Malaria Vaccines

Adrian V. S. Hill

Jenner Institute, Oxford University
Malaria Mortality and Morbidity

• Currently about 500,000 deaths each year from *Plasmodium falciparum*
  – Mostly in young children
  – Mostly in Africa

• About 250,000,000 clinical cases a year

• Malaria control now costing >$2 billion annually
  – Tools such as spraying, drugs and impregnated bed nets have a finite period of utility
  – Current economic cost of malaria to Africa: ~$12bn
Edmond & Etienne Sergent

Les Comptes Rendu de l’Academie des Sciences
151: 407-409, 1910

Immunity in avian malaria: maintenance in vitro of Plasmodium relictum sporozoites. Partial immunity by inoculation of sporozoites
Malaria Vaccine Design

• Attempts to make a malaria vaccine go back many years
  – Attenuated or killed parasites grown in blood have been considered unsafe for widespread use
  – So subunit vaccines preferred

• There are three central challenges
  – Choosing the right antigen(s)
  – Generating strong enough immune responses
  – Avoiding immune escape mechanisms
By 2030, license vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* that encompass the following two objectives, for use by the international public health community:

- Development of malaria vaccines with protective efficacy of at least 75 percent against clinical malaria suitable for administration to appropriate at-risk groups in malaria-endemic areas.

- Development of malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection. This will enable elimination in multiple settings. Vaccines to reduce transmission should be suitable for administration in mass campaigns.
Malaria: Complexity

• > 5000 genes
• Substantial stage-specificity of antigen expression
• Antigenic variation
• Antigenic polymorphism
• Evolution of parasite to subvert and evade host immunity
Malaria
Four Stages for Vaccines to Target

1. Sporozoite Stage
2. Liver Stage
3. Blood Stage
4. Mosquito Stage
Malaria
Four Stages for Vaccines to Target

1. Sporozoite Stage
   - R21 VLP

2. Liver Stage
   - Viral vectors

3. Blood Stage
   - PfRh5 VLP

4. Mosquito Stage
   - Pfs25 VLP
Main Approaches to Malaria Vaccine Development

1. Protein-adjuvant vaccines
   - RTS,S/AS01
   - R21/matrix-M
   - PfRH5/AS01
   - Pfs25/alum

2. Vectored vaccines
   - Adenovirus-MVA
   - DNA-Adenovirus

3. Whole parasite vaccines
   - Irradiated sporozoites
   - Genetically attenuated parasites
   - Low dose blood-stage parasites
Malaria Vaccines
Multiple Strategies in Clinical Development

• **Pre-erythrocytic:**
  – RTS,S/AS01: phase III in infants
  – Prime-boost vectors: reached phase IIb in African children
  – R21/matrix-M

• **Blood-stage:**
  – MSP142/AS02, AMA1: reached phase IIb in children
  – MSP3 & GLURP: in phase IIb – no efficacy
  – PfRH5 in Phase I/II

• **Transmission-blocking:**
  – Three new candidates based on Pfs25

*P. vivax*: just one blood-stage candidate
The RTS,S Malaria Vaccine Candidate

Sporozoites

Liver-stage parasites

Circumsporozoite protein

Target of neutralizing antibodies

T cell epitopes

RTS,S Particle

Rutgers et al., 1988; Biotechnology 6:1065-1070
Protection Is Dependent On Adjuvantation

GSK adjuvant systems tailored to induce strong antibody and Th-1 targeted cell mediated immune responses

- Saponin extract of *Quillaja saponaria* +
- 3-O-desacyl-4′-monophosphoryl lipid A
  - Oil-in-water emulsion (= AS02)
  - Liposome suspension (= AS01)

RTS,S Phase III Program

8 Countries
11 Trial Centres
15,459 Subjects
# RTS,S Vaccine Final Efficacy Data

36 – 48 months median follow-up

<table>
<thead>
<tr>
<th>Vaccinees Age</th>
<th>6-12 weeks</th>
<th>5-17 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Malaria</td>
<td>18% [12 - 24]</td>
<td>28% [23 - 33]</td>
</tr>
<tr>
<td>Severe Malaria</td>
<td>10% [-18 - 32]</td>
<td>1% [-23 - 21]</td>
</tr>
</tbody>
</table>

