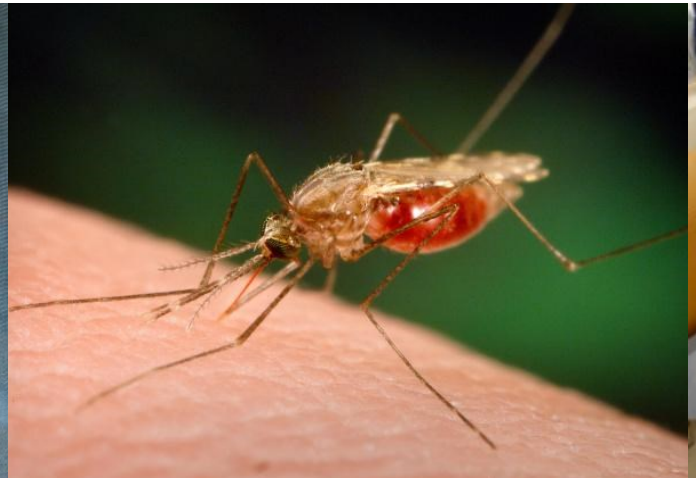
THE JENNER INSTITUTE
DEVELOPING INNOVATIVE VACCINES

UNIVERSITY OF OXFORD

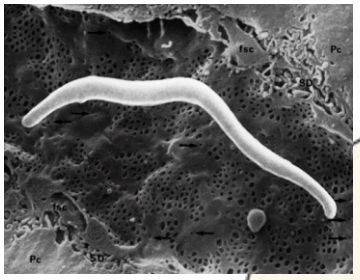

Development of Broadly Neutralising Vaccines against Blood-Stage Malaria

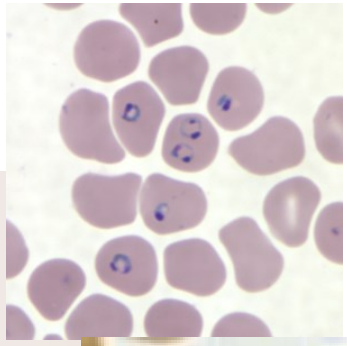
Simon Draper

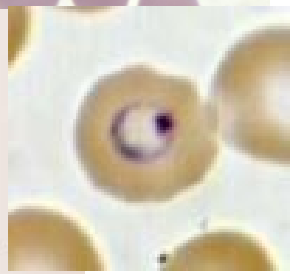
Vaccinology 2017 – Hanoi, Vietnam

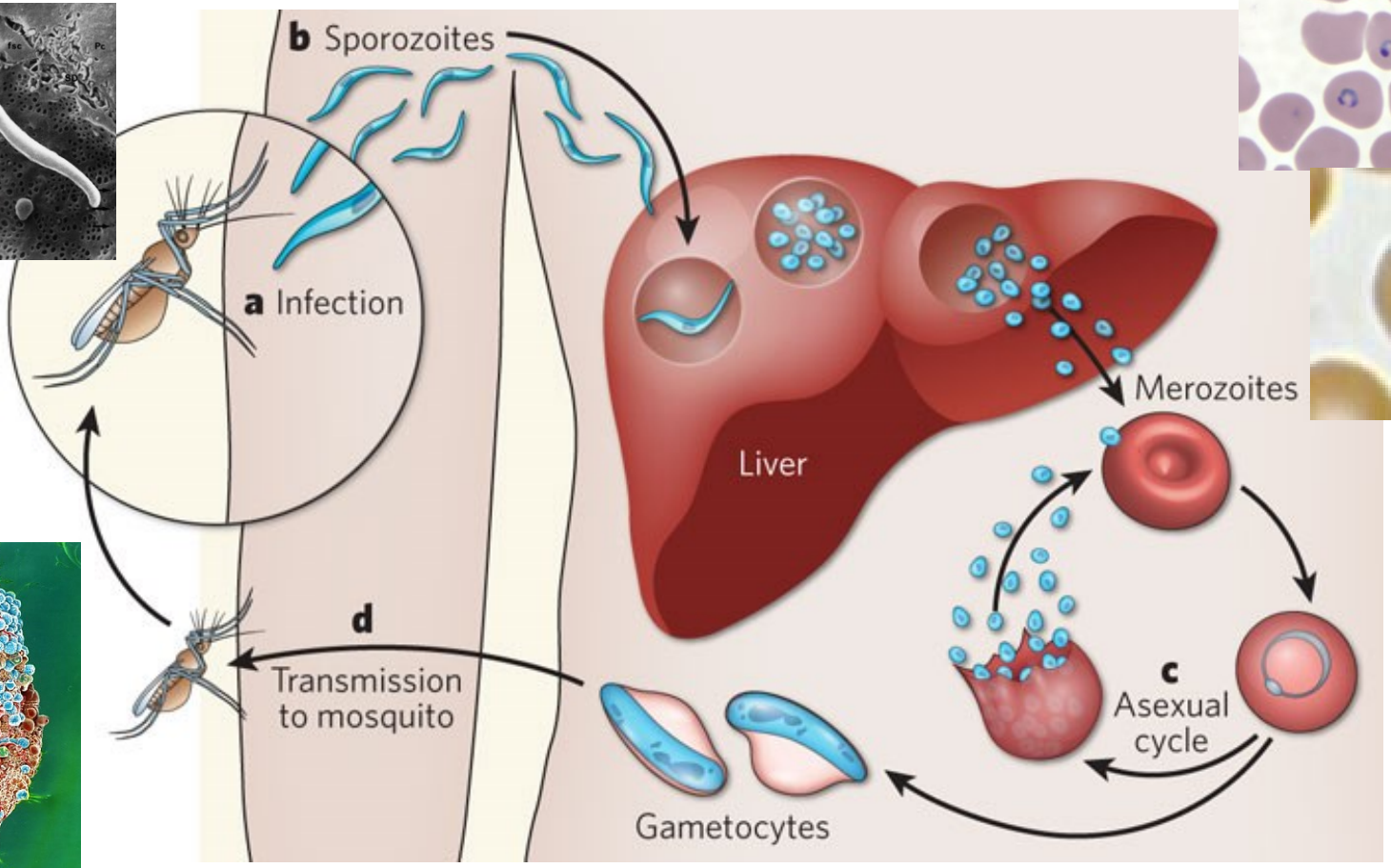
17th October 2017

Plasmodium falciparum Malaria Life-Cycle



