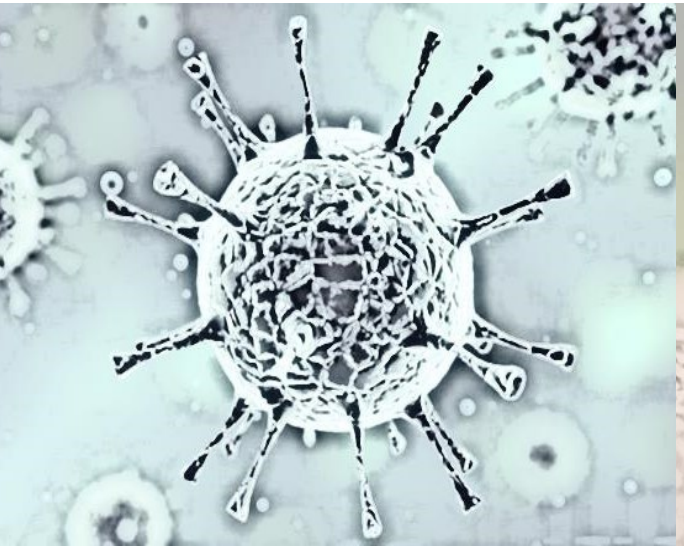
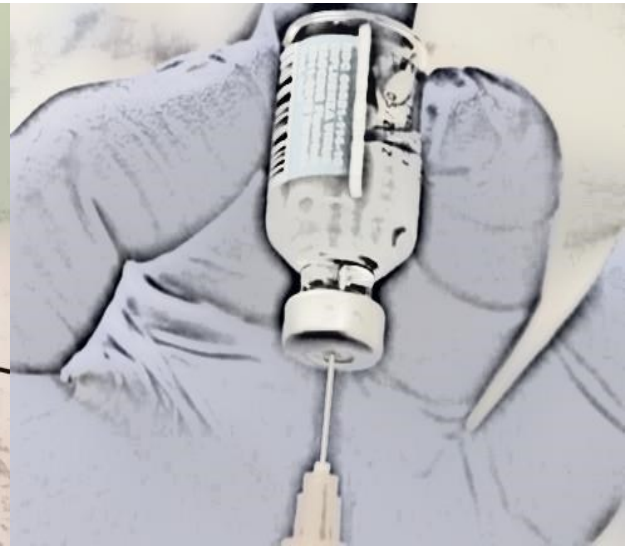
THE JENNER INSTITUTE
DEVELOPING INNOVATIVE VACCINES

UNIVERSITY OF OXFORD





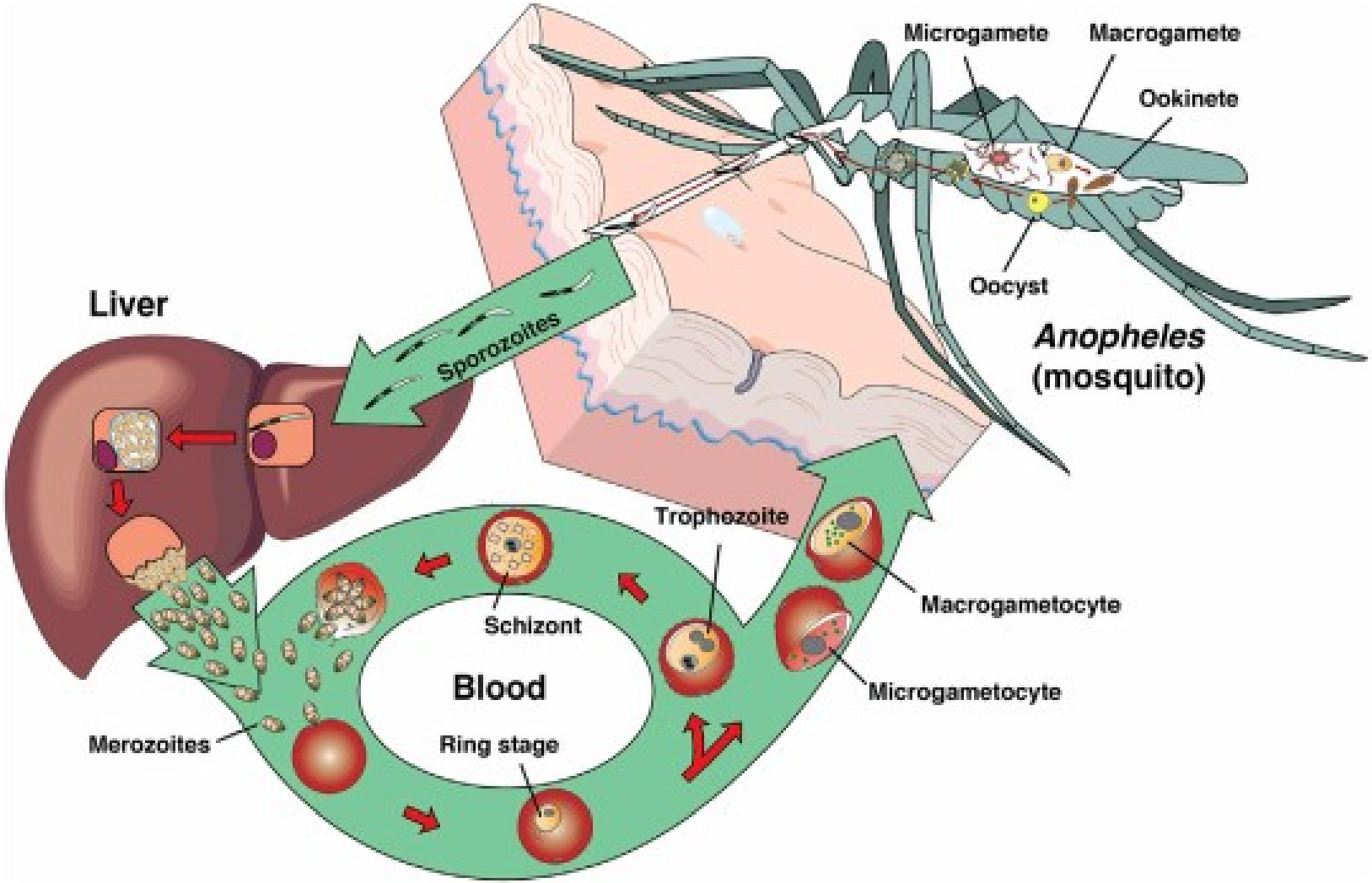
Vaccines for Malaria – Recent Progress and New Horizons

