New Medicines for Eradicating Malaria: Lessons for Drug Discovery

Defeating Malaria Together

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MMV Medicines for Malaria Venture
Malaria: Leading cause of child mortality

- 800,000 deaths: 85% in children under five
- Selectively targets pregnant women
- 225 million cases per year
- Half the world’s population at risk
MMV at a glance

- Non-profit ‘product development partnership’ established 1999 in Geneva
- Mission: Discover, Develop and Deliver safe and effective antimalarials
- Two products launched, two products submitted
- Largest-ever pipeline of antimalarial drugs with over 50 projects from Discovery to Registration
- Funded by Foundations, Governments, Companies, Individuals
- Nine pivotal phase III in three years: 11 000 patients
Artemisinin Combination Therapies

- Resistance concern: WHO recommended withdrawal of monotherapy in 2006
- Long half-life eliminate residual parasites and protect against re-infection
- Challenge: formulation, dose and clinical trials
- Treated over 160 million patients in 2010
- $0.25 - $0.37 for small children
ACTs can now reach the majority of patients

Source: MMV discussion with Manufacturers 02-2010
**Why do we need many ACTs?**

Sulphadoxine-pyramethamine-artesunate  
Amodiaquine-artesunate

**Threat of resistance against partner drug**  
Multiple First Line therapies may slow resistance

*Graphs: Dr Pascal Ringwald WHO Global Malaria Program*
Filling the gaps

• Child-friendly formulations
• Infants < 5kg
• Longitudinal studies
• Effectiveness studies
• Medicines for use in Pregnancy (MiP)
• Aquamat (Dondorp et al., 2010): iv artesunate superior to iv quinine: 5000 patient study
• Guilin first prequalified (Dec 2010) with MMV’s support
• Only Chinese manufacturer with WHO approval
• Cost: approximately $1 per vial
Radical Cure of Plasmodium vivax

- 100 million infections per year
- Hypnozoites: relapse without reinfection
- Primaquine: 14 days, G6PD liability
- Tafenoquine: single dose?
- Pivotal Phase II/III starts 2Q 2011
  - Efficacy
  - Safety

Thanks to Ric Price
Quality Medicines are a human right

- Under-dosing produces ineffective medicines, and promotes resistance
- Overdosing significantly increases adverse events
- Stability depends on formulation and packaging
- Generics must meet WHO standards
Safe medicines are a human right

All patients

G6PD deficient patients

DACART  CoartemD
Artemisinin resistance is emerging

- Parasite Clearance Times increased in Cambodia
- Small increase? in IC50 for artesunate
- ACTs still work >95% at day 28
- Increased pressure on partner drug
Endoperoxides: the stealth warhead

- OZ439 collaboration: MMV, Monash, Basel and Nebraska
- Same warhead, different scaffold
- Should fool ACT resistance: test in patients
- High plasma concentration 48–72 h
- The first partner for a ‘single dose cure’
- Launch date beyond 2016
Target Product Profile: start with a view of what’s needed
(All available at www.mmv.org)

1. SERC: single exposure, (radical cure, prophylaxis)
2. NACT (3 day non-artemisinin combination therapy)
3. Severe malaria (adjunct therapy)
4. Radical cure (liver stage *P. vivax*)
5. Transmission blocking
6. IPT (intermittent preventative therapy)
7. Prophylaxis

Ideal (SERCaP) contains 1, 4 and 5 and is long acting
Managing Discovery Projects

- Proposals from Annual Call
- Approved projects: collaborations with MMV and Mentors
- Projects reviewed annually, and at key decision points

**Enabling Technology**
- Assay Validation
  - MMV/Technology Review panel

**Screening**
- Screening Hit:
  - On receipt of data

**Active-to-Hit**
- Validated Hit
  - Project team

**Hit-to-Lead**
- Early Lead
  - Project team
  - MMV

**Lead Optimisation**
- Late Lead
  - MMV/ESAC sub-committee

**Candidate Profiling**
- Preclinical Candidate
  - MMV/ESAC Candidate Selection Meeting
  - Full report required

**Preclinical Development**
What makes us excited?

- Going to be efficacious: No cross resistance or resistance induction
- Safe: High therapeutic margin; no serious toxicity
- Fast killing (especially ring stage)
- Low predicted human dose
- Transmission- and relapse- blocking potential
- High bioavailability, good half-life
Parasite Reduction Rate

