QIMR Berghofer
Medical Research Institute

Induced Blood Stage Malaria: a tool to facilitate development of antimalarials

Dr James McCarthy
Senior Scientist, QIMR Berghofer Medical Research Institute
Infectious Diseases Physician, Royal Brisbane and Womens Hospital

Disclosures

- Funding from Novartis and Sanofi to support clinical trials

Outline

The method

Study endpoints

Generalisability?

Safety issues

Future options

Clinical trial design

Parasite Inoculation

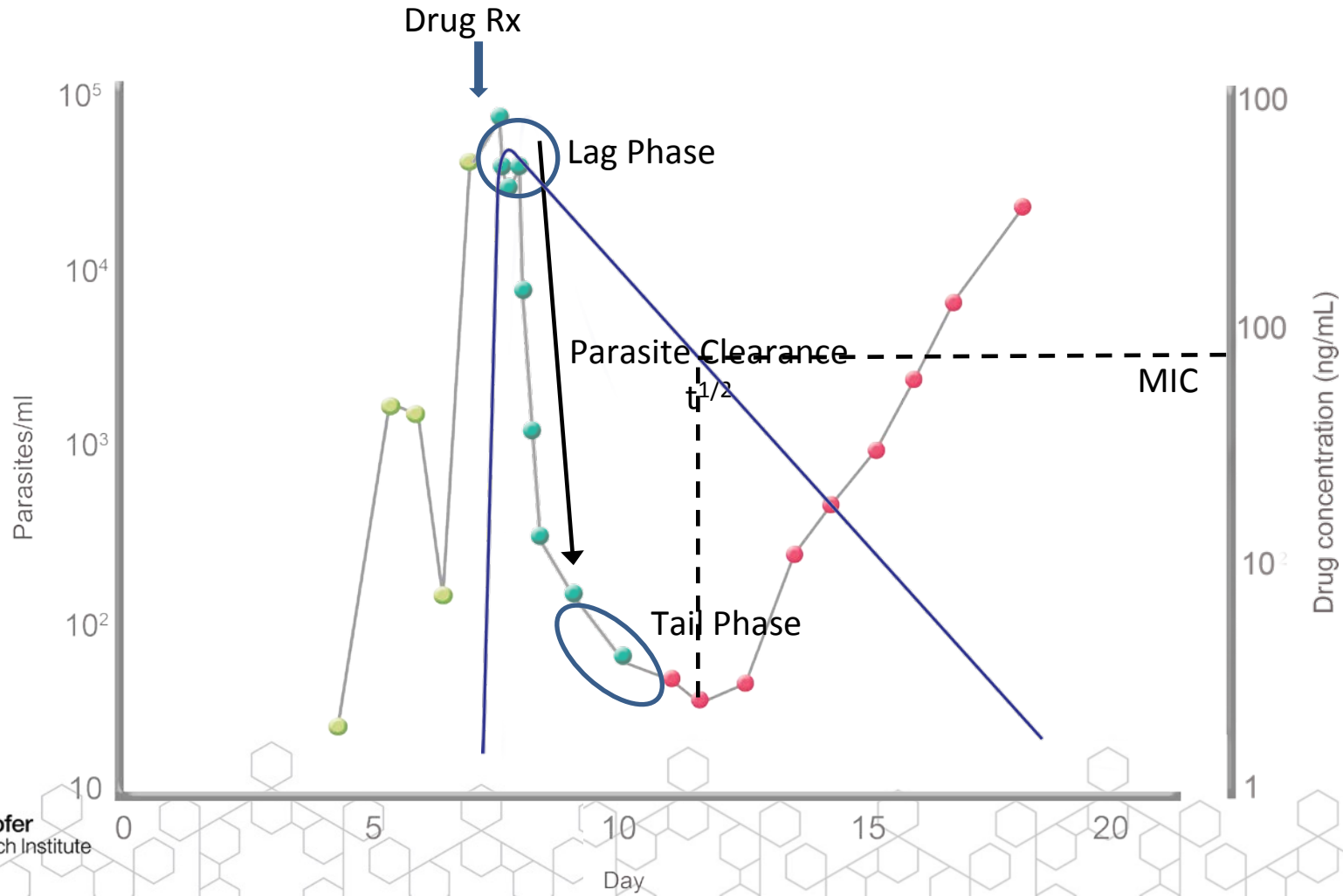
Test drug

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	28
Outpatient		x	x	x	x	x	x	x			+	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Confinement									Q-Pharm																			
Drug Rx																Rescue Drug Treatment as needed												
PCR (parasites)					x	x	x	x	xxxxxxxxxxxxxxxxx				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PCR (gametocytes)														x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mosquito transmission															x		x		x	x		x	x		x		x	x