With a booster dose at month 20

<table>
<thead>
<tr>
<th>Vaccinees Age</th>
<th>6-12 weeks</th>
<th>5-17 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Malaria</td>
<td>26% [20 - 32]</td>
<td>36% [32 - 41]</td>
</tr>
<tr>
<td>Severe Malaria</td>
<td>17% [-9 - 38]</td>
<td>32% [14 - 47]</td>
</tr>
</tbody>
</table>

Possible Rebound in Susceptibility

in 5-17 month old RTS,S vaccinees followed from months 21 to 48 (ATP)

Efficacy against severe malaria in 5-17 month olds

Vaccination to month 20: 36% [15, 51%]

Month 21 to study end with booster: -10% [-67, 27%]
Month 21 to study end without booster: -52% [-123, -4%]

Month 21 to study end without booster in young infants: 11% [-35, 42%]

Greenwood et al. Lancet 2015
RTS,S Vaccine Efficacy Wanes Rapidly

6 – 12 week olds

5 – 17 month olds

Greenwood et al Lancet 2015
Antibodies to CSP Wane Rapidly but can be increased with a 20 month booster dose

Greenwood et al 2015
WHO Delay Pre-Qualification of RTS,S/AS01

• July 2015: positive EMA scientific opinion

• 23 October 2015 WHO SAGE decision
  – Pilot deployment for 3 – 5 years
  – Only the 5 – 17 month age group to be considered
  – Licensure delayed until 2023

• Concerns
  – Modest efficacy – but “cost-effective”
  – Safety: ?meningitis and cerebral malaria signals
  – Lack of demonstrated impact on malaria mortality in phase III
  – Need for four immunisations after 5 months
    • Logistic feasibility unclear

• Later, increased female mortality signal identified
  – Odds ratio: 1.91  \( P < 0.0006 \)  (Klein et al. *MBio* 2016 7:e00514-16)
RTS,S/AS01 Efficacy against Death attributed to Malaria

Malaria Deaths: 68 in total (ICID10 definition)

Efficacy against malaria mortality in babies: -67% (Table S19)

Efficacy against malaria mortality in toddlers: -25% (Table S12)

Babies 6 / 2179 in controls 20 / 4358 vaccinees

Toddlers 12 / 2974 in controls 30 / 5948 vaccinees

Overall 18 / 5153 controls 50 / 10306 vaccinees

P = 0.23 Odds Ratio = 1.39 [0.81 – 2.39]

Greenwood et al. Lancet 2015
RTS,S/AS01 Efficacy against All Cause Mortality

Deaths: 304 in total

Efficacy against mortality in babies: -25% (Table S20)
Efficacy against mortality in toddlers: -22% (Table S13)

Babies 42 / 2178 in controls  104 / 4356 vaccinees
Toddlers 46 / 2974 in controls  112 / 5948 vaccinees
Overall 88 / 5152 controls  216 / 10304 vaccinees

P = 0.10 Odds Ratio = 1.23 [0.96 – 1.59]

Greenwood et al. Lancet 2015
# Female Sex and Mortality in the Phase III RTS,S/AS01 Trial

<table>
<thead>
<tr>
<th>Sex and age of group</th>
<th>No. of deaths overall [no. of deaths due to malaria]/no. of persons in group (%)</th>
<th>RTS,S recipient/control risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R3R(^a)</td>
<td>R3C(^b)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–17 mo</td>
<td>26 [4]/1,509 (1.7)</td>
<td>19 [9]/1,472 (1.3)</td>
</tr>
<tr>
<td>6–12 wk</td>
<td>24 [3]/1,116 (2.2)</td>
<td>26 [8]/1,118 (2.3)</td>
</tr>
<tr>
<td>Total</td>
<td>95 [24]/5,215 (1.8)</td>
<td>55 [11]/2,550 (2.2)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–17 mo</td>
<td>35 [9]/1,467 (2.4)</td>
<td>32 [8]/1,500 (2.1)</td>
</tr>
<tr>
<td>6–12 wk</td>
<td>27 [5]/1,064 (2.5)</td>
<td>29 [4]/1,060 (2.7)</td>
</tr>
<tr>
<td>Total</td>
<td>123 [26]/5,091 (2.4)</td>
<td>33 [7]/2,603 (1.3)</td>
</tr>
</tbody>
</table>

\(^a\) R3R, 3× RTS,S plus booster RTS,S.  
\(^b\) R3C, 3× RTS,S plus comparator vaccine.  
\(^c\) C3C, controls (comparator vaccines).
RTS,S vs R21

