CNAP Artemisia Research Project

Fast-track breeding of *Artemisia annua*

Meeting Global Demand

25 June 2007

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CNAP

CENTRE FOR NOVEL AGRICULTURAL PRODUCTS

The Queen's Anniversary Prizes
For Higher and Further Education
2006

The University of York

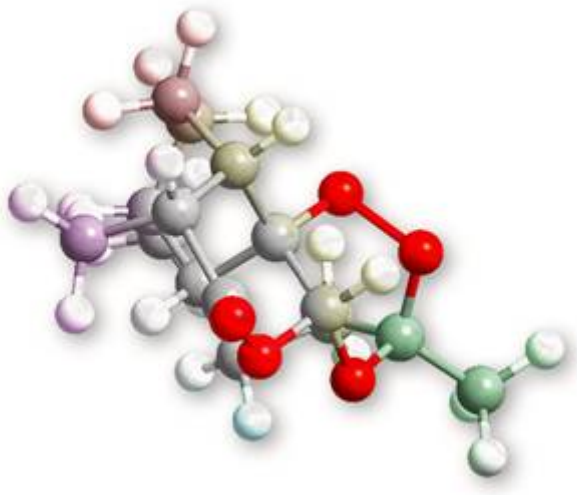
Department of Biology

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

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

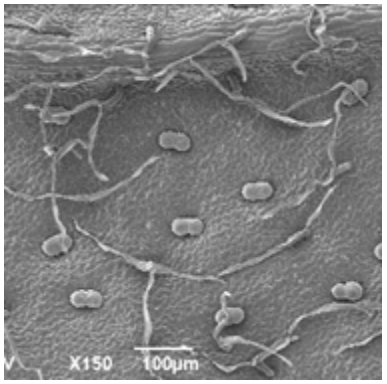
cheaper artemisinin

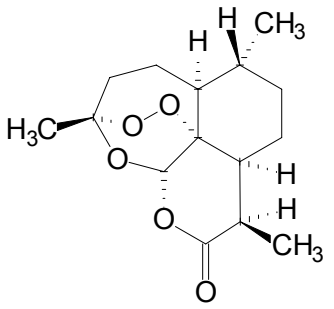
Impact of high yield varieties on price

- 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



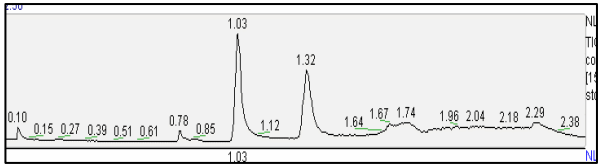


- increasing the leaves on a plant
- increasing the trichomes on a leaf
- increasing the artemisinin per trichome

Scientific strategy

increase the genetic diversity of *A. annua*

identify individuals with high artemisinin



develop robust new varieties

Increased genetic diversity

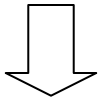
EMS-treated populations of *A. annua*

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

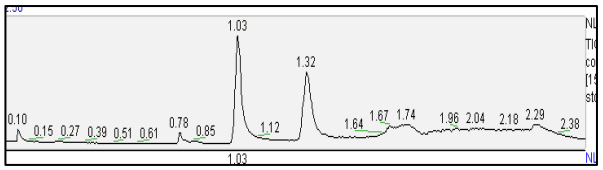
Timescale – plants currently under cultivation

