Towards the future: medicines and the elimination of malaria

Defeating Malaria Together

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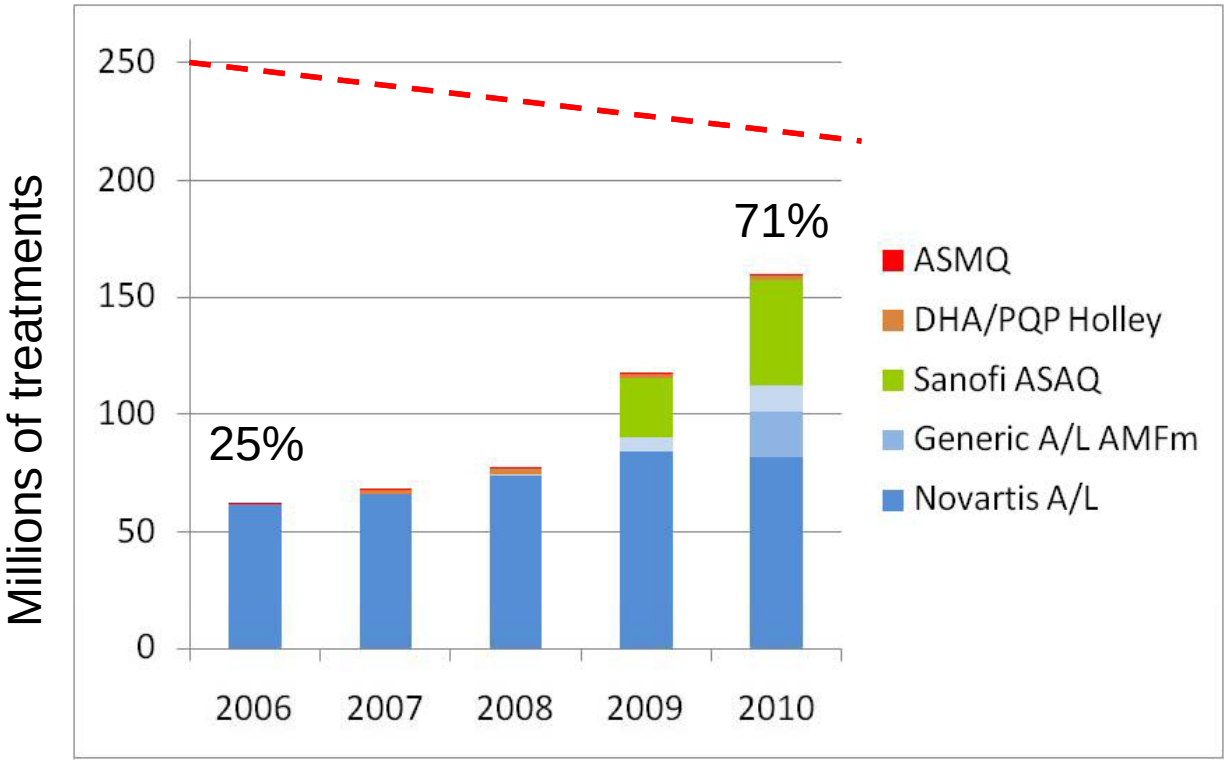
Changing the landscape: ACTs available to all



Coartem-D (Novartis)has treated 65 million children so far

150 million treatments of fixed dose ACTs delivered in 2010

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Adult medicines for un-complicated malaria

- Resistance is a fact of life
- Not all medicines work in all populations
- Different risk-benefit profiles – allows choice

- DHA-piperaquine (sigma-tau)
  - EMA decision expected August 2011
- Pyronaridine-artesunate (Shin-Poong)
  - EMA decision expected 1Q’2012