R21 is produced in *Picha pastoris* yeast from a single fusion protein

- without co-expressing HBsAg

20% of molecules encode CS  100% of molecules encode CS
**RTS,S compared to R21**

**RTS,S**
- Produced in *S. cerevisiae*
- Highly immunogenic for both CSP repeat and HBsAg
- Completed Phase III trial
- Efficacy < 50% in field trials

**R21**
- Produced in *P. pastoris*
- Very high immunogenicity for CSP repeat
- Non-immunogenic for HBsAg
- 100% efficacy in transgenic challenge in mice
- Phase I/II trials (matrix-M, AS01)
R21 and Rv21 Pre-Clinical Data

Enhancing protective immunity to malaria with a highly immunogenic virus-like particle vaccine

Katharine A. Collins, Rebecca Snaith, Matthew G. Cottingham, Sarah C. Gilbert & Adrian V. S. Hill

Received: 09 November 2016
Accepted: 03 March 2017
Published: 19 April 2017

Rational development of a protective *P. vivax* vaccine evaluated with transgenic rodent parasite challenge models

Ahmed M. Salman†, Eduardo Montoya-Diaz†, Heather West†, Amar Lall†, Erwan Atcheson†, Cesar Lopez-Camacho†, Jai Ramesar†, Karolis Bauza†, Katharine A. Collins†, Florian Brod†, Fernando Reis†, Leontios Pappas†, Lilía González-Cerón†, Chris J. Janse†, Adrian V. S. Hill†, Shahid M. Khan† & Arturo Reyes-Sandoval†

Received: 02 November 2016
Accepted: 15 March 2017
Published: 18 April 2017
R21 Induces Low Levels of HBsAg Antibodies in Mice

Anti-HBsAg IgG ELISA

Endpoint titre (log 10)

- R21 + No Adjuvant
- R21 + Alhydrogel
- R21 + Abisco
- HBsAg + Alhydrogel

- ● 3 wks post 1 shot
- ■ 3 wks post 2nd shot
- ▲ 3 wks post 3rd shot

• BALB/c mice immunised with 3 shots of 0.5ug R21 or HBsAg + adjuvant at 3 week intervals
R21 Induces High Levels of CSP Antibodies and protects against transgenic parasite challenge

Anti-NANP IgG ELISA

R21 + No Adjuvant
R21 + Alhydrogel
R21 + Abisco

Endpoint titre (log 10)

3 wks post 1 shot
3 wks post 2nd shot
3 wks post 3rd shot

BALB/c mice immunised with 3 shots of 0.5ug R21 + adjuvant at 3 week intervals

R21 challenge

Percent survival

Time to 1% parasitaemia

- R21+Abisco
- R21+Matrix M
- R21 +AddaVax
- Ad-M CS
- Adjuvant only

Collins et al. Sci Reports 2017
Hepatitis B VLP Technology

**R21 VLP**
- Construct similar to RTS component of RTS,S
- No free S subunits so higher ratio of CSP:HepBsAg
- GMP manufacture of R21 completed in May 2015
- Four clinical trials completed

**New generation VLPs**
- 2nd malaria antigen fused to C-terminus of HepBsAg
- Testing in progress with sporozoite and transmission blocking candidates
Matrix-M Adjuvant

• Saponin based: purified fractions of *Quillaja saponaria*

• Nano-particulate formulation (approx 40 nm particles)

• Synergistic mixture of Matrix-A and Matrix-C
  – Manufactured in Uppsala, Sweden

• Good safety profile in >1400 subjects
Progress with R21/Matrix-M

- GMP batch produced
- Four clinical trials completed
  - With a good safety profile
  - Various doses assessed
  - Durability of response being followed
    - And avidity
- One trial completed in Burkina Faso
- Matrix-M: a less complex adjuvant than AS01
  - Lower cost of goods?
- A phase IIa Controlled Human Malaria Infection completed in Q1 2017 in UK
  - Re-challenge study scheduled for September 2017
Malaria
Four Stages for Vaccines to Target

1. Sporozoite Stage
2. Liver Stage
3. Blood Stage
4. Mosquito Stage
Killer T-Cell Attack on an Infected Liver Cell

Parasites
Cytoplasm
Liver Cell
Killer T Cell

HLA = Human Leucocyte Antigen
Receptor

KILLING
Vaccines that Stimulate the Cellular Arm of the Immune System

• Viral carriers
  – Insert microbial (e.g. malaria) gene into the virus
    • Modified Vaccinia Ankara
    • Adenovirus (simian or human)
    • Yellow fever virus
    • Vesicular stomatitis virus?
    • CMV vectors
A PolyEpitope-Protein Construct

pSG.ME.TRAP

ME: Malaria Epitopes
TRAP: Thrombospondin-Related Adhesion Protein

TRAP strain is T9/96
In this vaccine
Viral Vector Vaccines
Designed to Maximise Cellular Immunogenicity