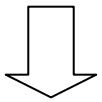
Scientific strategy

increase the genetic diversity of *A. annua*



identify individuals with high artemisinin





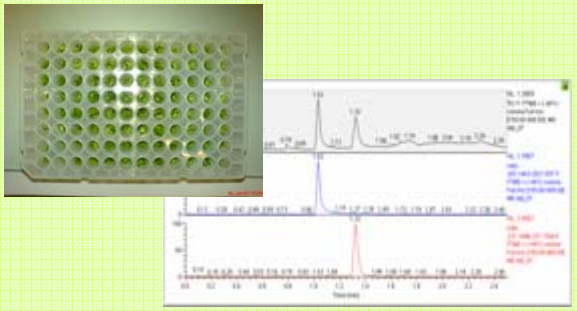
develop robust new varieties

Identify individuals with high artemisinin

HT screen for metabolites

~25,000 plants

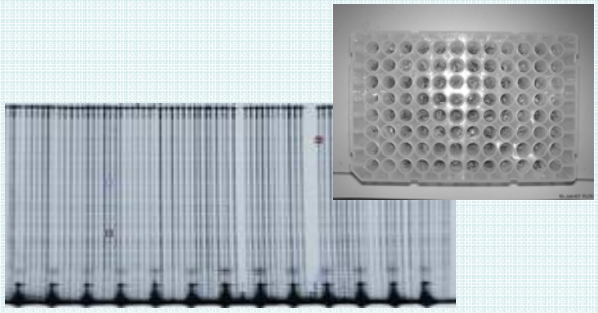
UPLC-MS, FTIR, MALDI. ELISA



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

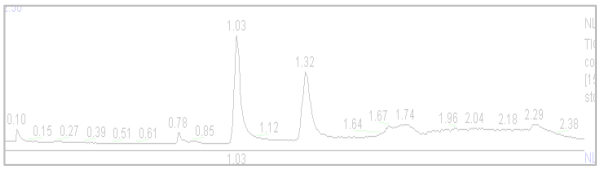
Genes controlling development

- Trichomes: size, number, distribution
- Flowering: number of flowers and timing
- Size/shape of leaves
- Plant architecture

Scientific strategy

increase the genetic diversity of *A. annua*

identify individuals with high artemisinin



develop robust new varieties

Develop robust new varieties

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

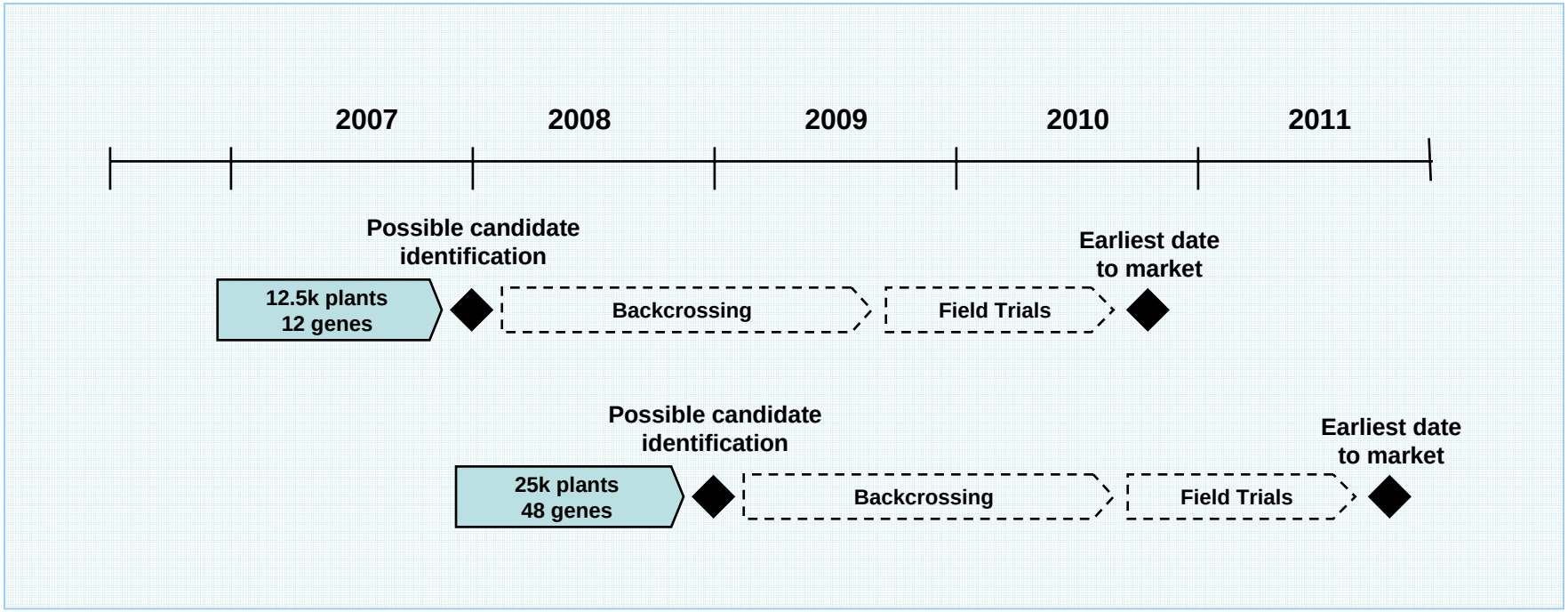
timescale – 3 years from identification of high yielding individual
earliest likely date – 2010

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

A continuum of forward and reverse screening

Earliest date to market 2010



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

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

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

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