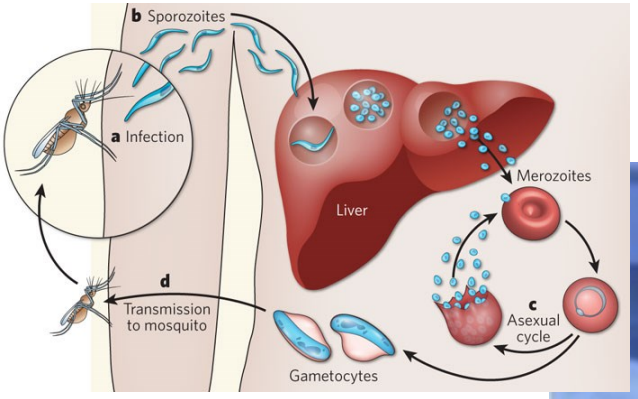
Simon Draper

Vaccinology 2018 – Panama City, Panama

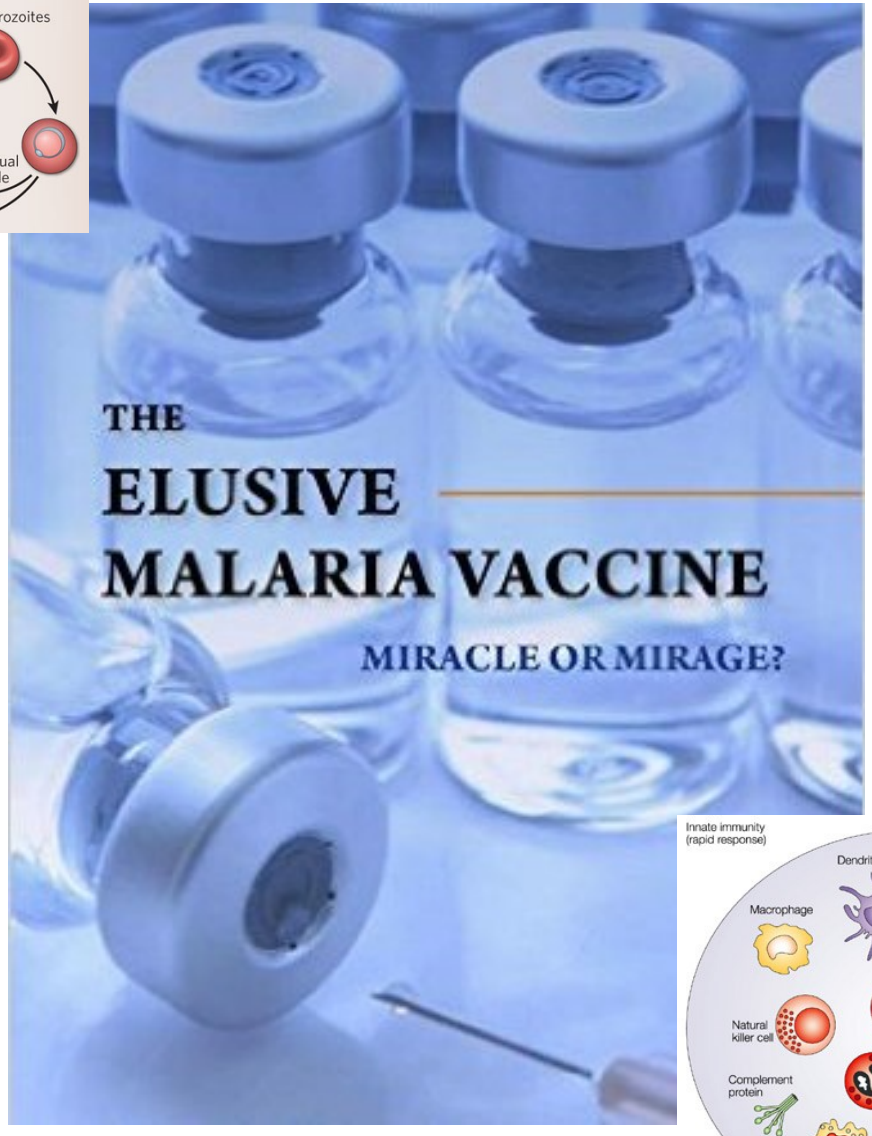
18th October 2018

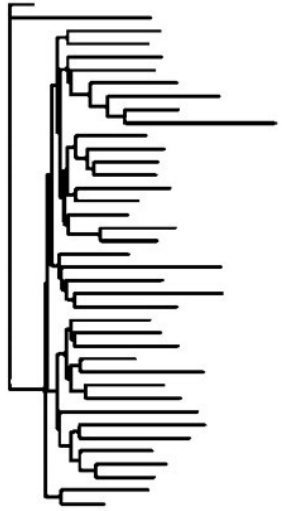
Malaria Parasites: A Complex Lifecycle





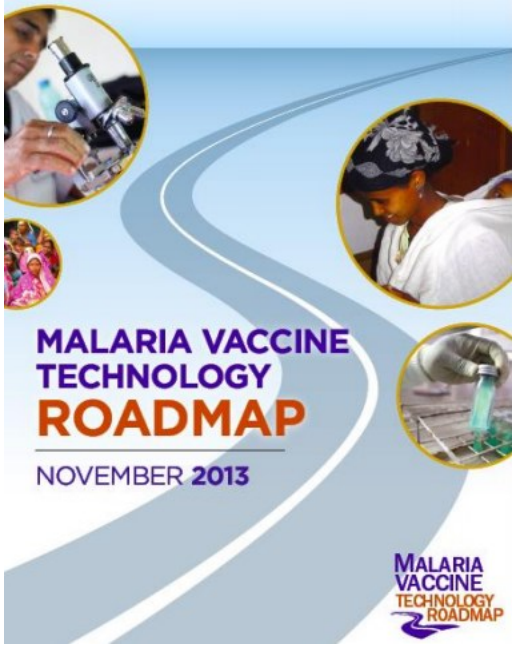
Complexity



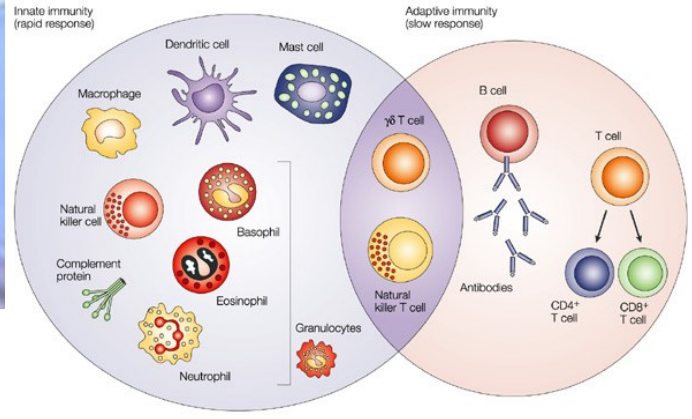


Antigenic Diversity

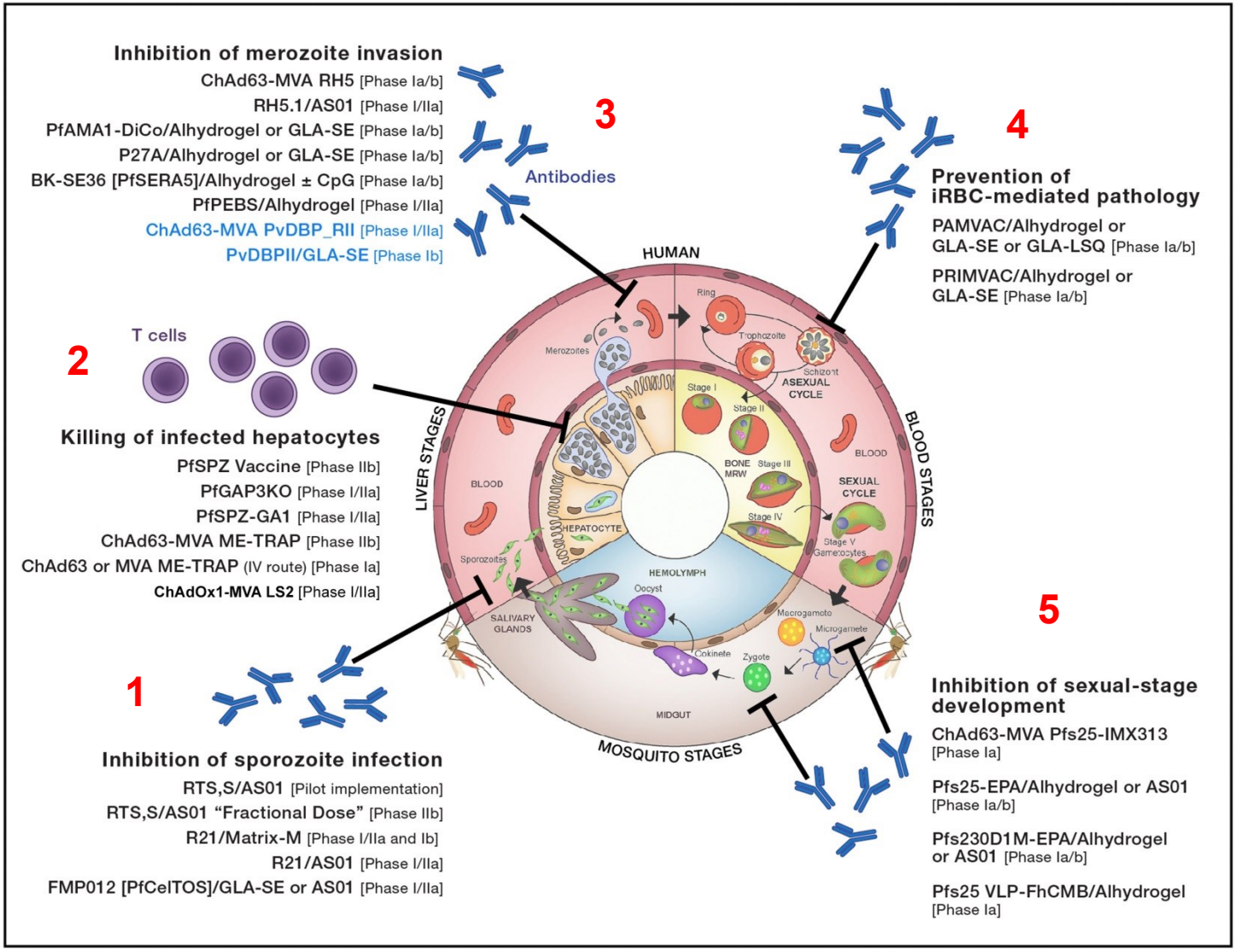
Technological



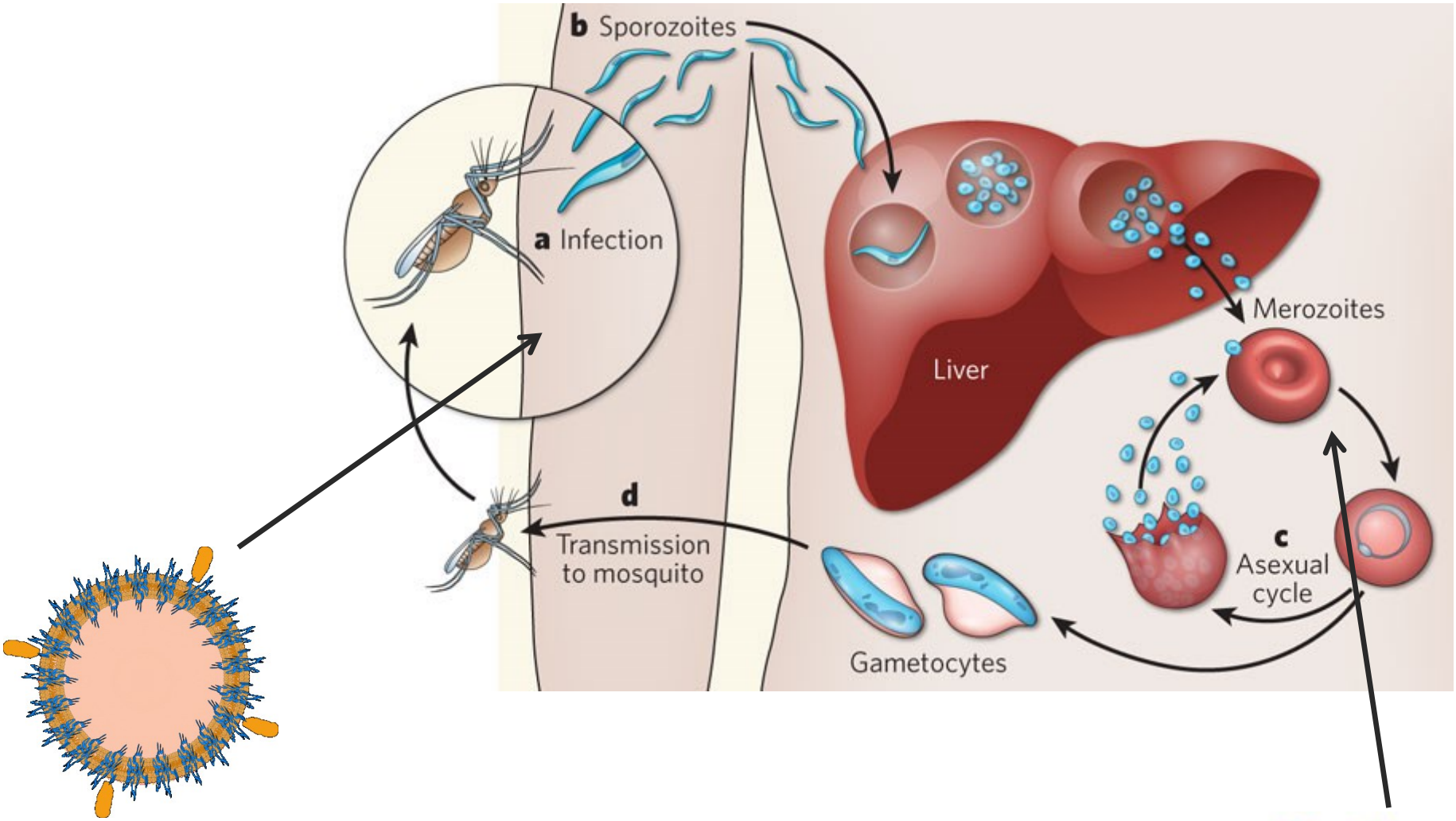
Mechanisms of *in vivo* Immunity



Malaria: Five Stages for Vaccines to Target



