

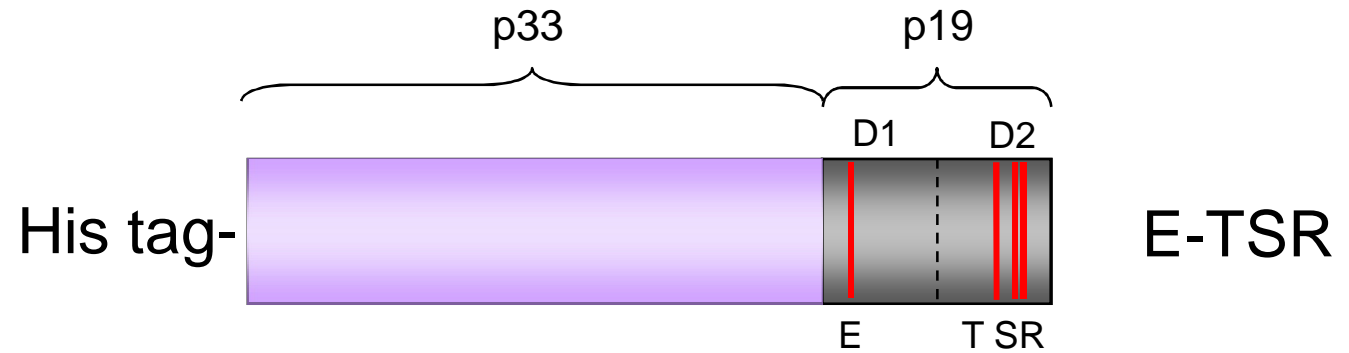
U.S. Military Malaria Vaccine Program
USAID Malaria Vaccine Development Program
Field Trials Collaboration

Outline

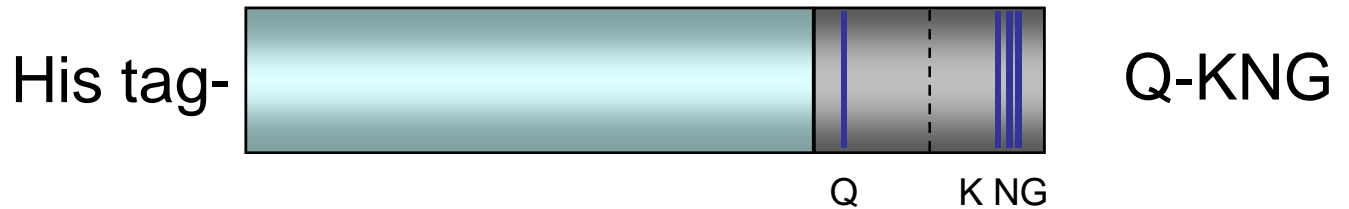
- **Three vaccines**
 - **MSP1**
 - **FMP1/AS02A**
 - **FMP010/AS01B**
 - **AMA1**
 - **FMP2.1/AS02A**
- **Three topics**
 - **Vaccine concept and rationale**
 - **Clinical Development Plans**
 - **Influence of postulated vaccine effect on parasite relationship on efficacy trial design**

WRAIR MSP1₄₂ Antigens

FMP1
MSP1₄₂ (3D7)
Angov, et. al. (2003)
MBP, 128, 195-204



FMP010
MSP1₄₂ (FVO)
Unpublished
Codon harmonized



1st Generation Vaccines

- **FMP1/AS02A (MSP1 3D7)**
 - Antigen developed at WRAIR (Lyon/Angov)
 - Formulated with GSK adjuvant AS02A
 - Field trials
 - Conducted at USAMU-K/KEMRI (Kenya) and Bandiagara Malaria Project, MRTC (Mali)
 - Supported by MVI/USAID/WRAIR/NIAID/MRTC
- **FMP2.1/AS02A (AMA1 3D7)**
 - Antigen developed at WRAIR (Lanar/Dutta)
 - Formulated with GSK adjuvant AS02A
 - Field trials
 - Conducted at Bandiagara Malaria Project, MRTC (Mali)
 - Collaboration: Center for Vaccine Development, UMD
 - Supported by NIAID/USAID/MRTC