Simian Adenovirus Prime  →  MVA Boost

1 - 8 weeks

Malaria, HCV, HIV, influenza, TB, RSV
Ebola, prostate cancer
# Outbreak Pathogen Vaccine Progress

Current status at Jenner Institute

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Construct Made</th>
<th>Immuno-Genicity</th>
<th>Neutralisation</th>
<th>Animal Efficacy</th>
<th>GMP funded</th>
<th>Phase I/II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandemic Flu</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Rift Valley Fever</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>MERS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Zika</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Chikungunya</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>CCHF</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lassa</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebola Zaire</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebola Sudan</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebola x2 + Marburg</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marburg</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nipah</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plague</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ChAd63-MVA MeTRAP
partial efficacy correlated with CD8\(^+\) T Cells

57\% (8/14) of volunteers show vaccine efficacy
21\% (3/14) show sterile protection
3/3 showed efficacy at 8 months

Vac046: Study Design

- Randomized controlled trial
- ChAd63 + MVA ME-TRAP vs Rabies control
- Healthy adult volunteers in Kilifi, Kenya, N=120
- Primary Endpoint: Time to PCR +ve infection after anti-malarial drug treatment to clear any baseline infection
- Drugs = Atovaquone, Proguanil, Artesunate

Software

Day

Screen

ChAd63 ME-TRAP Vaccine

MVA ME-TRAP Vaccine

Drug treatment Day 63-65

Intense PCR monitoring Day 70 - 126
### Efficacy with Vectors in a Field Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ME-TRAP</th>
<th>Rabies</th>
<th>Unadjusted Efficacy</th>
<th>Adjusted Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PCR positivity*</td>
<td>60</td>
<td>11</td>
<td>67% (33-83%)</td>
<td>66% (31-83%)</td>
</tr>
<tr>
<td>&gt;10 parasites/ml</td>
<td>60</td>
<td>4</td>
<td>82% (46-94%)</td>
<td>81% (42-94%)</td>
</tr>
<tr>
<td>New parasite genotype</td>
<td>60</td>
<td>5</td>
<td>67% (7-88%)</td>
<td>65% (2-87%)</td>
</tr>
</tbody>
</table>

T cells to the major immunogenic TRAP peptide pool correlated with efficacy
Mean peak ELISPOT response: 1694 SFU/M

Primary endpoint *

Sukuta Vaccine Clinic
The Gambia
Coadministration with Gambian EPI schedule: Vac058

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Polio</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pneumococcal Conjugate</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTP HiB HepB</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Yellow fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

| Group 1                         | ChAd  | MVA      |          |          |          |          |
| Group 2                         | ChAd  | MVA      |          |          |          |          |
| Group 3                         |       | ChAd     | MVA      |          |          |          |
| Controls                        |       |          |          |          |          |          |

15 infants per group plus 20 control infants

SFU/M
750
1760
1440
Screening for New Liver-Stage Target Antigens

• Eluting and sequencing *Plasmodial* peptide epitopes from hepatocyte HLA molecules
  – 80 *P. falciparum* epitopes sequenced from HLA class I molecules of human hepatocytes
  – Collaboration with V Soulard and D Mazier, Paris

• Transgenic parasite technology
  – Insert *P. falciparum* antigens into *P. berghei*
    • Replacements or additions
    • Collaboration with Chris Janse and Shahid Khan, Leiden
PfLSA1 and PfLSAP2 are more Protective than CSP or TRAP in Balb/c and CD-1 Outbred Mice

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Balb/c Efficacy (%)</th>
<th>CD-1 Efficacy (%)</th>
<th>P &lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>PfCSP</td>
<td>25</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>PfTRAP</td>
<td>0</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>PfLSA1</td>
<td>87.5*</td>
<td>87.5*</td>
<td>* P &lt; 0.0001</td>
</tr>
<tr>
<td>PfLSAP2</td>
<td>87.5*</td>
<td>70*</td>
<td>* P &lt; 0.0001</td>
</tr>
<tr>
<td>PfLSAP1</td>
<td>0</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>PfUIS3</td>
<td>12.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PfLSA3</td>
<td>12.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PfETRAMP5</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Pf Falstatin</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>PfCelTOS</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