Parasite viability at 10xIC₅₀

- Artemisinin
- Azithromycin
- Atovaquone

48h treated parasites

Javier Gamo GSK Tres Cantos
Dose and cost of goods

- Current combinations cost $1 for adults
- Ideally we should target < $0.10
- Of this $0.03 - $0.30 is for each ingredient (API)
- At $300/kg maximum total dose 100 - 1000 mg

- If daily dose < 10 mg, slow release formulations can be acceptable
Transmission Blocking

Key assays set up to study sexual stages

- Key assays set up to study sexual stage parasites
- Testing 100 key antimalarials
- Automate assay to allow testing of Malaria Toolbox
- uHTS on stage V gametocytes
Hypnozoites

- No cell assay with *P. vivax* (yet)
- New assay with *P. cynomolgi* and primary rhesus cells
- Stable small forms at 10 days, validated pharmacologically
- Testing 100 key antimalarials
- Future: Identifying hypnozoite biomarkers to make better assay
### Not all candidates are perfect

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Finding new clinical candidates

Classical ‘Forward’ approach

Genome: All drugable targets → Validate Knock-out organisms → Assay Set-up Validation → HTS Specific Target

Reverse approach

Chemistry: All available molecules → HTS Whole parasite → Hits to leads Identify resistance
Next generation: guided by structure

- Best used for fast followers – valid targets
- One target: resistance concerns

Changing the anti-infective discovery paradigm

Drugs for bad bugs: confronting the challenges of antibacterial discovery

David J. Payne, Michael N. Gwynn, David J. Holmes and David L. Pompliano

Abstract | The sequencing of the first complete bacterial genome in 1995 heralded a new era of hope for antibacterial drug discoverers, who now had the tools to search entire genomes for new antibacterial targets. Several companies, including GlaxoSmithKline, moved back into the antibacterials area and embraced a genomics-derived, target-based approach to screen for new classes of drugs with novel modes of action. Here, we share our experience of evaluating more than 300 genes and 70 high-throughput screening campaigns over a period of 7 years, and look at what we learned and how that has influenced GlaxoSmithKline’s antibacterials strategy going forward.

Experience suggests that it is easier to find the cellular target of an antibacterial compound than it is to engineer permeability into an enzyme inhibitor. Therefore whole-cell assays are favoured for finding a lead compound that has a modicum of antibacterial activity, but biochemical assays and genetic studies are vital to determine the MOA of these leads. Using engineered
Guided by biology

Chemistry: All available molecules
HTS Whole parasite
Hits to leads Identify resistance

- Screening parasites faster and cheaper
- Five million compounds; 0.5% < 1 uM
- Easy collaboration with Industry
- Genome helps characterise resistance
- Fast track to man

Wells TNC Science 329 1153-1154 (2010)
Hits to Leads Bottleneck

- Dedicated teams 6 medicinal chemists, cell pharmacology
- Partnering, capacity building in disease endemic countries
  - India
  - South Africa
- MMV experienced Mentors
- Common *in vivo* centres of excellence
- Goal: active in mice <10 mg/kg, potential for single dose cure
The MMV Malaria Box – *The Concept*

- 500 structurally diverse compounds from whole cell screens plus standards
- Compounds in 10 nM DMSO solutions: purity and solubility carefully controlled
- Contains both leads for drug discovery and probes for biological mechanism
- Validated data should be sent back to MMV for posting on the web-site

- Available from the summer 2011. Further details please e-mail malarialog@mmv.org
Phenotypic hits in molecular screens

90 targets, 18 screens: only 2 identified ‘tool compounds’
Implications for the future of drug discovery

• Pharma has over 4000 compounds, with pre-clinical packages which are ‘on-hold’ or inactive
• Randomly: we know 1:200 compounds have IC50 < 1 μM
• Source the high value compounds and test
  • *In vitro*
  • *In vivo* – huSCID mouse model
Repositioning compounds: human challenge

Collaboration with Queensland Institute for Medical Research/Q-pharm
Natural Products: back to our roots?

