New Medicines for Eradicating Malaria: Lessons for Drug Discovery

Defeating Malaria Together

Timothy N.C. Wells PhD ScD

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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

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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

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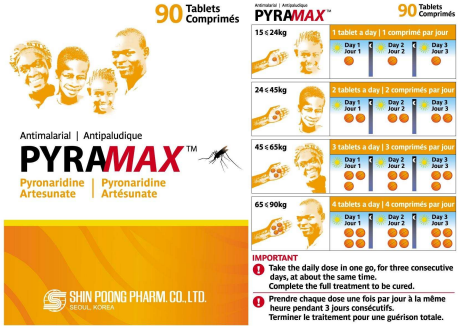
Artemisinin Combination Therapies

- 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

Draft



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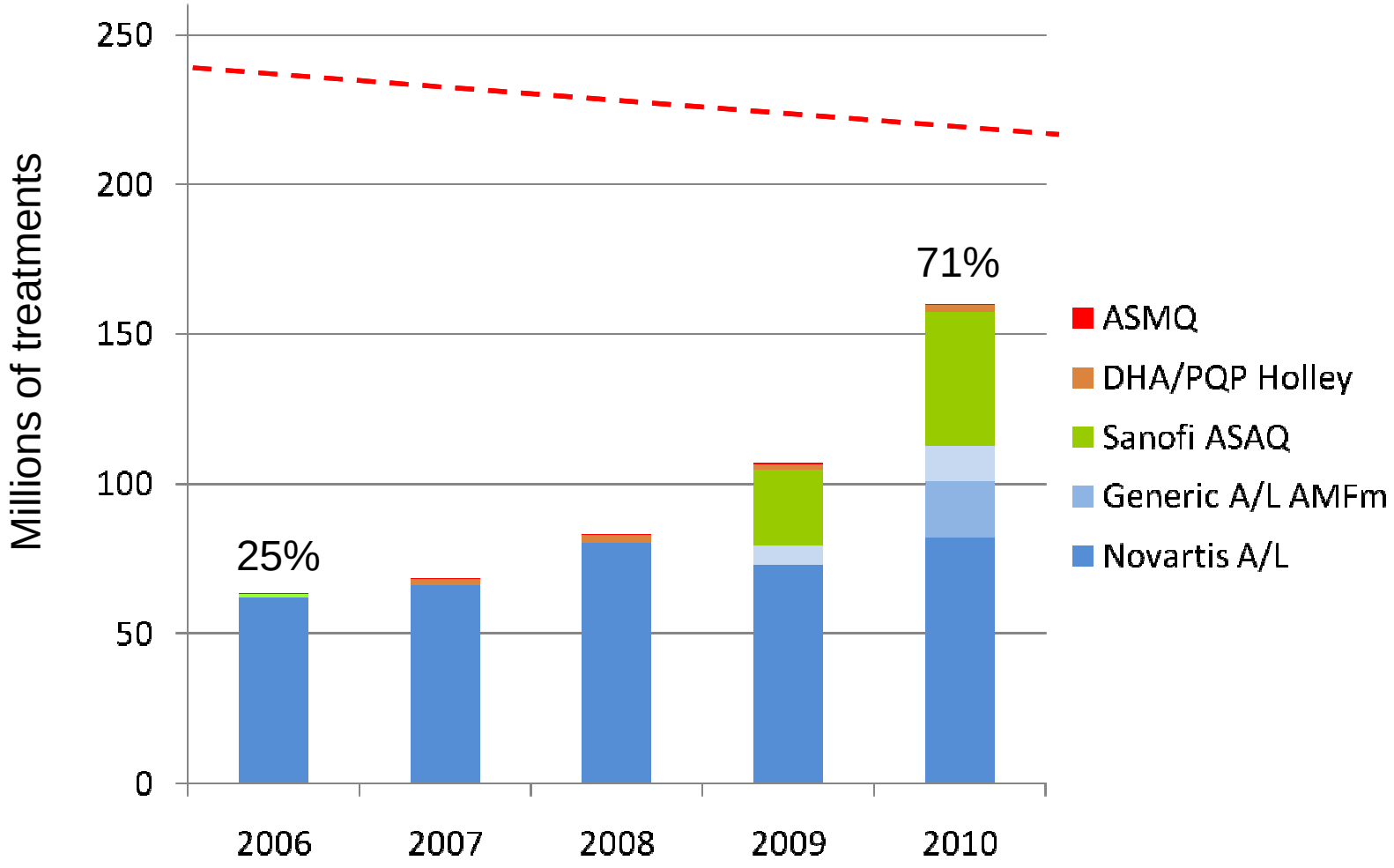
ACTs can now reach the majority of patients



Source: MMV discussion with Manufacturers 02-2010

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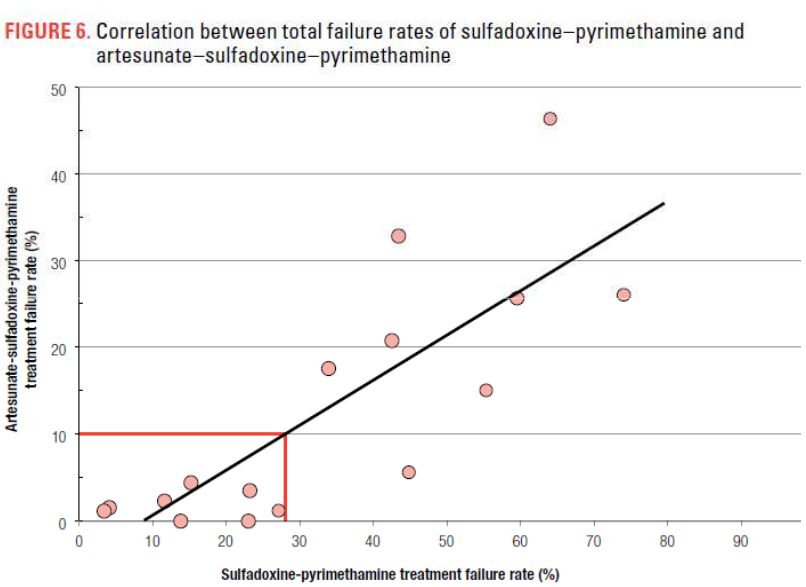
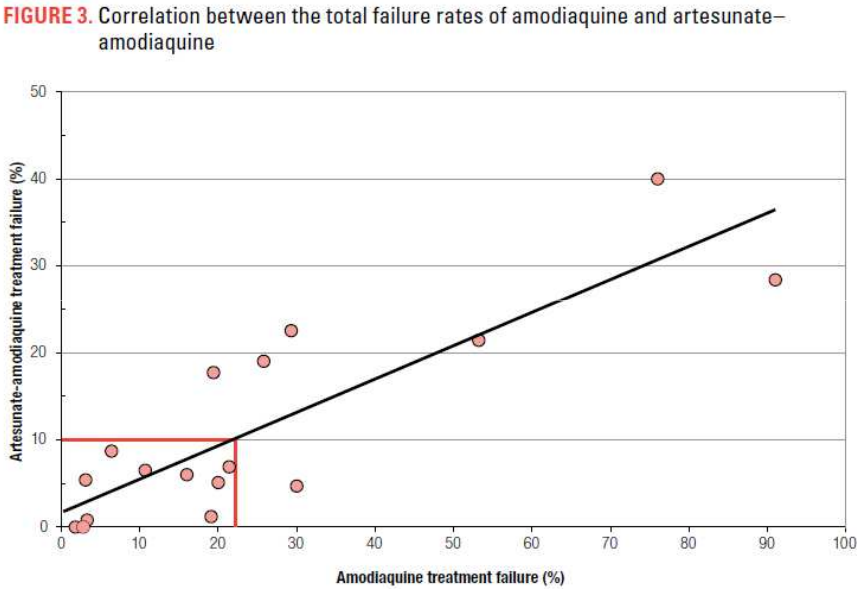
Why do we need many ACTs?