• Both LSA1 and LSAP2 localise to the parasitophorous vacuole membrane
• For both protection is CD8 T cell dependent

Prime-Target Vaccination

- A new means of targeting CD8\(^+\) T cells to the liver

- Requires a priming intramuscular immunisation followed by an intravenous boost to target the liver

- Induces high levels of resident memory T cells in the liver

- Markedly increases malaria vaccine efficacy!
Intravenously Administered Viral Vectors Express Antigen in the Liver increasing CD8+ T Cell “Targeting”

Liver T cells have a resident memory phenotype:

- up-regulated CXCR6
- up-regulated CD69
- down-regulated CD127
Potential of Prime-Target Immunisation

• Should substantially enhance viral vector efficacy against liver-stage malaria

• May do so with a single (simian) adenoviral vector

• Should allow a two dose, short interval regime
  – but the second dose will likely need to be i.v.

• Could be combined with R21/matrix-M

• Particularly application to elimination campaigns and travellers

• Clear potential applicability to immunotherapy of HBV and HCV
Malaria

Four Stages for Vaccines to Target

1. Sporozoite Stage
2. Liver Stage
3. Blood Stage
4. Mosquito Stage
Most natural immunity targets blood-stage

Multiple target antigens are available

A major target, PfEMP1, shows antigen variation

Many show substantial polymorphism
Blood-Stage Antigens: Problems

• The B cell epitopes are conformational
  – Correctly folded protein requirement
• Very high level antibody required for protection
• The major antibody target, Pf EMP1, undergoes spectacular antigenic variation
  – Like trypanosomes, so not a vaccine candidate
• The leading major antigens are di-morphic
  – Both forms required as a mixture in a vaccine
• >24 clinical candidates
  – No convincing efficacy
PfRH5: now the leading candidate antigen for blood-stage vaccines

• A conserved blood-stage candidate antigen

• The first subunit blood-stage vaccine to show efficacy against heterologous challenge in monkeys

• Difficult to express
  – Recently achieved in S2 Drosophila cells

• Phase I trial with vectors shows cross-strain responses
  – trial with protein in adjuvant underway

• Can be added to pre-erythrocytic components

Simon Draper et al.
Antigen Screening: *P. falciparum* Merozoites
Screen for Growth Inhibitory Activity (GIA)

Douglas AD (2011) *Nat Commun* 2, 601
PfRH5 Vaccines Mediate Heterologous Strain Blood-Stage Efficacy in Aotus monkeys

A = anaemia; + = death

Controls  RH5 Freund’s  ChAd63-MVA RH5

Parasites / µL

Untreated (%)
Early Parasite Control and Peak Parasitaemia are Associated with Anti-PfRH5 IgG level and GIA

Douglas et al. *Cell Host and Microbe* 2015
PfRH5 Structure: Basigin and MAbs

Wright KE et al. (2014) Nature
Clinical Development of PfRH5

- PfRH5 antigen well expressed in S2 Drosophila cells
  - Very difficult in E. coli, yeast, mammalian cells
- Second generation VLP with PfRH5.2 in progress
- GMP batch of PfRH5.1 produced
- Phase I trial ongoing with AS01 adjuvant in Oxford
- Phase IIb controlled human malaria infection efficacy trial in Q4 2017
  - Using i.v. blood-stage parasites

Simon Draper et al.
Transmission Blocking Vaccines
Parasite Candidate Antigens

- Pfs48/45
- Pfs230
- PfsHAP2

**a:** Expressed in host

**b:** Expressed in vector
Standardised Membrane Feeding Assay Used to Down-Select Clinical Insert

Mosquitoes feeding on blood

Malarial oocysts in the mosquito midgut

Oocyst number per mosquito


0.041 mg/ml

Sumi Biswas et al.
Pfs25-IMX313 Nanoparticle

Antigen fused to IMX313 self-assembles to form a heptamer

Log improvement in antibody titre

Significantly better transmission-blocking activity in the Standard Membrane Feeding Assay

5 µg protein in Alhydrogel i.m.