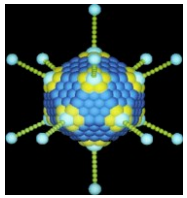


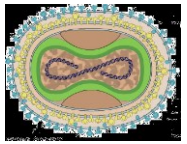




SANARIA

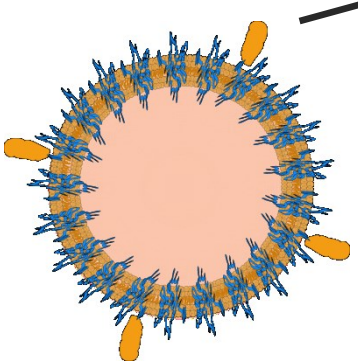
MALARIA ERADICATION THROUGH VACCINATION



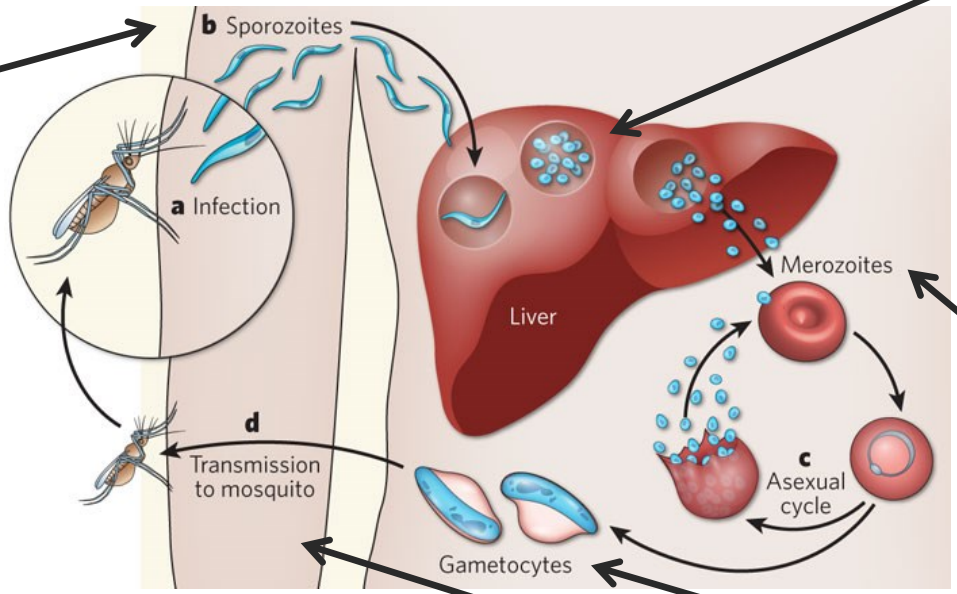


Adenovirus

MVA Poxvirus



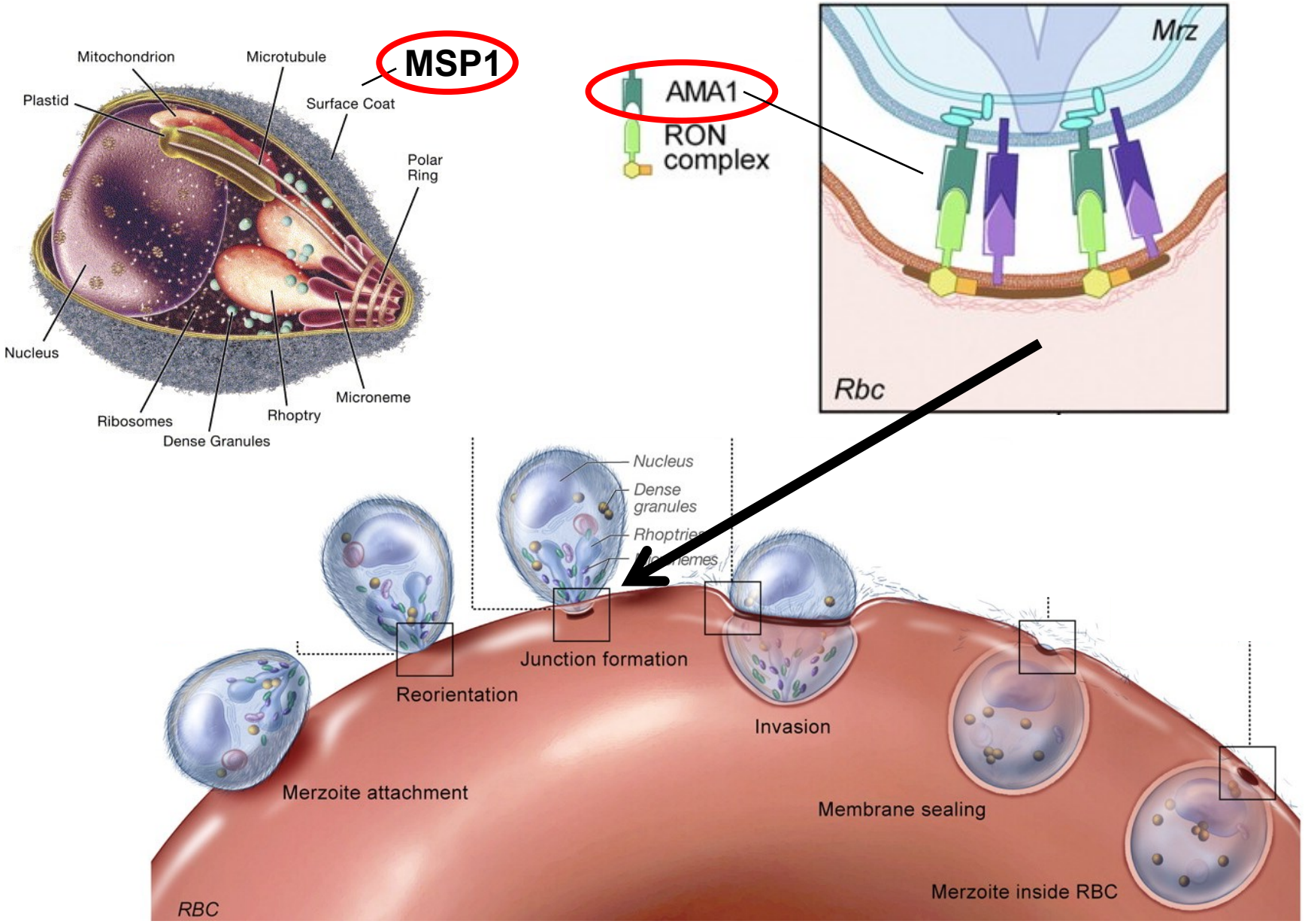
RTS,S / AS01



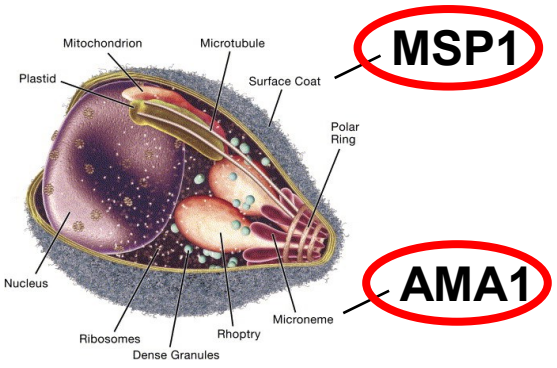
Protein-in-Adjuvant

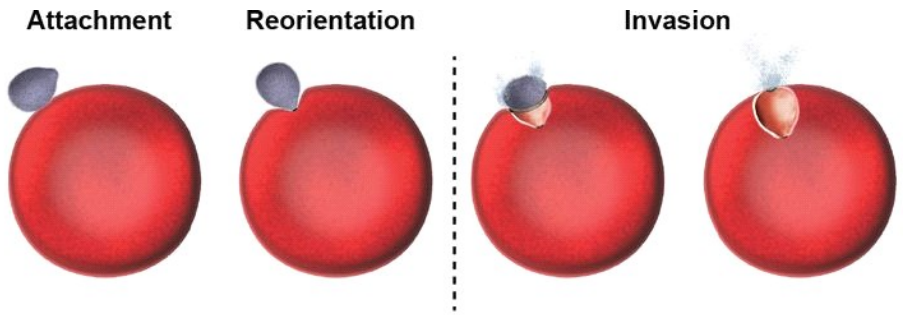
gsk

Red Blood Cell Invasion