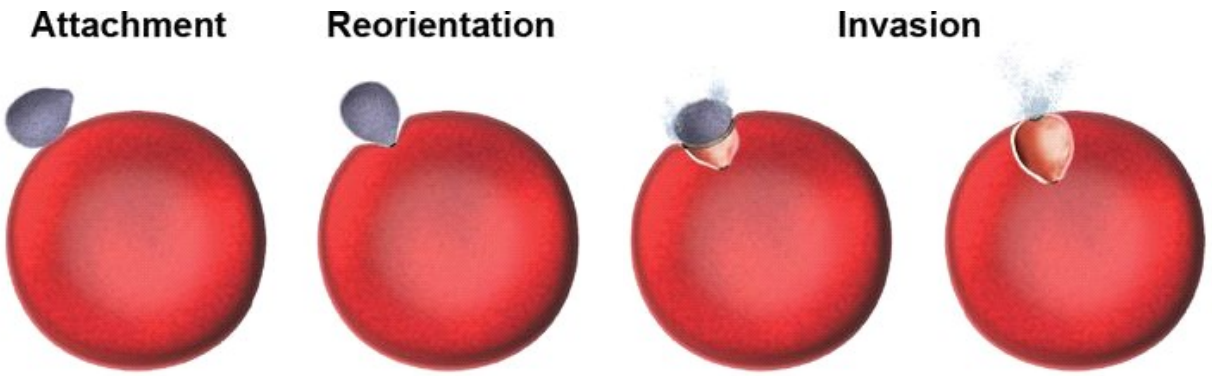
Draper SJ *et al.* (2018) *Cell Host Microbe* 24:43



RTS,S / AS01

- **Completed Phase III**
- **In pilot implementation trials**
- **Moderate-to-low short-term efficacy**

Blood-Stage Merozoite Vaccine Difficulties



1. Antigenic **polymorphism** and **redundancy** of invasion pathways

   New conserved and essential targets

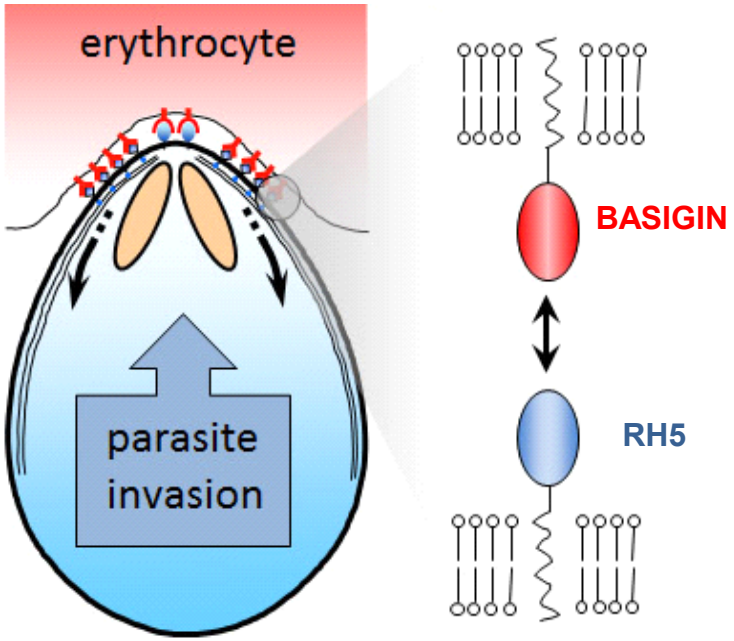
2. Antibody **mechanism of immunity**? Lack of *in vitro* assays that associate with *in vivo* protection in humans