1st Generation Vaccines Concept and Rationale

- **FMP1/AS02A & FMP2.1/AS02A have similar rationale**
 - **Test hypothesis of allotype transcending immunity**
 - **Initial study of vaccine allotype relationships**
 - **Analysis of immune response to vaccines in face of coexisting ongoing malaria transmission**

1st Generation Vaccines Clinical Development Plans

- **FMP1/AS02A & FMP2.1/AS02A plans similar**
 - **U.S. Phase 1a safety**
 - **Endemic areas**
 - **Phase 1b (adult) safety**
 - **Phase 1b (pediatric) safety**
 - **Phase 2b (pediatric) preliminary efficacy**
 - **If high efficacy: further development as stand alone**
 - **If medium efficacy: development in combination with RTS,S**
 - **If no efficacy: stop development of formulation**

1st Generation Vaccines

Influence of presumed vaccine mode of action on trial design

- **Presumed vaccine mode of action is direct interference with blood stage parasite growth and development by**
 - Interaction of antibody with merozoite associated antigen
 - Parasite killing through immune mediate cytokine cascade
- **CMI vs liver stages ?**
- **Clinical episode chosen as unit of disease occurrence**
 - Anti blood stage parasite immunity expected to retard disease
 - Immunity to clinical malaria a more direct predictor of public health impact
- **Time to first episode chosen as primary measurement parameter**
 - Most sensitive methodology
 - Trade off is public health impact interpretation

1st Generation Vaccines

Current Status of FMP1/AS02A

- **Vaccine induced high antibody titers (ELISA)**
- **Time to first episode in vaccinees no different than in comparator group (rabies vaccine)**
- **No evidence of a vaccine effect on parasitemia**
- **No evidence of increased serum growth inhibitory activity as a result of vaccination**
- **No plans for further development of formulation**
- **Allelic analysis ongoing**

Allele distribution*

- 400 children (12-47 month) stratified by age into two groups (vaccine and placebo)
- Blood samples for RT-PCR collected and scored as clinical malaria (fever > 37.5 + PDNS >0); parasite density (PDNS) determined by thick & thin blood smear
- Vaccine haplotype: **E – T – SR** (non-vaccine haplotype **Q – K – NG**)
- Vaccine alleles: position 1644 (**E/Q**); 1691 (**T/K**); 1699 & 1701 (**SR/NG**)
- Total # samples for analysis included presence of at least 1 allele at each locus at positions 1644, 1691, and 1699/1701 = 998 cases

# samples	Locus 1644 (E/Q)	Locus 1691 (T/K)	Locus 1699&1701 (SR/NG)
Single allele per sample	518 E = 394 Q = 124	722 T = 65 K = 657	753 SR = 45 NG = 708
Mixed allele per sample	480 (E and Q)	276 (T and K)	245 (SR and NG)