Blood-Stage Merozoite Vaccine Difficulties





- Antigenic polymorphism
- Redundant invasion pathways

'RH5 complex' conserved and essential

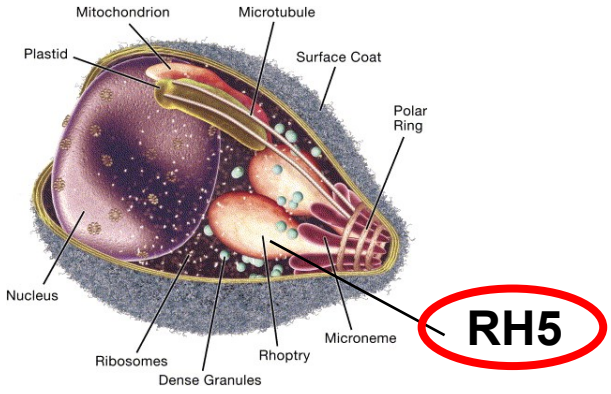
- Lack of *in vitro* assays that associate with *in vivo* protection in humans

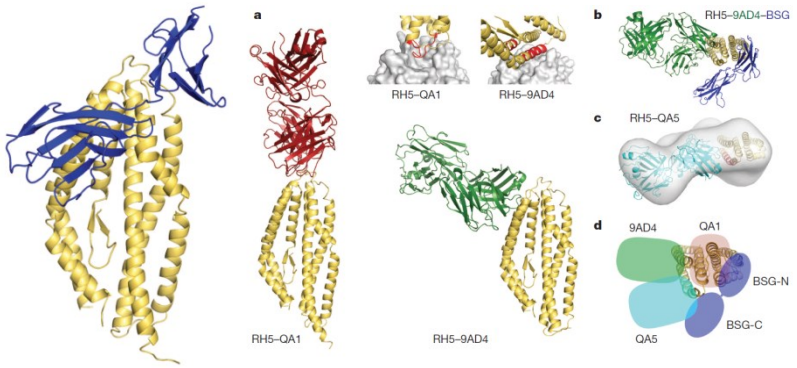
Functional assay correlates with protection in NHP

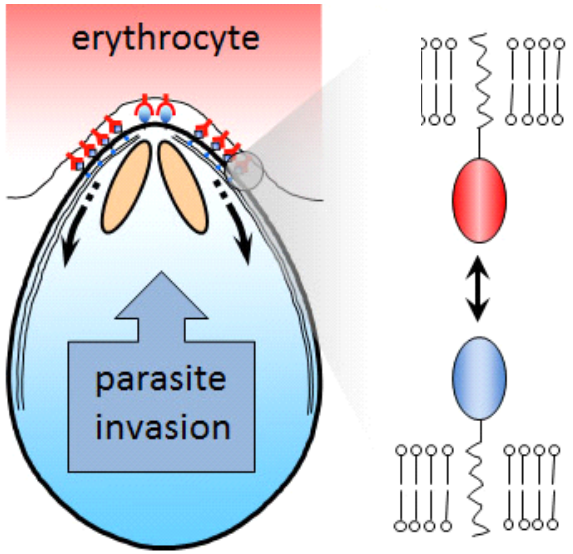
- Need for very high antibody concentration

