Federal Malaria Vaccine Coordinating Committee
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The US Military Malaria Vaccine Program

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USMMVP Approach

- Objective: completely prevent infection
- Pre-erythrocytic stage vaccines prioritized
- Current research in blood stage antigens focusing on overcoming antigenic heterogeneity
Targets: Induce Antibodies to Sporozoites

Antigens:

- CSP
  - Pf: RTS,S & new full length CSP
  - Pv: VMP001
- CelTOS
- New antigens (Joao Aguiar, Urszula Krzych, LMIV / MVI)

Platforms:

- Soluble protein vs particle
- Adjuvant
Induce T cell Responses to Attack Liver Stage Parasites

**Antigens:**
- CSP + AMA1
- New antigens

**Platforms:**
- Adenovectors
- Prime-boost
  - DNA-Ad
  - Ad-Protein

PF106

4 days Post-Infection

PF106

6 days Post-Infection
NMRC-M3V-D/Ad-PfCA Vaccine

Test articles:
- DNA plasmids CSP, AMA1
- Adenovectors CSP, AMA1 (AdHu5)

Partners:
- GenVec, Vical
- USAID

DNA/Ad: sterile protection (4/15)
Ad alone: no protection (0/18)

Pathway forward
- AdHu5 for PoC
- New simian vector program
- Collaboration with Adrian Hill to add antigens & compare platforms (AdCh63 prime MVA boost, ME-TRAP)
- Glycolipid adjuvant (ADARC)
Sanaria: Production of aseptic, purified sporozoites & storage in liquid nitrogen to allow needle/syringe administration

Radiation – attenuated (PfSPZ Vaccine)
- Two volunteers protected with intermediate dose
- Antigen potent in NHP when administered IV
- New route of administration needed (eg. microneedle)
- Sponsor is planning IV administration trial

Gene knock-out attenuated
- p52/36: trial with Seattle BioMed halted due to breakthrough blood stage infection
WRAIR Malaria Vaccine Efforts
Liver Stage Antigen -1 (LSA-1)
- Cummings JF et al.; Recombinant Liver Stage Antigen-1 (LSA-1) formulated with AS01 or AS02 is safe, elicits high titer antibody and induces IFN-gamma/IL-2 CD4+ T cells but does not protect against experimental Plasmodium falciparum infection. Vaccine. 2010 12;28 (31): 5135-44.

RTS,S/AS01B

MSP-1 (3D7 allele)

MSP-1 (FVO allele)
- Spring M et al; Phase 1a Open-label Dose Escalation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of the Candidate Plasmodium falciparum Merozoite Surface Protein-1 (MSP-142) Administered Intramuscularly with GSK Biologicals’ Adjuvant System AS01B in Healthy Malaria-Naive Adults, 2008, ASTMH

MSP-1 (FVO allele)
- Spring M et al; Growth inhibitory activity of antibodies generated to vaccine candidate Plasmodium falciparum Merozoite Surface Protein-1 (MSP-142) Administered Intramuscularly with GSK Biologicals’ Adjuvant System AS01B in Healthy Malaria-Naive Adults, 2009 ASTMH

AMA-1 (3D7 allele)

- Thera et al; Randomized, controlled, phase 2B clinical trial to evaluate the safety, immunogenicity, and efficacy of WRAIR’s AMA-1 malaria vaccine (FMP2.1) adjuvanted in GSK Biologicals’ AS02A vs Rabies Vaccine in 1-6 year old children in Bandiagara, Mali, ASTMH 2009
Toward 2nd generation malaria vaccines

A. CS-based vaccines

1. Prime-boost regimens that augment successful 1st generation recombinant protein-based RTS,S vaccines

   • 2011; Ad35-RTS,S prime boost study – GSK, Crucell, Walter Reed Army Institute of Research, U. Maryland

   • 3 sequential cohorts; 56 subjects each
   • Double blinded study
   • Randomized equally to:
     • a) three doses RTS,S/AS01B
     • b) 1 dose Ad35CS, 2 doses RTS,S/AS01B
     • c) 0, 1, 2 month intervals
     • d) *P. falciparum* challenge
1. Soluble PfCS – full-length
   • 90-100% sterile protection using transgenic P. berghei/PfCS parasite challenge
   • Adjuvant – IDRI
   • GMP production

2. Particle-based CS vaccines
   a) ICMVs – Interbilayer-Cross-linked Multilamellar Vesicle (MIT)s
   b) Q-beta – phage display (Cytos)
3. Nanoparticles – self assembling polypeptides
   - B cell epitopes; CS repeats
   - Pf CD8 epitopes
   - Universal CD4 epitope

4. Genetically-modified killed bacteria
   (Shigella expressing CS, CelTOS, MSP1)
1. **Sporozoite – Ookinete antigen**
   a) Recognized by PBMC from subjects immunized with irradiated spz.
   b) PfCelTOS immunized mice protected against heterologous challenge with P. berghei parasites
   c) Mechanism of protection – antibody and CD4 and CD8
   d) Functional role in cell transversal in host and mosquito
   e) Compatible with IDRI adjuvants
   f) Phase 1/2a clinical trial – September 2011
P. vivax vaccines

1. Establish human challenge model
   - Challenge # 1 November 2009; 6 subjects
   - Challenge # 2 May 2010; 6 subjects

2. VMP001/AS01B Phase 1/2a clinical trial
   - July 2010 – November 2010
   - soluble PvCSP chimeric antigen – VK210/VK247
   - 10 ug, 30ug, 60 ug Ag doses with AS01B adjuvant
   - Pv human challenge to assess efficacy – Nov 2010
   - Partners – GSK; funding MVI