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

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Filling the gaps

- Child-friendly formulations
- Infants < 5kg
- Longitudinal studies
- Effectiveness studies
- Medicines for use in Pregnancy (MiP)

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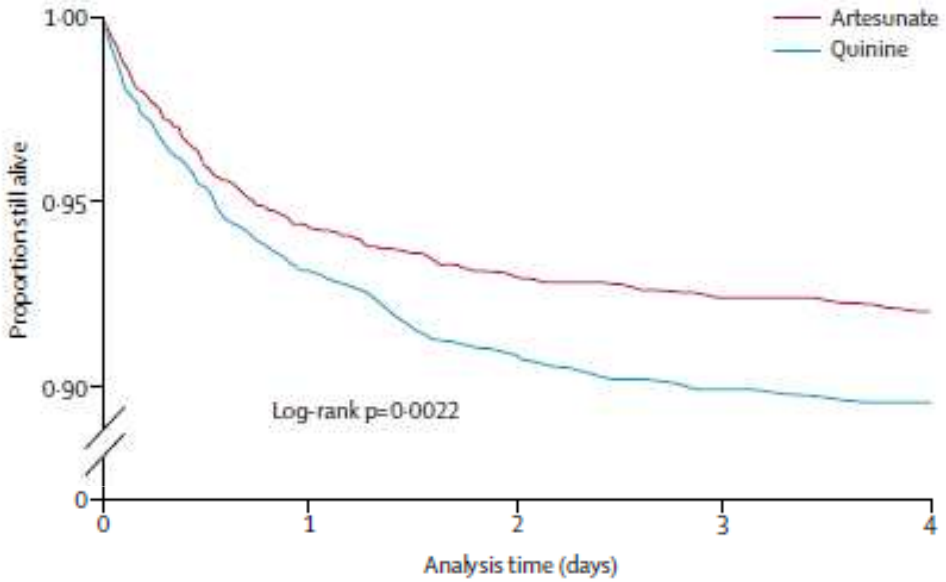
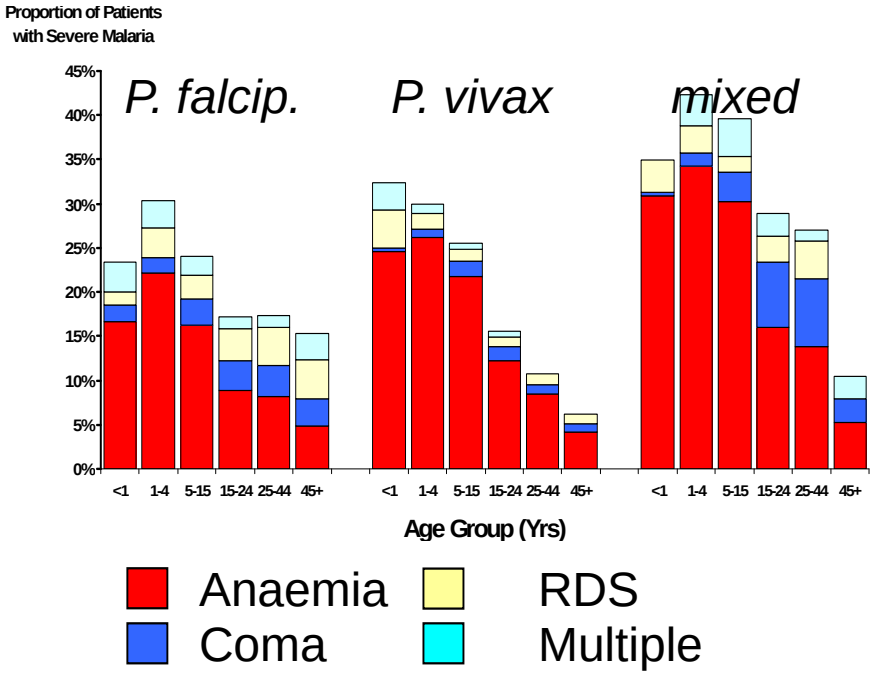
Severe Malaria

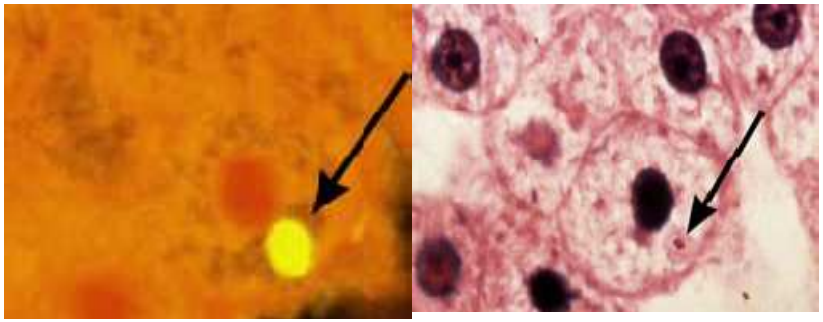


- Aquamat (Dondorp et al., 2010): iv artesunate superior to iv quinine: 5000 patient study
- Guilin first prequalified (Dec 2010) with MMV's support
- Only Chinese manufacturer with WHO approval
- Cost: approximately $1 per vial

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

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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

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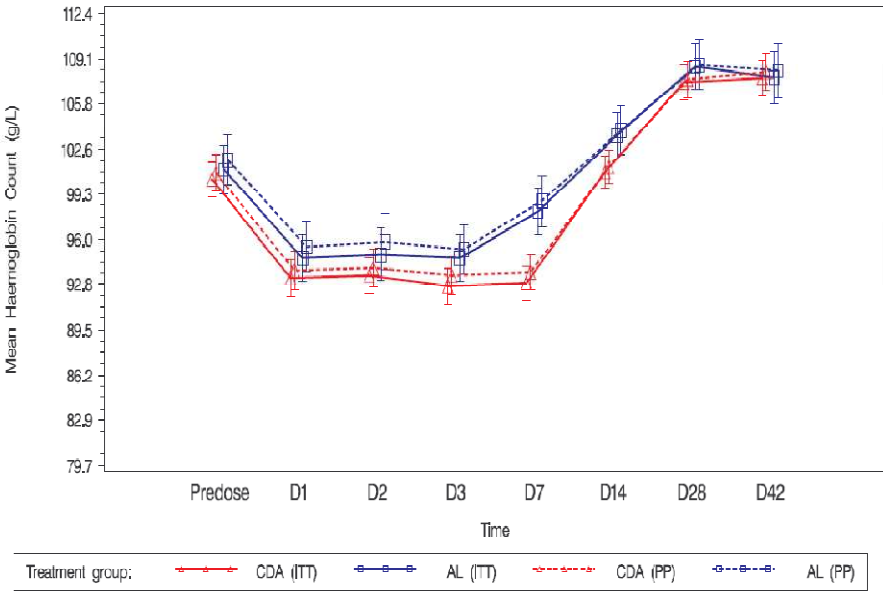
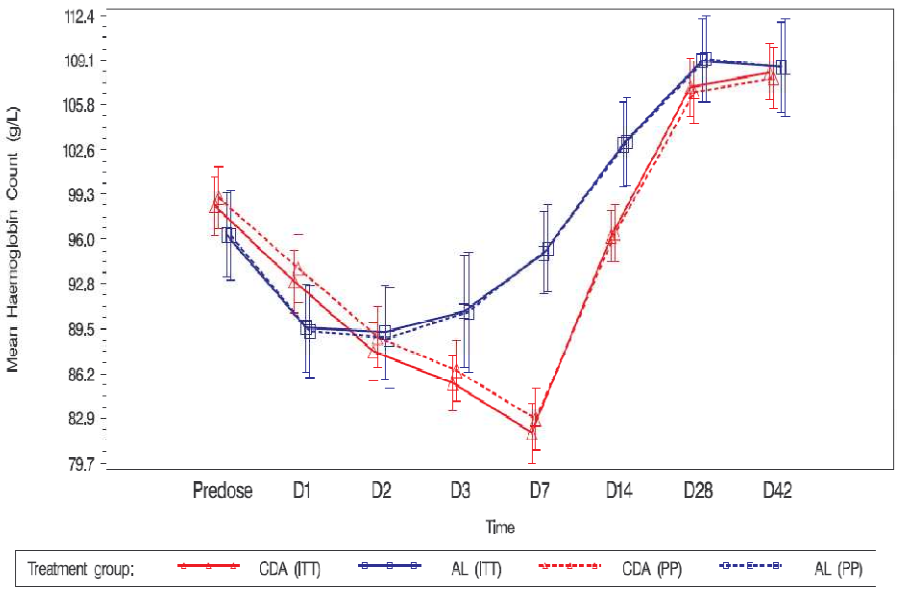
Safe medicines are a human right

