



Malaria Vaccines 2002

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We believe...

...that sustained control of malaria cannot be achieved without a malaria vaccine...



Our Goal

To develop a malaria vaccine that is...

... safe

...effective

...affordable for all

Malaria Vaccines 2002

- How far have we come?
- Where are we going?
- How will we get there?
- Who is leading the way?
- Are we there yet?

How Far Have We Come?

Highlights

- Product profiles under serious discussion
- More vaccines being tested than ever before
- Pediatric malaria vaccine trials in Africa
- Unparalleled level of public/private funding

Where Are We Going?

Product profile (minimum acceptable?)

- For children 3 months and older
- Safe and well tolerated
- At least 50% efficacy against clinical malaria
- May require annual booster
- No “malaria rebound” effect

Product Profile: Example of Desired Characteristics

- For all age groups (6 wks +)
- Safe, affordable, compatible with EPI
- Efficacy > 70% against clinical malaria
- Efficacy >30% against severe malaria
- Durable (1-3 years?)
- Decreases childhood mortality

Which Leads Us to an Indication

- For active immunization of individuals (6 weeks of age and older) in endemic areas against *Plasmodium falciparum*, to prevent clinical malaria, **including severe disease and death** due to falciparum malaria
- The indication informs the series of clinical studies required for licensure

How will we get there?

Component Vaccines Are Being Developed Independently

Pre-erythrocytic
(Sporozoite – liver)

N = 8

Sexual
(Mosquito)

N = 1

Asexual
(Blood)

N = 3



Big
Progress!

Leading the Way

Recent Vaccine Progress
Reported at MIM 2002

Progress in Transmission Blocking Vaccines

- Transmission blocking assay allows rapid screening of candidates
- Leading targets have been technically difficult to produce (proper folding)
- Proof of concept fairly direct, but validation in field very complex
- Importance of staying focused on this strategy – impact could be huge

PVS25 Transmission Blocking Vaccine (MVDU, NIAID)

- PVS25 (*P. vivax*) has been successfully expressed and purified, PFS25 coming along
- Preclinical immune sera completely block development of oocytes in mosquitoes
- Phase I clinical trial of PVS25 in progress

Progress in Blood Stage Vaccines

- Surface expressed antigens on merozoites and schizonts
- Strong epidemiologic basis plus protection in rodent and primate models
- Antibodies directed against epitopes that are frequently conformational and strain-specific

MSP-3 Long Synthetic Peptide (Institute Pasteur / EMVI)

- B and T cell epitopes from MSP-3 identified by analysis of immune sera
- Induce cytophilic antibody (ADCI)
- Phase I trial with alum, Montanide inhibitory antibodies develop in 30-50%
- Recombinant protein version in development to increase response rate

GLURP Long Synthetic Peptide (Staten Serum Institut / EMVI)

- Long synthetic peptide from glutamine rich protein (GLURP) on schizont surface
- Includes conserved B and T epitopes, induces cytophilic Ab
- Phase I study revealed significant reactogenicity issues
- Recombinant in development as back-up strategy

MSP-1 Recombinant Protein (FMP-1)

- *E. coli* expressed protein derived from C terminal 42 kD fragment
- Developed at WRAIR with support from USAID, GSK, NIMR
- Formulation with ASO2 adjuvant was immunogenic in non-immune adults (US)
- Overview of Phase I trial in Kenyan adults reported at MIM (in progress)
- Possible Phase I pediatric trial 2003

Project supported by MVI

MSP-1 42 kD (*E. coli*)

Strengths

- Scalable *E. coli* expression
- FVO version protects Aotus

Weaknesses

- Protection required Freund's adjuvant and was allele-specific
- May require two allelic forms

Progress in Pre-erythrocytic Stage Vaccines

- Protects from sporozoite challenge
- Potential market as traveler's vaccine
- Validation of technology platforms
- Most well studied vaccine type

Pre-erythrocytic Vaccines Based on CS Protein

Mechanism of action includes:

- Antibodies against CS repeats
- INF- γ from CD4+ and CD8+ T cells

CS Repeats Expressed in HepB Core Particles (Apovia)

- Includes CS repeat plus universal T cell epitope
- Stimulates high antibody titers in mice
- Two Phase I studies underway
- Testing with and without alum as adjuvant

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HepB core Particles

Strengths

- Commercially viable expression system
- Highly immunogenic in animal models

Weaknesses

- Limited capacity for foreign sequences
- Primarily stimulates antibody responses
- No protection data available yet

CS Peptides (U. Lausanne)

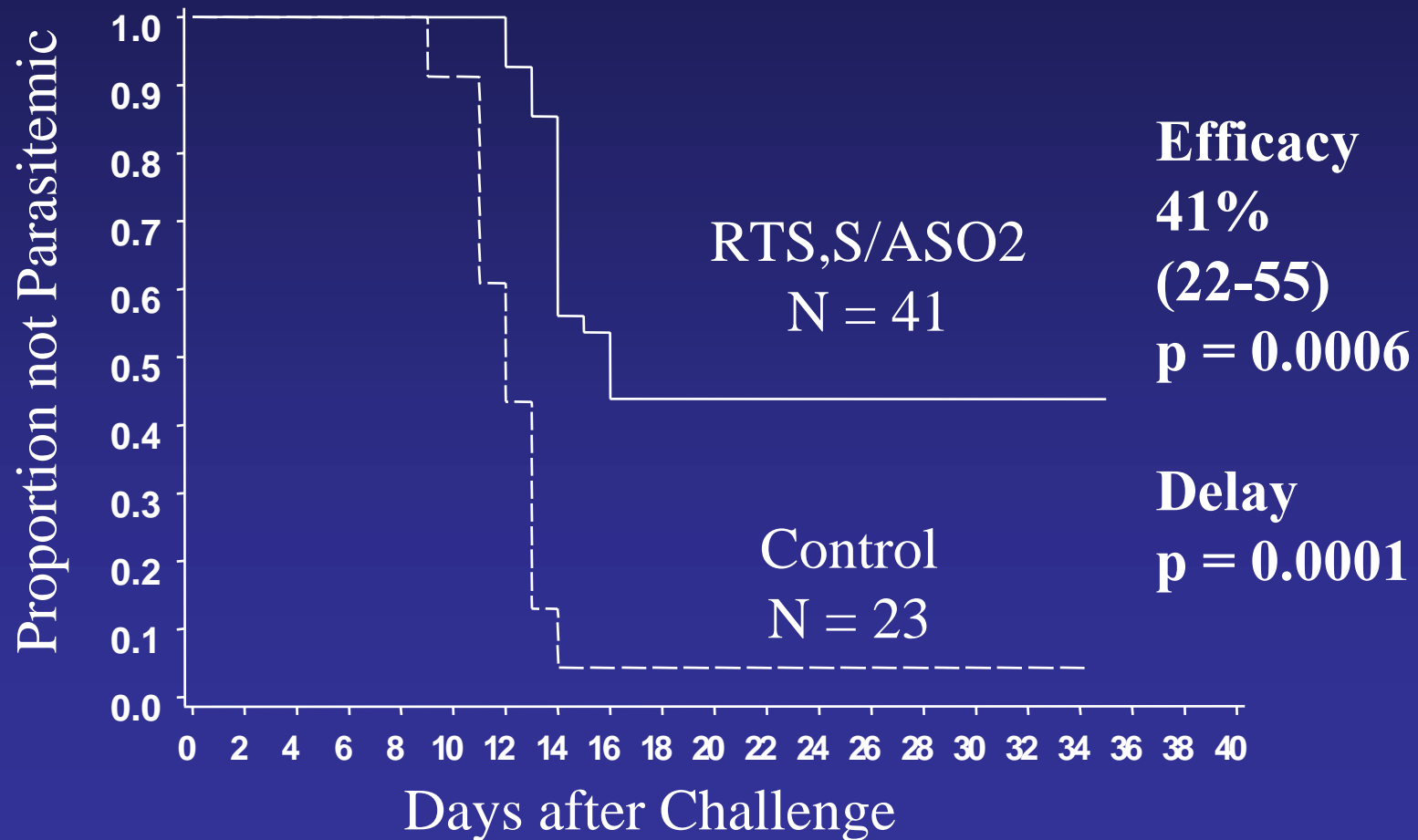
- Peptide 282-383 from the CS protein
- Phase I studied with alum or Montanide 720
- High titer antibodies, T help and CTL responses
- No industrial sponsorship
- No protection data yet