Draft

Draft

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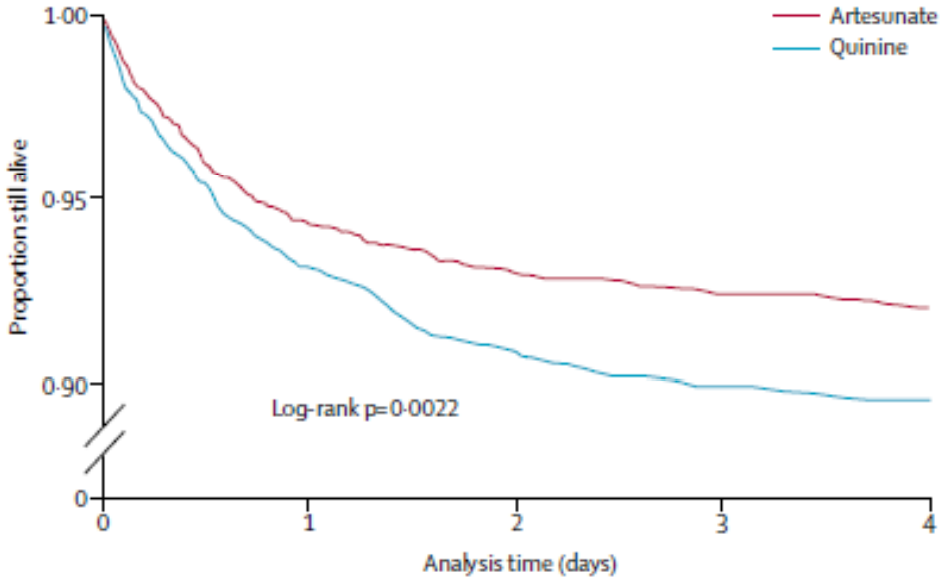
New child friendly medicines

- Pyronaridine-artesunate granule formulation – submission early 2012
- DHA-piperaquine: taste-masked dispersible formulation - submission late 2012

- Coartem-D: child-friendly formulation: extend to available < 5kg babies

Severe Malaria



- Aquamat artesunate superior to quinine: 5000 patient study
- Guilin first prequalified (Dec 2010) with MMV's support
- Only Chinese manufacturer with WHO approval
- Cost: approximately $1 per vial

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Protecting expectant mothers

- Neither azithromycin nor chloroquine are optimal on their own
- Synergy: azithromycin blocks chloroquine resistance clinically
- 60% of mothers have bacterial infections (STI): impact on peri-natal mortality
- Both drugs treat both diseases

- New fixed dose formulation (Pfizer)

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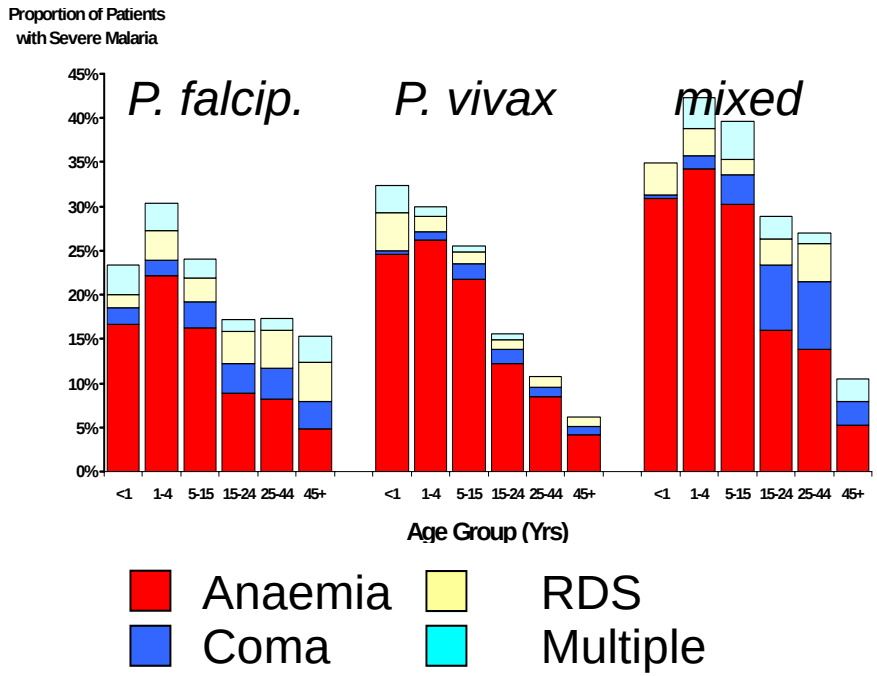
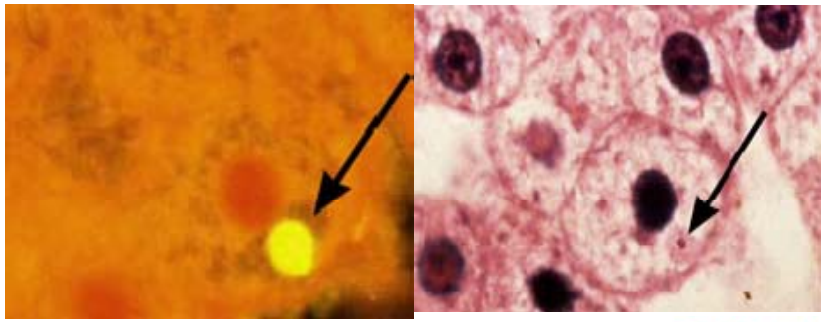
Stopping the relapses from *P vivax*