All patients



G6PD deficient patients



DACART CoartemD

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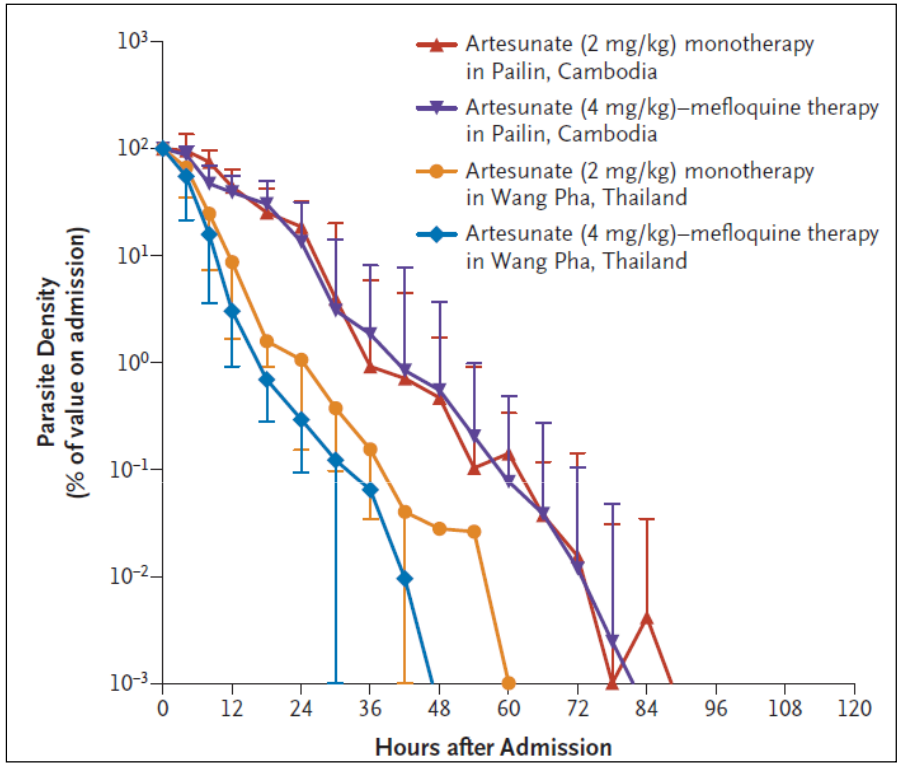
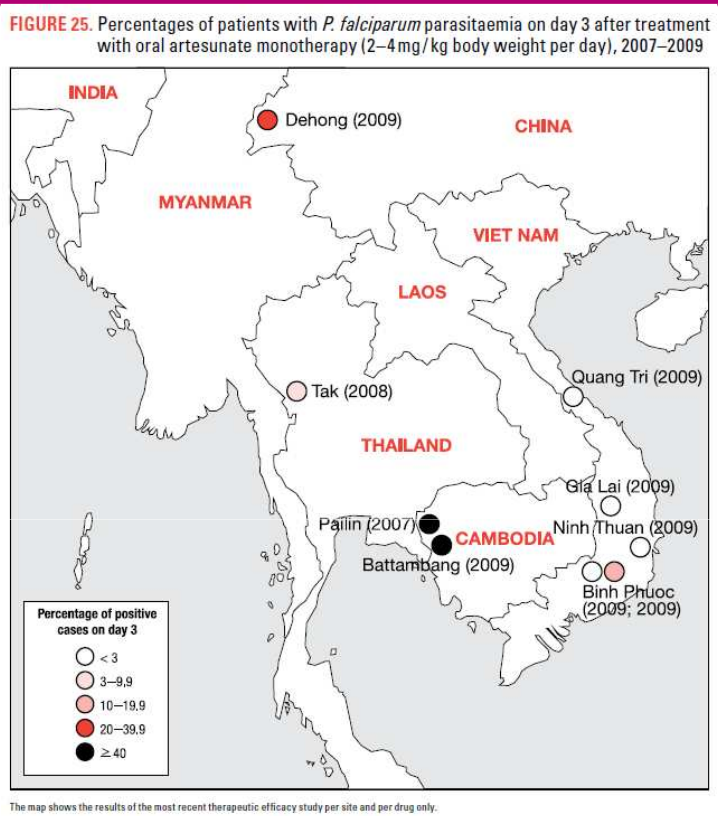
Artemisinin resistance is emerging





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

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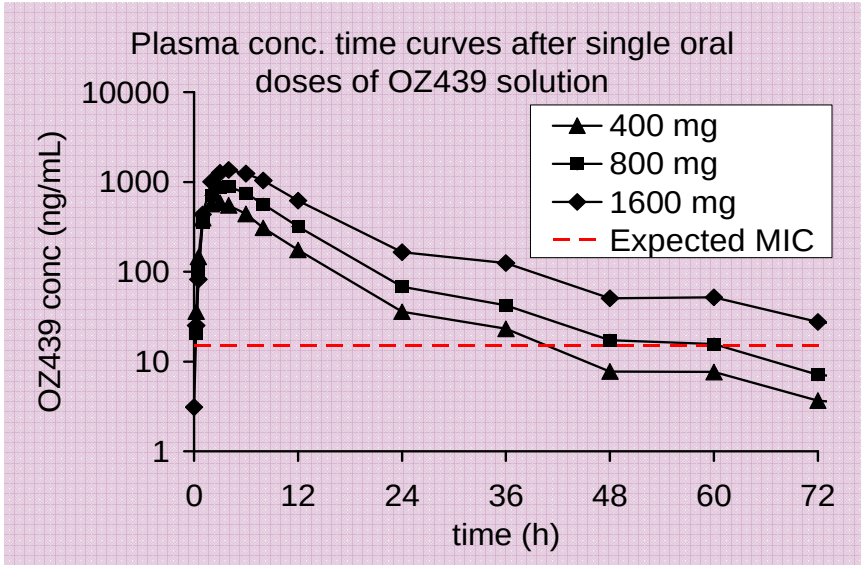
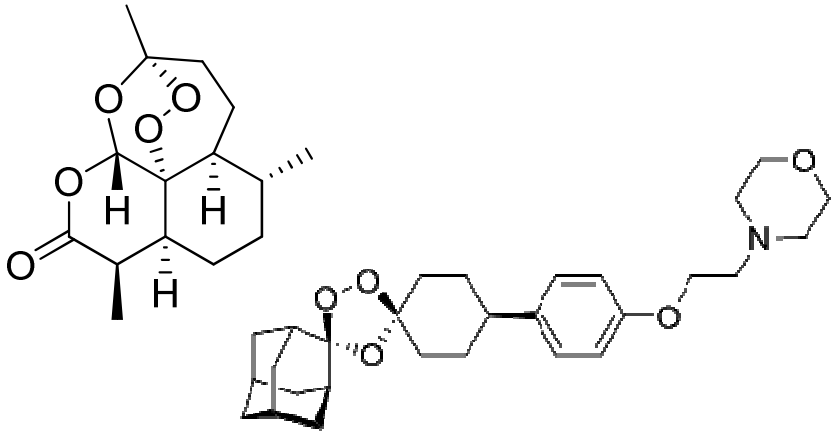
Endoperoxides: the stealth warhead