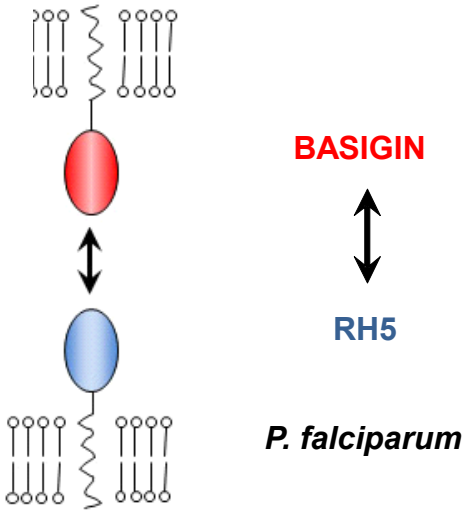
Quantitative assessment of Ab responses

Introducing *P. falciparum* RH5



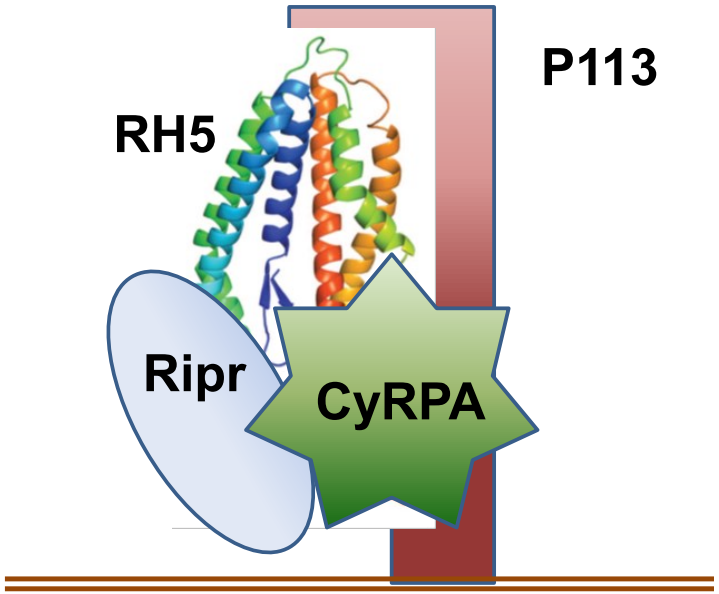


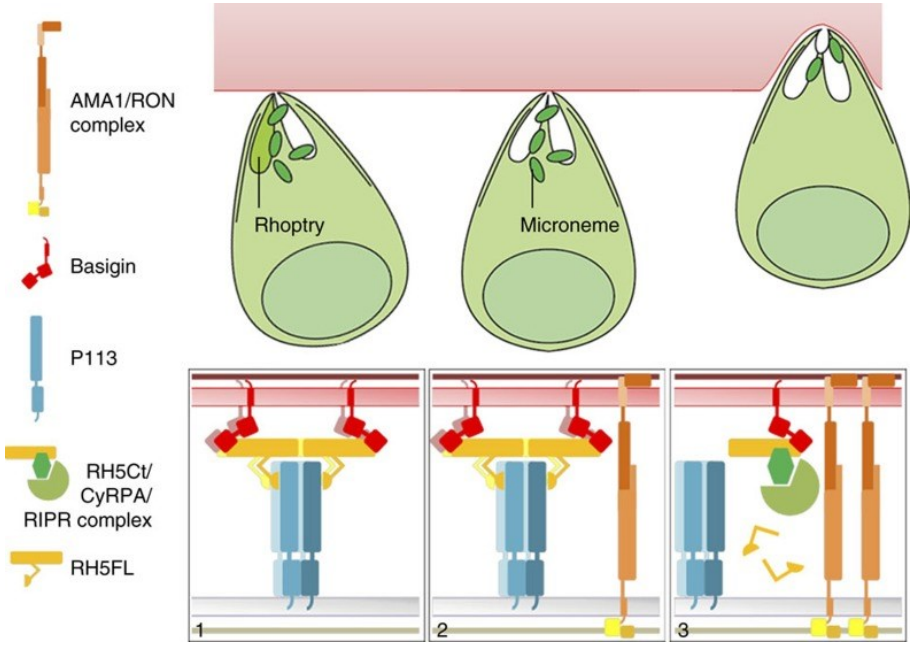


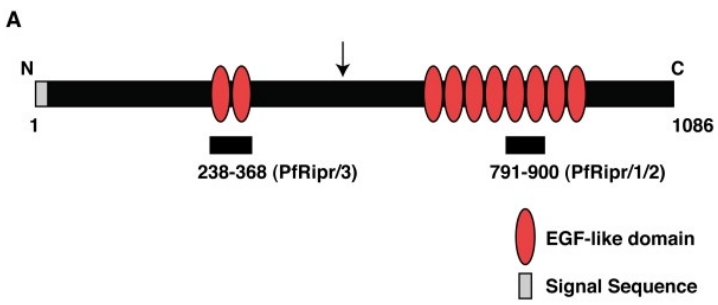


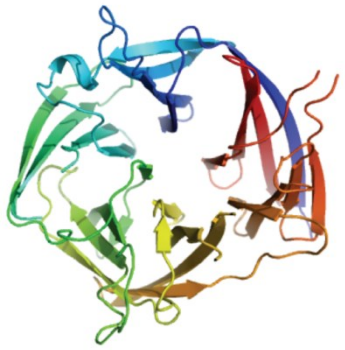
- **The first <u>highly conserved</u> target within the *P. falciparum* blood-stage merozoite to be susceptible to vaccine-induced broadly neutralising polyclonal antibody (Douglas *et al.* 2011, Nat Commun)**
- **Forms an <u>essential</u> interaction with basigin (CD147) on the erythrocyte surface (Crosnier *et al.* 2011, Nature)**
- **<u>Structure</u> reported of RH5 bound to basigin and neutralising mAbs (Wright *et al.* 2014, Nature)**

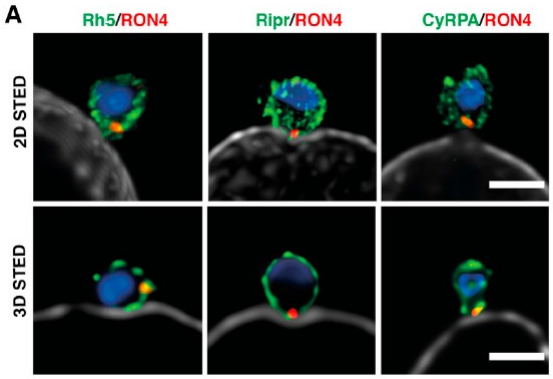
RH5 Invasion Complex





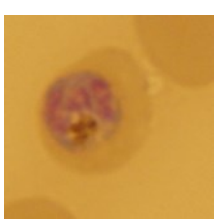






Chen 2011 PLoS Pathog ; Dreyer 2012 J Immunol ; Reddy 2015 PNAS ; Volz 2016 Cell Host Microbe ; Favuzza 2016 Malar J ; Galaway 2017 Nat Commun ; Favuzza 2017 eLife ; Chen 2017 eLife

Does the assay of GIA associate with *in vivo* protection?



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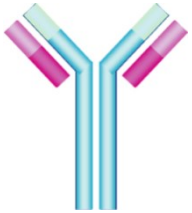
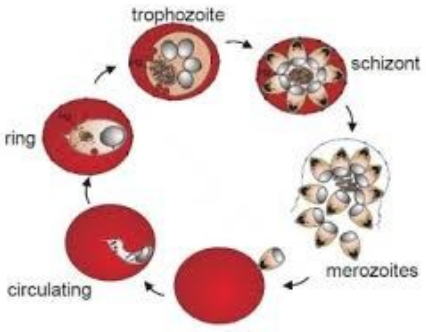
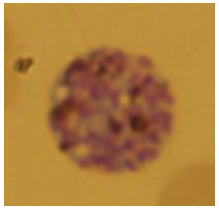


IgG from Serum
or mAb

Wait 48 hours





Growth Inhibition Activity (GIA)

1. Poor association with naturally-acquired malaria immunity

   Duncan *et al.* (2012) *Hum Vaccin Immunother* 8:706

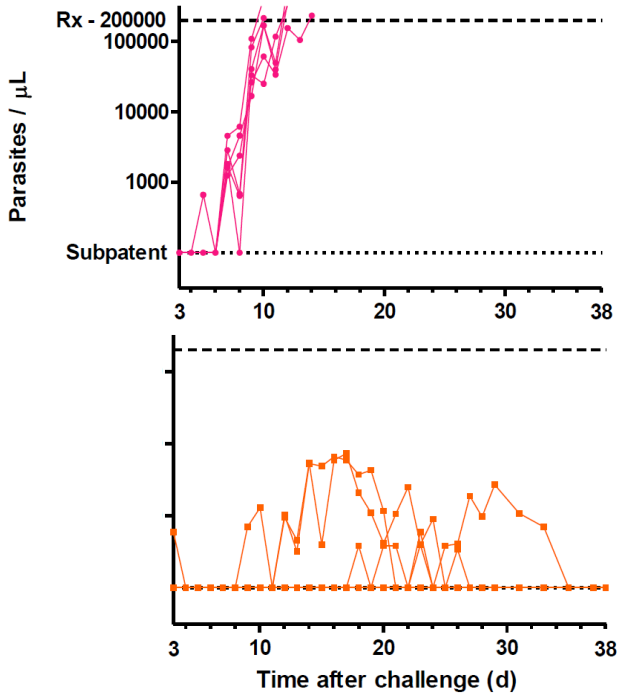
2. Three NHP studies associated *in vitro* GIA with *in vivo* protection:
   - Singh et al (2006) *Infect Immun* : MSP1 – *Aotus* – *falciparum*
   - Douglas et al (2015) *Cell Host Microbe* : RH5 – *Aotus* – *falciparum*
   - Hamid et al (2011) *PLoS One* : AMA1 – Rhesus – *knowlesi*

