Advances on the development of next generation differentiated antimalarials

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Bangkok, Dec 2017

Tres Cantos Medicines Development Campus

Scope of the Presentation

Brief outline

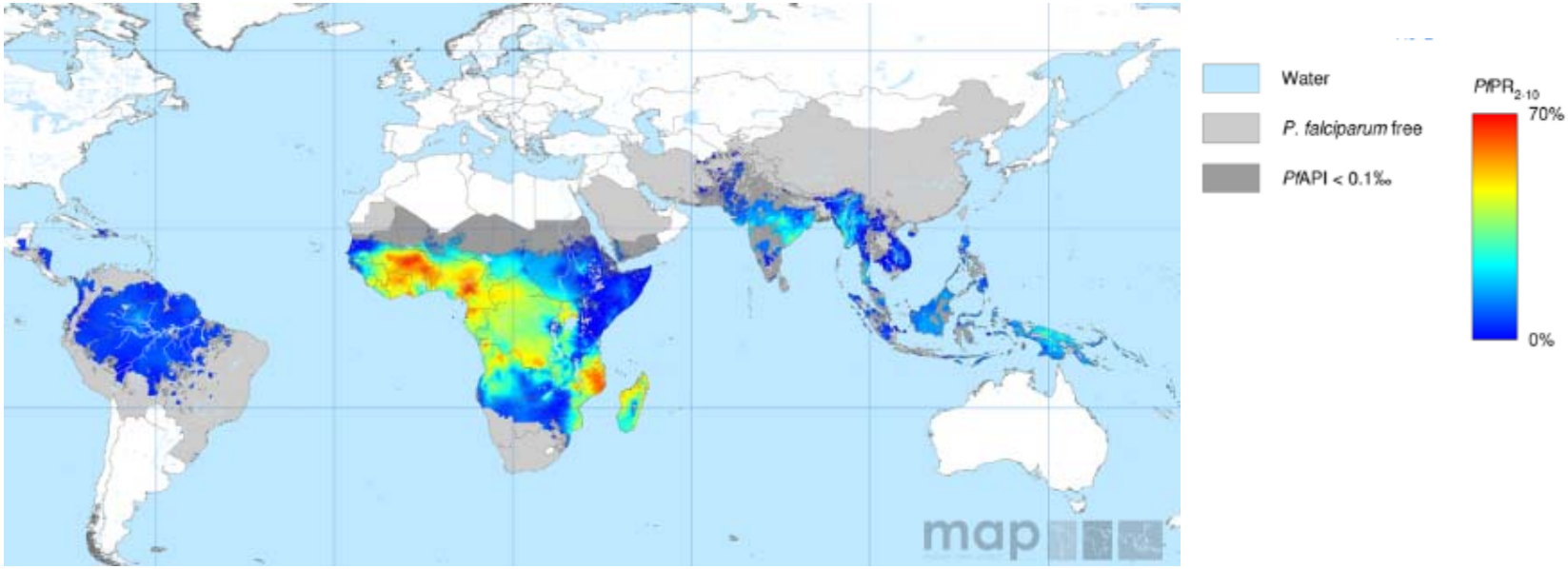
- Introduction
  - Resistance makes urgent discovery of new antimalarials
- Overview of Malaria DPU
  - Mission, priorities and business model
- Antimalarial discovery strategy
  - Most desired antiparasitological profiles
  - Biological profiling and MoA tools
- Case study:
  - Novel antimalarials with dual mode of action
  - Novel “irresistible” blood stage inhibitors
- Summary and conclusions

All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on the Care, Welfare and Treatment of Animals. The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents

Malaria numbers are not acceptable

- Malaria still one of the deadliest infectious disease
  - 50% of world population is at risk
  - ca. 200 million people yearly affected
  - 429,000 deaths estimated in the last WHO report

Clinical burden of *P. falciparum* infection



- Most deaths are associated with *P. falciparum* infection with Sub-Saharan Africa accounting for more than 90% of the observed mortality

New antimalarial therapeutic options are urgently needed

- Despite progress achieved recently, current antimalarial therapeutic arsenal is very limited
  - No new class of antimalarials into clinical practice since 1996
- Resistance to historic antimalarials has rendered these drugs ineffective
- Emerging evidences of resistance to ACTs threaten all the recent advances in malaria control
- Combinations of novel antimalarials should be the strategy to deploy new treatments

Malaria Drug Discovery in GSK

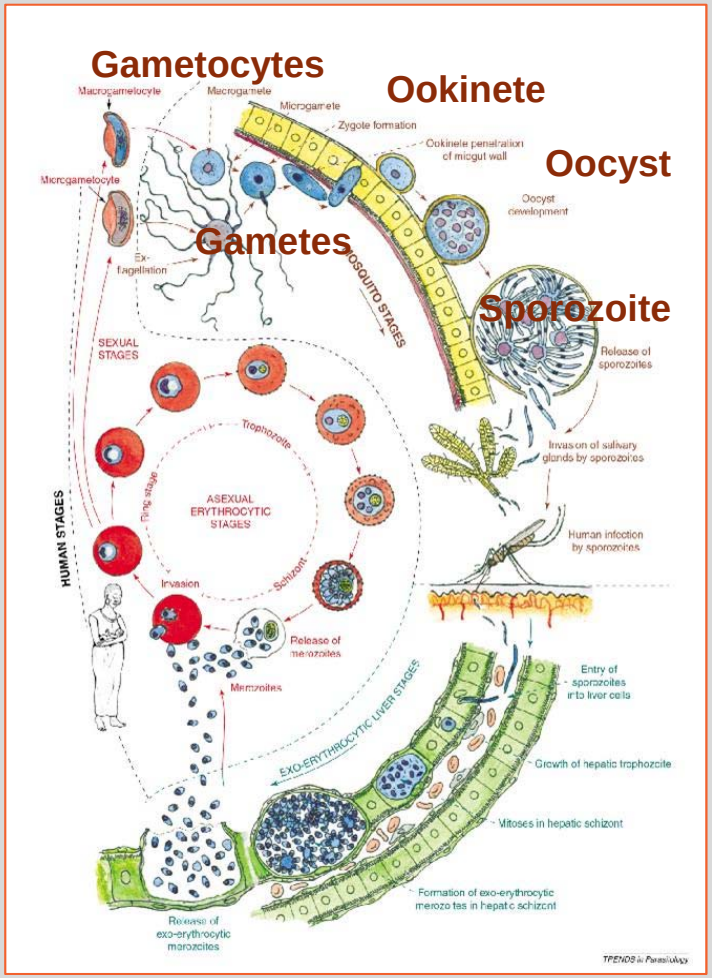
Differentiated antimalarials for control and eradication

Scientific Opportunities

- WGS and Target ID
- Phenotypic screening assays (*e.g.* TCAMS)
- Recognition that gametocytes and liver stages are important targets
- “Open source” approach with TCAMS

Discovery Approaches

- Fully exploit phenotypic hits
- Identify and use novel antimalarial targets
- Build capability to test all aspects of the malaria lifecycle
- Build full *in vitro* and *in vivo* PK/PD modelling knowhow
- Exploit combination approach to avoid resistance and improve efficacy



Malaria DPU: Business model

wellcome trust

gsk

Platform Technology & Science

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P. falciparum In Vitro Killing Rates Allow to Discriminate between Different Antimalarial Mode-of-Action

Laura M. Sanz[1], Benigno Crespo[1], Cristina De-Cózar[1], Xavier C. Ding[2], Jose L. Llergo[1], Jeremy N. Burrows[2], Jose F. Garcia-Bustos[1¤], Francisco-Javier Gamo[1*]

