



Canadians Make a Global Advance against the Scourge of Malaria

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On March 18th 2011, an announcement at the National Research Council Plant Biotechnology Institute in Saskatoon promised to turn the world's fight against malaria on its head (Major breakthrough in Malaria fight; 2011, March 18). A collaborative effort between Canada's National Research Council (NRC) and researchers at the University of California in Berkeley has enabled a potent, naturally occurring antimalarial called artemisinin to be semisynthetically produced.

Artemisinin, or *quinhaosu* in Chinese, is a compound produced by the leaves *Artemisia annua*, the sweet wormwood plant used for thousands of years in Chinese medicines (Heyerick, A. n.d.). The compound was first isolated in 1972 (Purcell, K. 2004) by Chinese scientists investigating the antimalarial properties of almost 200 traditional medicines (Defeating the curse. n.d.), and artemisinin was found to be very effective in curing patients infected with malaria. Indeed, Artemisinin Combination Therapies (ACTs), which administer artemisinin together with one or more other anti-malarial drugs, constitute today's most effective pharmaceutical response to the disease, as determined by the World Health Organization (WHO) (Artemisinin combination therapies. n.d.). ACTs have a cure rate better than 95% (Marketing of oral artemisinin. n.d.) and are efficacious where disease variants have become resistant to standard drugs such as chloroquine (Artemisinin derivatives, n.d.).

However, artemisinin has not been without its problems, most notably its high cost. Due to the lengthy time it takes to grow and process *Artemisia annua*, as well as the extremely low concentration of artemisinin in the plant (only 0.01% - 0.08%) (Lei, CY. 2011), a single dose of an ACT, such as Coartem, is up to 24 times as expensive as an equivalent dose of chloroquine (\$2.40 compared to \$0.10 - \$0.15) (Artemisinin & malaria treatments. n.d.), (Artemisinin combination therapies. n.d.). This represents a significant barrier in treating those afflicted with malaria, as almost all of the hundreds of millions affected are the world's most impoverished and vulnerable citizens: women and children living in developing countries. 90% of those infected with malaria are in Africa (Malaria in Africa. n.d.), and most of the 800,000 persons that die annually are children under five and pregnant women (Munthali, A. 2005.). Artemisinin price and provision issues are further exacerbated because the world's supply of naturally occurring is viable, susceptible as it is to the drought, flood, pests, and diseases which can disrupt sweet wormwood crops. As a result, there are severe limitations on the widespread supply of artemisinin, and consequently of ACTs, to the 300-500 million people who suffer malaria every year (About malaria. n.d.).

Given these problems inherent in natural source artemisinin, the scientific community recognized the need for developing a synthetic supply of the compound. Patrick Covello, senior researcher with the NRC, and his team of scientists at the University of Saskatchewan secured over \$800,000 in funding from the Canadian government (Haight, L. 20011, May 20.) to conduct research aimed at isolating the sweet wormwood genes which lead to the production of artemisinin in the plant. Nearly six years of research finally yielded the identification of the four



genes which code for the proteins responsible for artemisinin production.

Meanwhile, a team of scientists at the University of California in Berkeley, led by Jay Keasling, had been conducting a parallel, independent stream of research in the fight against malaria under the auspices of the Artemisinin Project, whose goal it was to synthetically produce artemisinin at a much lower cost than the naturally occurring version. This innovative private-public partnership, led by the Institute for OneWorld Health (iOWH) and funded by a \$43 million grant from the Bill and Melinda Gates Foundation (Sanders, R. 2004, December 13.), had yielded the ability to genetically engineer *E. coli* to produce amorphadiene, a close precursor to artemisinin, by mixing certain chemicals with the bacteria (Lynn, Y. 2006, May 30.).

Cognizant of the potential benefits of collaboration, Covello of the University of Saskatchewan contacted Keasling at his spin-off company, Amyris Biotechnologies, an endeavour birthed out of the successes of the Artemisinin Project. Keasling embraced the opportunity, and in 2008 “the NRC and Amyris signed a license agreement, allowing the company to incorporate NRC’s discovery of two key genes in the artemisinin pathway into Amyris’ proprietary system.” (Innovative Canadian research. 2011, March 18.)

In response to this turn of events, the California team began to use yeast as a platform in their research, as it was much easier to splice the wormwood genes into yeast than into bacteria (Lynn, Y. 2006, May 30). Yeast was genetically modified in a very similar way as the *E. Coli* had been, so that it would likewise produce amorphadiene; the two sweet wormwood genes that the plant uses to convert amorphadiene into artemisinic acid— genes which had been isolated by the NRC team in Saskatoon— were then inserted into the yeast. These modifications would allow the yeast to produce artemisinic acid rather than ethanol as it fermented (Major breakthrough in malaria fight. 2011, March 18) . After that, as Keasling describes it, “The synthesized artemisinic acid can be transported out and retained on the outside of the engineered yeast. This means that a simple and inexpensive purification process can be used to obtain the final product [artemisinin].” (Lynn, Y. 2006, May 30).

These amazing breakthroughs promise huge benefits for our world. The biosynthetic version of artemisinin, already in the early stages of production, is much cheaper to produce than natural artemisinin, only \$0.25 per dose (. According to an April 18, 2011 news release by OneWorld Health, “its development of an alternative source of artemisinin using pioneering synthetic biology... has successfully entered the production and distribution phase...with an estimated goal to begin distribution in 2012.” (The Institute for OneWorld Health. 2011, April 18.). In order to maximize the benefits to those affected by malaria, the drug will be manufactured by the pharmaceutical company sanofi-aventis (The Institute for OneWorld Health. 2011, April 18) on a strictly not-for-profit basis.

This huge accomplishment, strongly reliant on work done by Canadian researchers, is a substantial benefit to the world and to iOWH’s goal that “one day no child will die from malaria.” (The Institute for OneWorld Health. 2011, April 18.).



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