   Functional assay correlates with protection in NHP

3. Need for very **high antibody concentration** for *in vivo* neutralisation

   Quantitative assessment of antibody responses

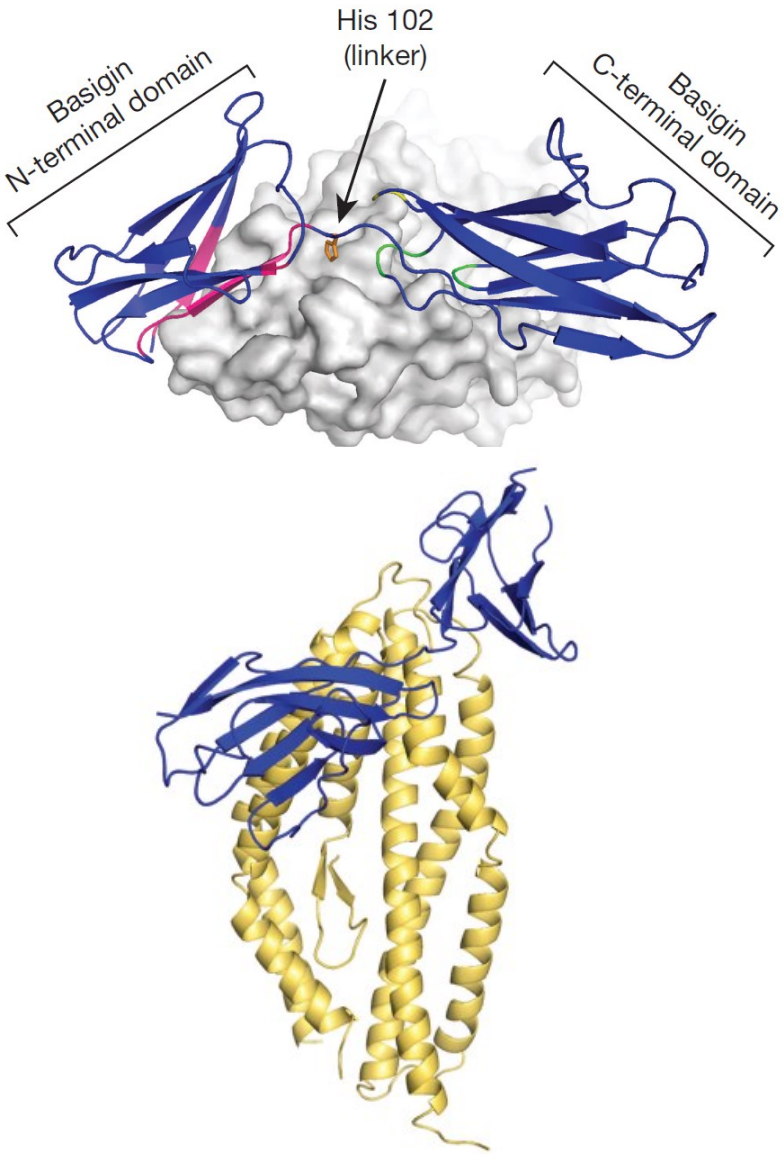
Introducing *P. falciparum* RH5

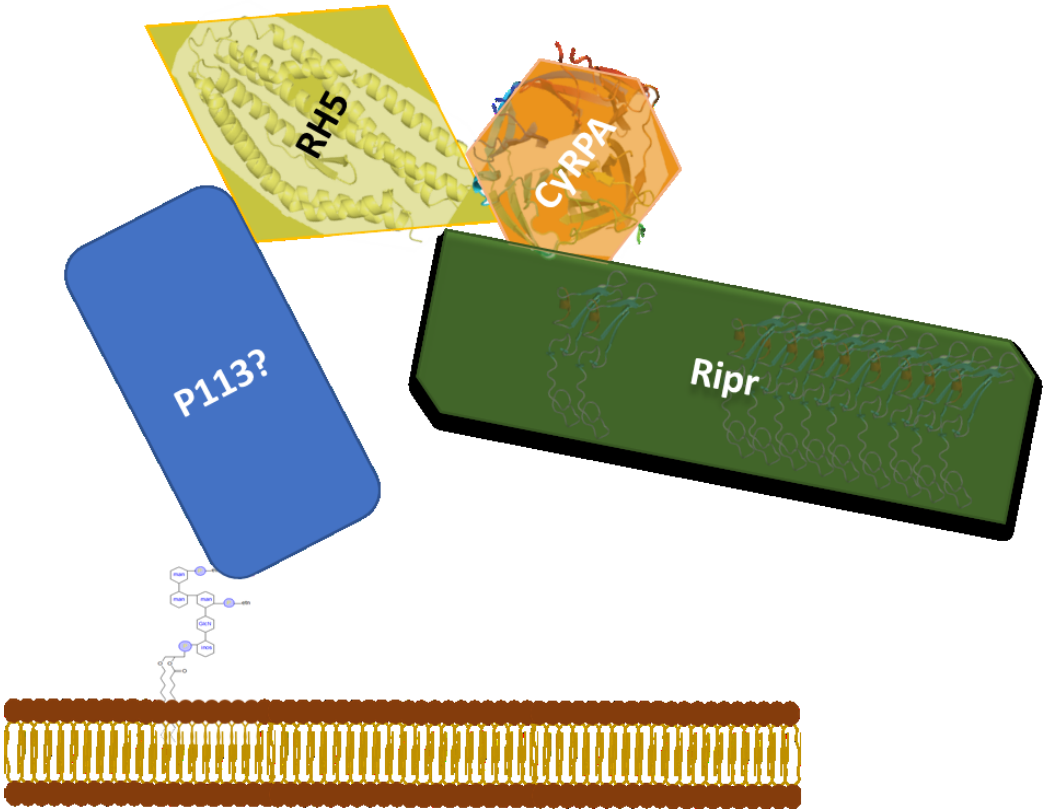


- **The first highly conserved target within the *P. falciparum* blood-stage merozoite to be susceptible to vaccine-induced broadly neutralising polyclonal antibody (Douglas *et al.* 2011, Nat Commun)**

- **Forms an essential interaction with basigin (CD147) on the erythrocyte surface (Crosnier *et al.* 2011, Nature)**

RH5 Invasion Complex and Basigin

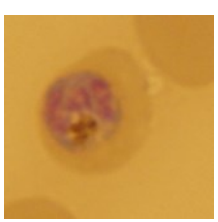




Wright KE *et al.* (2014) *Nature* 515:427

Volz JC *et al.* (2016) *Cell Host Microbe* 20:60
Galaway F (2017) *Nat Commun* 8:14333

An assay to predict *in vivo* protection?