375 µg/ml

188 µg/ml
SpyTag + SpyCatcher = Plug & Display VLPs


Mark Howarth

Sumi Biswas
Transmission-Blocking Vaccines
to sexual stage and mosquito antigens

• Fascinating science
  – with proof-of-concept
  – community rather than individual protection
  – renewed momentum

• Reached clinical development more recently
  – three candidates now in phase I trials
    • NIH, Fraunhofer, Oxford

• Significant challenges for deployment
  – >90% population coverage required
Malaria

Four Stages for Vaccines to Target

1. Sporozoite Stage
   - R21 VLP

2. Liver Stage
   - Viral vectors
   - PfRH5 VLP

3. Blood Stage
   - Pfs25 VLP

4. Mosquito Stage
Vaccines for *P. vivax*

- Far less investment
  - For the most widespread malaria parasite

- Will be needed for malaria eradication
  - Likely also for a traveller’s vaccine

- One sporozoite vaccine evaluated clinically for efficacy in a challenge study
  - No sterile efficacy

- One blood-stage vaccine in a phase I trial
  - PvRII in vectors (Draper group, submitted)
SANARIA
The quest for a whole sporozoite vaccine
Efficacy of Sporozoites Administered by the Bites of Irradiated Mosquitoes

<table>
<thead>
<tr>
<th># IMMUNIZING BITES</th>
<th># PROTECTED/ # CHALLENGED</th>
<th># PROTECTED/ # CHALLENGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1000 Immunizing Bites</td>
<td></td>
<td>33/35</td>
</tr>
<tr>
<td>1st challenge</td>
<td>13/14 (93%)</td>
<td>13/14 (93%)</td>
</tr>
<tr>
<td>Re-challenge &lt;10 wk</td>
<td>6/6 (100%)</td>
<td>15/15 (100%)</td>
</tr>
<tr>
<td>Re-challenge 23-42 wk</td>
<td>5/6 (83%)</td>
<td>5/6 (83%)</td>
</tr>
<tr>
<td>&lt;1000 Immunizing Bites</td>
<td></td>
<td>5/15</td>
</tr>
</tbody>
</table>

Courtesy  S Hoffman
The Whole Irradiated Sporozoite Vaccine Approach

- **Manufacturing**
  - One batch per day, implies very high cost

- **Storage and Transport**
  - Liquid nitrogen required

- **Lack of efficacy with non-intravenous routes**

- **But high efficacy 75-90% with i.v. parasites: 4-5 doses**
  - Now a 3 dose regime at 2 monthly intervals (0.45M sporozoites)

- **With intravenous administration of 135K parasites x 5**
  - Duration of efficacy short
  - Efficacy against a heterologous strains is lower

- **African efficacy appears much lower**
  - 9% (anti-disease), 28% (anti-infection) efficacy in Malian adults
  - Much lower vaccine immunogenicity in Africa
Perspective

- Malaria vaccination is possible
- A wide range of approaches are being assessed actively
- Exceptionally potent immune responses are required for efficacy: “unnatural immunity”
- Durability of protection is a major issue
  - so is lower immunogenicity in Africa
Summary

• There is exciting progress in vaccine development for malaria
  – A remarkable range of technologies being used
  – One vaccine candidate has been reviewed positively by the European Medicines Agency
  – RTS,S/AS01 leads the way but is now targeting licensure about 2023

• Further components should increase efficacy
  – Vectored liver-stage
  – Conserved blood-stage antigen
  – Mosquito-stage component
Pre-Erythrocytic Malaria Acknowledgements

Jenner Pre-Clinical
Katharine Collins
Rhea Longley
Ahmed Salman
Florian Brod
Anita Gola
Sarah Gilbert
Alex Spencer

Kilifi, Kenya
Caroline Ogwang
Philip Bejon

GSK
Ripley Ballou
Johan Vekermans

MRC, The Gambia
Muhammed Afolabi

PATH MVI, USA
Ashley Birkett
David Kaslow

Leiden University
Shahid Khan
Chris Janse

Imaxio
Fergal Hill

CNRFP, Burkina Faso
Sodiomon Sirima

UK Clinical Trials
Tommy Rampling
Navin Venkatraman
Ruth Payne
Danny Wright
Carly Bliss
Georgie Bowyer
Rachel Roberts
Nick Edwards
Alison Lawrie
Babatunde Imoukhuede
Katie Ewer

Novavax
Russell Wilson
Greg Glenn
Acknowledgements


Companies. Janssen: Johan van Hoof; Novavax: Greg Glenn; Imaxio: Fergal Hill; GSK: Ripley Ballou; Okarios: Alfredo Nicosia; ExpreS²ion Biotechnologies: Wian de Jong