Clearance of parasitemia over 48-96 hrs

n=178 subjects

QIMR Berghofer Medical Research Institute



QIMR Berghofer
Medical Research Institute

Defining the PRR and Parasite clearance $t^{1/2}$

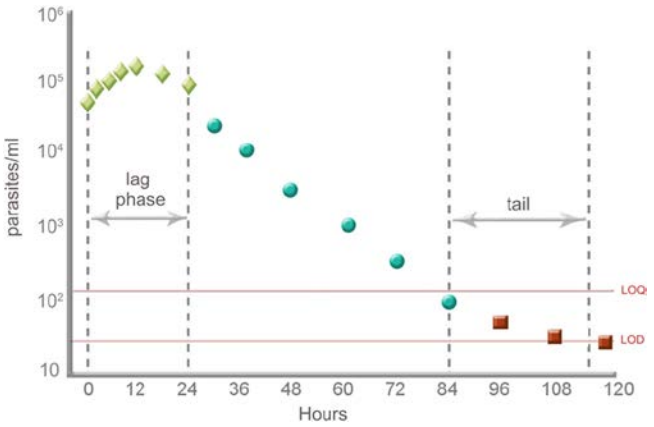
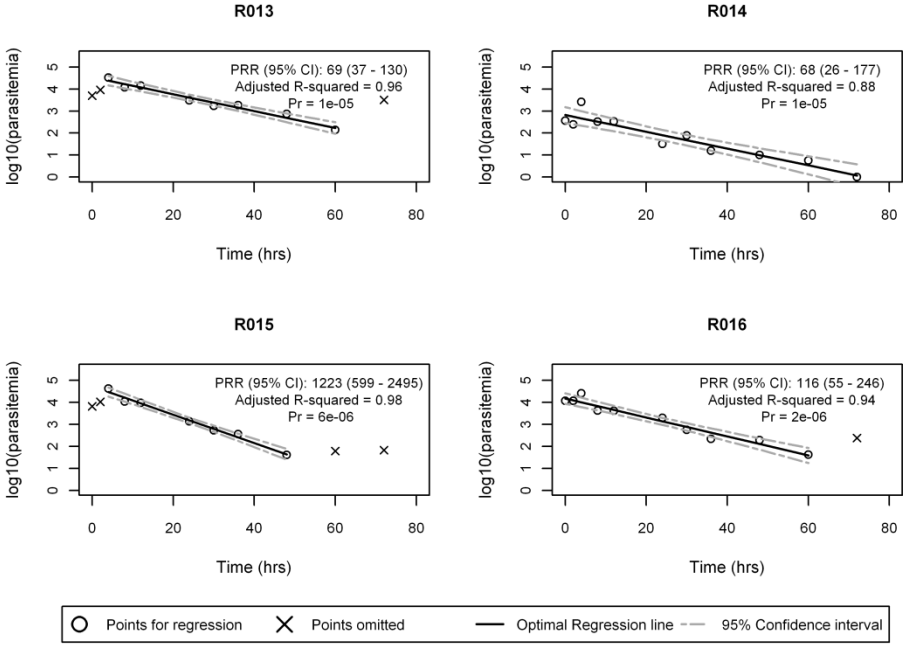


FIG 1 Effect of lag phase and tail exclusion on the calculation of the clearance rate constant. (Modified from Flegg et al. with permission of the author.)