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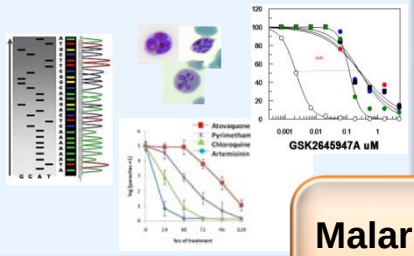
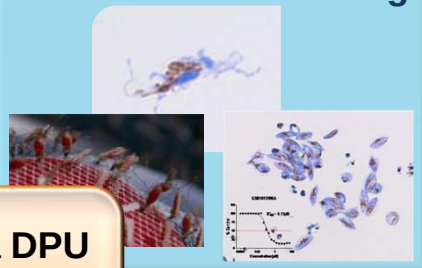
Activity of Clinically Relevant Antimalarial Drugs on *Plasmodium falciparum* Mature Gametocytes in an ATP Bioluminescence "Transmission Blocking" Assay

Joël Lelièvre[1*¤], Maria Jesus Almela[1¤], Sonia Lozano[1], Celia Miguel[1], Virginia Franco[1¤], Didier Leroy[2], Esperanza Herreros[1*]

Blood Stage Parasitology



Transmission blocking



Clinical Development

Business Development

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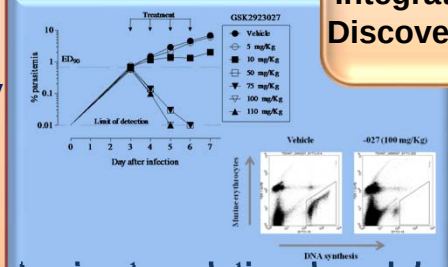
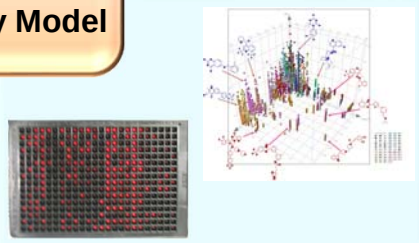
Malaria DPU Integrated Drug Discovery Model

Global Regulatory

Animal Sciences



In vivo translational models



Chemistry & Screening

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GSK core servicies

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A Murine Model of *falciparum*-Malaria by *In Vivo* Selection of Competent Strains in Non-Myelodepleted Mice Engrafted with Human Erythrocytes

Iñigo Angulo-Barturen[1*], María Belén Jiménez-Díaz[1], Teresa Mulet[1], Joaquín Rullas[1], Esperanza Herreros[1], Santiago Ferrer[1], Elena Jiménez[1], Alfonso Mendoza[1], Javier Regadera[2], Philip J. Rosenthal[3], Ian Bathurst[4], David L. Pompliano[5], Federico Gómez de las Heras[1], Domingo Gargallo-Viola[1]

MMV Medicines for Malaria Venture

ARTICLES

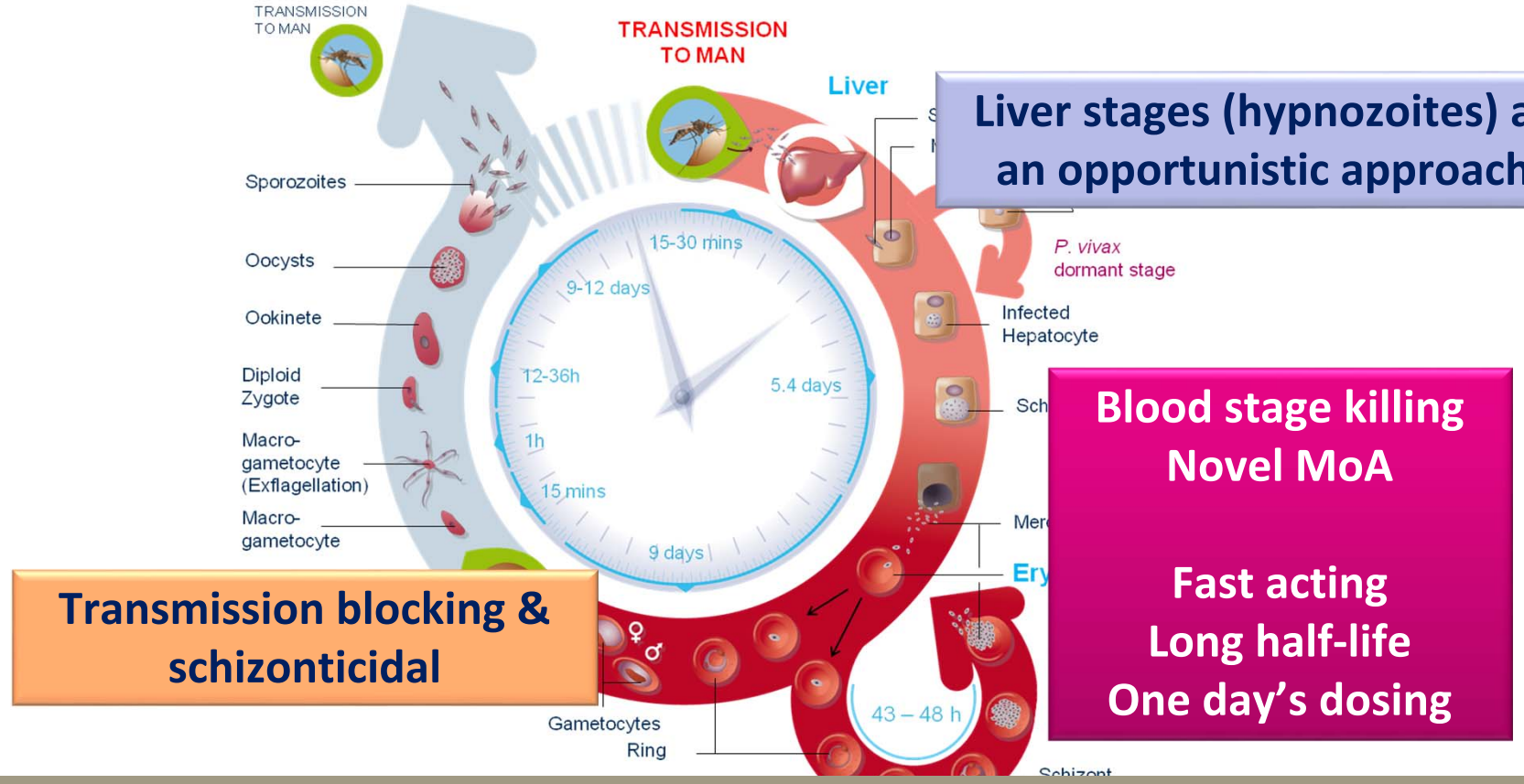
Thousands of chemical starting points for antimalarial lead identification

Francisco-Javier Gamo[1], Laura M. Sanz[1], Jaume Vidal[1], Cristina de Cozar[1], Emilio Alvarez[1], Jose-Luis Lavandera[1], Dana E. Vanderwall[2], Darren V. S. Green[3], Vinod Kumar[4], Samiul Hasan[4], James R. Brown[4], Catherine E. Peishoff[5], Lon R. Cardon[5] & Jose F. Garcia-Bustos[1]

Malaria Discovery Performance Unit (DPU)

Our mission:

Deliver next generation of antimalarial drugs to improve current SoC



Liver stages (hypnozoites) as an opportunistic approach

Blood stage killing
Novel MoA

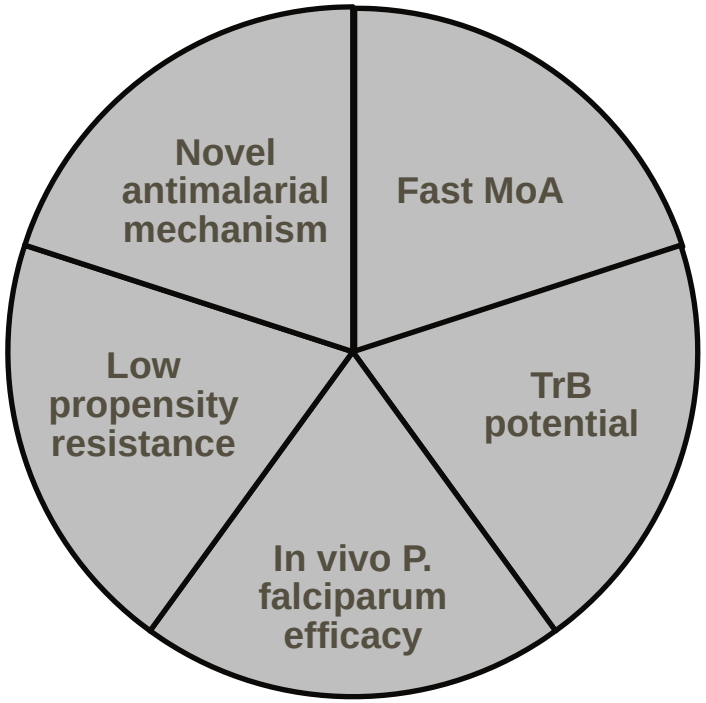
Fast acting
Long half-life
One day's dosing

Transmission blocking & schizonticidal

Novel modes of action avoiding resistance and enabling combination therapies

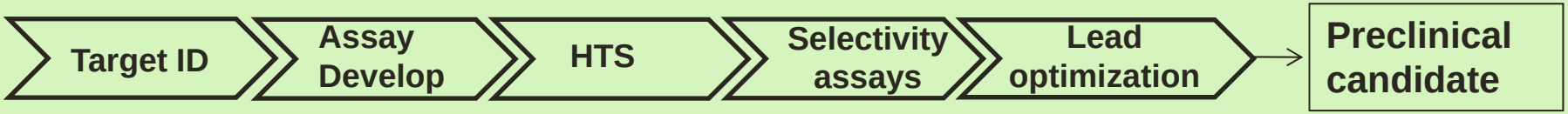
Differentiated antimalarials for control and eradication

– Strategy focused on identifying molecules with the most desirable parasitological profile



The best strategy for antimalarial lead discovery?

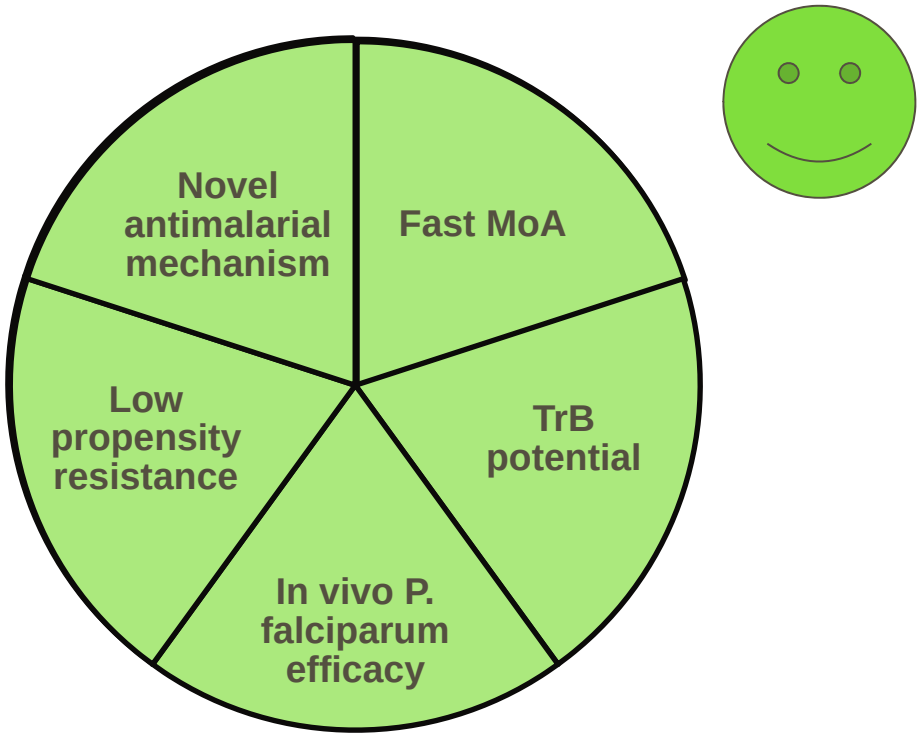
Target-based drug discovery



- **Validated target can provide desirable the clinical therapeutic profile**

Differentiated antimalarials for control and eradication

– Validated target can provide desirable the clinical therapeutic profile



The best strategy for antimalarial lead discovery?

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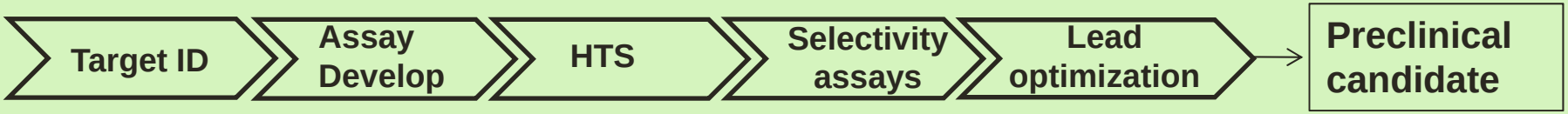
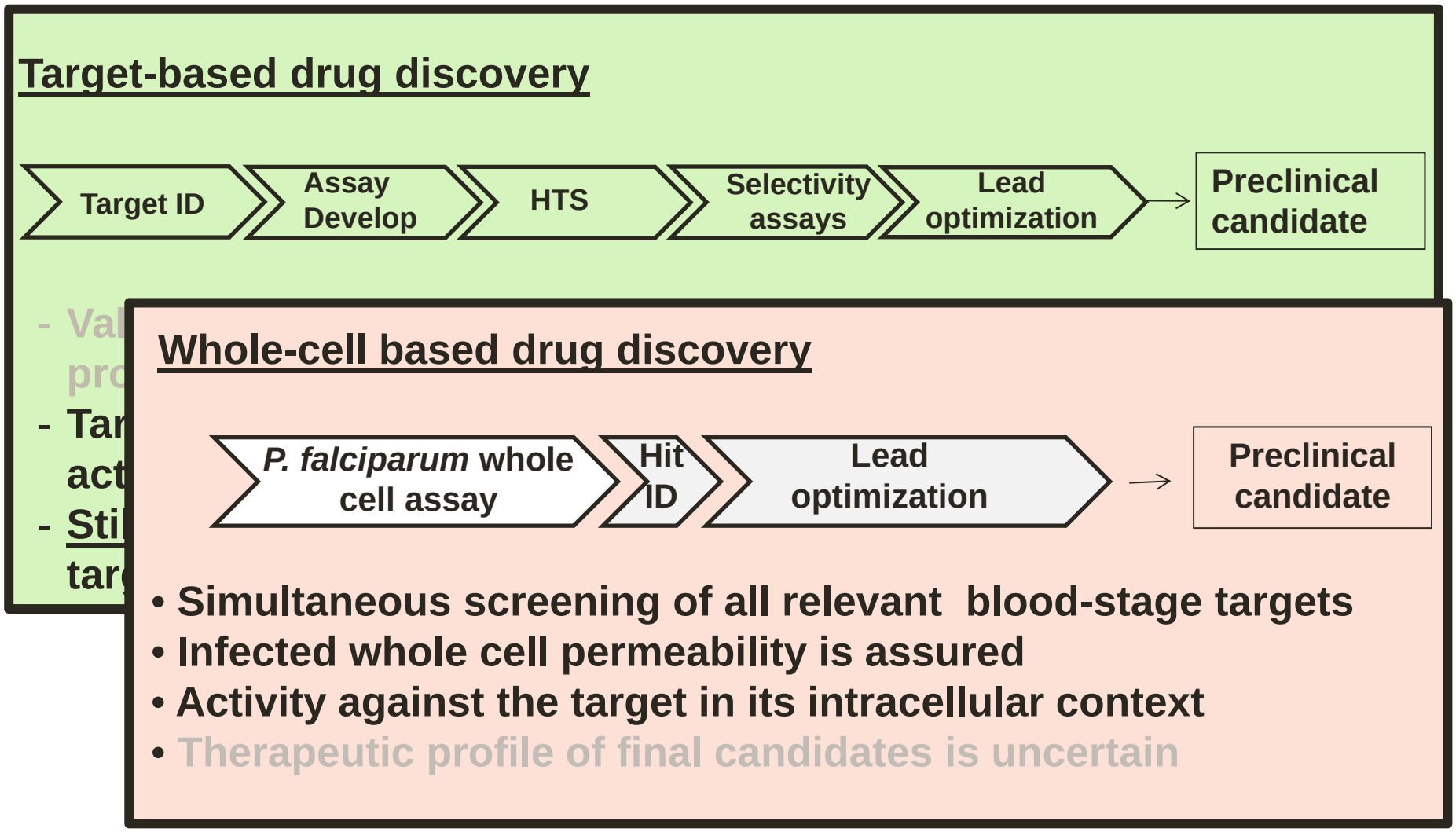


