Development of a Multi-Component Multi-Stage Malaria Vaccine

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Immunity in avian malaria: maintenance in vitro of *Plasmodium relictum* sporozoites. Partial immunity by inoculation of sporozoites
Malaria
Four Stages for Vaccines to Target

1. Sporozoite Stage
2. Liver Stage
3. Blood Stage
4. Mosquito Stage
Some Current Candidates
Pre-Erythrocytic

**Sporozoite stage**
- RTS,S / AS01
- R21
- DNA + Ad5 CSP
- Ad35 + Ad26 CSP
- PfCelTOS

**Liver-stage**
- ChAd63 ME-TRAP
- MVA ME-TRAP
- EP-1300 electroporated DNA
Some Current Candidates

Blood-Stage

- GMZ2 (GLURP + MSP3)
- MSP3
- AMA1 (NIH + WRAIR) and AMA1-DiCo
  - DNA and vectors
- MSP1 (protein and vectors)
- SE36
- PEV3a
- P27A
- Pf11.1
- PvRII (*P. vivax*) in vectors
- PfRH5 in vectors
Some Current Candidates
Sexual-Stages

- Pfs25-EPA
- Pfs25+Pfs230-EPA
- Pfs25 VLP-FhCMB
- Pfs25 IMX-313 (vectored)
- R0-PF10C (Pfs48/45)
FP7 “MultiMalVax” Clinical Trials

Trial 1: R21/adjuvant + MeTRAP in vectors

Trial 2: PfRH5 in vectors (Simon Draper)

Trial 3: Pfs25 in vectors (Sumi Biswas)

Trial 4: Combination of all of the above
Multi-Component Malaria Vaccine Strategy

• A Four-Stage High Efficacy Modular Vaccine against *P. falciparum* malaria
  – Sporozoite Stage: CSP
  – Liver Stage: TRAP
  – Blood Stage: PfRH5
  – Mosquito Stage: Pfs25
The RTS,S Malaria Vaccine Candidate

Rutgers et al., 1988; Biotechnology 6:1065-1070
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
R21 VLPs – Electron Micrograph

Positive control – HepB vaccine

R21 VLPs
Killer T Cell Attack on an Infected Liver Cell

Parasites

Cytoplasm

Liver Cell

Killer T Cell

HLA = Human Leucocyte Antigen Receptor

KILLING
Viral Vector Vaccines
to Maximise Cellular Immunogenicity

Adenovirus Prime 8 weeks MVA Boost

Malaria, HCV, HIV, influenza, TB, RSV, Ebola

27 trials completed: over 1300 vaccinees
ChAd63-MVA MeTRAP Efficacy against heterologous strain *P. falciparum* sporozoites

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

CD8 T cells correlate with efficacy specifically γ-interferon +ve cells

Vac55: Vectors with RTS,S/AS01
Challenge December 2013; Re-Challenge May 2014

<table>
<thead>
<tr>
<th>Week</th>
<th>Group 1 (n=20)</th>
<th>Group 2 (n=20)</th>
<th>Group 3 (n=6)</th>
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# Vac059 Trial: recruiting

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Blood-Stage PfRH5
Simon Draper’s Lab

• A conserved blood-stage candidate antigen
  – that induces cross-strain growth inhibitory activity in vitro

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

• Difficult to express with high yield
  – Recently achieved in S2 Drosophila cells

• Phase I/IIa trials in 2014 - 2015
  – First vaccinees with vectors in August 2014 in Oxford
  – S2 cell-expressed protein to be tested clinically in 2015
  – Blood-stage challenge planned

IMX313 Platform

IMX313 is a hybrid chicken equivalent of C4bp oligomerization domain (less than 20% homology to human C4bp)

Spontaneously forms a heptamer when fused to antigen of interest: 10 nm in diameter

Currently being tested in a phase I clinical trial with a tuberculosis vaccine candidate in Oxford
Multi-Component Malaria Vaccine Strategy

• A Four-Stage High Efficacy Vaccine against *P. falciparum* malaria:
  – Sporozoite Stage: RTS,S or R21
  – Liver Stage: ME-TRAP
  – Blood Stage: PfRH5
  – Mosquito Stage: Pfs25-IMX313
MultiMalVax 2013-2014

• R21 progress
  – GMP manufacturing progressed
  – High level efficacy in murine models

• Proof of concept evaluated with RTS,S + vectors
  – Promising efficacy

• Vectored RH5 in phase I
  – Excellent T cell immunogenicity

• Pfs25-IMX313 downselected
  – GMP manufacture of both vectors completed
## Pre-Erythrocytic Acknowledgements

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<th>Jenner Pre-Clinical</th>
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<th>UK Clinical Trials</th>
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