*Ockenhouse, 2008, unpublished

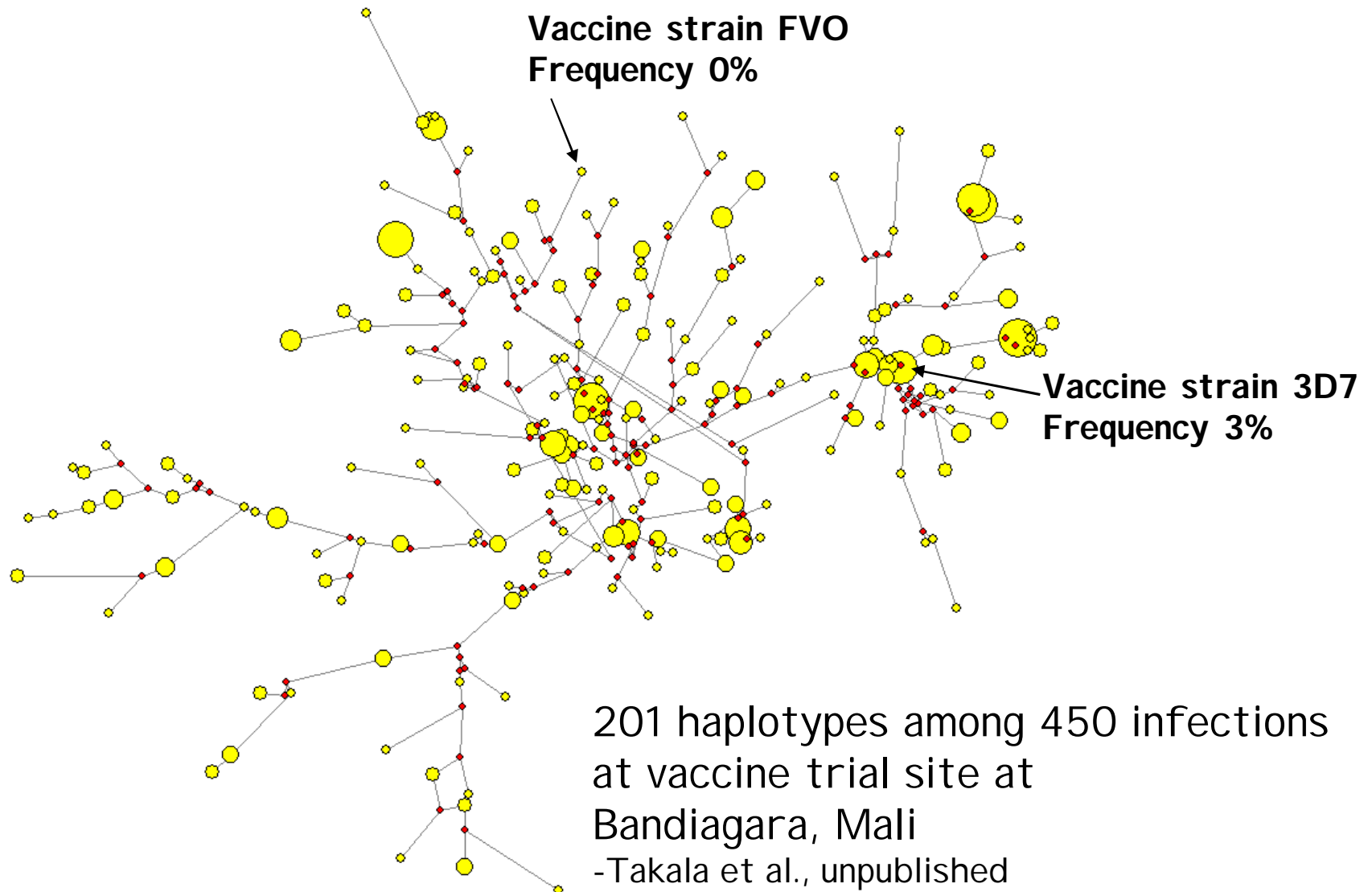
1st Generation Vaccines

Current Status of FMP2.1/AS02A

AMA1 3D7

- **Phase 2b (pediatric) still blinded**
- **Allelic analysis from phase 1b indicates extreme polymorphism**

