Drugs for treatment and chemoprevention of malaria

Tim Wells, Chief Scientific Officer, MMV
Ideal Product has several activities

- Clears blood stages rapidly
- Long acting
- Blocks transmission
- Kills dormant forms
- Active against all current and emerging resistance
- Safe enough to give to all

Malaria Drug Resistance

- Artemisinin resistance in the Mekong: slower rate of killing parasites
- Puts pressure on partner drugs: multidrug resistance

Focus on simplifying treatment or fighting resistance?

- **Districts where ACTs have failed**
  - **One Dose**
    - ✓ High compliance
    - ✓ Directly observed therapy
    - ✓ Low cost of goods
    - ? Need to show activity in artemisinin resistant malaria
  - **Split Dose**
    - ✓ Back-up therapy where ACTs fail
    - ✓ Some compliance benefit vs. ACTs
    - ? Cost of goods benefit vs. ACTs

- **Districts where ACTs still effective**
  - **One Dose**
    - ✓ High compliance
    - ✓ Low cost of goods
  - **Split Dose**
    - ❌ Limited interest to replace ACTs where they are still active
    - ❌ No compliance benefit vs. ACTs
    - ? Cost of goods benefit vs. ACTs

Trade-Off
Balancing Efficacy and Safety

Increasing the drug dose increases the chance of side effects

- Ideally the compound needs to be active (above the minimum threshold) for 28 days or more
16 new candidates 2009-2016
SETTING THE GOALS

FINDING THE MOLECULES

MEASURING SUCCESS

WINNING COMBINATIONS
Building on an existing template

OZ03
Reduce logP
Improve solubility

OZ277/ RBx11160
Decrease interaction with ferrous iron (single electron)

OZ439
Less potent on embryos and on granulocytes
Active vs artesunate resistance

Molecular Design: DHODH

- Phase IIa completed December 2015

**DSM1**
EC$_{50}$ 3D7 79 nM
No oral efficacy

**DSM191**
EC$_{50}$ 3D7 220 nM
ED$_{90}$ Pf SCID 57 mg/kg

**DSM265**
EC$_{50}$ 3D7 8 nM
ED$_{90}$ Pf SCID 8.1 mg/kg

Optimising phenotypic hits
New targets from parasite screening

<table>
<thead>
<tr>
<th>Chemotype and related series</th>
<th>New Biological Target</th>
<th>Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple diverse series</td>
<td>ATP4 Na channel</td>
<td>KAE609, SJ733, GSK030, PA92</td>
</tr>
<tr>
<td>Imidazolopiperazine</td>
<td>CARL</td>
<td>KAF156</td>
</tr>
<tr>
<td>Triazolopyrimidine</td>
<td>DHODH</td>
<td>DSM265 (DSM421)</td>
</tr>
<tr>
<td>Aminopyridine</td>
<td>PI4K</td>
<td>MMV048 (UCT943)</td>
</tr>
<tr>
<td>Quinoline</td>
<td>eEF2</td>
<td>DDD498</td>
</tr>
<tr>
<td>Triaminopyrimidine</td>
<td>V-type H+ ATPase</td>
<td>AZ412</td>
</tr>
</tbody>
</table>

Target Identification Consortium: 50 compounds from Malaria Box 10-15 new targets
Collection of ‘irresistable scaffolds’
New Chemotypes by calculation

Sequence alignments

Homology models/docking

Validating models to drive compound design

Prioritization of new chemistry
SETTING THE GOALS

FINDING THE MOLECULES

MEASURING SUCCESS

WINNING COMBINATIONS
Standard Phase II data
Response in patients for first 36h

$\log_{10}\text{PRR}(48h)$ $P.\ falciparum$ 2.76 - 3.62
$log_{10}\text{PRR}(48h)$ $P.\ vivax$ 3.92 - 4.80
Measuring the MIC clinically

\[ P_t = \int_0^t P \cdot \left[ G - D_0 \cdot \frac{C_t^H}{C_t^H + IC_{50}^H} \right] \, dt \]
Early data in CHMI models saves time and money

Australian Volunteers (100-500mg)

1 month per cohort, 1 centre
All year round

Thai Patients (100 mg)

6 months, 4 centres, seasonal
Human volunteer challenge – early readout that the drug works

150 mg DSM265 predicts Human Effective Dose as 400 mg
SETTING THE GOALS | FINDING THE MOLECULES | MEASURING SUCCESS | WINNING COMBINATIONS
Development for combination medicine

New Chemical Entity

Discovery
Discovery and Candidate Profiling
- in vitro and in vivo activity
- DMPK
- Solid state characterization
- Salt/Form screen

Candidate Profiling

Pre-clinical
Preclinical
- GLP Tox
- DMPK
- Pre-formulation studies

Single agent

Phase I (h.v.) and Phase IIa (adult pts)
- Single agent
  - Safety
  - PK
  - Parasite clearance and time to recrudescence (up to Day 28)
- Combination
  - Safety
  - Drug-Drug interactions
  - PK/PD modeling

Phase I and Phase IIa formulation

Phase I
Phase I (h.v.)