- 100 million patients annually
- Hypnozoites: relapse without reinfection
- Gold standard: Primaquine 14 days, G6PD liability
- Tafenoquine (WRAIR, GlaxoSmithKline)
- Pivotal Phase II/III starts 2Q 2011
- Single dose
  - Efficacy
  - Safety





Thanks to Ric Price

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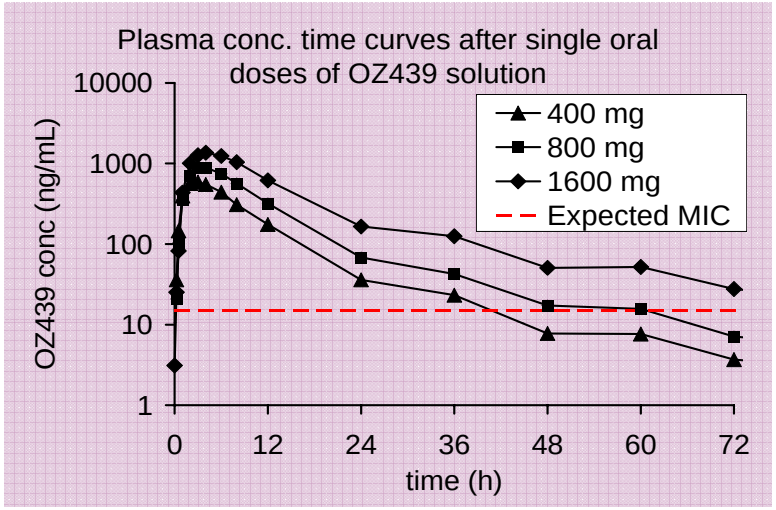
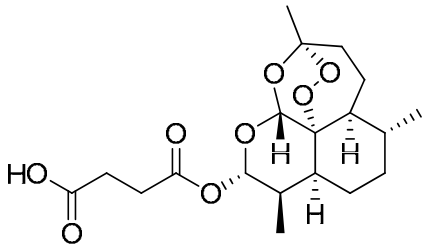
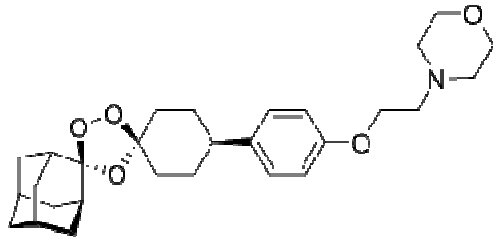
Powering the single dose cure: OZ439

- OZ439 collaboration: MMV, Monash, Basel and Nebraska
- Same warhead, different scaffold
- High plasma concentration 48–72 h
- Active in ‘resistant malaria’?
- Currently being tested in patients (phase IIa)





artesunate



OZ-439

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New medicines driving eradication

- Efficacy: No cross resistance or resistance induction, fast killing
- Safe: High therapeutic margin; no serious toxicity
- Long time above the IC_{90} in plasma
- Low predicted human dose