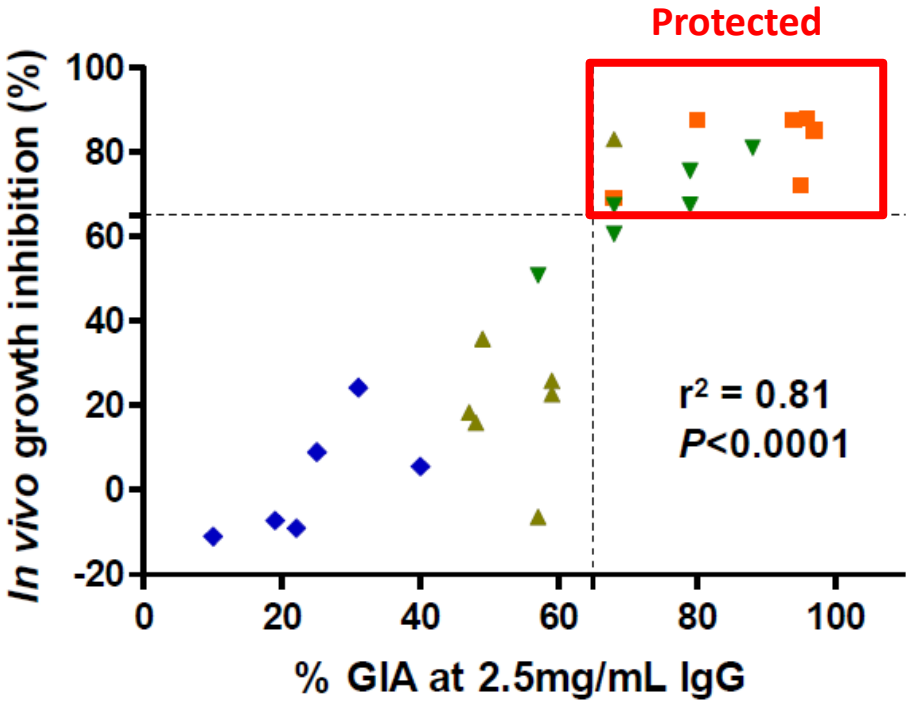
Vaccine-induced GIA reflects "non-natural" immunity

PfRH5 vaccine testing in *Aotus* monkeys

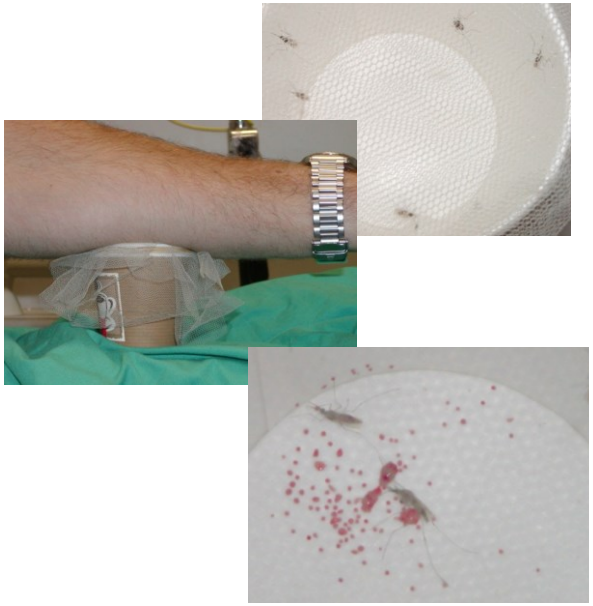
- Protected monkeys showed:
  - >60% reduction in growth rate (PMR) *in vivo*
  - >200 µg/mL anti-PfRH5 polyclonal IgG in serum
  - >60% *in vitro* GIA using purified total IgG at 2.5 mg/mL (=1:4 serum dilution)

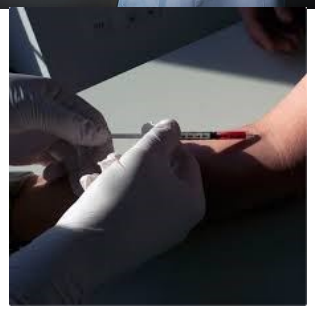
Douglas AD (2015) *Cell Host Microbe* 17:130-9

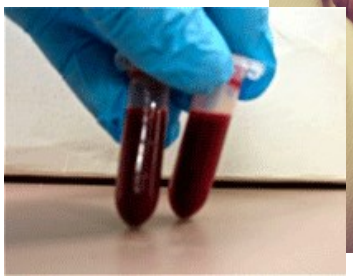


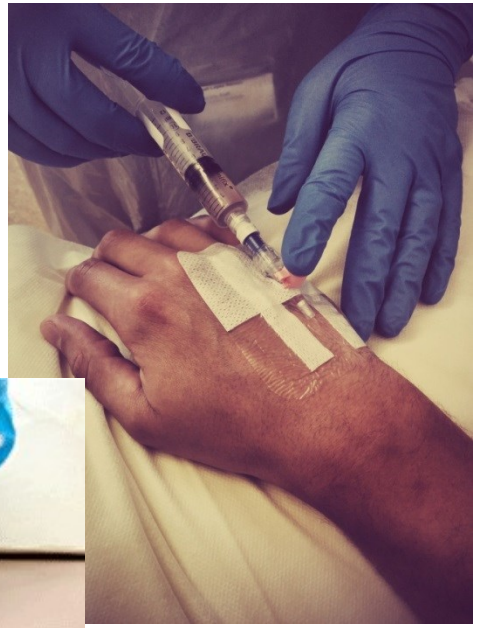


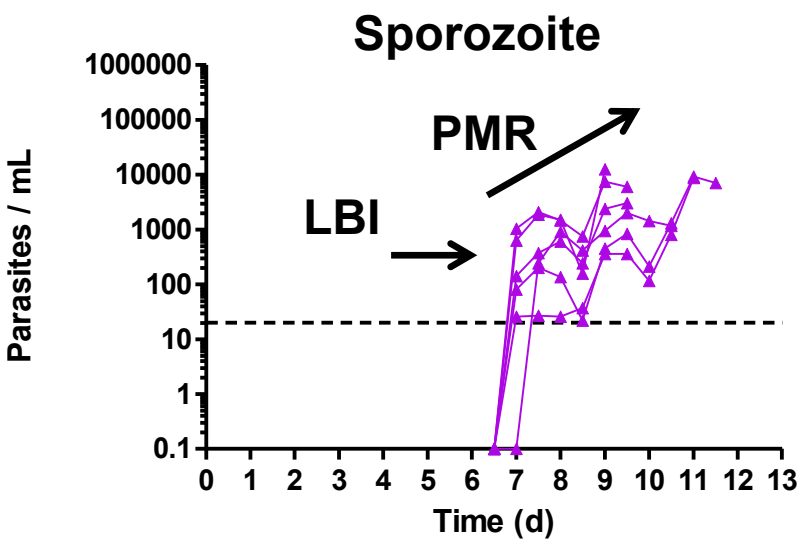
Assessing Immunity by Controlled Human Malaria Infection (CHMI)