QIMR Berghofer Medical Research Institute

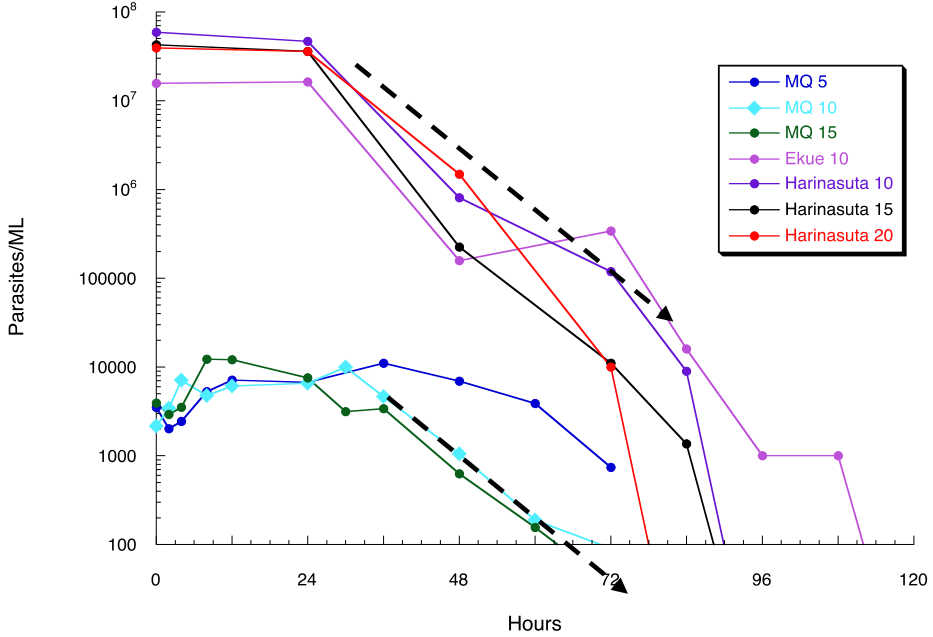
Marquartet al. Evaluating the pharmacodynamic effect of antimalarial drugs in clinical trials by quantitative PCR. AAC. 2015;59:4249-59

PK/PD modelling

$$\frac{dP}{dt} = P\left(G - D\frac{c^{\gamma}}{c^{\gamma} + {IC_{50}}^{\gamma}}\right)$$

P: parasite concentration in count/ml; t: time in hr; G: the first order parasite growth rate in absence of drug; D: the maximum drug-specific parasite reduction rate; c: the drug concentration in µg/L; IC_{50}: the drug concentration required to achieve half the maximum parasite reduction rate. γ: an optional nonlinearity parameter defining the steepness of the concentration-effect curve.

How do clearance kinetics in challenge model compare to field studies?



McCarthy et al. Linking Murine and Human *P. falciparum* Challenge Models in a Translational Path for Antimalarial Drug Development. AAC 2016
Kofi Ekue et al. A double-blind comparative clinical trial of mefloquine and chloroquine in symptomatic falciparum malaria. Bull WHO. 1983
Harinasuta et al. A phase II clinical trial of mefloquine in patients with chloroquine-resistant falciparum malaria in Thailand. Bull WHO. 1983

Safety issues

- Inoculum
  - Adventitious contaminants
    - Bacteria, viruses, prions
  - Red cell alloimmunization

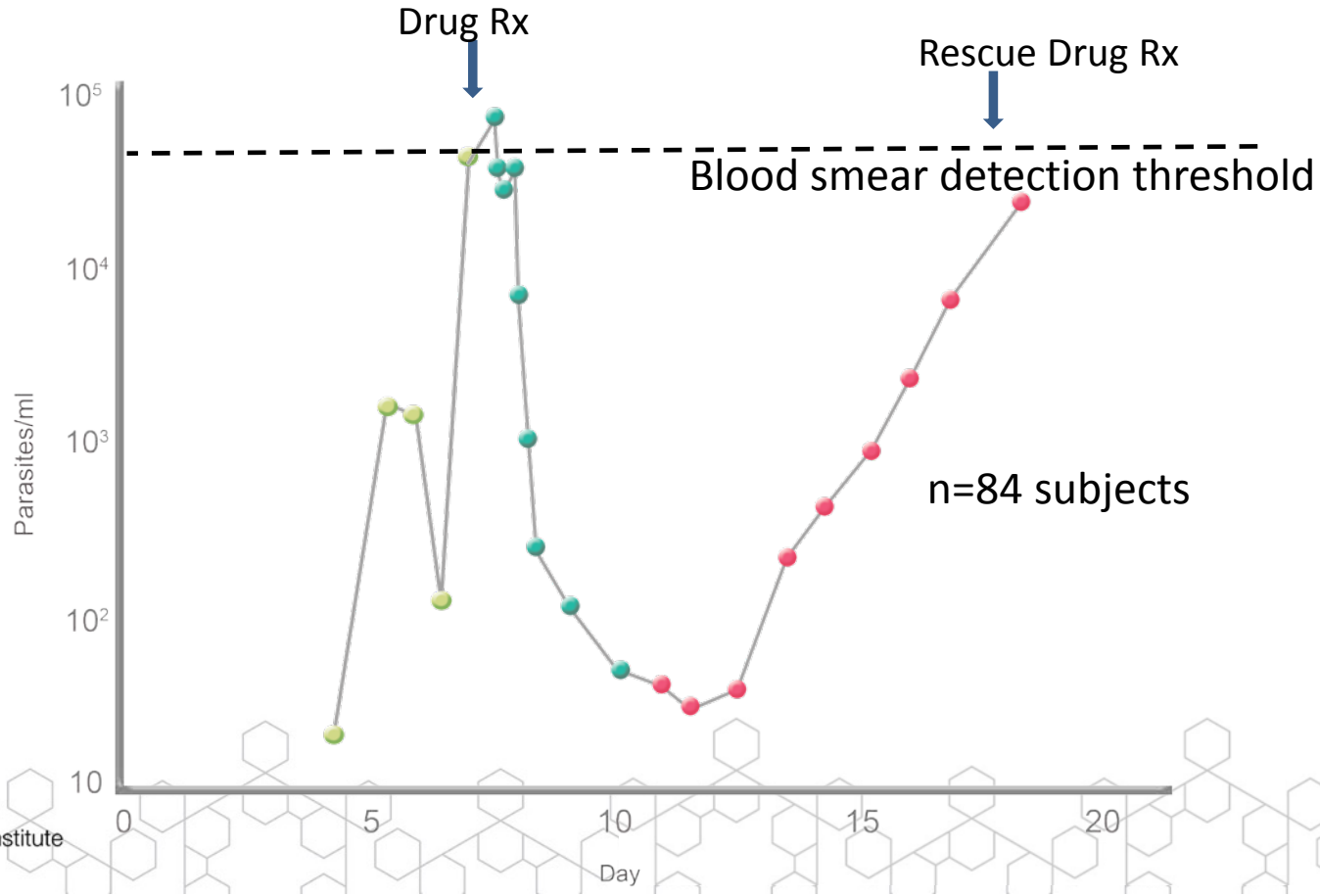
- Malaria
  - Malaria-induced AEs and SAEs
  - Onward Transmission
    - Gametocytemia