Genetic diversity of blood stage vaccine antigen AMA-1



2nd Generation MSP1 Vaccine

The approach

Build on 1st generation results and take advantage of current opportunities

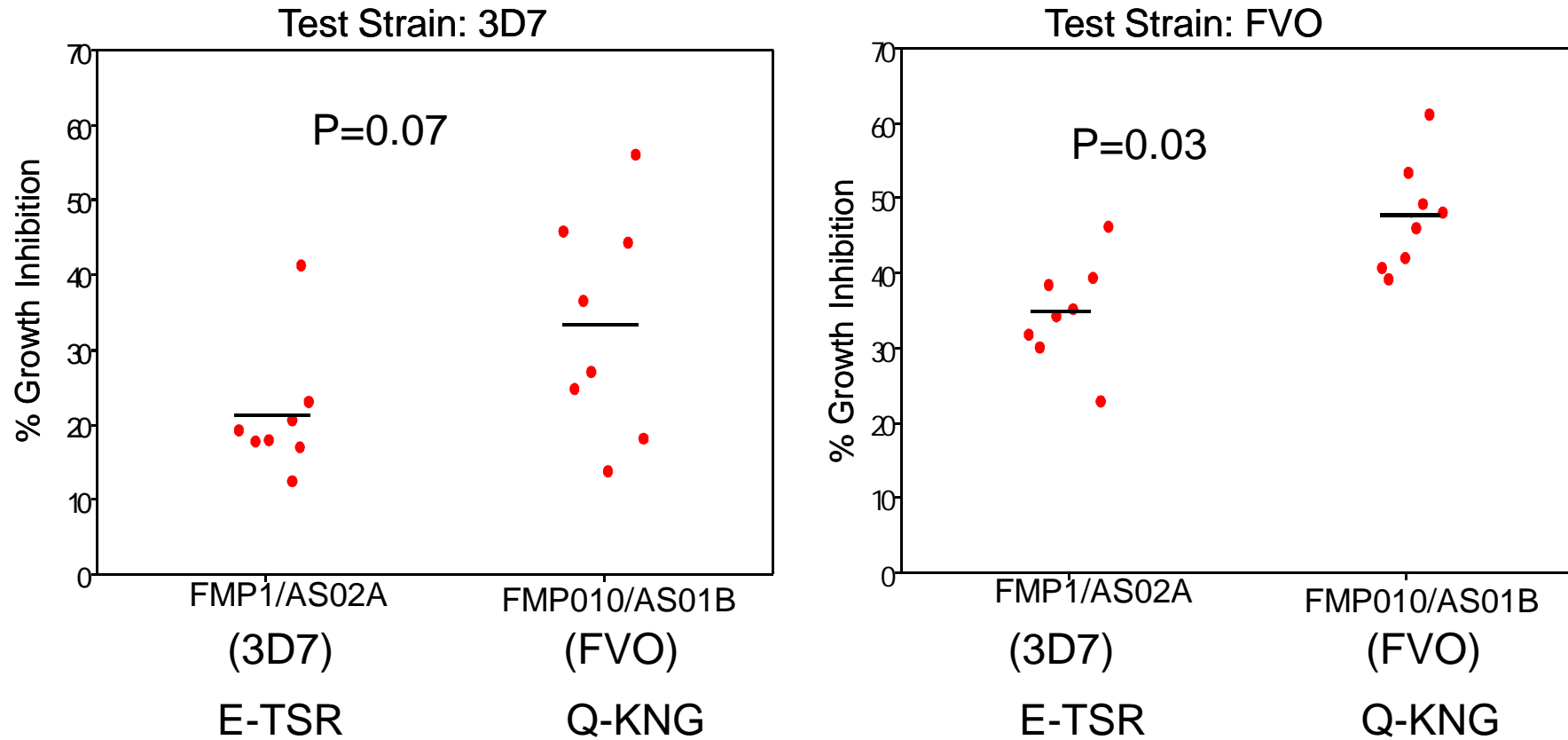
– Available data suggests that allelic specificity plays a role in protective efficacy

– FMP010

- contains two of the three most prevalent alleles (K & NG)
- provides broader GIA specificity than FMP1
 - Antibody against FMP010 inhibits growth of 3D7 parasites better than antibody against 3D7
- is available as clinical product

Analysis of Rabbit IgGs for Growth Inhibitory Activity (by WRAIR miniaturized GIA-384 wp format)

Tested at 2mg/mL Purified IgG (Final)



Angov and Bergman-Leitner, 2008, unpublished

FMP010/AS01B Development Plan

- **Phase 1a & 1b trial (ongoing)**
- **Progress to pediatric studies if:**
 - **Safe in Phase 1a and 1b**
 - **Phase 1a trial sera meets immunogenicity criteria:**
 - Greater than 30% GIA at 1/5 serum dilution in at least 70% of subjects against both 3D7 (E-TSR) and FVO (Q-KNG) parasites
 - **Phase 2b trial would be powered to test efficacy vs Q-KNG (FVO)**