The role of academia in combating malaria.

A member of the Russell Group
This talk

• What does academia have going for it?
• DISCOVERY rooted in (a) genome sequencing (b) intelligent redesign.
• DEVELOPMENT the Lapdap and CDA projects.
• POST LICENSURE STUDIES the MiP and iPTI Consortia and EDCTP.
• REFLECTIONS ON PARTNERSHIP
What does academia have going for it?

- Wide diversity.
- Implicit commitment to research capacity development.
- A hotbed environment for excellence.
- Drivers that differ from (are complementary to) those of industry.
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- Relative stability.
- Much opinion-leading expertise.
What does academia have going for it?

• Wide diversity.
• Implicit commitment to development.
• A hotbed environment.
• Drivers that differ from those of industry.

• Much opinion-leading expertise.
• Chemists, Pharmacologists, Physicians, Public Health.
• But also Ethicists, Economists, Social Scientists.
• The ability for upstream-downstream discussion.
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- Drivers that differ from (are complementary to) those of industry.
- Relative stability.
- Because we teach.
- Identification of young talent.
- Nurturing and retention.
- In the developed world.

Wellcome Trust Research Training Programmes for Clinicians

Applications are invited for the autumn 2003 intake to the Wellcome Trust Research Training Programme for Clinicians across the UK.

These programmes are designed to support the next generation of clinically active doctors who wish to undertake higher research training.

Successful candidates will develop their potential to become active clinicians within a dedicated and mentored training environment. There are three broad types of programme, each with a focus on a specific area:

- PhD Programme for Clinicians
- Joint Basic and Clinical PhD Programme
- Interdisciplinary Training Programme for Clinicians in Translational Medicine and Therapeutics

PhD Programmes for Clinicians

Seven PhD programmes – at Cambridge, Dundee, Edinburgh, Liverpool, Imperial College, King’s College London, and the School of Hygiene & Tropical Medicine and Oxford – have been established to support a range of centres of excellence throughout the UK, which can provide research opportunities that will support a wide range of careers.

Each programme has been structured to reflect the expertise of individual institutions and the needs of individual candidates. Candidates will have the potential to pursue a career as an academic clinician. It is anticipated that many will also have already completed their specialist training but have not yet commenced their higher research training.

Support includes a research salary, PhD registration fees, travel and research grants, and accommodation costs.

Information on the programme is available at the Wellcome Trust website.
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- Because we teach.
- Identification of young talent.
- Nurturing and retention.
- In the developed world.
- But also in Africa.

Alexis N’Zila: Royal Society Prize 2006; EDCTP prize 2009.
What does academia have going for it?

- Wide diversity.
- Implicit commitment to research capacity development.
- A hotbed environment for excellence.
- Drivers that are different from (are complementary to) those of industry.
- Nurturing takes place in a very competitive environment.
- Darwinian processes select for survival in the Professoriate.
What does academia have going for it?

• Wide diversity.
• Implicit commitment to research capacity development.
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• Drivers that differ from (are complementary to) those of industry.

• Publications
• Grant income
• The ability to follow an idea, even if it moves from malaria to tuberculosis and back again!
Discovery rooted in genome sequencing.

Alternative complex-I as a drug target in malaria
Type II NADH:quinone oxidoreductase (PfNDH2)
- Essential parasite enzyme
- Absent from human host

Potential value in Chemotherapy, prophylaxis and eradication
- Enzyme essential *all* human parasite stages
PfNDH2 is Essential

- Responsible for >90% of the flux through the pathway.
- HDQ (a non-drugable inhibitor) collapses membrane potential.
Enzyme amenable to HTS

- Recombinant enzyme available
- Simple end-point assay monitoring
- Hits currently being studied
Discovery rooted in intelligent redesign.

The MMV Isoquine project
Designing a Non-Toxic Replacement for Amodiaquine

- >200 analogues designed and tested

ISOQUINE

- Isoquine is cheap and easy to synthesise
- Highly effective against malaria parasites *in vitro* and *in vivo*
- Does not form toxic metabolites *in vivo*
- Advanced to Phase-I
In the absence of a vaccine, drug treatments remain fundamental to the battle against malaria. With drug resistance & development of multi-drug allergies, a major problem at the moment is the treatment of malaria. The only drugs available are chloroquine and Fansidar, both of which are becoming less effective due to growing resistance. The World Health Organization recommends a combination of these drugs to slow the spread of resistance. However, even with this approach, the treatment of malaria remains a significant challenge.

In addition to drug treatments, there are other strategies being explored to combat malaria. One of these is the use of insecticides, which can be applied to bed nets or sprayed directly on walls. Another approach is the development of a vaccine, which has shown promise in clinical trials. However, the development of an effective vaccine remains a major challenge due to the complexity of the Plasmodium vivax parasite.

Overall, the battle against malaria is a complex one that requires a multifaceted approach involving drug treatments, insecticides, and research into new prevention strategies. Efforts are ongoing to develop more effective treatments and vaccines, with the ultimate goal of eradicating malaria worldwide.

In conclusion, malaria is a serious disease that continues to pose a significant threat to global health. While progress has been made in recent years, there is still much work to be done to eliminate this disease from the world. Continued investment in research and development is essential to achieving this goal.