Safety of Inoculum

- This 3D7 blood stage *P. falciparum* line has been given to 260 human volunteers
  - 205 subjects at QIMR (27: <2009; 178: 2009-16 [30 cohorts, 15 studies])
  - 55 subjects elsewhere (Nijmegen, Oxford)
- Other blood stage *P. falciparum* strains used in IBSM
  - "Wild type" *P. falciparum* (n=2)
  - Remanufactured under GMP blood stage *P. falciparum bank*
    - 3D7 (n=2)†; NF54 (n=4)††; 7G8 (n=2)†
- "Wild type" *P. vivax* (n=26)†††

† Unpublished
†† Stanasic I&I (In Press 2016)
††† McCarthy JID 2016, and Unpublished

Can we identify recrudescence and safely rescue?



QIMR Berghofer
Medical Research Institute

What is a safe treatment threshold?

- Drug potency
- Relationship between parasitemia and risk of clinical harm unknown

APPENDIX 2: CLINICAL SCORE FOR MALARIA[35]

Grading of the signs and symptoms specified in the table beneath will be performed at all relevant protocol-specified time points in accordance with the following:

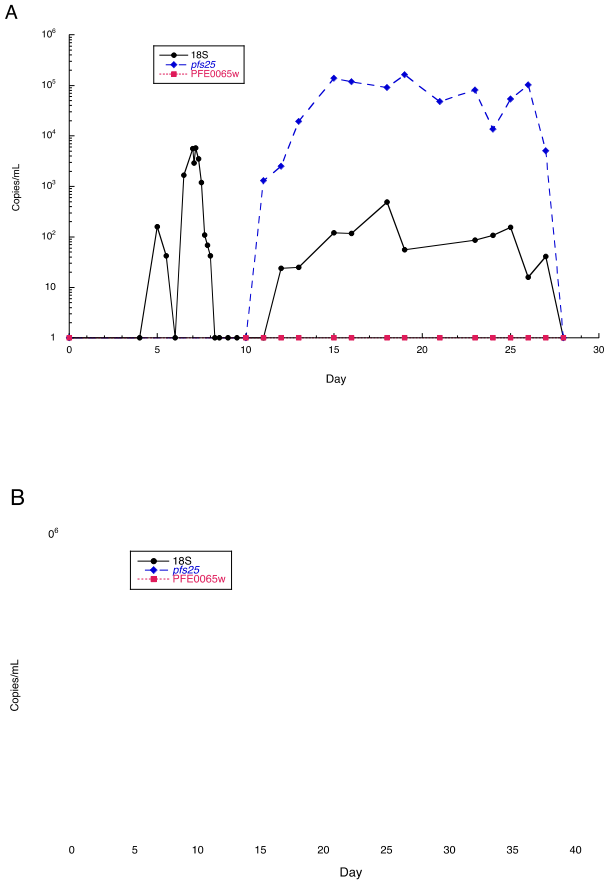
- Absent = 0
- Mild = 1
- Moderate = 2
- Severe = 3