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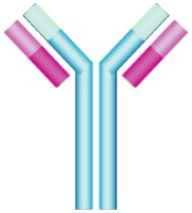
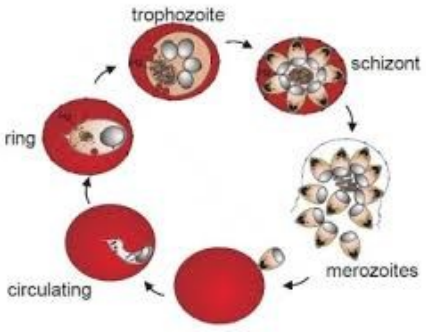
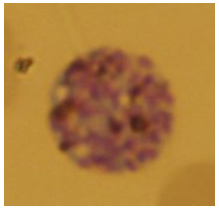


IgG from Serum
or mAb

Wait 48 hours





Growth Inhibition Activity (GIA)

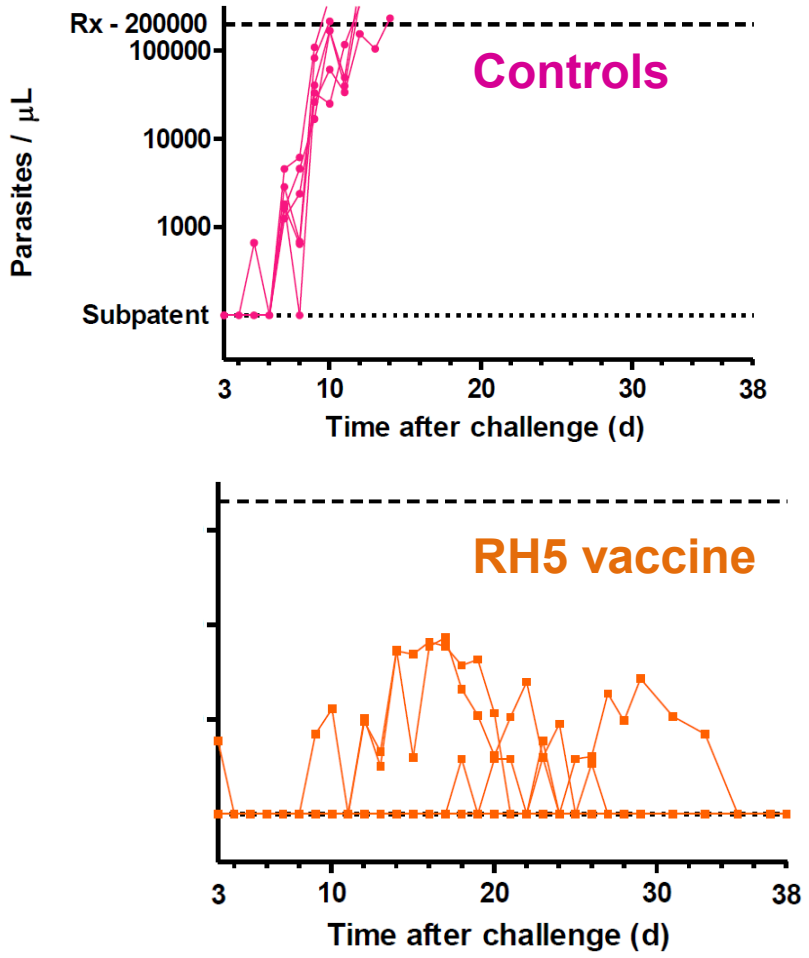
1. Poor association with naturally-acquired malaria immunity

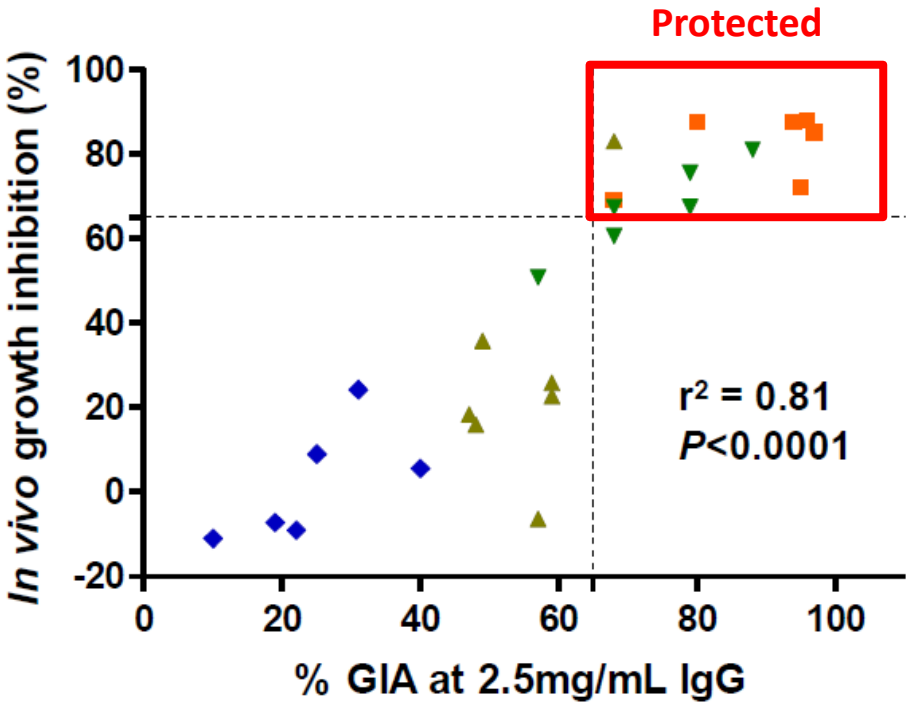
   Duncan *et al.* (2012) *Hum Vaccin Immunother* 8:706

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

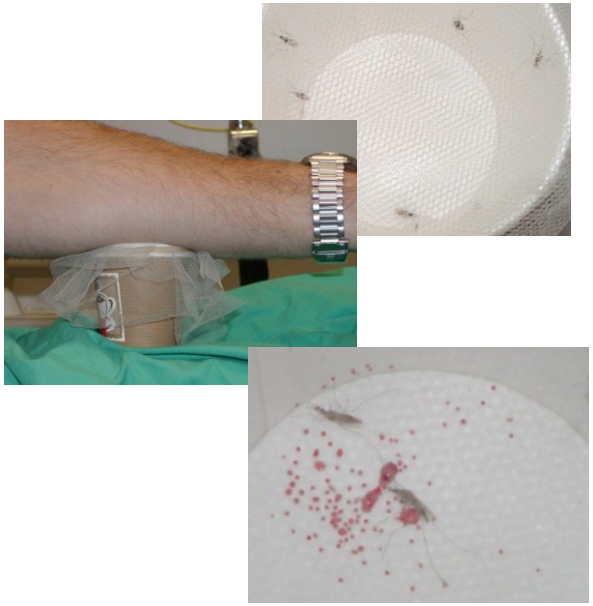


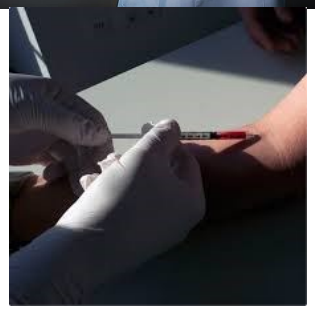


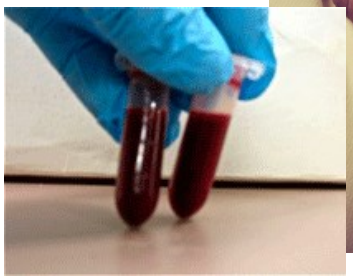
U.S. NAVAL MEDICAL RESEARCH UNIT - 6
NAMRU - 6

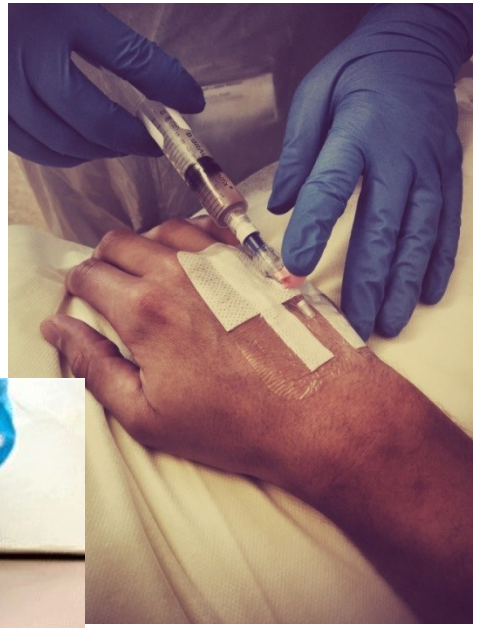
Douglas AD (2015) *Cell Host Microbe* 17:130-9