- 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





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Searching for new classes of molecules

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

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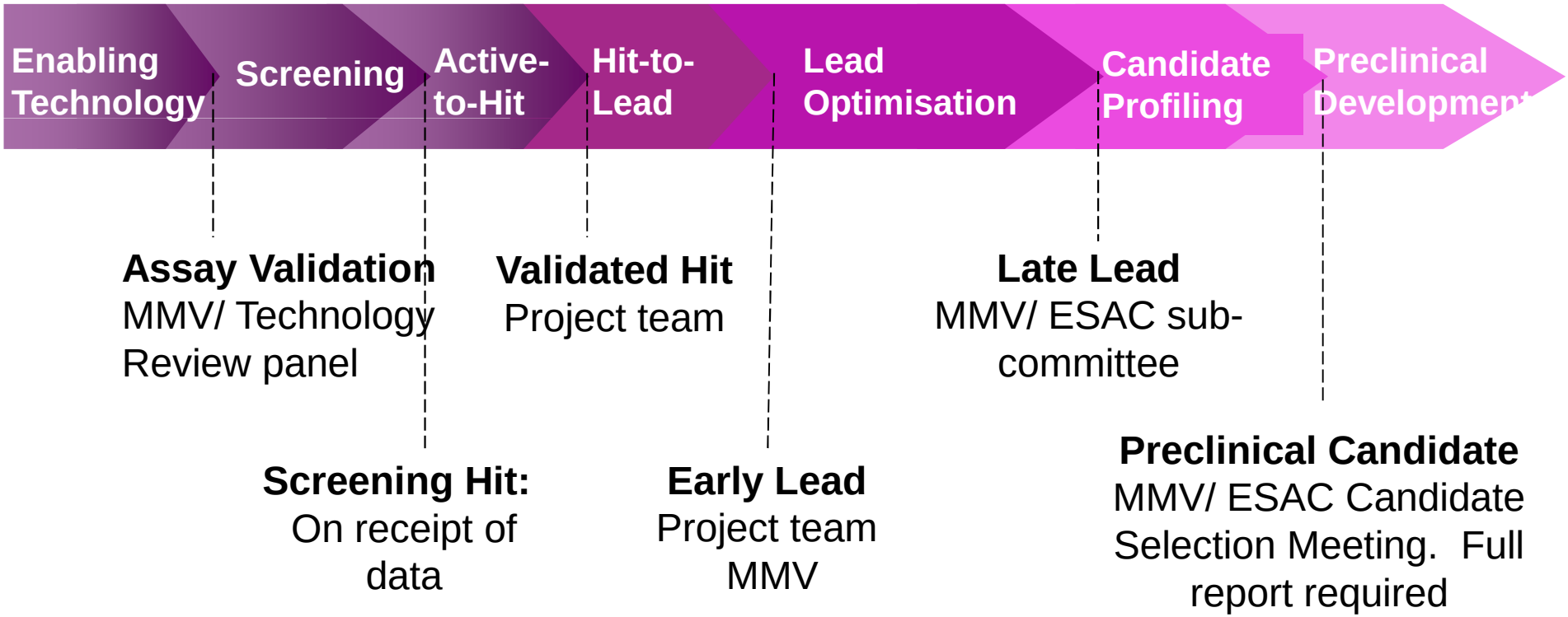
Managing Discovery Projects

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



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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

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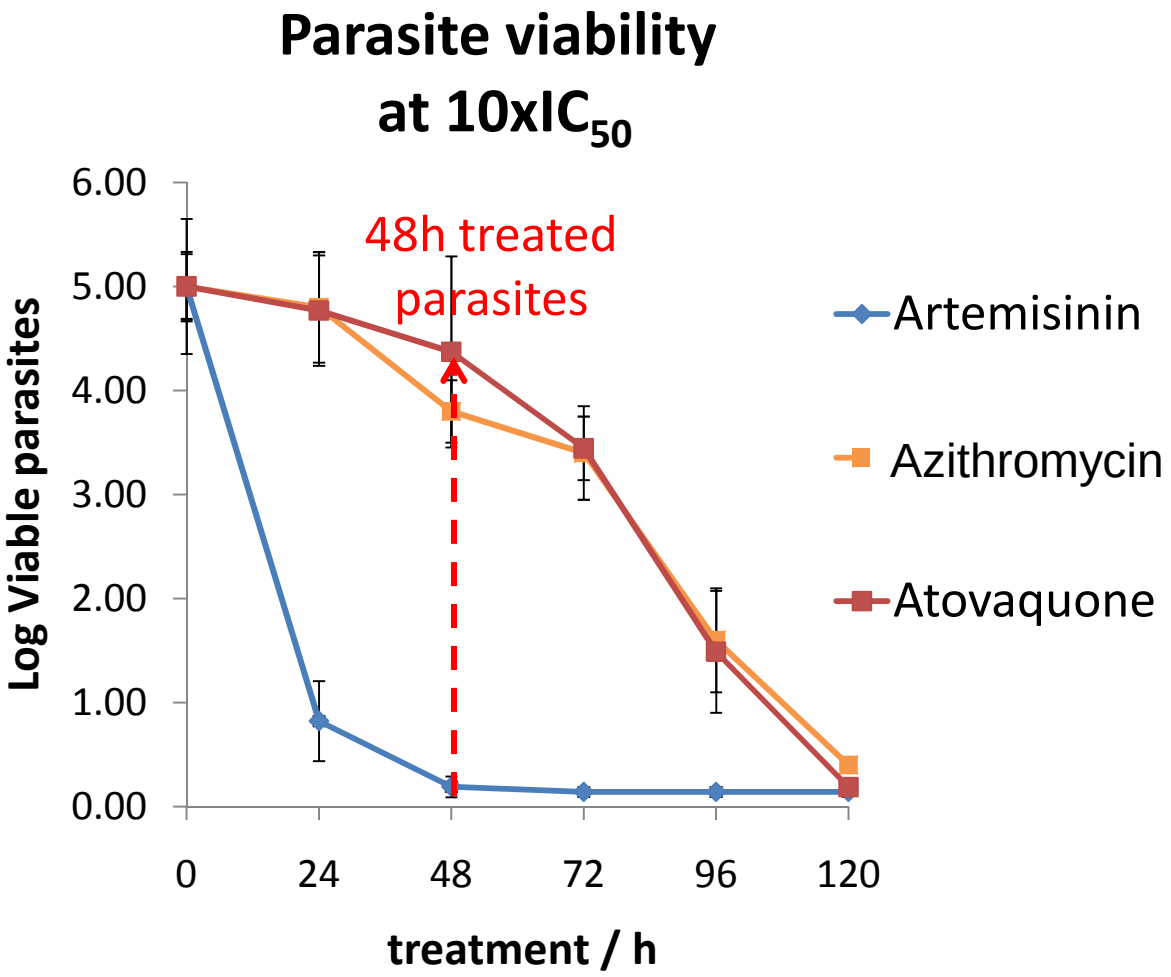
Parasite Reduction Rate