- Transmission-blocking
- Relapse- blocking
- Chemoprevention

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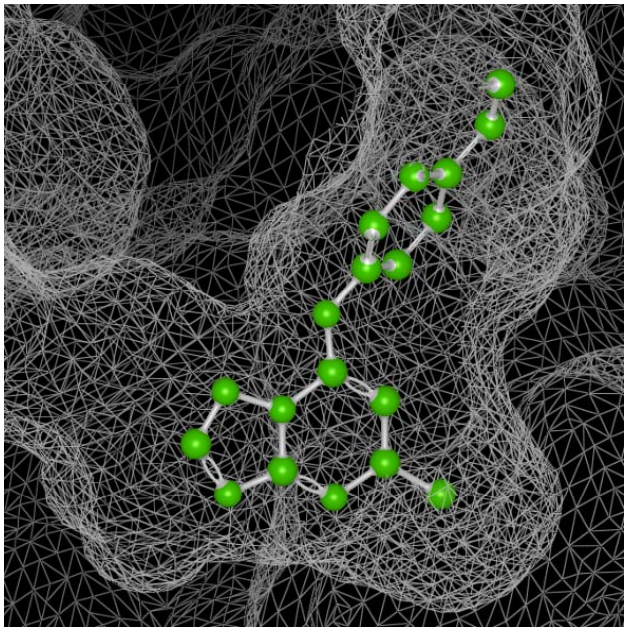
Next generation: guided by structure

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



- Rapid progression with validated targets

Deng X *et al*, J Biol Chem. 284: 26999-7009 (2009)

Booker ML *et al,* J Biol Chem. *in press*(2010)

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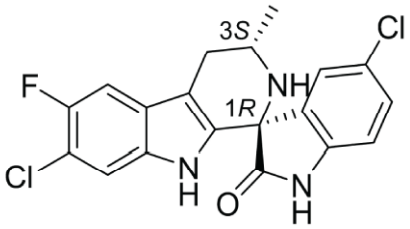
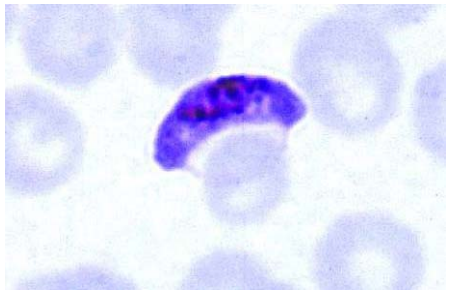
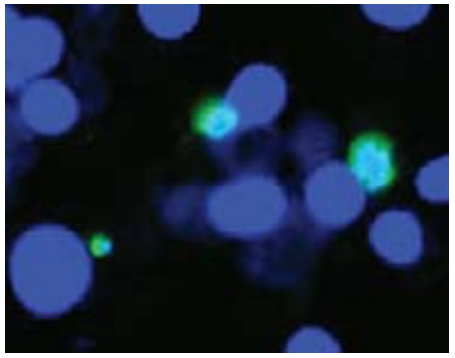
Next generation: guided by Biology

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



- Screening five million compounds
- 25’000 hits < 1 uM
- Fast track to man – less than four years





- *Now let’s look at the other stages: transmssion blocking and liver stages*

Gamo FJ, *et al.,* Nature 465 (7296): 305–310 (2010)
Guiguemde WA, et al., *Nature* 465, 311–315 (2010)
Rottman M., *et al,* Science 325 1175-1180 (2010)
Wells TNC Science 329 1153-1154 (2010)

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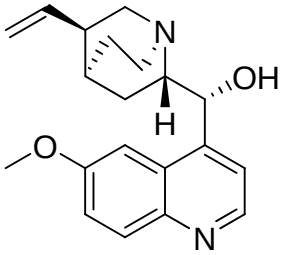
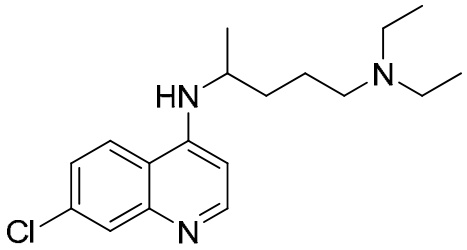
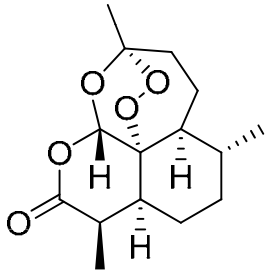
Dao-xing-ni-shi