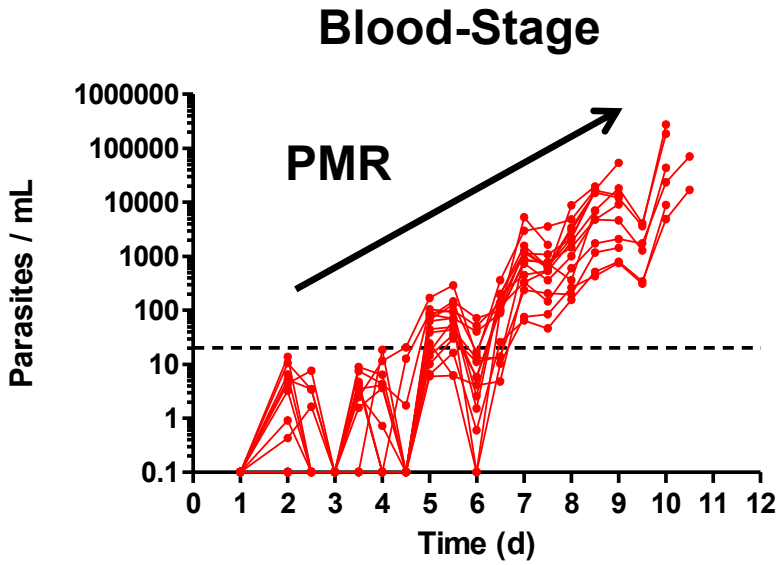




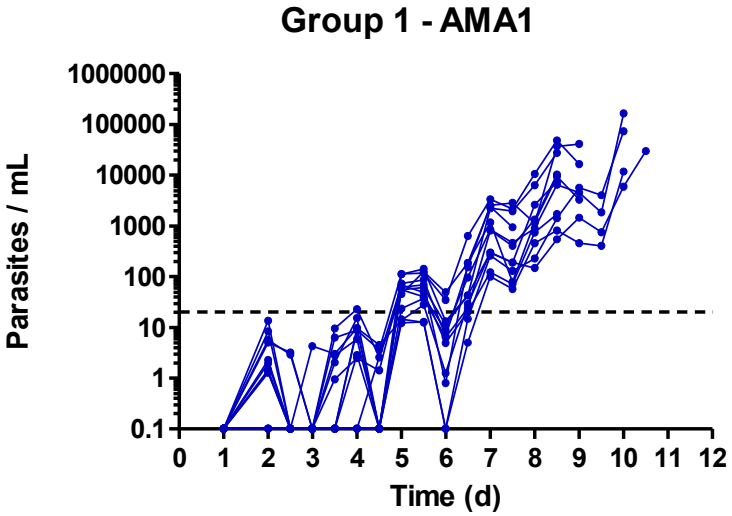


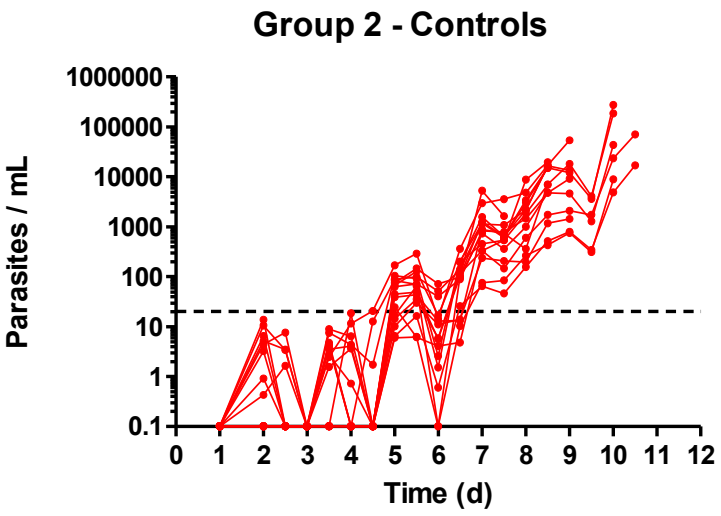


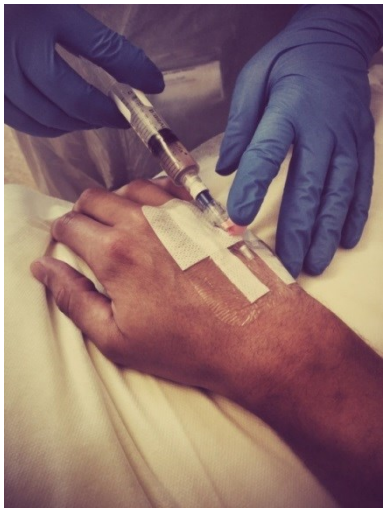




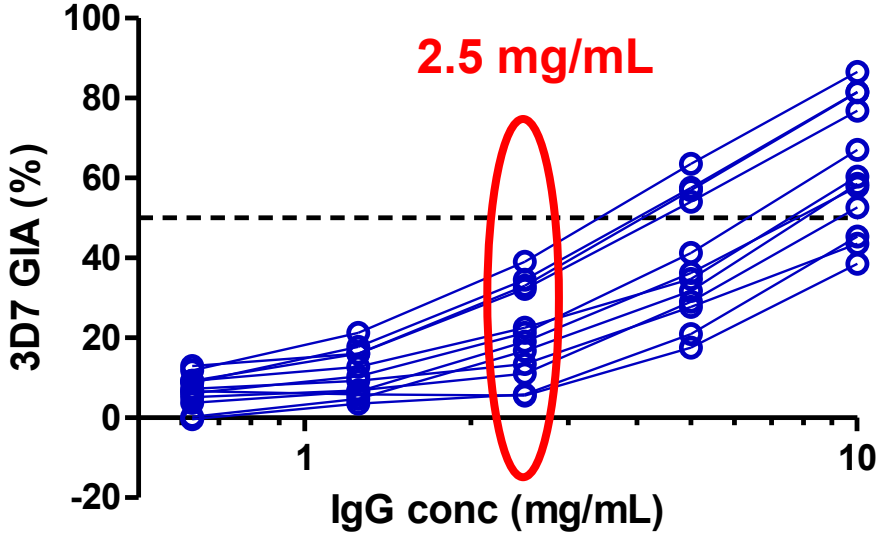
Assessment of GIA as a protective mechanism in humans







- AMA1 protein vaccine (from WRAIR)
- Formulated in AS01B adjuvant (GSK)
- 50µg dose given IM in a 0-28-56 day regimen; blood-stage CHMI on d70
- 100% homologous parasite challenge



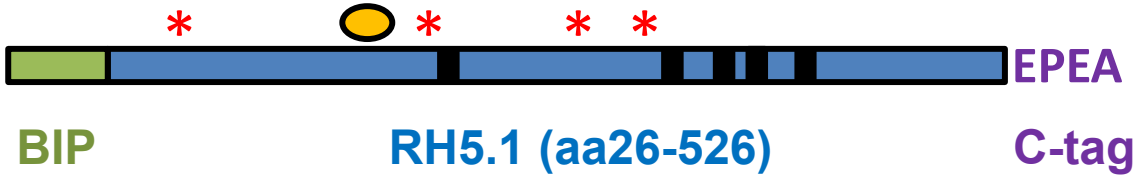
Payne RO *et al. J Infect Dis* (2016) 213:1743-51

1. **Can RH5-based vaccines really improve on historical candidates (AMA1 / MSP1)?**

2. **How to maximise antibody potency and durability against the blood-stage merozoite?**

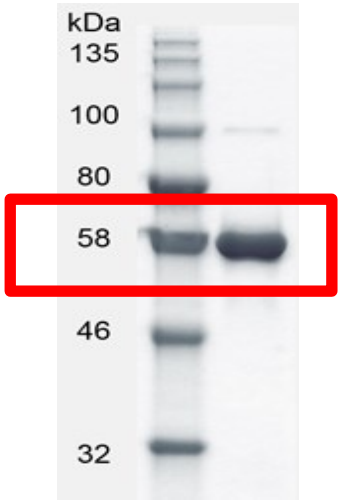
3. **Mechanism and potency of vaccines targeting other antigens within RH5 complex?**

Clinical Production of RH5.1 Protein Vaccine in a *Drosophila* S2 Stable Cell Line