Javier Gamo GSK Tres Cantos

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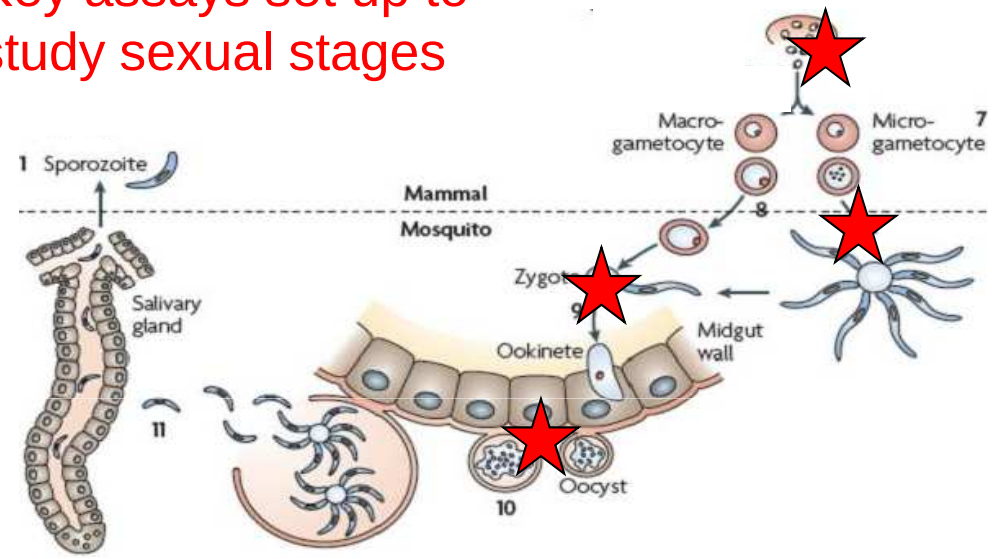
Dose and cost of goods

- 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

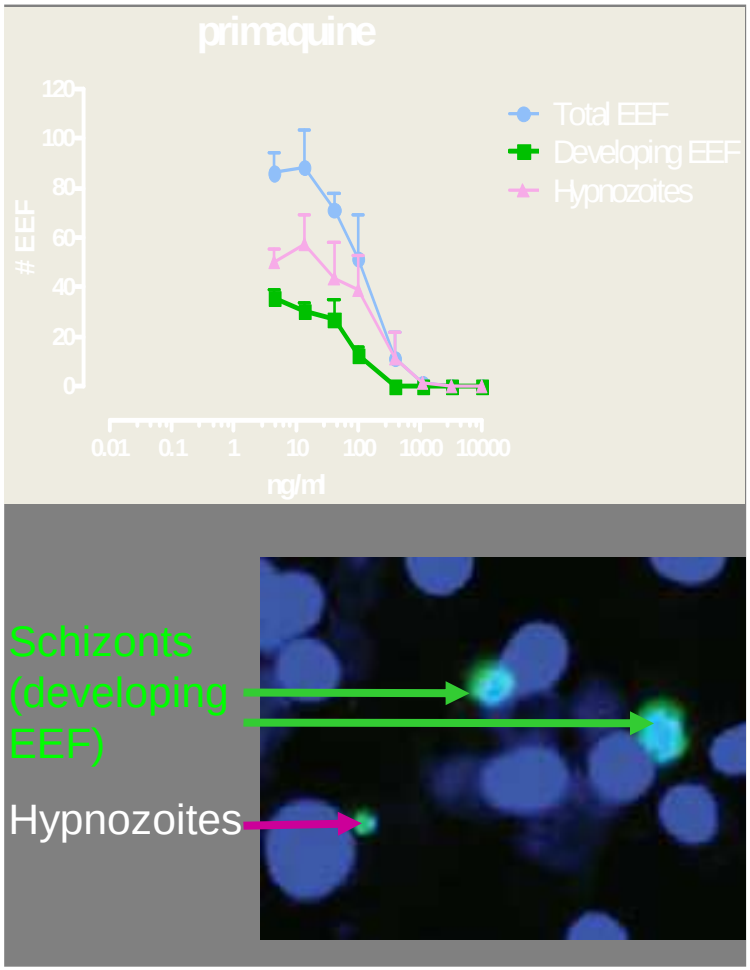


Ookinete

- 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



Clemens Kocken, BPRC Rijkswik NL
Wells TNC et al., Trends in Parasitol 26 1471-4922 (2010)

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Not all candidates are perfect

Parameters	A	B	C	D	E	F	G
Target profile	2	2	1?	2	2	2	2
Human Dose	30	30	<10	1000	1000	15	?
Human Half Life Time >IC90?	10-30	15-30	15-70	10-20	5	10-15	?
Parasite Reduction Rate	Slow	?	?	?	Fast Delay	Fast	?
Other activities Liver/Transmission	L,T	T	L,T	?	L,T	?	L
Cross resistance	Yes	Good	Good	Good	Good	Good	Good
Total	☹	☺	☺	😐	☹	☺	**?**

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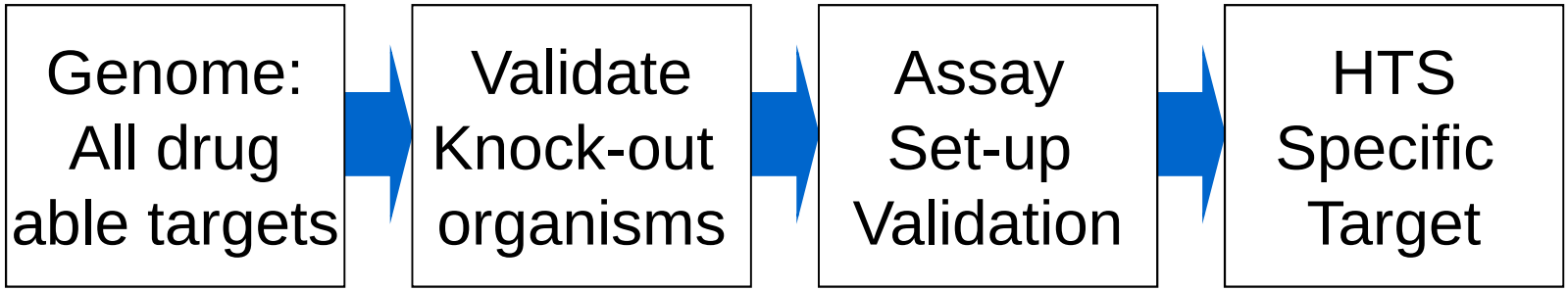
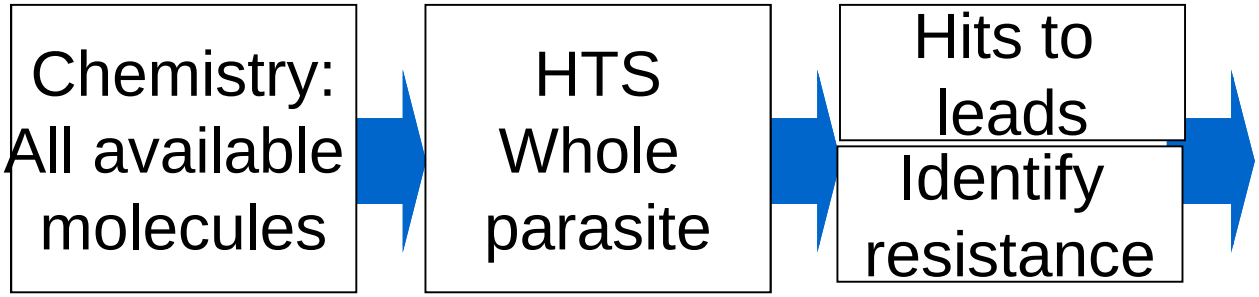
Finding new clinical candidates