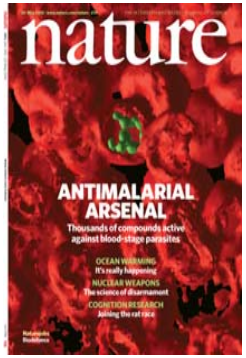
- Validated target can provide desirable the clinical therapeutic profile
- **Target-based discovery has been disappointing: lack of whole cell activity is one of the main causes**
- **Still the favoured approach but a lack of tractable antimalarial targets is the main handicap**

The best strategy for antimalarial lead discovery?



Phenotypic Screening

Current global portfolio reflects the success of the whole cell approach



Chemical genetics of *Plasmodi*

W. Armand Guiguemde[1], Anang A. Shelat[1], David Bouck[1], Sandra Duffy[2], Gr
David C. Smithson[1], Michele Connelly[1], Julie Clark[1], Fangyi Zhu[1], María B. Jir
Emily B. Wilson[6], Abhai K. Tripathi[7], Jiri Gut[8], Elizabeth R. Sharlow[9], Ian Bath
ve Castro[14], Iñig
ohn S. Lazo[9], Da
n Voorhis[3], Vick

ARTICLES

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Thousands of chemical starting points for antimalarial lead identification

Francisco-Javier Gamo[1], Laura M. Sanz[1], Jaume Vidal[1], Cristina de Cozar[1], Emilio Alvarez[1], Jose-Luis Lavandera[1], Dana E. Vanderwall[2], Darren V. S. Green[3], Vinod Kumar[4], Samiul Hasan[4], James R. Brown[4], Catherine E. Peishoff[5], Lon R. Cardon[6] & Jose F. Garcia-Bustos[1]

Malaria is a devastating infection caused by protozoa of the genus *Plasmodium*. Drug resistance is widespread, no new chemical class of antimalarials has been introduced into clinical practice since 1996 and there is a recent rise of parasite strains with reduced sensitivity to the newest drugs. We screened nearly 2 million compounds in GlaxoSmithKline's chemical library for inhibitors of *P. falciparum*, of which 13,533 were confirmed to inhibit parasite growth by at least 80% at 2 μM concentration. More than 8,000 also showed potent activity against the multidrug resistant strain Dd2. Most (82%) compounds originate from internal com
data suggest several novel mechanism
interaction related targets. Chemical st
lead identification efforts and further r

In silico activity profiling reveals the mec of action of antimalarials discovered in a high-throughput screen

David Plouffe*, Achim Brinker*, Case McNamara*, Kerstin Henson*, Nobutaka Kato*, Kelli
Francisco Adrián*, Jason T. Matzen*, Paul Anderson*, Tae-gyu Nam†, Nathanael S. Gray*‡,
Jeff Janes*, S. Frank Yan*, Richard Trager*, Jeremy S. Caldwell*, Peter G. Schultz*¶5, Yingy
and Elizabeth A. Winzeler*¶

Research Lead optimisation		Translational Preclinical	Translational Human volunteers	Development Patient exploratory	Development Patient confirmatory	Development Under review *	Access Post approval
Oxaboroles Anacor	1 Project Novartis	P218 DHFR BIOTEC (Monash/ LSHTM)	MMV048 UCT/TIA	OZ439/PQP Sanofi	Tafenoquine GSK	Rectal Artesunate CIPLA/Strides/TDR	Artemether-Lumefantrine Novartis
DHODH UTSW/UW/Monash	3 Projects GSK	SJ733 StJude/Eisai	ACT840 Actelion	OZ439/FQ Sanofi	DHA-Piperaquine Pediatric Sigma-Tau	Arterolane/PQP Ranbaxy **	Artemether-Lumefantrine Dispersible Novartis
Open Source Drug Discovery Sydney	Orthologue Leads Sanofi	DDD498 Merck Serono (Dundee)	CDRI 97-78 Ipca	KAE609 Novartis	Pyronaridine-Artesunate Paediatric Shin Poong		Artesunate for injection Guilin
Amino-alcohols Merck Serono	Tetraoxanes LSTM/Liverpool	PA92 (Drexel/UW/GNF)		KAF156 Novartis	Co-trimoxazole Bactrim Inst. of Trop. Med.		DHA-Piperaquine Sigma-Tau
Imidazolidinedion-es WRAIR	*Pf* NMT Imperial College London	MMV253 (AstraZeneca)		DSM265 NIH/Takeda	Artemisinin Naphthoquine KPC		Pyronaridine-Artesunate Shin Poong
dUTPase inhibitors Medivir	*Pf* NDH2 LSTM/Liverpool	GSK030 GSK		Fosmidomycin Piperaquine Jomaa Pharma GmbH	Artemether sub-lingual spray ProtoPharma Ltd		Artesunate Amodiaquine Sanofi/DNDi
Diversity Oriented Synthesis Broad Institute		NPC-1161-B Mississippi		Methylene Blue/AQ Heidelberg			Artesunate-Mefloquine CIPLA/DNDi
		RKA182 LSTM/Liverpool		SAR97276 Sanofi			Sulfadoxine Pyrimethamine + Amodiaquine Guilin
		JPC-3210 Jacobus		Artemisone UHKST			
		MK4815 Merck		AQ13 Immtech			
				DF02 Dilafor			

1 Brand name: Coartem®
2 Brand name: Coartem® Dispersible
3 Brand name: Artesun®
4 Brand name: Eurartesim®
5 Brand name: Pyramax®
6 Brand names: Coarsucam™, ASAQ/Winthrop®
7 Brand name: Synriam™
8 Brand name: ARCO®
9 Brand name: ArTiMist™

The best strategy for antimalarial lead discovery?