Symptom / Sign	Score (0 to 3)
Headache	
Myalgia (muscle ache) Arthralgia (joint ache)	
Fatigue/lethargy	
Malaise (general discomfort/uneasiness)	
Chilles/Shivering/Rigors Sweating/hot spells	
Anorexia	
Nausea	
Vomiting Abdominal discomfort	
Fever	
Tachycardia Hypotension	
TOTAL SCORE	/ 42

The total score will serve as a clinical indication of the severity of the induced malaria infection. The clinical threshold for the commencement of treatment with the IMP (interpreted in conjunction with the parasite load as determined by qPCR) is >6.

QIMR Berghofer
Medical Research Institute

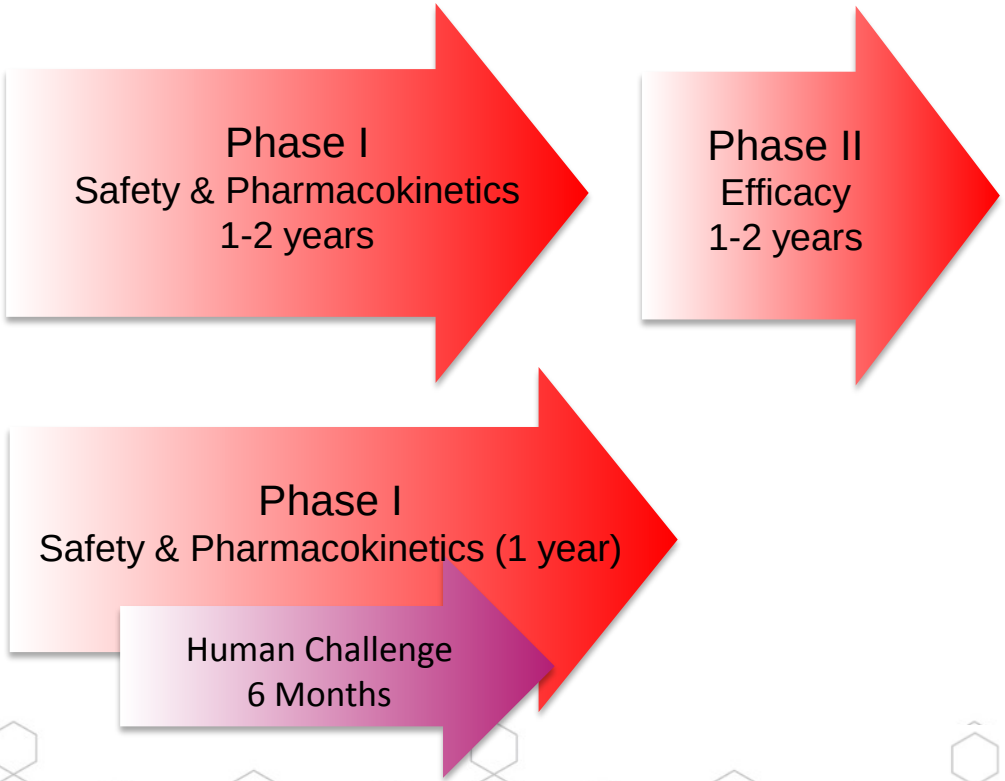
Can we distinguish gametocytemia from recrudescence?