Classical ‘Forward’ approach



Reverse approach



Wells TNC Science (2010) 329 1179-1180

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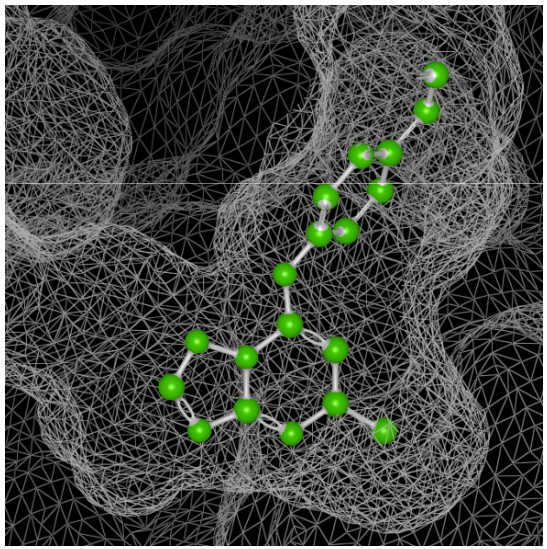
Next generation: guided by structure

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



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

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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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

Payne D., et al Nature Reviews Drug Discovery 6 29-40 (2007)

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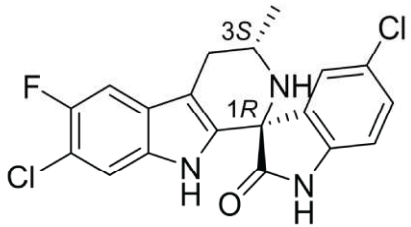
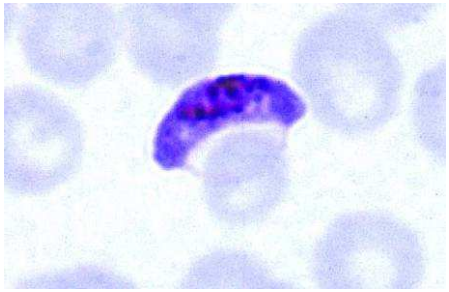
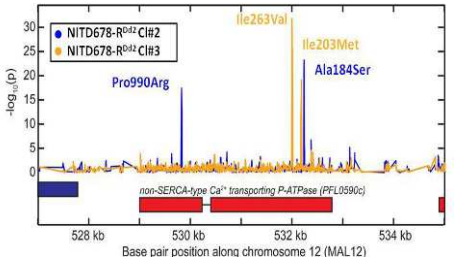
Guided by biology

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





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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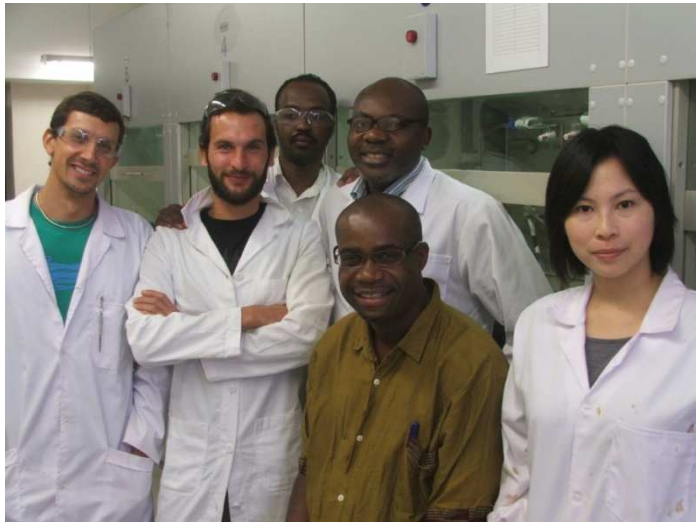
Hits to Leads Bottleneck

- 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



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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 malariabox@mmv.org

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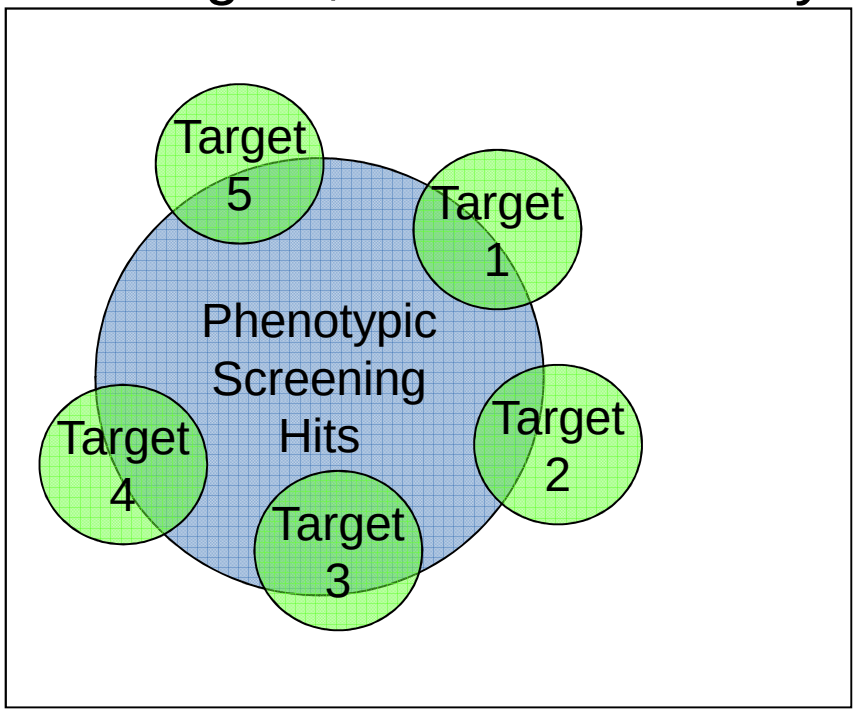
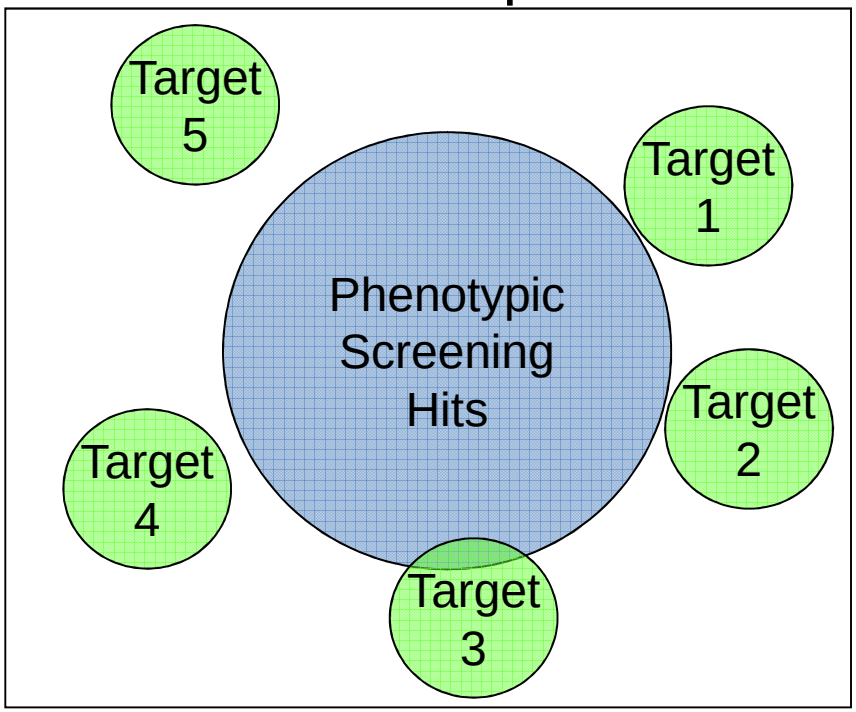
Phenotypic hits in molecular screens