Target-based drug discovery

Target ID → Assay Develop → HTS → Selectivity assays → Lead optimization → Preclinical candidate

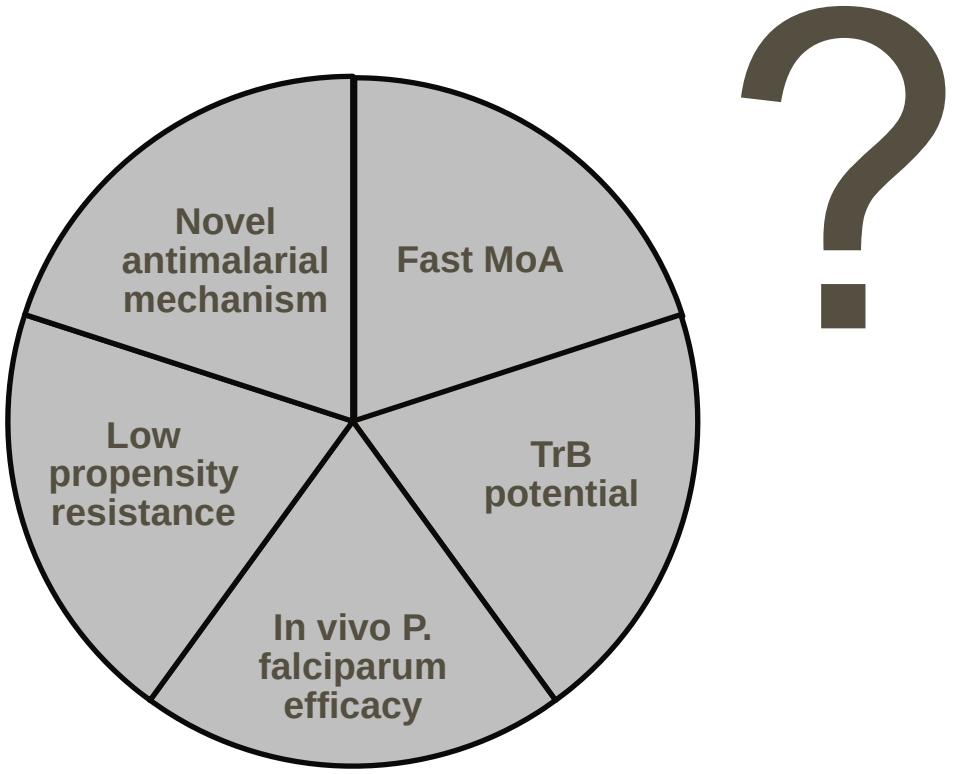
- Val
  pro
- Tar
  act
- Sti
  tar

Whole-cell based drug discovery

P. falciparum whole cell assay → Hit ID → Lead optimization → Preclinical candidate

- Simultaneous screening of all relevant blood-stage targets
- Infected whole cell permeability is assured
- Activity against the target in its intracellular context
- **Therapeutic profile of final candidates is uncertain**

Phenotypic hits: therapeutic profile of final candidates is uncertain

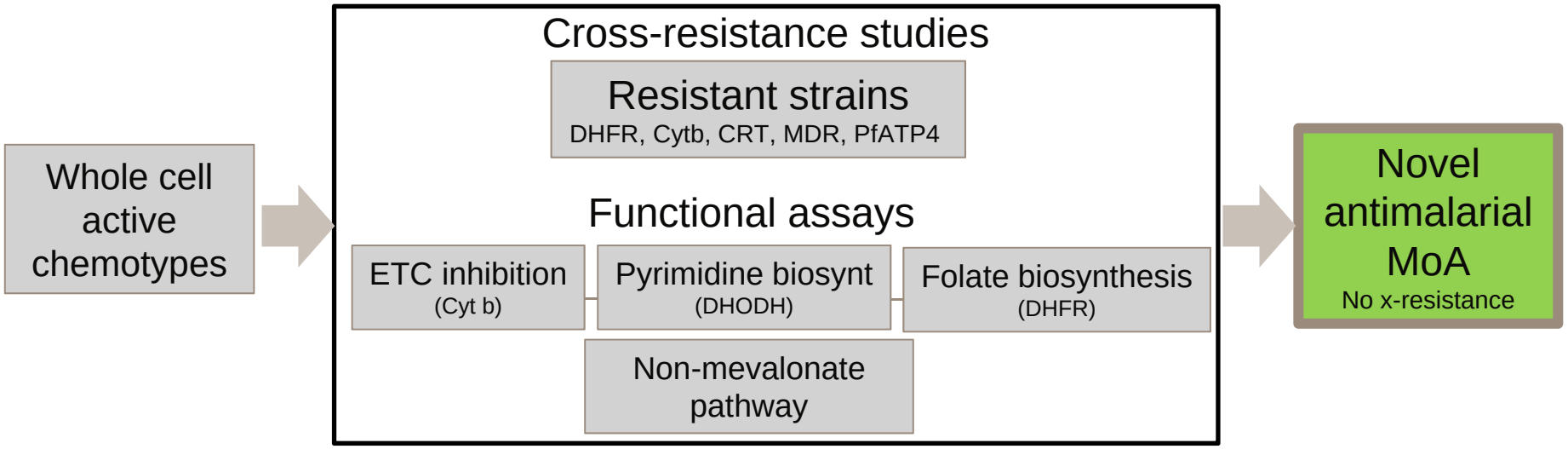


- **How to identify molecules with the most desirable profile?**

Selecting scaffolds with a novel mode of action

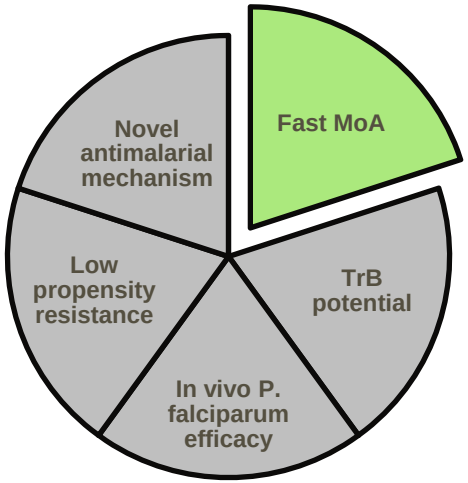
….discarding know MoA

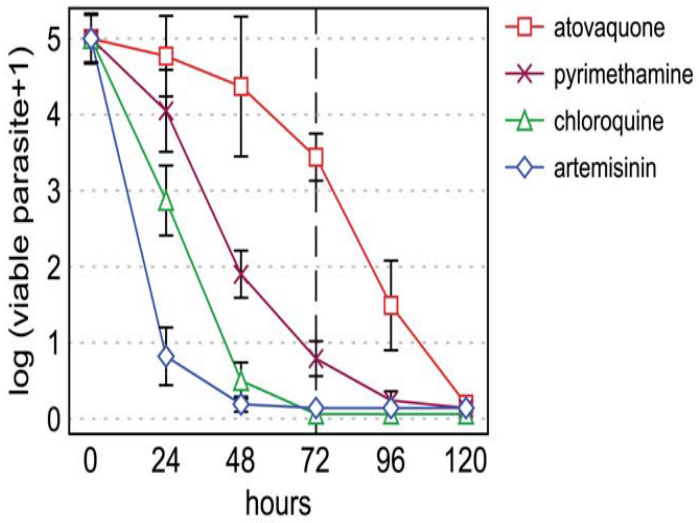
- Hits from phenotypic screens are examined to identify inhibitors with known antimalarial mechanism of action



