

The Artemisinin Consortium

MMV joins forces with the Institute for OneWorld Health and York University to address the critical issue of satisfying global demand for artemisinin.

Three complementary scientific approaches together aim to improve artemisinin production technologies. This will consequently stabilize the supply of artemisinin, lower the cost of artemisinin production, and ultimately make ACTs cheaper and therefore more accessible to patients who need them. These approaches constitute a revolution.

In 2001, the World Health Organization (WHO) recommended that countries where malaria is resistant to conventional treatments, such as chloroquine, should switch to artemisinin-based combination therapies (ACTs). Since then, orders for ACTs have increased exponentially each year, with WHO alone initially requesting 220,000 treatment courses for the public sector, later increasing their order to 10 million treatment courses in 2004, and to 60 million in 2005. This surge in demand led to a global shortage of ACTs, raising the cost of the drug and making it inaccessible to those populations in desperate need of treatment. In addition, it left the ACT production system straining to keep pace with demand.

Artemisinin, the essential active ingredient of ACTs, costs at least ten times as much as chloroquine. It is extracted from the herb *Artemisia annua*. Cultivation of this plant requires a minimum of six months. The extraction, processing and manufacturing of the final products take an additional three to five months, depending on the product formulation.

It became obvious to WHO, national malaria control programmes, and initiatives researching new treatments for malaria, such as the Institute for OneWorld Health (IOWH) and MMV, that reliable, low-cost supplies of artemisinin were urgently needed if the situation was to be resolved.

In response to this situation, three projects have joined forces to satisfy the projected global demand for ACTs. Known as the Artemisinin Consortium,

this collaboration aims to ensure maximum impact on ACT supply chains, and to ensure that the new technologies do not enter supply chains for substandard drugs or monotherapies. The projects are outlined briefly below:

- ▶ The Institute for OneWorld Health (IOWH), in partnership with the University of California, Berkeley, and Amyris Biotechnologies, is using synthetic biology to develop microbially-derived artemisinin through fermentation.
- ▶ The Centre for Novel Agricultural Products (CNAP) at York University is applying fast-track breeding technologies with the aim of creating new, non-GM cultivars of *Artemisia annua* with increased yield of artemisinin.
- ▶ Medicines for Malaria Venture (MMV) is working towards developing a new class of antimalarial compounds — synthetic peroxides — that is safe, potent, and could mimic the rapid action of artemisinin.

These three complementary scientific approaches constitute a revolution. Together, they aim to improve artemisinin production technologies, which will consequently stabilize the supply of artemisinin, preventing vast fluctuation in prices and shortage-driven price rises; lower the cost of artemisinin production; and ultimately make ACTs cheaper and therefore more accessible to patients.



**Microbially-derived artemisinin
Institute for OneWorld Health,
USA**

The Institute for OneWorld Health and its partners, Amyris Biotechnologies and the laboratory of Professor Jay Keasling at the University of California, Berkeley, are using synthetic biology to help reduce the price of artemisinin. The project aims to create, optimize, and scale-up microbial production systems to augment current supplies and make high-quality bulk artemisinin available to ACT manufacturers year-round at a price much lower than the current cost to them.

The project is addressing the price of artemisinin derivatives, which are a significant cost component of ACTs. The price of artemisinin, the starting material for the synthesis of artemisinin derivatives is extremely volatile and in recent years has ranged from USD 400 to USD 1700/kg. The price that the Institute for OneWorld Health project is targeting is USD 100/kg for microbially-derived artemisinin, with the goal of reducing final treatment costs and helping to stabilize the ACT market.

This project aims to develop and validate a cost-effective, commercial-scale process using fermentation combined with synthetic chemistry to produce artemisinin. It is anticipated that bulk production of this important compound will significantly reduce the price of these

medicines, making them accessible to the hundreds of millions of impoverished people who contract malaria each year. The industrial fermentation process also offers advantages in scalability, reliability, and flexibility, which allow for a greater and faster ability to adjust to market changes.

There are two stages in the production of microbially-derived artemisinin: biological and chemical. The biological stage employs an engineered microbe to convert simple sugars into artemisinic acid using microbial fermentation. Several chemical synthesis steps then convert artemisinic acid into the final product, artemisinin.

Production using the highest manufacturing quality standards is expected to begin by 2010, with the goal of making enough medicine for 200 million of the estimated 500 million treatments needed. OneWorld Health is in the process of selecting a manufacturing partner.

**High-yielding *Artemisia annua*
Centre for Novel Agricultural
Products (CNAP), York University,
UK**

The medicinal plant *Artemisia annua* is currently the sole source of artemisinin and will continue to be an essential element for supply in the foreseeable future. However, it usually yields less than 1% dry weight, making production expensive. High-yielding varieties would reduce the costs associated with both cultivation and extraction, and would improve returns for the farmer.

Based at the Centre for Novel Agricultural Products (CNAP), a research centre in the Department of Biology at York University, this project aims to produce new, non-genetically modified (GM) cultivars of *Artemisia annua* with increased artemisinin yield, using fast-track plant breeding techniques.

A population of *Artemisia annua* seeds with increased genetic variety has been created by means of a chemical treatment, widely used in plant breeding. Two complementary approaches will be used to screen this population for individuals with increased artemisinin yields. The first approach screens their DNA for gene alleles that are predicted to improve yield. The second approach measures the artemisinin levels in leaf tissue.



Once high-yielding individuals have been selected, classical crop breeding methods will be used to convert them into agronomically robust varieties. Field trials in a range of global environments will be conducted on the new varieties. Roll-out will include a sustainable supply of high-quality seed, supplied at cost, accompanied by a handbook for growers. It is vital that the new varieties are not used in the manufacture of monotherapies or substandard drugs. To this end, it is anticipated that seed distribution will be overseen by a stakeholder cooperative, who will ensure that the crop is to be used only by approved ACT manufacturers. The use of hybrids further mitigates this risk, as growers will achieve greatly reduced yields from seed they save from such varieties.

Synthetic peroxides Medicines for Malaria Venture (MMV)

In collaboration with a number of research partners, including the University of Nebraska, Monash University, and the Swiss Tropical Institute, MMV is working towards developing a new class of antimalarial compounds that is safe and potent. This class of synthetic peroxides, coined the 'OZ compounds', could potentially have a different mode of action or molecular target in the parasite, compared with artemisinin.

Many synthetic antimalarial peroxide compounds have been identified as having antimalarial activity, but almost all suffer from low oral activity. Therefore, scientists are eager to discover new peroxide antimalarial agents that can be easily synthesized, are inexpensive, have high oral activity, and which are devoid of the known toxicities associated with artemisinins. The synthetic peroxides appear on initial evidence to be potentially safer in early pregnancy than the artemisinins; and safety in early pregnancy has been one of the concerns about deploying ACTs to women of childbearing age. The goal is to identify new antimalarial agents which have the requisite pharmacokinetic properties to allow curative doses to be administered over a one to three day period.

An extensive investigation of the existing OZ compound library has been undertaken to identify the key features contributing to single-dose cures, which include high oral bioavailability, a longer half-life, and possible prophylactic activity. The research team will select the most promising OZ compound for clinical development during the second half of 2007.

