Progress in the Hunt for a Malaria Vaccine

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Why do we need a malaria vaccine?

- In 2018, 405,000 deaths
- In 2018, 228 million cases
- In 2017, for the first time in a decade, the WHO reported an increase in the global incidence of malaria.
- Disruptions to healthcare and control programs caused by COVID could result in a doubling of malaria-related deaths.

Existing control methods (insecticides and anti-malarial drugs) increasingly less effective.
Why don’t we have a malaria vaccine?

Which Plasmodium species should a vaccine target?
- There are 6 species of malaria that infect humans.

What Plasmodium stage should be targeted?

What do we want a malaria vaccine to do?
Requirements: affordable, capable of inducing long-term immunity, well tolerated and non-toxic
- eliminate infection?
- reduce disease?
- prevent transmission?
2 Broad Malaria Vaccine Approaches

Sub-unit vaccines

- Contain a small part of the parasite eg a single protein
- Require adjuvants (substance that enhances immune response)
- Proteins that are targeted are often variable between different parasite strains
- Immune responses often not long-lived
- Low and variable protection
Many different protein targets including proteins conserved between parasite strains
May overcome issues associated with protein variation.

**Approaches:**

- **Pre-erythrocytic:**
  - Irradiated sporozoite vaccine
  - Chemically attenuated sporozoite vaccine
  - Genetically attenuated sporozoite vaccine

- **Erythrocytic:**
  - Genetically attenuated blood-stage vaccine
  - Chemically attenuated blood-stage vaccine
### Evaluation and testing of vaccines

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<th>Phase</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb/III</th>
<th>Phase IV</th>
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<th>Local application</th>
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<td>Lab studies</td>
<td>Animals</td>
<td>Tens Healthy adults</td>
<td>Hundreds Target people</td>
<td>Thousands Target people</td>
<td>Hundreds of thousands</td>
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<td>Safety</td>
<td>Minimizing adverse effects</td>
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**Prelicensure tests**
- Immune response
  - Use challenge model
- Placebo controlled
  - Double-blind
  - Rarer side effects

**Postlicensure tests**
- Safety monitoring
  - Potential adverse effects

**Average time:** 12-15 years
**Cost:** $US200-500 million per attempt.
Leading malaria vaccine candidates

Development of a chemically attenuated whole parasite blood-stage vaccine (PlasProtect)

- Tafuramycin-A binds to malaria parasite DNA and stops it replicating.
- In rodent models, chemically treated parasites \((1 \times 10^6 \text{ pRBC})\) can protect mice from challenge.
- Protection is dependent on CD4+ T cells.
- Red blood cell membranes must be intact for vaccine efficacy.

*MF Good et al 2013 J Clin Invest 123(8): 3353-3362*
*A Raja et al 2016 Infect Immun 84(8): 2274-88*
Development and Evaluation of a Chemically Attenuated Malaria Vaccine

1. Pre-clinical Development: Establish protective efficacy and immune mechanisms in a rodent model of malaria.

2. Pre-clinical Development: Develop key reagents for the chemically attenuated vaccine in humans.


Clinical Vaccine Development
Development of *Plasmodium falciparum* cell banks

Required:
- To make the vaccine
- For challenge to examine if the vaccine protects

*P. falciparum* parasites expanded in transfusion-grade Blood Group O Rh negative red blood cells in the cleanroom at Griffith University and then frozen.

Characterized according to specific release criteria eg sterility, viability of parasites, drug sensitivity profile, viral testing.
Suitable for administration to humans in early phase clinical studies.

*DI Stanisic et al 2015 Malaria J 14: 143.*
Development and Evaluation of a Chemically Attenuated Malaria Vaccine

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Clinical study: Malaria Vaccine

Pilot Study
1. Identify correct dose of chemical to completely attenuate parasite
2. Examine safety and tolerability
3. Does it induce an immune response?

Study participants screened according to inclusion/exclusion criteria
- Healthy males 18-60 years of age
- No history of clinical malaria or travel/residence (>2 weeks) in malaria endemic area within last 12 months
Vaccine Preparation

1. *P. falciparum* cell bank parasites thawed and cultured in Blood Group O Rh D negative red blood cells in cleanroom at Griffith University.

2. Parasites harvested.

3. Parasites treated with Tafuramycin-A.

4. Parasites washed.

5. Chemically treated parasites injected intravenously.
Clinical study: Malaria Vaccine

Study Group B:
Injected with one dose of chemically attenuated parasitised red blood cells
Broad T cell responses are induced by chemically attenuated blood-stage malaria parasites.
Cytokine producing memory T cells increase following inoculation with chemically attenuated blood-stage malaria parasites
Chemically attenuated purified *P. falciparum* blood-stage vaccine

Vaccine has been reformulated  
- contains purified parasitised red blood cells

- We have shown in a small pilot study that the fresh, purified form of the vaccine is safe and immunogenic.
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2. Pre-clinical Development: Develop key reagents for the chemically attenuated vaccine in humans.


4. **Clinical Development:** Examine protective efficacy of vaccine in humans.
Phase Ib Efficacy Study (commenced)

Aims

Safety, immunogenicity and protective efficacy following blood-stage challenge

-2 study groups receiving different doses of parasite run sequentially

-1 or 2 infectivity controls per study group

-3 doses of the vaccine on Day 0, 28 and 56

-Challenge one month later with infectious *P. falciparum* blood-stage parasites

-A proportion of vaccinees were fully protected against the challenge infection
Field deployable malaria vaccine

- Field-deployable vaccine = malaria parasites + liposomes
- Protective in rodent models of malaria
- Optimising vaccine candidate
- Produce vaccine candidate for toxicology tests and for clinical studies
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