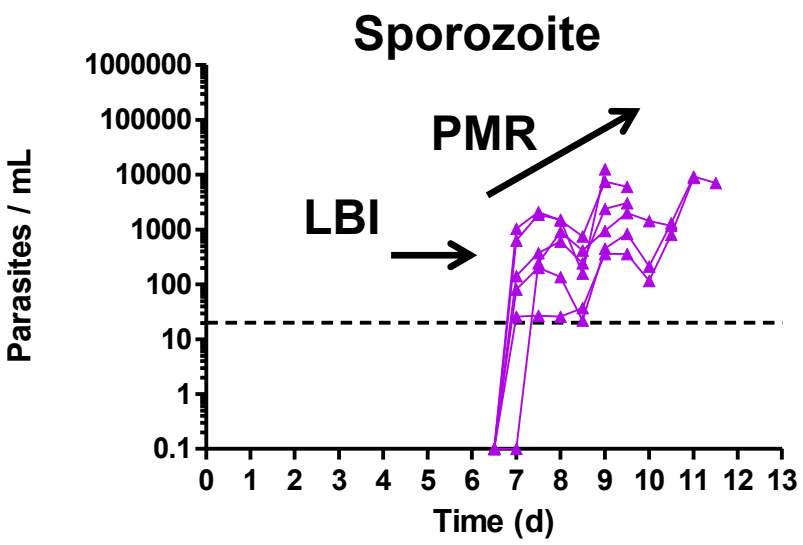
Assessing Immunity by Controlled Human Malaria Infection (CHMI)

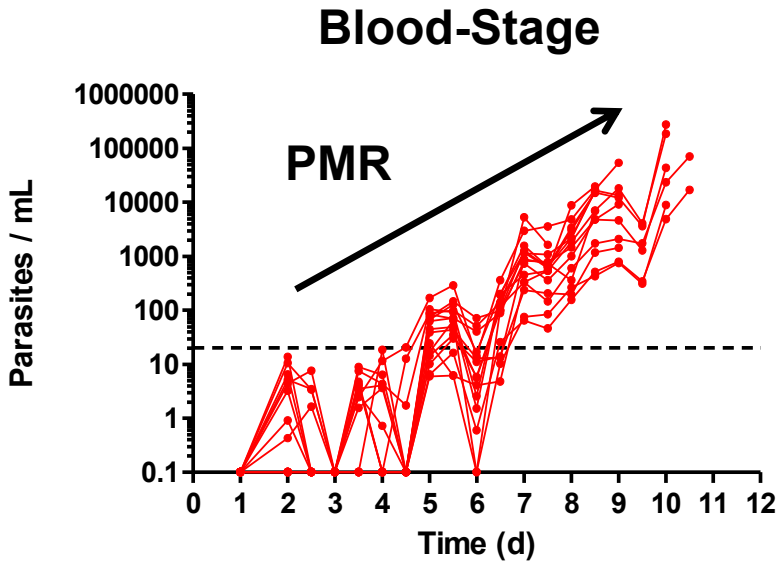




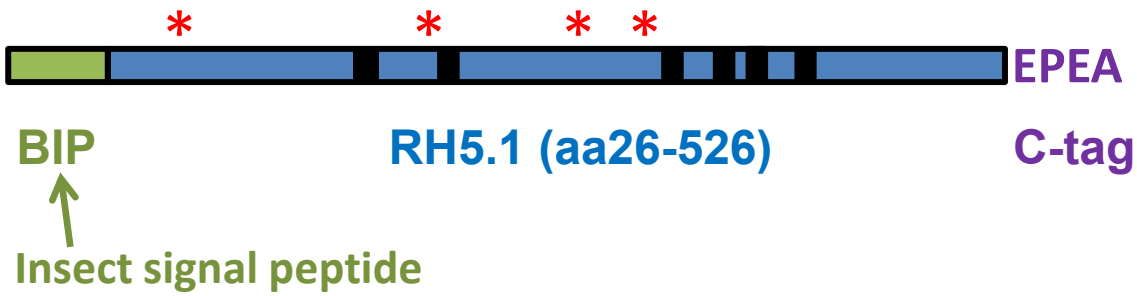








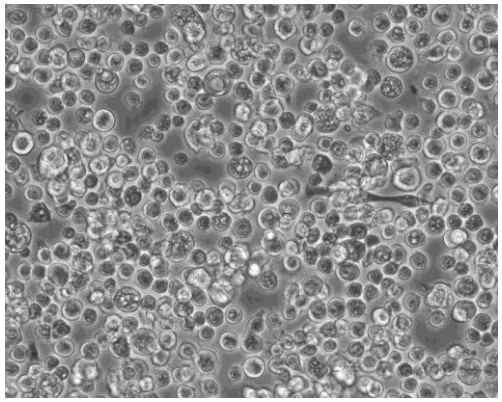
RH5.1 Protein Vaccine for Clinical Trials



* = Mutated N-linked glycosylation sites (Thr to Ala)

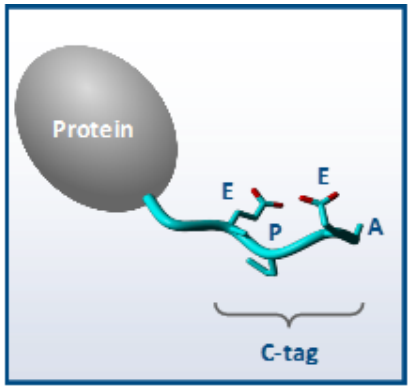
■ = Cysteine

EXPRES^{2}ION BIOTECHNOLOGIES



Hjerrild KA *et al.* 2016 Sci Rep

BAC part of life technologies



Jin J *et al.* 2017 Int J Parasitol

Jin J *et al.* 2018 NPJ Vaccines

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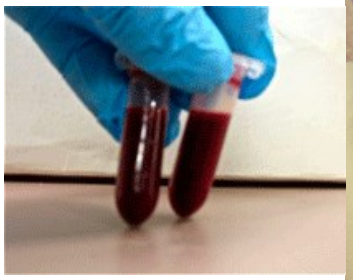
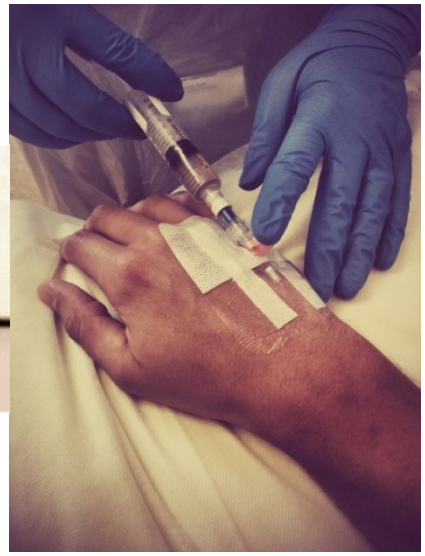
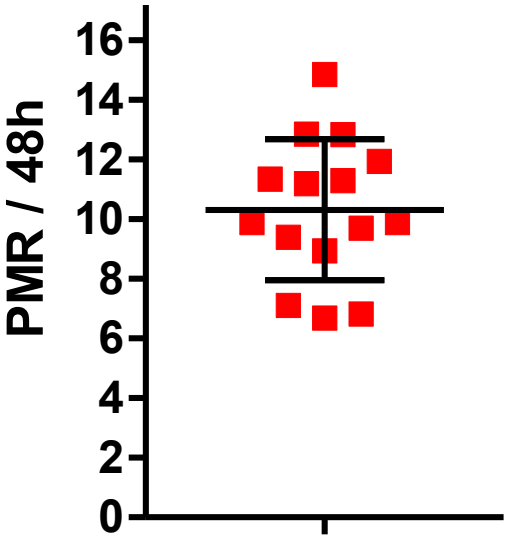