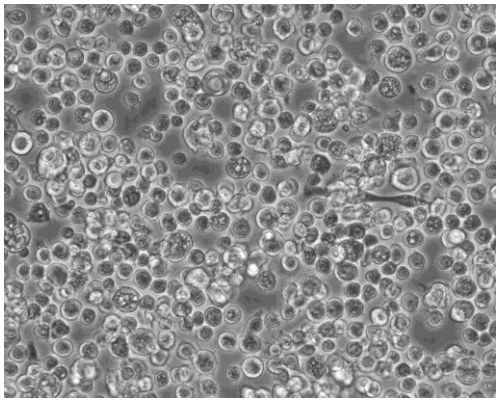


RH5.1 , 4 x T-A glycan subst

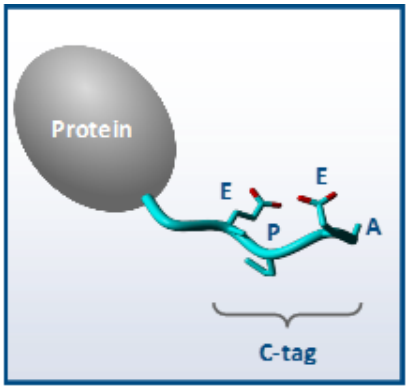
T40A C203 T216A T286A T299A



EXPRES^{2}ION BIOTECHNOLOGIES



BAY part of life technologies



Hjerrild KA *et al.* 2016 Sci Rep Jin J *et al.* 2017 Int J Parasitol

Phase I/IIa trial of RH5.1/AS01B

	Group	N =	Day 0	Day 28	Day 56	Day 70	Day 182
Phase Ia	1	12	2 µg	2 µg	2 µg		
	2	12	10 µg	10 µg	10 µg		
	3	12	50 µg	50 µg			10 µg
	4	12	50 µg	50 µg	50 µg		

Clinicaltrials.gov NCT02927145

1. Can RH5-based vaccines really improve on historical candidates (AMA1 / MSP1)?

2. How to maximise antibody potency and durability against the blood-stage merozoite?

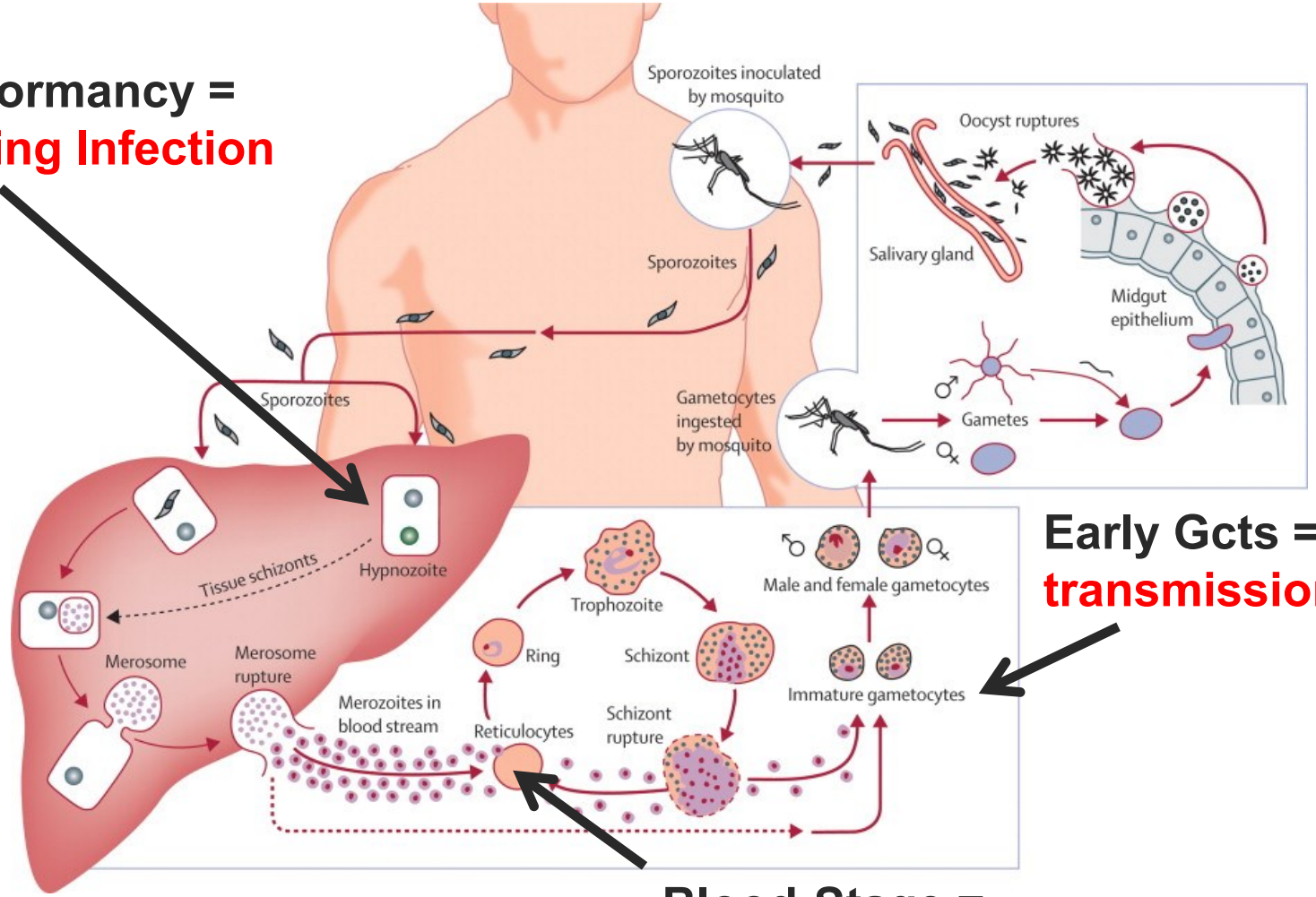
3. Mechanism and potency of vaccines targeting other antigens within RH5 complex?

The Enemy: Ab Concentration (and Durability)

- Antigen selection – careful quantification of Ag-specific polyclonal antibody concentrations to "rank" antigens
  - Assessing candidates from the RH5 invasion complex
  - Antigen combinations – synergistic Ab responses
- Vaccine platform – protein or VLP/adjuvant
- Immunogen optimisation
  - Functional analysis of human mAbs
  - Structure-based vaccine design
  - Immune-focussing on critical region(s) of RH5
  - Assess "quality" and "quantity" of vaccine-induced Abs