RTS,S/AS02 Vaccine (GSK)

- HBsAg particles incorporating CS protein with AS02 adjuvant
- Safe and well tolerated by children >1 year of age
- Current benchmark for efficacy 30-80% (challenge) and 70% in immune adults (field trial in The Gambia)
- Phase I pediatric trials underway in Mozambique, Phase IIb planned for 2004?

Project supported by MVI

Combined Efficacy Data for One, Two or Three Doses of RTS,S/ASO2 (WRAIR)



RTS,S/AS02 Vaccine (GSK)

Strengths

- Consistent, reproducible, boostable efficacy
- High seroconversion rates against CS
- Very immunogenic HepB vaccine
- Compatible with EPI schedule

Weaknesses

- Durability of efficacy (<6 months)
- Novel adjuvant raises safety barrier

Malaria Vaccines Based on Other Pre-erythrocytic Antigens

- Antigens based on analysis of immune populations, irradiated sporozoite model, genome
- Epitopes that drive CD8+ and CD4+ T cells to express INF- γ *in vitro* and kill liver schizonts

DNA and Attenuated Viral Vectors Expressing Malaria Ags (Oxford)

- Prime-boost with DNA, Fowlpox or MVA expressing multi-epitope string+TRAP (ME-TRAP)
- Several trials completed, some protection vs sporozoite challenge
- Phase I pediatric studies in progress, Phase IIb studies planned in the Gambia

DNA, Live Vector Prime-Boost

Strengths

- Inclusion of multiple epitopes/targets
- Strong stimulation of cellular responses
- Evidence for protection in challenge studies

Weaknesses

- Weak stimulation of antibody responses
- Complex regulatory approval
- Uncertain commercial development path

DNA Vaccines Encoding Pre-erythrocytic Stage Antigens (NMRI/VICAL)

- Multiple DNA vaccines tested alone and in combination in Phase I/IIa
- No protection observed in humans with homologous challenge
- DNA vaccines can be boosted by sporozoites, RTS,S
- Studies ongoing to enhance immunogenicity (prime-boost)

DNA Vaccines

Strengths

- Inclusion of multiple genes
- Strong stimulation of cellular responses
- Evidence of protection in rodent models

Weaknesses

- Not yet optimized for humans
- Protection in primates requires poxvirus boost
- DNA and live viruses raise safety barrier
- Complex regulatory pathway to licensure

Are We There Yet?

- Three vaccines will have begun safety studies in young children in malaria endemic regions by end of 2003
- Earliest proof-of-concept studies begin 2004
- If successful, could lead to expanded Phase II and to Phase III by 2006-2007
- But clearly, there is a long way to go....

The Good News

- Many new investigators are involved
- North-South collaborations are in place
- Vaccines for each stage are being tested
- Industry sees need to plan for success
- Greater access to public sector funding
- A growing sense of momentum

The Not So Good News

- Critical demand for investigators with strong clinical development skills
- Vaccine pipeline exceeds \$\$ and resources
- Complex strategies abound, but most are currently too unwieldy to be implemented
- Risk is still seen as too high for most industrial sponsors

The Way Forward...

- Continue to refine product profiles
- Encourage greater public-private partnering
- Seek buy-in on strategies from industrial sector
- Establish and live by Go/No Go decisions
- Demonstrate the ability to make hard choices

“Malaria Delenda Est”