90 targets, 18 screens: only 2 identified ‘tool compounds’





Applicant / status			Screening partner / status												
16-Feb-2010			Novartis			GSK			Broad Genzyme						
Target	Originator	Application status	Assay approved date	Malaria hca screen completed (IC50s)	Secondary assay completed	Assay approval status	Malaria hca screen completed (IC50s)	Secondary assay completed	Assay approval status	Malaria hca screen completed (IC50s)	Secondary assay completed	Active in enzyme assay? (Full-length?)	PlasmoDB ID	EC #	TDRtargets percentile rank	
Plasmodium Surface Anion Channels (PSAC)	S. Desai (NIAID)	Received	15-May-08	15-Sep-08	15-Jun-08											
Choline Kinase	G. McGrowther (UV)	Received	30-Nov-08	1-May-09								active	PF14_0020	2.7.1.32	97.9%	ATP +
S-adenosylhomocysteine hydrolase (SAHH)	G. McGrowther (UV)	Received	30-Nov-08	15-May-09								active	PFE1050w	3.3.1.1	99.9%	S-ado homo
Orotidine 5' monophosphate decarboxylase (OMPDC)	G. McGrowther (UV)	Received	30-Nov-08	1-May-09		29-Aug-09			1-May-09			active	PF10_0225	4.1.1.23	98.6%	OMP
Glutamate dehydrogenase (NADP-specific)	G. McGrowther (UV)	Received	15-Feb-09	31-May-09								active	PF14_0164	1.4.1.4	99.7%	L-glut NH3 +
Adenylosuccinate synthetase	G. McGrowther (UV)	Received	15-May-09	30-Jun-09					1-May-09			active (full-length)	PF13_0287	6.3.4.4	99.5%	GTP + (L2-4

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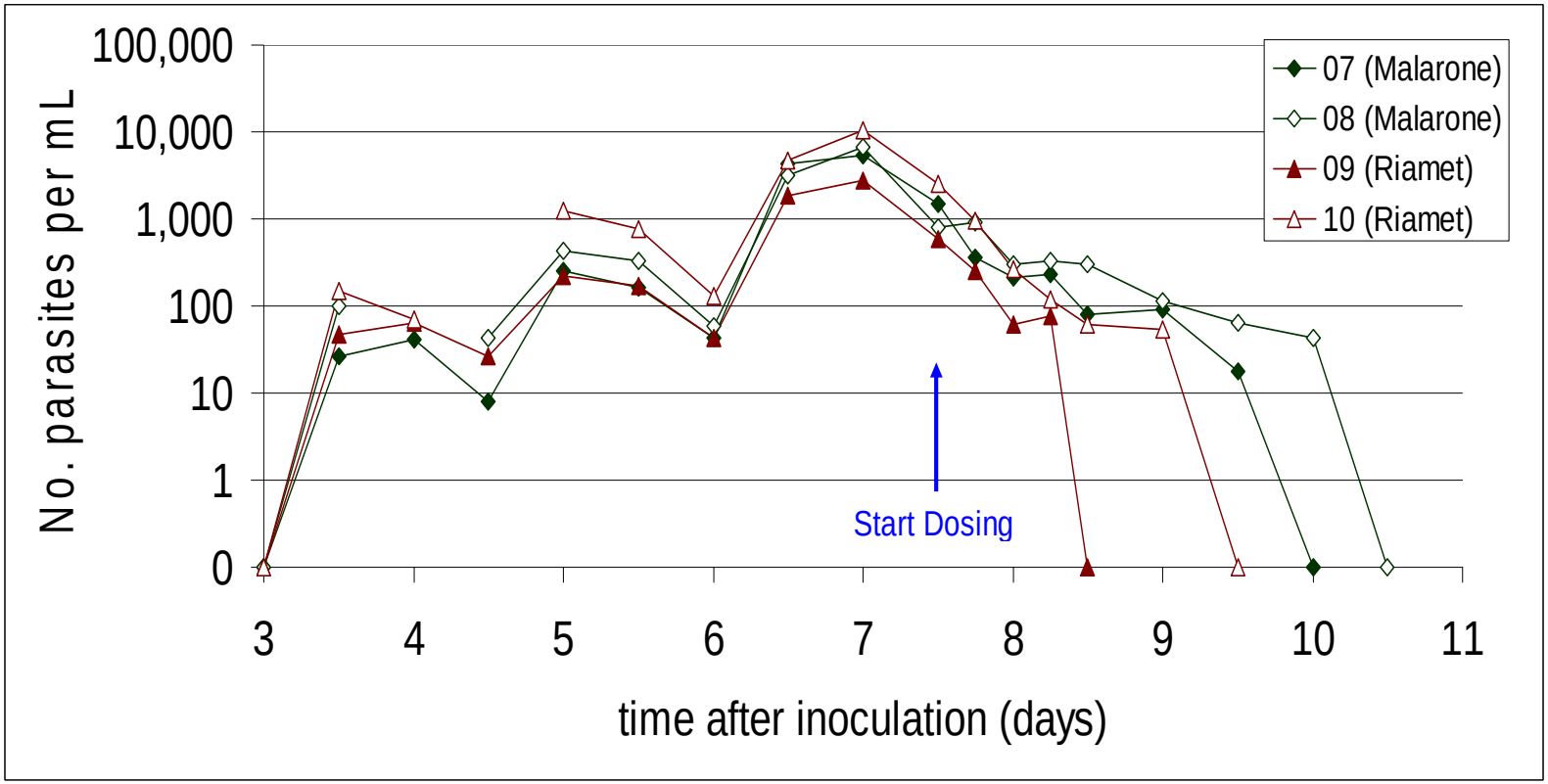
Implications for the future of drug discovery

- Pharma has over 4000 compounds, with pre-clincal 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

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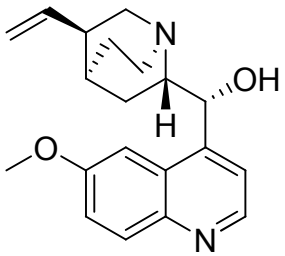
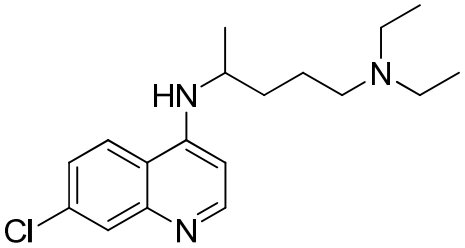
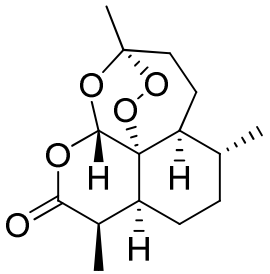
Natural Products: back to our roots?