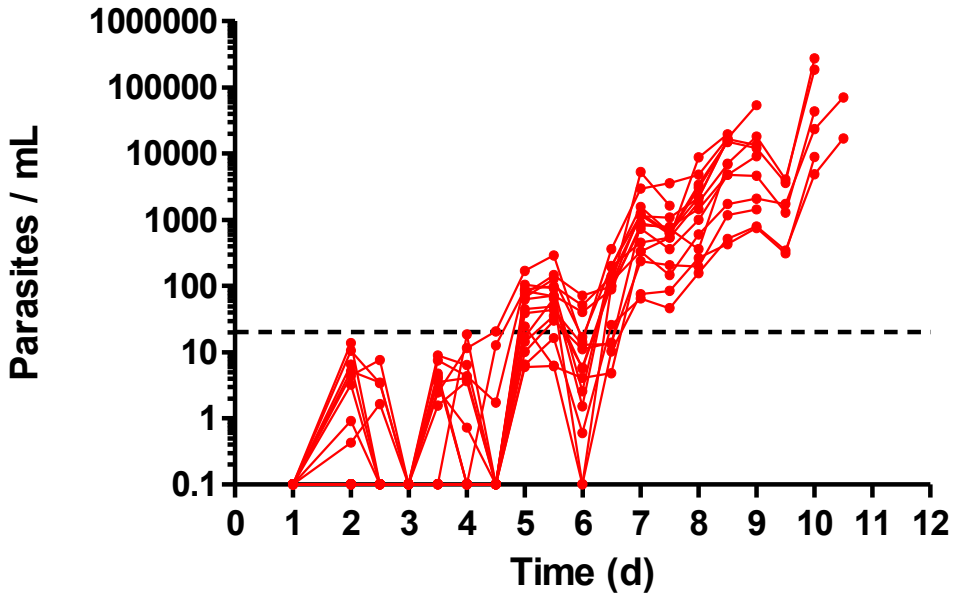




Mean **PMR** = 10.3 per 48 h

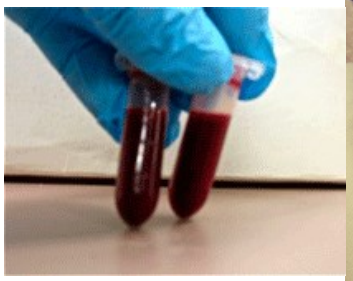
SD = 2.36

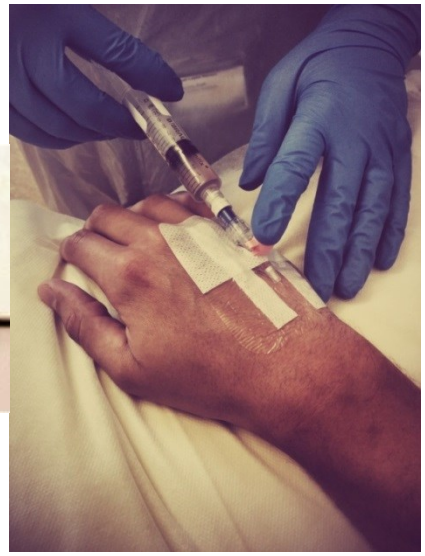
n=15

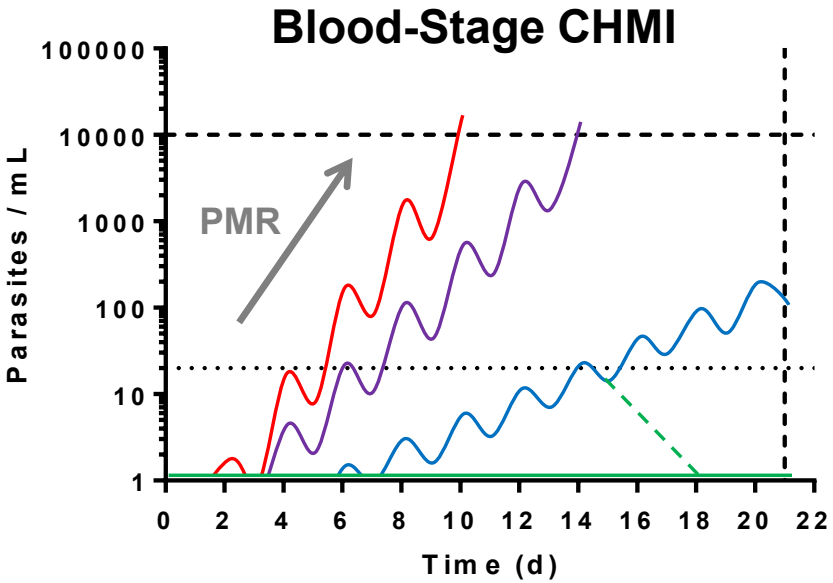


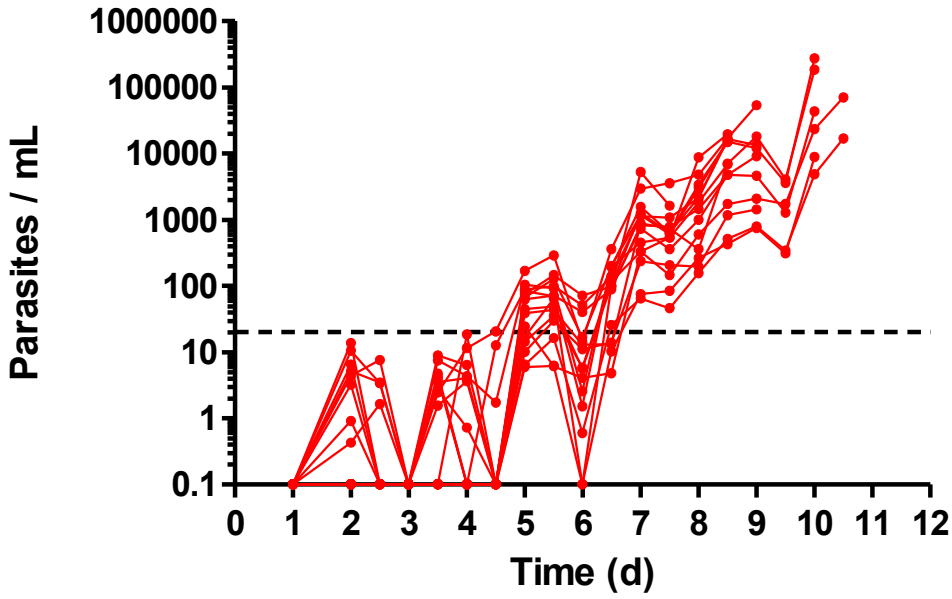
Payne RO *et al. J Infect Dis* (2016) 213:1743-51

Assessing Immunity by Controlled Human Malaria Infection (CHMI)