[The image includes a logo and text related to the University of Liverpool and Wellcome-KEMRI Research Programme.]

[The text is overlaid on the image, making it difficult to read clearly.]
Chlorproguanil-dapsone: the underpinning idea

- **Mid-1980s**
- Pyrimethamine and sulfadoxine are eliminated very slowly, and this was always held to be a GOOD THING.
- Bill Watkins wondered whether slow elimination was a BAD THING – slow elimination accelerates decline in sensitivity.
Three clinical trials and much lab work later (WHO-TDR funded)

- CD was more efficacious than SP (Kenya). *AAC*
- CD offered promise as inexpensive ‘rescue therapy’ after SP failure (Tanzania). *Lancet*
- Risk of new episode of clinical malaria no higher after CD than after SP – 12 months of follow up (Kenya and Malawi). *Lancet*
- Greater emergence of resistance with SP than with CD. *JID*
Lapdap: move to public-private partnership

• Academics cannot develop drugs *alone*.
• Receptive company, WHO-TDR and DFID.
• Supportive Wellcome Trust.
• Phase-III trials focused on safety (more anon).
• MHRA registration in 2003.
• US$ 0.20 per treatment
CDA (Dacart)

- I need not set out the logic underpinning ACT.
- Chlorproguanil-dapsone-artesunate (CDA).
  - Greater efficacy
  - Reduce the rate of development of resistance to CD
  - Low cost - a high priority.
CDA phase-II

Artesunate dose-finding.
• Children and adults
• CD plus: 0, 1, 2 and 4 mg/kg/day
• Primary endpoint: time to 90% parasite clearance (PC90).
PC90 - time to 90% drop in parasitaemia

Mean PC90 by artemunate dose

Mean PC90 (hours)

Artemunate dose group (mg/kg)

Note: error bars show 95% C.I.s
CDA phase-III: CDA v Co-artem

Focus on CDA safety – following WHO criticism of earlier trials.

• 11 sites in 5 countries.
• Frequent measurement of haemoglobin
• G6PD genotyping and phenotyping in all patients.
We concluded that CDA and Lapdap would not be safe under usual conditions in Africa.
Post-Licensure assessment

Clinical trials for the File
• Clear requirements by Regulatory Authority.
• Carefully defined patient group with Directly Observed Therapy.
• Certain groups avoided – e.g. Pregnant women.
• Some academic involvement.

Beyond the File
• Data needed for the Public Health much less clear.
• The real world – diverse population in diverse settings.
• Real world populations studied – including pregnant women.
• Great academic involvement.
**MiP Consortium**  A wide research portfolio, not confined to drugs. Drug studies include:

- 5-centre trial of Coartem v AQ-AS v MQ-AS v DHA-PPQ in women >16/52 with malaria infection.
- Trials of MQ v SP, and MP in HIV+ women on cotrimoxazole.

**iPTI Consortium**

- Effectiveness and safety of alternatives to SP
Some reflections on partnership
Academic role in Drug Development Partnerships

• Getting things started:
  • The scientific case – downstream-upstream dialogue

• Within the team:
  • Leadership
  • Specific expertise – Biology, Medicine and Trial Sites

• Communication:
  • With the Community
  • Within the team – PPPs need ATP-driven processes to keep them functioning.
In summary

• Making drugs is not for the faint-hearted at the best of times.
• It’s harder to make drugs for malaria than for baldness.
• Some pharmaceutical companies do want to engage, but MMV is vital:
  • Sharing the risk
  • Sharing the cost
  • Prominent partnership when things are not going so well
• Academics **should** play an important part.
RESERVE SLIDES
Which rapidly-eliminated antifolate combination is most potent and has the widest Therapeutic window?

<table>
<thead>
<tr>
<th>Antifolate-R Parasite strain</th>
<th>Normal human marrow cells</th>
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Log_{10} Concentration

**DHFR inhibitors**
- Pyrimethamine
- Chlorcycloguanil
- Two other triazines
- Three quinazolines
- Trimethoprim
Pyrimethamine-resistant falciparum

Log$_{10}$ Concentration

Pyrimethamine

Parasite

Human marrow
Log\textsubscript{10} Concentration

Pyrimethamine-resistant falciparum

Chlorcycloguanil
4-Aminoquinoline Antimalarials

Chloroquine
RESISTANCE

Amodiaquine
TOXICITY
Hit identification against PfNDH2 (<10 µM)

Identified via medicinal chemistry

Chemical structures of identified compounds.

Identified via preliminary search of Zinc™ database

Additional chemical structures of identified compounds.
Manoeuvrability in Academia.

CHAPTER SEVENTEEN

TYPE II NADH: QUINONE
OXIDOREDUCTASES OF Plasmodium
Falciparum AND Mycobacterium
Tuberculosis: Kinetic AND
HIGH-THROUGHPUT ASSAYS

Nicholas Fisher, Ashley J. Warman, Stephen A. Ward, and
Giancarlo A. Biagini
Selectivity - malaria mitochondria are different to human mitochondria

**HUMAN**

**MALARIA**

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[Diagram showing the comparison of mitochondrial processes in human and malaria organisms]
Rapid drug elimination would reduce the length of the selection window.