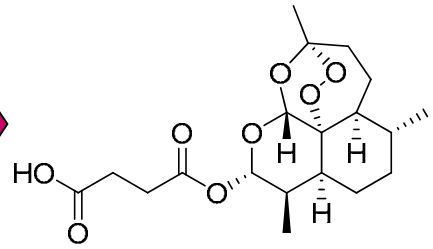
Half life 8 h



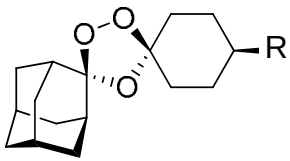
Half life 278 h



Insoluble



Soluble
half life <1h



Soluble
half life >24h

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

Natural products as starting points for future anti-malarial therapies: going back to our roots?
Wells TN *Malaria Journal* 2011, 10(Suppl 1):S3

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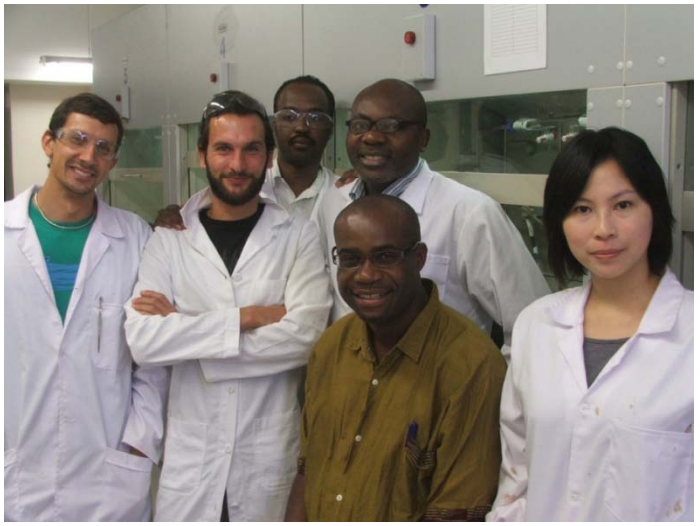
Miniportfolios – built on chemistry

- New Hits to leads model
- Dedicated teams: medicinal chemists, cell pharmacology
- Partnering in disease endemic countries
  - India
  - South Africa
- MMV experienced Mentors
- Common *in vivo* centres of excellence



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This potential treasure trove of compounds, selected from publically available hits, will be a resource to catalyze malaria drug discovery and research. It includes:

200 diverse "drug-like" compounds as starting points for oral drug discovery and development

200 diverse "probe-like" compounds for use as biological tools in malaria research

Available Autumn 2011
Further details malariabox@mmv.org

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Delivering game changing molecules

NITD609 (Novartis): new class, phase IIa 4Q'11
AN3661 (Anacor): fast acting, potent, safe. phase I 4Q'11

GNF156 (Novartis): liver schizonticide, phase I 1Q'12

New candidates
2011 Aminoindole (Genzyme) no *in vitro* resistance
DHODH inhibitors (DSM, Genzyme, GSK)
2012 *new series*: fast killers
new series: liver stages
new series: transmission blocking
new series: stage 4, 5 gametocytes
… targeting the eradication agenda

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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

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Today's agenda

- *New medicines for protection during pregnancy* Dr Joshua Kimani KEMRI Kenya
- *DHA/PQP: a new once-per-day treatment for uncomplicated malaria* Dr Ambrose Talisuna WWARN East Africa
- *Artesunate for injection: new evidence for the management of severe malaria* Dr Antoinette Tshefu University of Kinshasa, DRC
- *DHODH: structure based design of a new class of drugs* Dr Margaret Philips University of Texas Southwestern USA

- Panel discussion: chaired by Dr Bernards Ogutu and Dr Timothy Wells