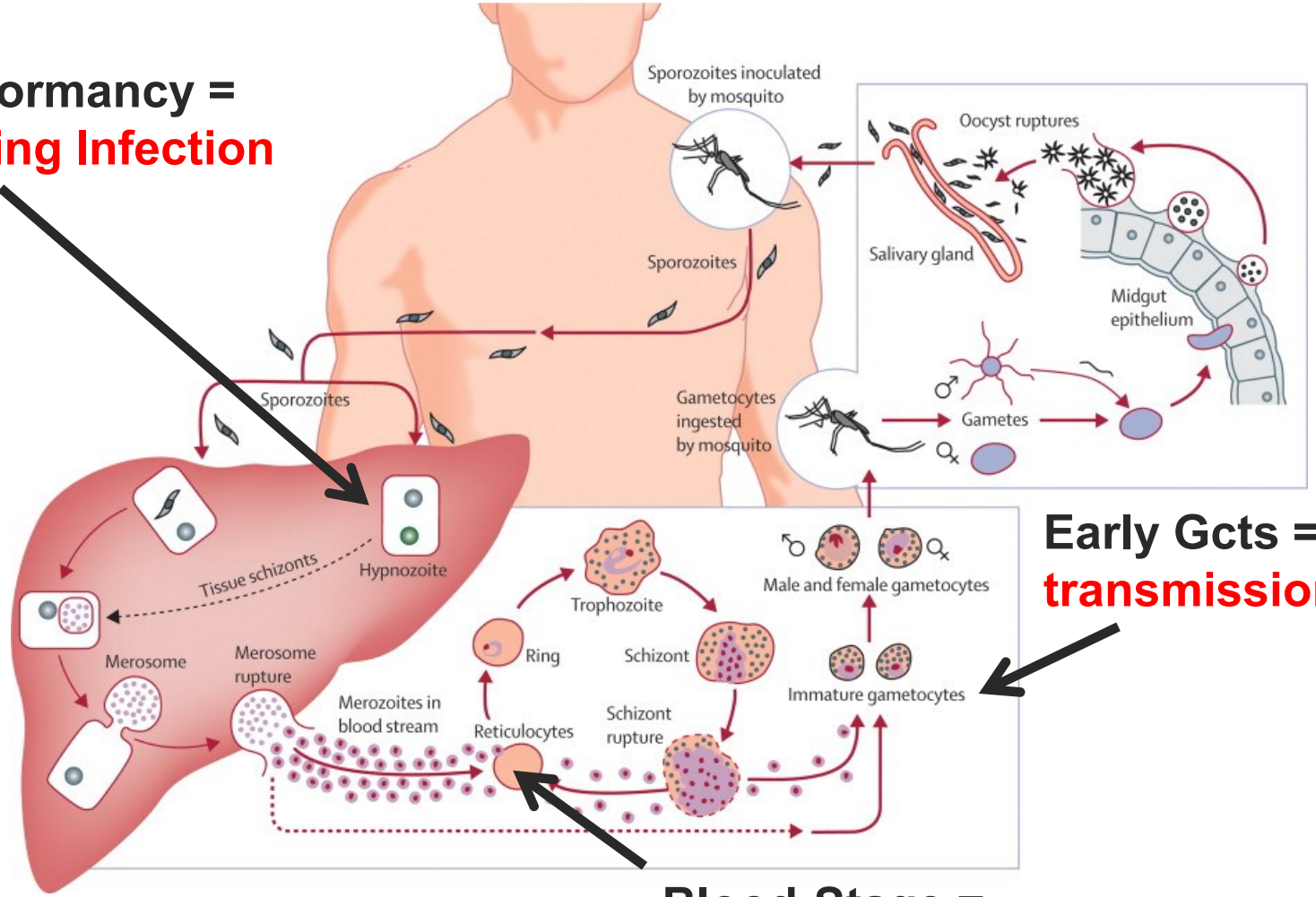


0% Efficacy & Controls (PMR = 10)
50% Efficacy (PMR = 5)
80% Efficacy (PMR = 2)
Sterile Protection
Clearance

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

Plasmodium vivax : Unique Challenges

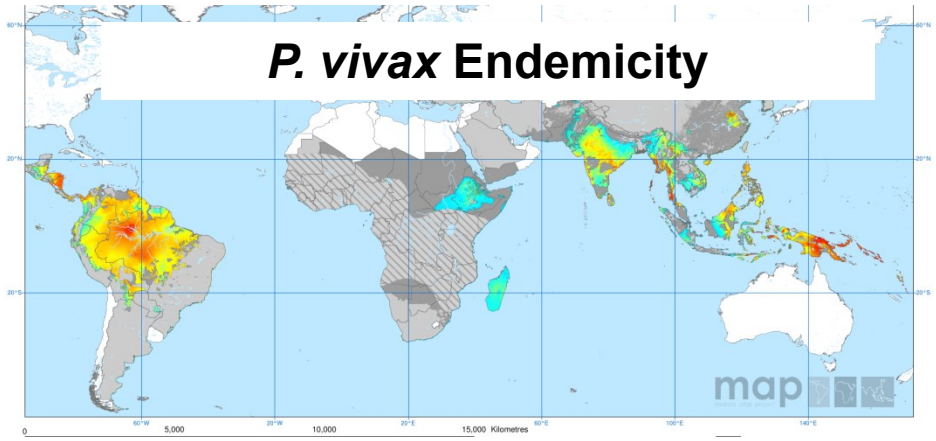
Liver Dormancy =
Relapsing Infection

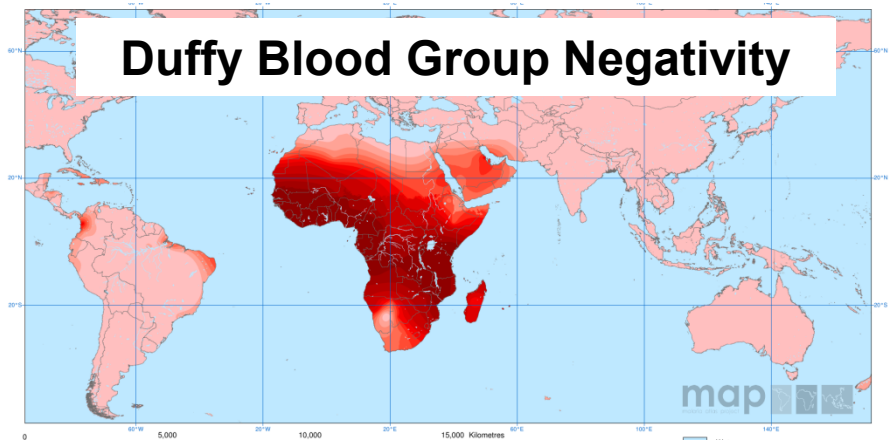


Early Gcts = Faster transmission

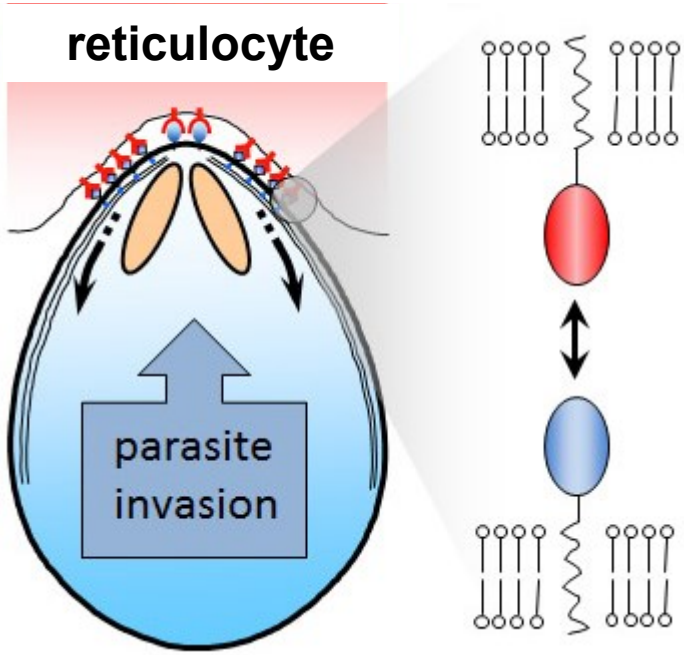
Blood-Stage =
Reticulocyte Tropic & Duffy-Positive

P. vivax Red Blood Cell Invasion



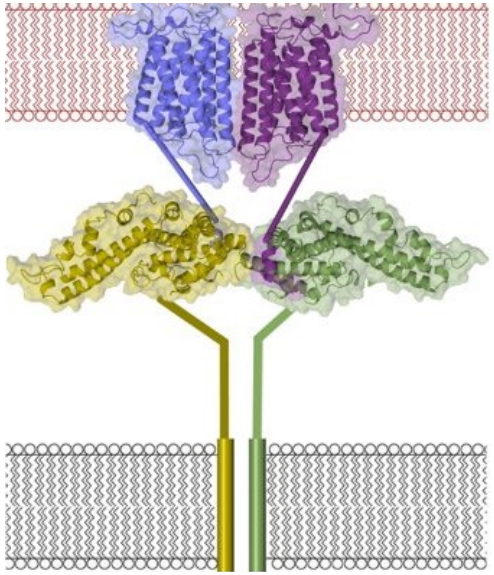


Miller LH (1976) *N Engl J Med* 295:302



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 and the biology of the RH5 complex.
- RH5 vaccine can elicit strain-transcending antibodies.
- First-generation vaccines are in Phase I/II clinical trials.
- Structural vaccinology is leading to improved second-generation VLP-based vaccines.
- *P. vivax* vaccine now entering Phase II efficacy testing in Oxford.