Phase IIa
Phase IIa (adult pts)
- Safety, tolerability
- Dose finding
- Contribution of each agent to the efficacy of the combination (FDA rule)
- Efficacy (ACPR Day 28 and 42)

Phase IIb
Phase IIb (adult and pediatric pts)
- Safety, tolerability
- Confirm efficacy of fixed dose combination (ACPR Day 28, 42 and 63)

DDI Phase I
Phase IIb
Phase III
Combination (with Pharma Partner)

Phase III (adult and pediatric pts)

Preclinical formulation
Phase I and Phase IIa formulation
Phase IIb loose combination or dose scalable formulation
Phase III FDC market formulation

Preclinical formulation

SRA filing

End of Phase IIa
Initiate Phase III

Development for combination medicine
Find the right partner

Differentiated partner protects against resistance trusted friend or beautiful stranger? can you afford to wait for the next best thing?

https://plus.maths.org/content/kissing-frog-mathematicians-guide-mating
## Partner selection Matrix

<table>
<thead>
<tr>
<th>Factor</th>
<th>High Score (5)</th>
<th>Low Score (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPP - SERCap</td>
<td>TCP1, 2 and 3</td>
<td>Insufficient TCP1 &amp; 2</td>
</tr>
<tr>
<td>Safety</td>
<td>Different organ tox &amp; manageable</td>
<td>Same organ tox + SAEs</td>
</tr>
<tr>
<td>Dev Stage</td>
<td>Both drugs approved</td>
<td>Both preclinical stage</td>
</tr>
<tr>
<td>PK- time &gt; MPC</td>
<td>Complete overlap &gt; MPC for &gt; 2wk</td>
<td>Very short acting + very long acting</td>
</tr>
<tr>
<td>Total Dose (mg)</td>
<td>&lt;150mg</td>
<td>&gt;1200mg</td>
</tr>
<tr>
<td>BCS -Formulation</td>
<td>No challenges</td>
<td>Two drugs with bad formulation</td>
</tr>
<tr>
<td>Prophylaxis-Liver Stage</td>
<td>Both drugs 3-4wks &gt; MPC</td>
<td>Neither has &gt;1 wk prophylaxis</td>
</tr>
<tr>
<td>Resistance</td>
<td>None to either drug</td>
<td>Widespread to 1 or 2 drugs</td>
</tr>
<tr>
<td>Food Effect</td>
<td>No food effect for both</td>
<td>Both food effect + severe safety issue</td>
</tr>
<tr>
<td>DDI between partners</td>
<td>No predicted DDI</td>
<td>Clinically concerning DDI</td>
</tr>
<tr>
<td>DDI with other conc-med</td>
<td>No predicted DDI</td>
<td>Clinically concerning DDI</td>
</tr>
<tr>
<td>MOAs</td>
<td>Complementary</td>
<td>Identical MOA + resistance mutation</td>
</tr>
<tr>
<td>IP Flexibility</td>
<td>Two drugs from same group</td>
<td>Owner unwilling to partner</td>
</tr>
</tbody>
</table>

Wes van Voorhis, MD PhD, Stephan Challon MD PhD
Two new combination phase II studies are ongoing.
Options for clinical development

Phase IIb
One day – three days
Adults and children
Dose range to satisfy FDA combination rule 2017-18

Single dose cohort safe and >95% efficacy

Single Dose Phase III program
Confirm safety 2019-20

Multiple dose Phase III program
Confirm safety 2019-20

Drug interaction studies with third partner (at risk)

Three day cohort safe and >95% efficacy

Launch single dose cure 2021

Launch multiple dose cure 2021

Phase III with three drug combination 2021-2
Eliminating the last parasite

Are medicines safe and well tolerated enough to use in subjects with

- Repeated infection
- asymptomatic infection
- undiagnosed early pregnancies?
- in HIV patients (co-medication, immunosuppressed)?
- malnutrition?
## A glass half full? – How we are doing

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood stage killers: fast and long acting</td>
<td>6/10</td>
</tr>
<tr>
<td>Chemoprevention: liver schizonticides</td>
<td>5/10</td>
</tr>
<tr>
<td>Transmission blocking: safely sparing primaquine</td>
<td>4/10</td>
</tr>
<tr>
<td>Relapse Prevention</td>
<td>8/10</td>
</tr>
</tbody>
</table>
## A glass half full? – How we are doing

<table>
<thead>
<tr>
<th>Prevention Type</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood stage killers: fast and long acting: safe and well tolerated for asymptomatics?</td>
<td>3/10</td>
</tr>
<tr>
<td>Chemoprevention: liver schizonticides: once per month once per season</td>
<td>2.5/10</td>
</tr>
<tr>
<td>Transmission blocking: safely sparing primaquine</td>
<td>4/10</td>
</tr>
<tr>
<td>Relapse Prevention in G6PD-individuals</td>
<td>0/10</td>
</tr>
</tbody>
</table>
If you want to go fast, go alone
If you want to go far, go together
Our partnerships are our greatest strength
Drugs for treatment and chemoprevention of malaria

Tim Wells, Chief Scientific Officer, MMV
Products with impact
<table>
<thead>
<tr>
<th>Molecule</th>
<th>Dosage</th>
<th>Efficacy</th>
</tr>
</thead>
</table>
| Lumefantrine | 4 x 480 mg  
               | 2000 mg over 3 days | 90.0%          |
|            |                               | 96.0%           |
| Artemether | 4 x 80 mg                     | 45.5%           |
| Ferroquine | 3 x 200 mg                    | 79.4%*          |
| KAF156     | 1 x 800 mg                    | 67%             |
| DSM265     | 1 x 400 mg                    | 89%             |

* PCR corrected