Rapid parasite killing properties

Inhibition of targets that induce rapid killing are highly desirable

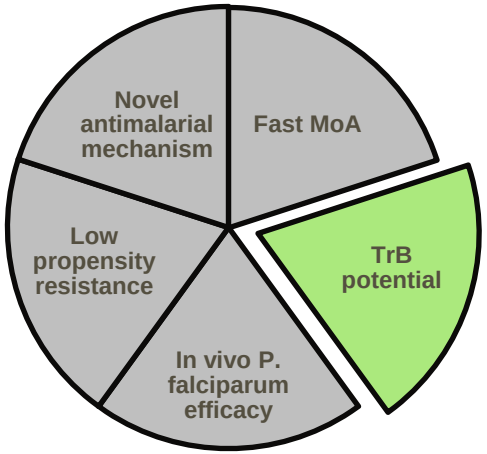


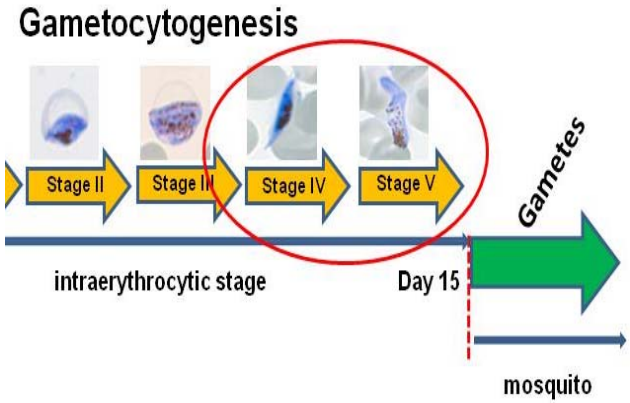


- Killing profiles can be readily determined *in vitro* and are specific to the MoA
  - Allows for differentation of MoA
- Fast acting compounds have a profound effect on disease progression
  - Avoids disease complications
- Rapid mode of action impairs gametocyte maturation
  - This favours transmission blocking
- Rapid decrease in parasitemia and parasite growth hampers selection of resistance

Discovering Transmission Blocking Potential

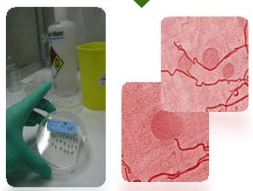
Selecting targets critical for asexual growth and gametocyte viability



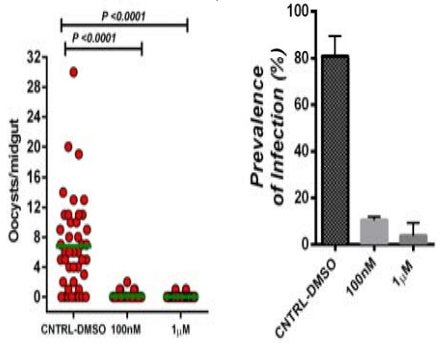


SMFA

Mosquito feeding
Infection of *A. stephensi* mosquitoes



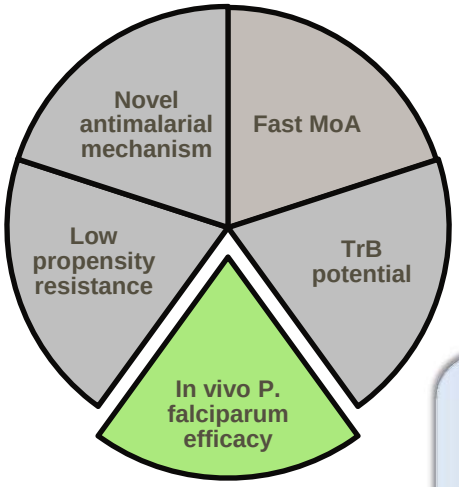
Decapitation, dissection and oocysts counting

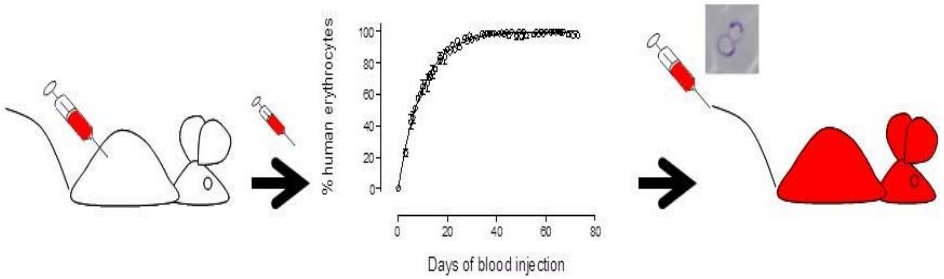


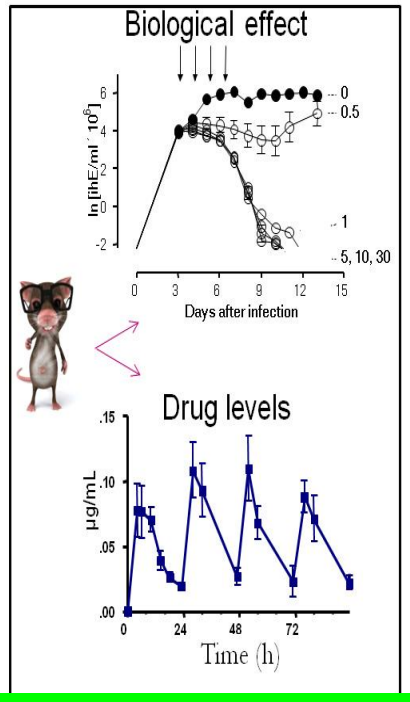
- Targets that are critical for both gametocyte and asexual forms are the most desirable
- Multiple assays available to assay gametocyte stages
  - mature gametocytes are a main target for transmission blocking
- Standard Membrane Feeding Assay (SMFA) providing the highest biological content

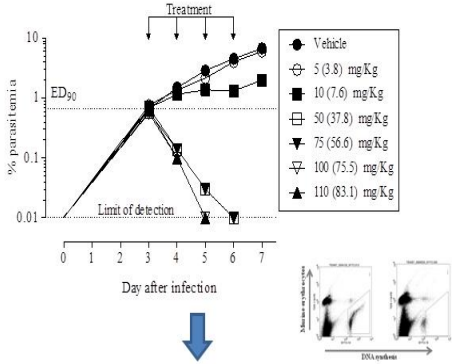
Translational Animal Models

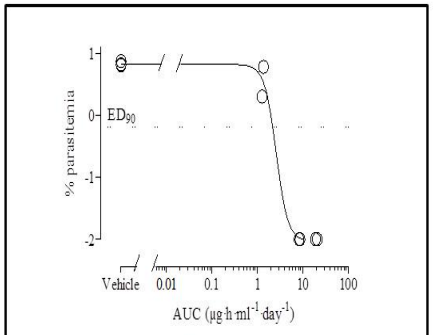
P.falciparum murine model enables rapid in vivo validation of antimalarial targets







