC Berkeley researchers are working to identify the genes involved in the artemisinic acid biosynthetic pathway in the wormwood plant, *Artemisia annua*. Using their expertise in synthetic biology, they are inserting this biosynthetic pathway into microbes to create hosts that manufacture this direct precursor to artemisinin. Optimizing artemisinic acid production in these host cells is being achieved through cutting-edge techniques in metabolic engineering, in collaboration with scientists at Amyris Biotechnologies.

Amyris Biotechnologies is collaborating with the Center for Synthetic Biology to build a better microbe. Amyris will optimize the microbial strain developed with UC Berkeley for commercial production. In addition, Amyris will develop a fermentation and purification process for the precursor. Simultaneously, Amyris is developing a scaleable, inexpensive chemical process to convert the precursor to artemisinin.

OneWorld Health is the product development lead and has responsibility for directing this collaborative effort. In addition, the organization is leading the project's regulatory and commercialization strategies and is conducting a risk-benefit analysis surrounding the use of artemisinin derivatives in malaria-endemic regions.

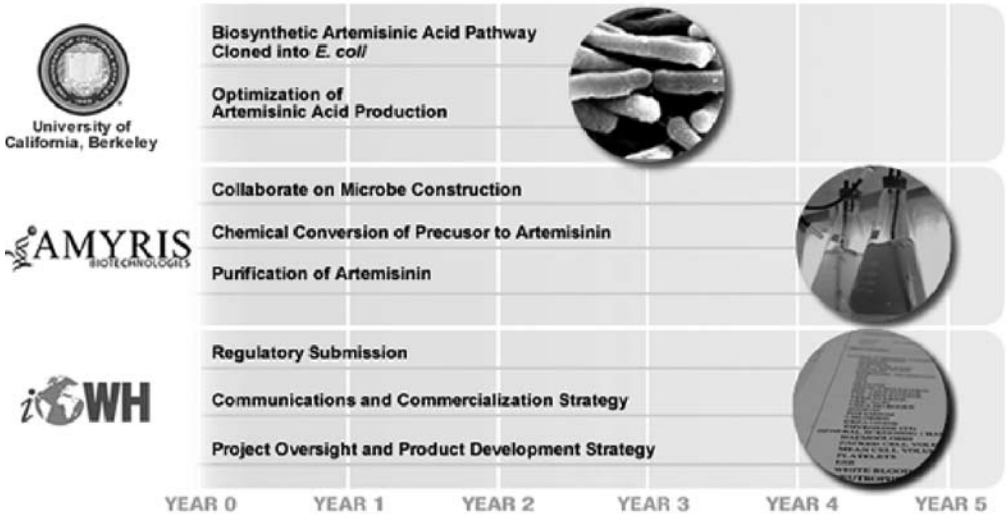
DEALS

Agreements between the partners include the following:

License Grants:

- The arrangement is governed by a three-party collaboration agreement and two license agreements (from UC Berkeley to each of Amyris and iOWH).
- UC Berkeley granted iOWH a royalty-free license for the manufacture of artemisinin-based malaria treatments used in the developing world. UC Berkeley further shall grant royalty-free licenses to iOWH for IP developed under the three-party collaboration agreement for use in manufacturing artemisinin-based malaria treatments used in the developing world. OneWorld Health is to establish partnerships for ACT manufacture and distribution.
- UC Berkeley granted Amyris licenses to develop the manufacturing process for the developing-world malaria market. Amyris also has licenses for the developed-world malaria market, nonmalaria indications of artemisinin, and alternative uses of the platform worldwide. UC Berkeley further shall grant similar licenses to Amyris for IP

Figure 1: Activities of Project Partners (to be carried out by the end of the grant period)



developed under the three-part collaboration agreement.
- Amyris shall grant iOWH a royalty-free license for IP developed under the three-part collaboration agreement for the manufacture of artemisinin-based malaria treatments used in the developing world.

Royalties:
- The license from UC Berkeley to iOWH is royalty free.
- The license from UC Berkeley to Amyris is royalty free for the developing-world malaria market (development for iOWH) and is royalty bearing for the developed world and nonmalaria indications in the developing world.

Patents:
- Patent costs for UC Berkeley's pre-existing patents are shared between iOWH and Amyris.
- UC Berkeley patents on IP arising from the collaborative research may be filed by UC Berkeley and licensed to iOWH and/or Amyris under the pre-arranged terms mentioned above. Costs are shared by the licensee on a pro rata basis. UC Berkeley has no obligation to file an application if it does not have a commitment by a licensee to pay patent costs.
- Patents that are the sole property of Amyris and/or iOWH may be filed by Amyris and/or iOWH, as the case may be, at their own expense.
- Logistics of filing and payment of costs on jointly owned IP will be negotiated in good faith by the joint owners when such joint IP arises. If the joint owners cannot agree and if iOWH has an ownership interest in a joint property, then iOWH may file and prosecute on behalf of the owners at its own expense.

Other:
- Amyris, as UC spinout company, is seeking venture funding to leverage applications in other markets.
- Using the process developed by Amyris and UC Berkeley, iOWH is to establish partnerships for ACT manufacture and distribution
- Similar licenses to all relevant third-party intellectual property will be obtained by iOWH as the need arises. ■

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1 Bill and Melinda Gates Foundation. www. gates foundation.org.

2 Institute for OneWorld Health. www.oneworldhealth.org/.

3 Office of Intellectual Property and Industrial Research, UC Berkeley. ipira.berkeley.edu/index.php.

4 Amyris Biotechnologies, Inc. www.amyrisbiotech.com.

5 The Artemisinin Project. www.artemisininproject.org.

6 Keasling Laboratory, UC Berkeley. www.cchem.berkeley.edu/%7Ejdkgrp/.

7 Martin VJ, DJ Pitera, ST Withers, JD Newman and JD Keasling. Engineering a Mevalonate Pathway in *Escherichia Coli* for Production of Terpenoids. *Nature Biotechnology*. 21 July 2003. (7): 796–802.