- Clinically characterise products ‘active in man’
- Show *ex vivo* activity of plasma, then purify

Wells TNC Malaria Journal *in press* (2011)
Global Portfolio of Antimalarial Medicines

### Translational
- **Preclinical**
  - SAR116242 Trioxaquinoine
  - RKA182 Liverpool
  - NPC-1161-B University of Mississippi
  - P218 DHFR (BIOTEC/Monash/LSHTM)
  - GNF156 Novartis
  - AN3661 Anacor
  - MK 4815 (Merck)

- **Phase I**
  - DF02 Dilafor
  - NITD 609 Novartis
  - CDRI 97-78 Ipca
  - GSK 932121 GSK
  - AQ13 Immtech

- **Phase IIa**
  - Ferroquine sanofi aventis
  - SAR97276 sanofi aventis
  - Fosmidomycin Clindamycin Joma Pharma GmbH
  - OZ 439 (Monash/UNMC/STI)
  - Artemisone UHKST

### Development
- **Phase IIb/III**
  - Artesunate i.r.
  - Co-artem RF Novartis
  - AZCQ Pfizer
  - Co-trimoxazole Bactrin Institute of Tropical Medicine

- **Registration**
  - Eurartesim™ sigma-tau
  - Pyramax® Shin Poong/University of Iowa
  - Mefloquine Artesunate Farmaguinhos/DNDi

- **Phase IV**
  - Coartem®-D Novartis
  - ASAQ Winthrop sanofi aventis/DNDi
  - IV artesunate Guillin

### ACT’s
- 2016+
- 2015
- 2013
- 2011

### Launch Probability
- 10%
- 20%
- 68%
- >90%

### Validated Mechanism
- P. vivax

### New Mechanisms
- On Hold
Global Portfolio of Antimalarial Medicines

Translational
Preclinical | Phase I | Phase IIa
---|---|---
SAR116242 | DF02 | Ferroquine sanofi aventis
Trioxaquine | Dilafor |
RKA182 | NITD 609 | SAR97276
Liverpool | Novartis | sanofi aventis
NPC-1161-B | Fosmidomycin | OZ 439
University of | Clindamycin | (Monash/UNMC/STI)
Mississippi | | |
P218 DHFR | Tafenoquine | |
(BIOTEC/Monash/LSHTM) | GSK | |
GNF156 | | |
Novartis | | |
AN3661 | | |
Anacor | | |

Development
Preclinical | Phase Iib/III | Registration | Phase IV
---|---|---|---
ARCO Coartem® | Eurartesim™ | Coartem®-D
Naphthoquine/ | sanofi aventis | Novartis
Artemisinin | | |
AZCQ Pyramax® | Pyramax® | ASAQ Winthrop
Pfizer | Shin Poong/University of Iowa | sanofi aventis/DNDi
Co-trimoxazole | Melfloquine | IV artesunate
Bachim | Artesunate | Guilin
Clindamycin | Farmagunhos/DNDi | |
Institut of Tropical Medicine | | |
OZ 439 | | |
(Monash/UNMC/STI) | | |
AN3661 | | |
Anacor | | |

ACT’s | Endoperoxides | Severe Malaria | Antibiotic | P. vivax | Validated Mechanism | New Mechanisms
---|---|---|---|---|---|---
Launch | 2016+ | 2015 | 2013 | 2011 | >90% Probability
| 10% | 20% | 68% | >90% |

MMV
Medicines for Malaria Venture
Priorities for the future

- Catalyse enhanced use of ACTs
  - Best medicines for each customer
  - Infants, mothers, special populations

- Next generation of therapy - combinations aiming at
  - Single dose
  - Transmission blocking
  - Anti-relapse
  - Affordable
Thanks to all our colleagues and partners – but especially to the children and their families who make the next generation of malaria therapy a reality.