Plasmodium vivax : Unique Challenges

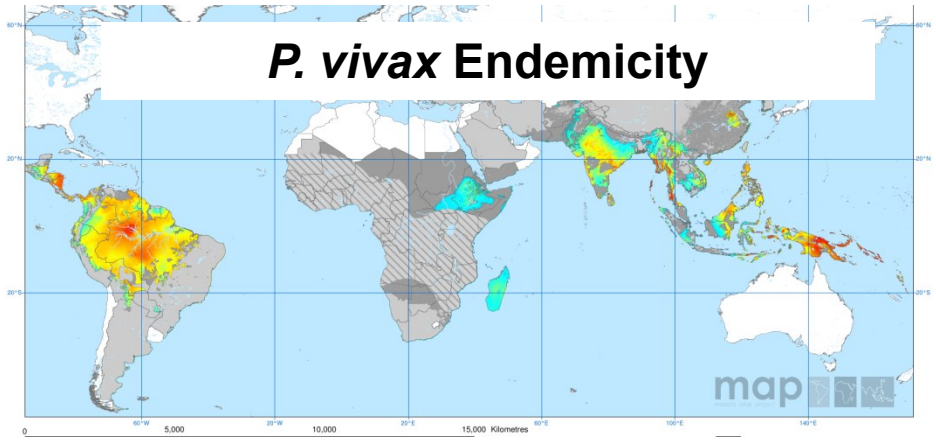
Liver Dormancy =
Relapsing Infection

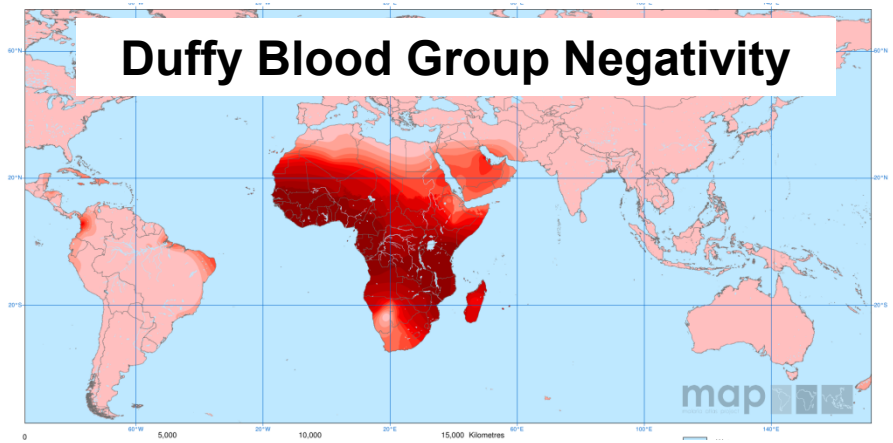


Early Gcts = Faster transmission

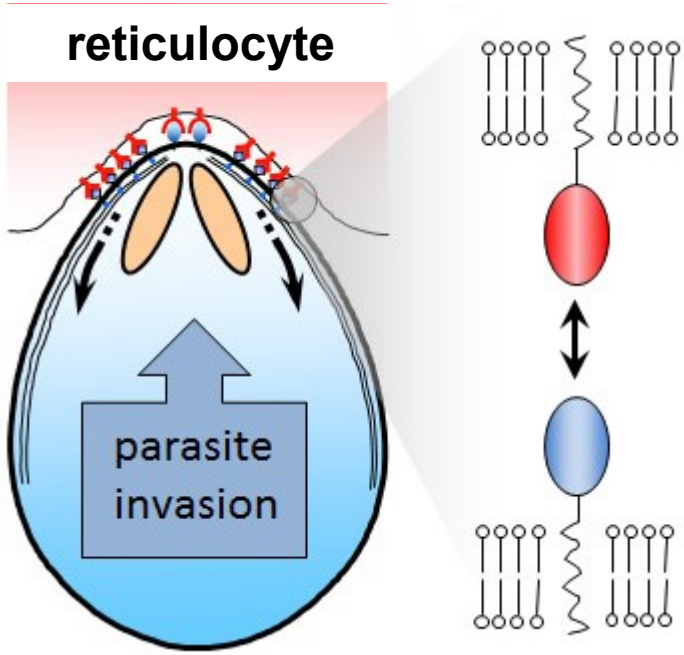
Blood-Stage =
Reticulocyte Tropic & Duffy-Positive

P. vivax Red Blood Cell Invasion



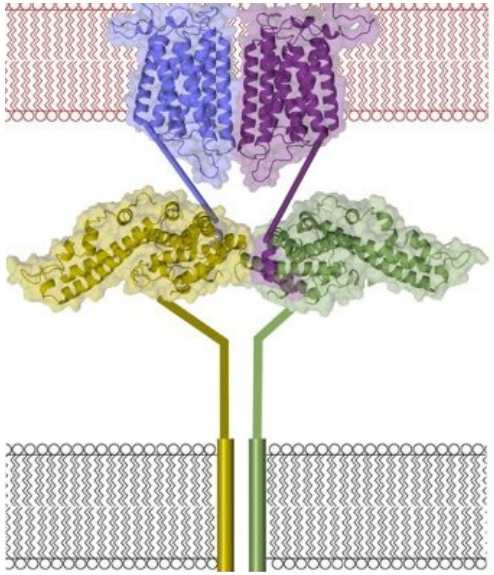


Miller LH (1976) *N Engl J Med* 295:302



Duffy Ag / Fy

PvDBP



P. vivax DBP vaccine: Phase I trial complete

JCI insight

CLINICAL MEDICINE

Human vaccination against *Plasmodium vivax* Duffy-binding protein induces strain-transcending antibodies

Ruth O. Payne,[1] Sarah E. Silk,[1] Sean C. Elias,[1] Kathryn H. Milne,[1] Thomas A. Rawlinson,[1] David Llewellyn,[1] A. Rushdi Shakri,[2] Jing Jin,[1] Geneviève M. Labbé,[1] Nick J. Edwards,[1] Ian D. Poulton,[1] Rachel Roberts,[1] Ryan Farid,[3] Thomas Jørgensen,[4] Daniel G.W. Alanine,[1] Simone C. de Cassan,[1] Matthew K. Higgins,[5] Thomas D. Otto,[6] James S. McCarthy,[3] Willem A. de Jongh,[4] Alfredo Nicosia,[7,8,9] Sarah Moyle,[10] Adrian V.S. Hill,[1] Eleanor Berrie,[10] Chetan E. Chitnis,[2,11] Alison M. Lawrie,[1] and Simon J. Draper[1]

[1]The Jenner Institute, University of Oxford, Oxford, United Kingdom. [2]International Center for Genetic Engineering and Biotechnology, Aruna Asaf Ali Marg, New Delhi, India. [3]QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia. [4]ExpreS[2]ion Biotechnologies, SCION-DTU Science Park, Hørsholm, Denmark. [5]Department of Biochemistry, University of Oxford, Oxford, United Kingdom. [6]Wellcome Trust Sanger Institute, Cambridge, United Kingdom. [7]ReiThera SRL (formerly Okairòs SRL), Viale Città d'Europa, Rome, Italy. [8]CEINGE, Naples, Italy. [9]Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Naples, Italy. [10]Clinical Biomanufacturing Facility, University of Oxford, Oxford, United Kingdom. [11]Institut Pasteur, Department of Parasites and Insect Vectors, Paris, France.

Payne RO *et al.* 2017 *JCI Insight* 2:93683

Summary

- Exciting developments in the *P. falciparum* blood-stage field surrounding the biology of the RH5 complex.
- As a vaccine RH5 can elicit strain-transcending antibodies.
- First-generation protein vaccine is in Phase I/IIa clinical trial.
- Analysis of human mAb responses is enabling rational structure-guided design of improved second-generation VLP-based vaccines.
- *P. vivax* finally receiving attention…