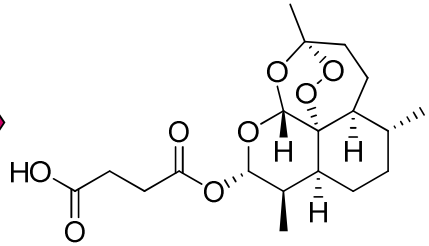
Half life 8 h



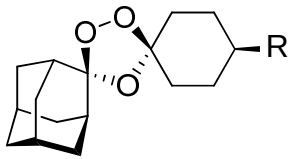
Half life 278 h



Insoluble



Soluble
half life <1h



Soluble
half life >24h

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

Wells TNC Malaria Journal *in press* (2011)

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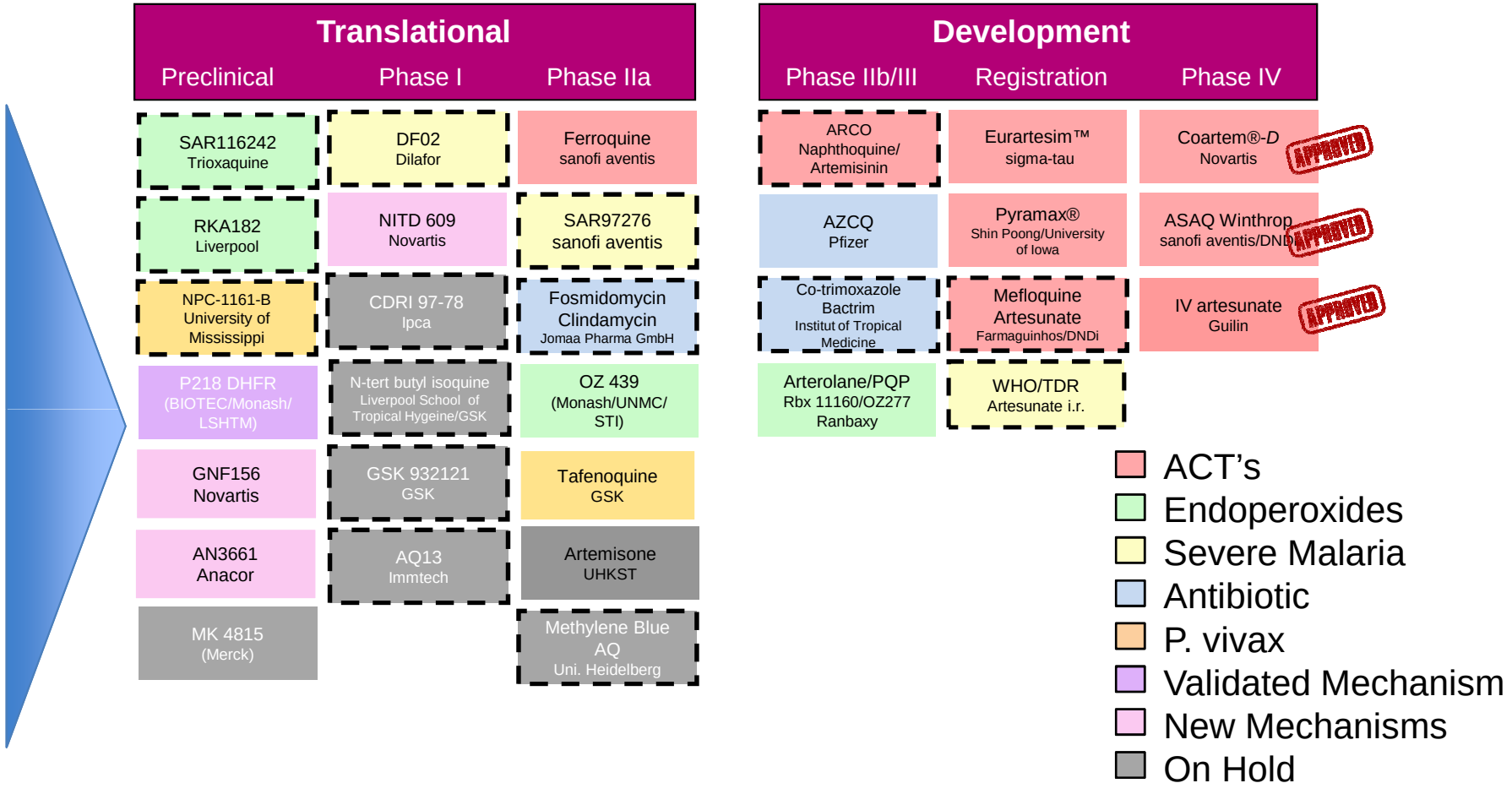
Global Portfolio of Antimalarial Medicines



2016+	2015	2013	2011	Launch
10%	20%	68%	>90%	Probability

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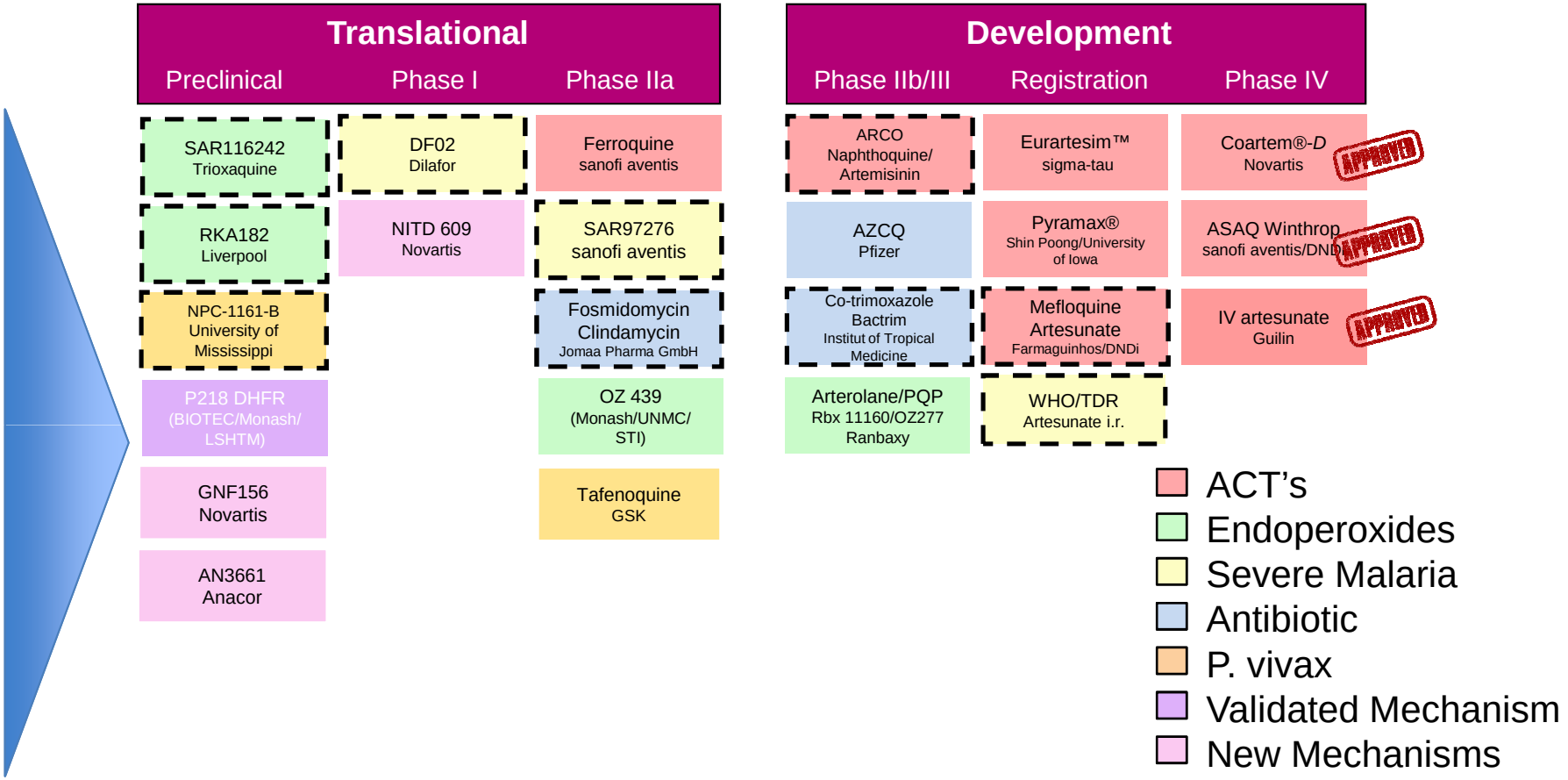
Global Portfolio of Antimalarial Medicines



2016+	2015	2013	2011	Launch
10%	20%	68%	>90%	Probability

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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

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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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