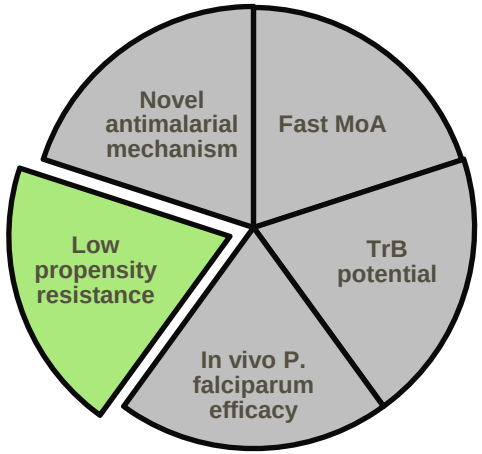




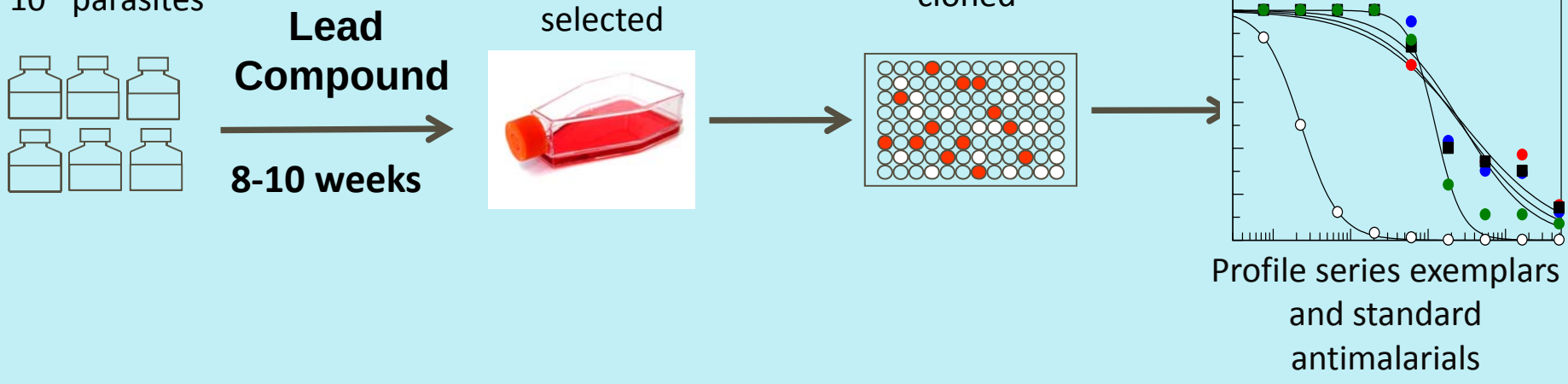
Essential in vitro targets not always required for in vivo growth

Understanding the Propensity for Resistance

Building confidence in the target

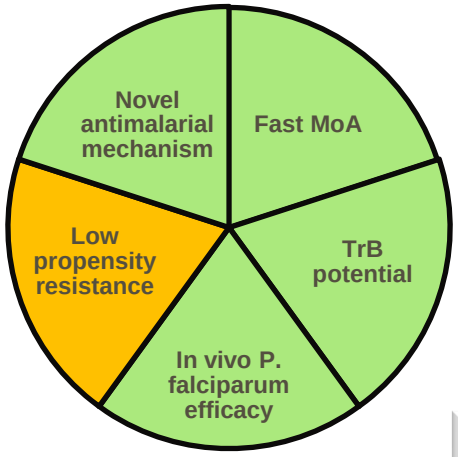


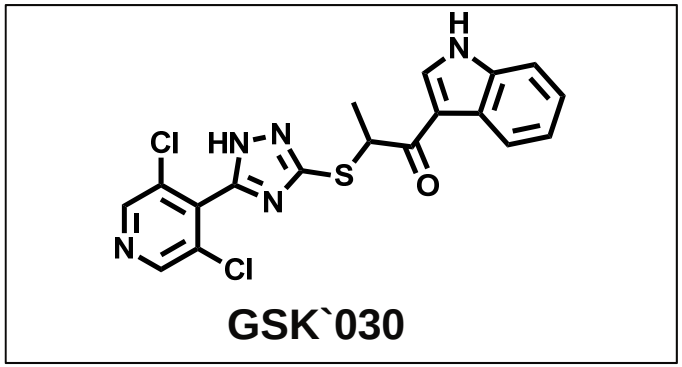
- Early resistance assessment for go/no go decisions
  - Resistance is the main antimalarial killer
- Preliminary genetic results can provide decisive tools
  - Facilitates target identification



Exemplars of GSK strategy on phenotypic screen

Thiotriazoles are novel PfATP4 inhibitors





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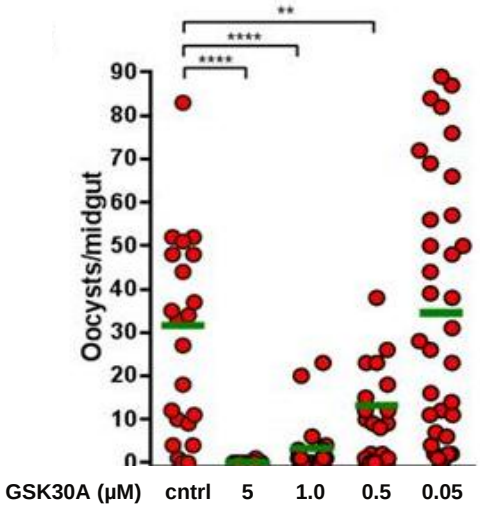
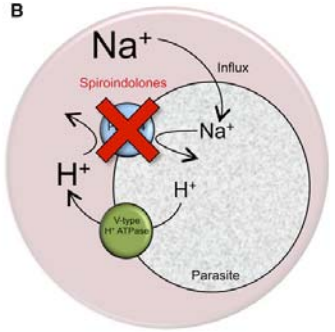


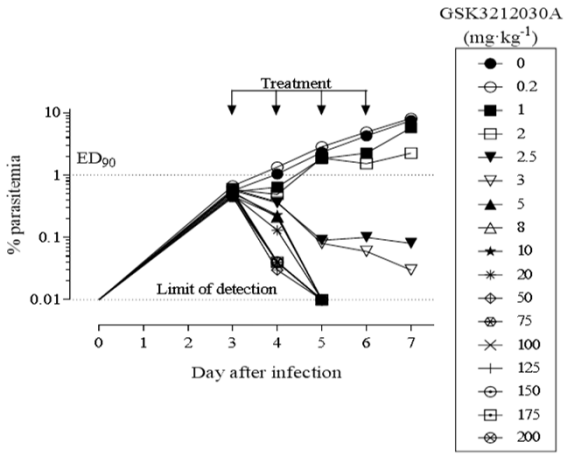
No X-resistance MDR

Active against clinical isolates
P.falciparum & P.vivax

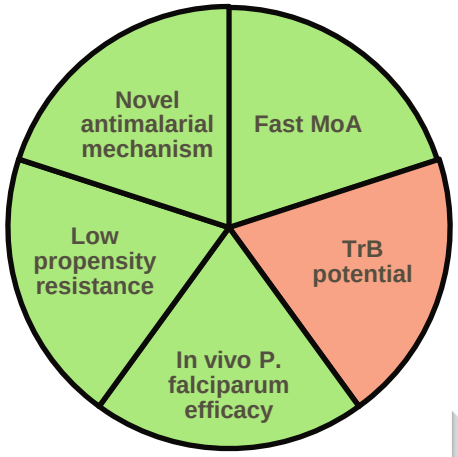
TrB potential validates in SMFA
- Reduce intensity &
prevalence of infection

