CNAP Artemisia Research Project

Fast-track breeding of *Artemisia annua*

Meeting Global Demand

25 June 2007

Dianna Bowles, Ian Graham, Maggie Smallwood

A sustainable supply of artemisinin from *Artemisia annua*
Project aim

To produce a cost-effective plant product which will stabilise supply and reduce production costs of artemisinin for artemisinin combination therapies.
Demand for artemisinin

- the global demand for ACTs will continue to increase
- over half of that demand must be met by *A. annua* plants even when alternatives succeed
- improvement of the plant production system is a continuing requirement

**Plant manufacturing**

- sustainable
- high capacity
- scaleable
- complex chemicals

A sustainable supply of artemisinin from *Artemisia annua*
Artemisinin made by plants

- *A. annua* is the only proven production system for artemisinin
- regulatory frameworks are already established
- the plant-based system has a known economy

However:
- yield in current varieties is low and unreliable
- the supply chain is not secure
- volatile prices and high production costs

High yield varieties will help
- secure the supply of artemisinin
- reduce the cost of production

**cheaper artemisinin**

A sustainable supply of artemisinin from *Artemisia annua*
Impact of high yield varieties on price

- Sustainable **price** for artemisinin using current technology and *A. annua* varieties ≥$400 per kg
- Cost of artemisinin production is directly proportional to yield in the plant
  - ↑ yield per hectare ⇒ ↓ cultivation costs
  - ↑ yield per unit biomass ⇒ ↓ extraction costs
- Yield of best current varieties ≤1% DW
- Increasing yield to 4% ⇒ artemisinin at ~ $100 / kg

However, **cost** of production is only one of many factors which impact on **price**
Parameters controlling plant artemisinin yield

- increasing the leaves on a plant
- increasing the trichomes on a leaf
- increasing the artemisinin per trichome
Scientific strategy

- Increase the genetic diversity of *A. annua*
- Identify individuals with high artemisinin
- Develop robust new varieties

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**Increased genetic diversity**

- Artemis – high yield F1 hybrid (0.8 – 1.5%)
- Starting population of 9,000 plants

**Timescale – plants currently under cultivation**
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**Scientific strategy**

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Identify individuals with high artemisinin

**HT screen for metabolites**
~25,000 plants

- UPLC-MS, FTIR, MALDI, ELISA

**HT screen for genes**
~50 genes

- Heteroduplex mapping

Timescale – probability increases with numbers screened
Earliest likely date – autumn 2007
Gene discovery programme

Genes controlling secondary metabolism
• Artemisinin biosynthetic pathway
• Precursor synthesis / competing pathways
• Regulation

Genes controlling development
• Trichomes: size, number, distribution
• Flowering: number of flowers and timing
• Size/shape of leaves
• Plant architecture

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Scientific strategy

increase the genetic diversity of *A. annua*

identify individuals with high artemisinin

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A sustainable supply of artemisinin from *Artemisia annua*
Develop robust new varieties

- back crossing into wild type parents
- field trials
- user-tests of artemisinin from new hybrid

timescale – 3 years from identification of high yielding individual earliest likely date – 2010

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Fast track breeding of *A. annua*

- **Scale**
  - orders of magnitude greater than previous efforts
    - metabolite screen of 25,000 plants
    - gene screen of 10,000 plants

- **Cutting edge technology**
  - Genomics - gene libraries, HDM, markers
  - HT LC and GC-MS metabolite profiling

- **Speed**
  - HT gene & metabolite technologies compress breeding timescale
  - Molecular markers further accelerate process

- **Information management**
  - Custom FLIMS designed for project

- **Achievable yield improvement**
  - Other species produce similar compounds in similar structures at 13% DW

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A continuum of forward and reverse screening

*Earliest date to market 2010*

Probability of success increases with number of homozygous genomes and genes screened

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Roll out of new varieties

strategy in early stages of development

• Sufficient high yield *A. annua* to meet demand of the ACT supply chain
• Reduced production **cost** ⇒ reduced **price** of artemisinin
• Low cost artemisinin is used for Artemisinin **Combination Therapies**
• Seed to be provided at cost to contractors/growers supplying ACTs
• Ensuring high yield seed is suitable for existing growers
  – Partnerships under development with contractors/growers North & South of equator
• Ensuring new varieties are suitable for ACT manufacture
  – Partnerships with pharmaceutical companies to undertake user tests

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**Acknowledgements**

**Collaborators**

Mediplant – sub-grantee
- Artemis variety
- Collection of *A. annua* accessions
- *A. annua* breeding and agronomics
- Field trials

Amyris biotechnologies
- Standards for intermediates

Jay Keasling (Berkeley)
- Access to EST libraries

Institute of One World Health
- Facilitating

Geoff Brown (Reading)
- Standards for intermediates

**Funding**

Bill and Melinda Gates Foundation
GlaxoSmithKline
Medicines for Malaria Venture
Garfield Weston Foundation

**Department of Biology**