QIMR Berghofer Medical Research Institute

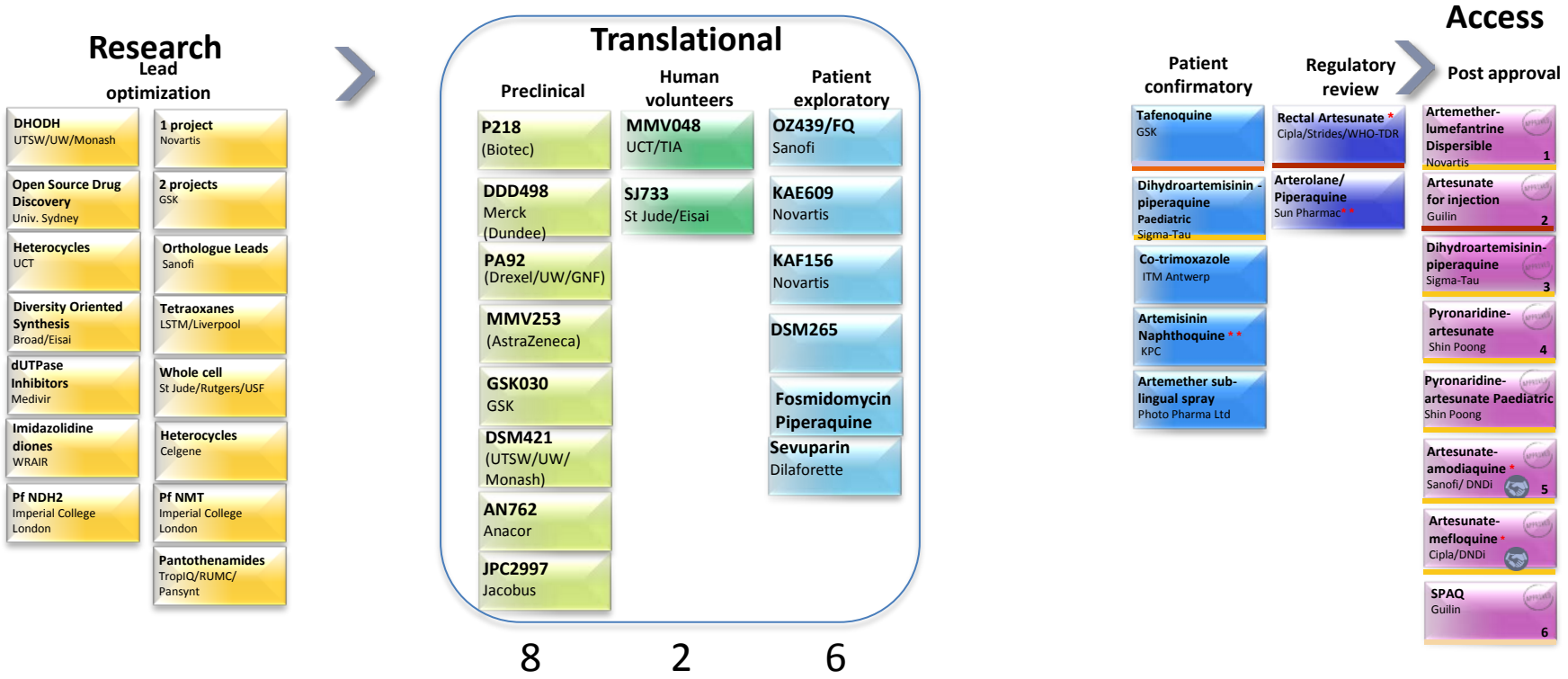
Pasay et al JID 2016

Integrated Phase I and Human Challenge



- Early Safety and PK Data
- Selection of dose for early look at efficacy in human challenge
- Adaptive design
  - Kill early
  - Reformulate

Global Portfolio of Antimalarials



16 Phase I studies (Safety & PK)
16 POC (Antimalarial activity)
120 possible combinations to be evaluated

MMV
Medicines for Malaria Venture

Conclusions

- Induced blood stage malaria
  - Provides a rapid, safe and efficient means of gaining pivotal early efficacy data
  - Can be integrated into a combined Phase I PK and Safety study design
  - Provides actionable data for modelling to predict clinical dose for later stage studies

QIMR Berghofer Medical Research Institute

Acknowledgments

QIMR Berghofer:

Silvana Sekuloski, Katharine Trenholme

Helen Jennings, Caroline Dobbin, Louise Marquet, Kere Klein, Peter O'Rourke, Steve Turner, Darron Laing, Rebecca Watts

Alan Saul

Greg Lawrence

Griffith University

Michael Good

Q-Pharm:

Suzanne Elliott, Nanette Douglas, Gem Mackenroth, Paul Griffin, Alice Lau

Medicines for Malaria

Jörg Möhrle, Tim Wells, Mark Baker, Andrew Humberstone, Stephan Chalon

QPID:

Rebecca Rockett

Jane Gaydon, Claire Wang

Theo Sloots

Australian Army Malaria Institute

Chris Peaty, Qin Cheng

Dennis Shanks

Volunteers

Funding: Wellcome Trust QLD Govt. Smart State, ACVD, PATH-MVI

Australian Government
National Health and Medical Research Council

Q-Pharm Pty Limited

Bill & Melinda Gates foundation

MMV Medicines for Malaria Venture