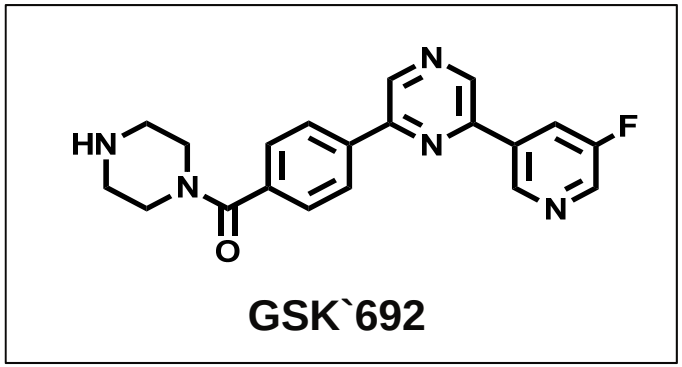
Resistant mutants map at *PfATP4*





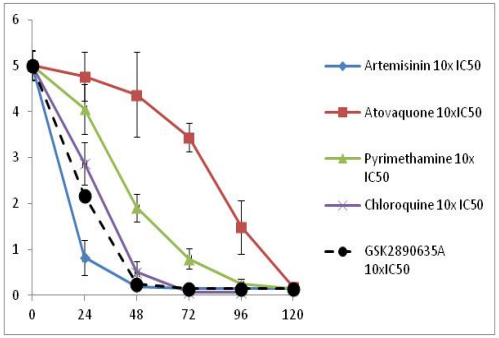
Pyrazines are “irresistible“ antimalarials





GSK`692

In vitro killing profile



No X-resistance MDR

Active against clinical isolates

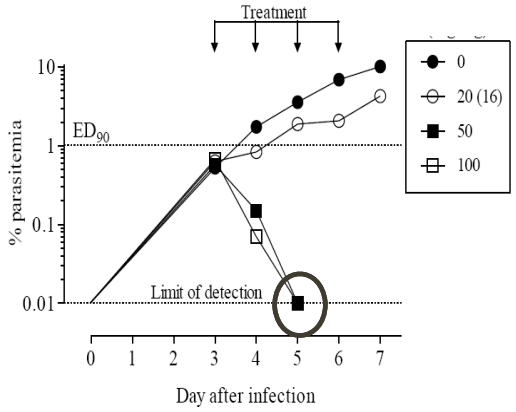
P.falciparum & P.vivax

Fast killing profile

No resistant mutants

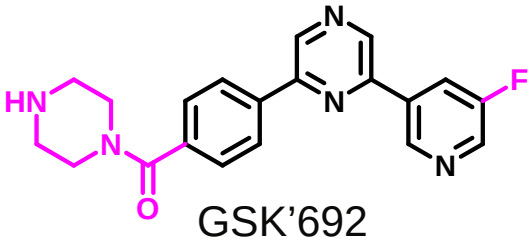
- ***Multiple conditions***
- ***Multiple strains***
- ***Multiple cmpds***

In vivo profile



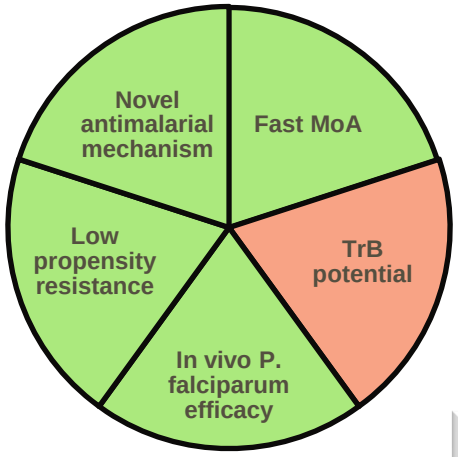
GSK'692 (Pyrazine): MoA is differentiated from known antimalarial mechanisms

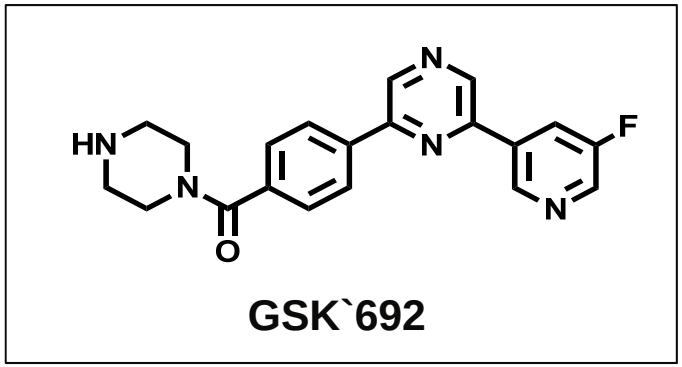
- Negative functional and cross-resistance studies with known antimalarial targets and pathways
  - Not linked to mitochondrial ETC, *Pf* DHODH, folate pathway inhibition, *Pf* ATP4 pathway, *Pf* PI4K
  - GSK692 does not inhibit hematin formation
- *P. falciparum* kinobead affinity assay (67 Pf kinases) didn't show any positives
- Standard approaches for target identification are not working with pyrazine
- **Proteomics (Cellzome)**:
  - Variety of linkable molecules prepared but not candidate target has been identified
- **Genomics**:
  - Pyrazine cannot select resistance *in vitro*
  - Multiple strains and genetic backgrounds used
  - Constant drug pressure *vs* ramping approaches
  - Multiple pyrazine derivatives
  - Selection periods up to 9 months
    - Different starting *inocula*



GSK'692

Pyrazines are “irresistible“ antimalarials





GSK`692

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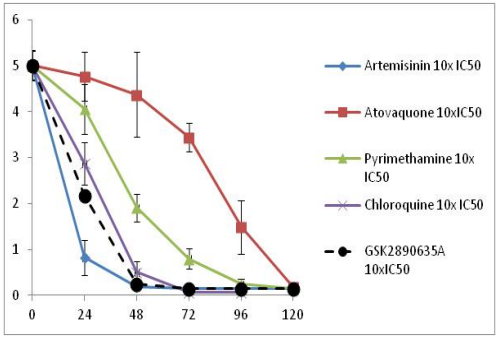
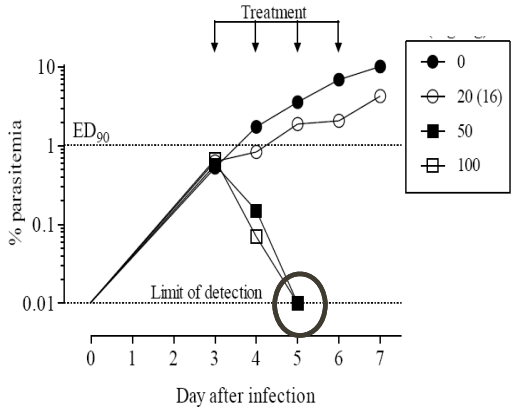
TARGET?

In vitro killing profile



In vivo profile



Summary

- Whole cell screening **is** delivering new antimalarial candidates
  - …but target based programs emerging
- Well populated pipeline but attrition high at this stage
- Phenotypic hits can be filtered using biological assays
  - …to select those affecting the most critical targets at different stages
  - ....molecules with low propensity to select for resistance
- It is possible to develop assets against tractable targets that simultaneously hit a number of parasite stages
  - *e.g. Pf*ATP4 molecules inhibit blood asexual and mature gametocyte stages *via* the same MoA
- "Irresistible" compounds possible but difficult to identify mechanism of action

Acknowledgements

Thank you to all our partners and those at GSK

If we are going to need combination therapies, we are all going to need to work together!