Ad35.CS.01 – RTS,S/AS01 prime boost
second generation malaria vaccine candidate

Johan Vekemans MD, PhD
Malaria vaccines
Global Vaccine Development
GSK Biologicals

NIH 2012
The need for a malaria vaccine: targets

Malaria Vaccine Technology Roadmap:

License by 2015 the first generation *P falciparum* malaria vaccine with 50% efficacy against severe malaria and deaths and lasts longer than one year

License by 2025 a *P falciparum* malaria vaccine of more than 80% efficacy against clinical malaria disease and last longer than four years
The pre-erythrocytic malaria vaccine development strategy

- Humoral responses: antibodies to sporozoites will block invasion of hepatocytes
- CD4$^+$ (TH1) and CD8$^+$ (CTL) effector T lymphocytes kill intra-hepatic parasites through IFN-$\gamma$ secretion or direct cytotoxicity

→ reduce incidence of new infections, hence malaria disease, severe disease, death and reducing transmission
The strategy: RTS,S antigen and Adjuvant Systems

The **RTS,S** vaccine particles:
- The **R** and **T** regions from CSP are fused to the Hepatitis B Surface protein (HBsAg)
- The fusion protein is co-expressed with HBsAg in yeast (*Saccharomyces cerevisiae*) where they spontaneously assemble into mixed particles

The **AS01** adjuvant system:
- Adjuvant system designed to induce strong antibody and Th-1 cell mediated immune responses
- Consists of MPL, QS21 and liposomes

---

**The Circumsporozoite Protein:**
- is the major surface protein of the sporozoite, also expressed by early liver forms
- liver entry function
- recent advances: conformational states, interferes with host cell pathways

**The RTS,S vaccine particles:**
- The **R** and **T** regions from CSP are fused to the Hepatitis B Surface protein (HBsAg)
- The fusion protein is co-expressed with HBsAg in yeast (*Saccharomyces cerevisiae*) where they spontaneously assemble into mixed particles

**The AS01 adjuvant system:**
- Adjuvant system designed to induce strong antibody and Th-1 cell mediated immune responses
- Consists of MPL, QS21 and liposomes

---

What do we know about RTS,S-induced protection?

Key RTS,S/AS01 vaccine efficacy results

Phase II Kenya & Tanzania, 5-17 mo old:

53% (95CI: 28-69) against malaria over 8 mo

Bejon et al. NEJM 2008; 359: 2521-32

Phase II Tanzania, Ghana & Gabon, 6-10 wks old, with DTPw-HepB/Hib co-administration:

53% (95CI: 26-70) against malaria over 17 mo


Phase III 11 research centres across Africa, 5-17 mo old:

56% (97.5CI 51-60) against malaria over 12 months

The RTS,S Clinical Trials Partnership. NEJM 2011; 365: 1863-1875
RTS,S/AS01 induced immune responses

- High and persistent Abs (ELISA) vs CSP repeat epitope
- B cell memory responses (B-cell ELISPOT)
- CD4+ T cell responses, characterized by secretion of IL2, TNFα and IFN-γ. Still detectable 1 year post immunization
- No CD8+ T cells detected in a consistent way

Which effectors mediate protection?

- Consistent association between anti-CSP (anti-repeat region) antibody responses and protection
- To a lesser degree, an association between magnitude of CD4+ T cell response (especially TNF-α producing) and protection has been found.
What role for CD4 T-cells in RTS, S/AS01 induced protection?

- Protective effectors or bystander helpers for antibody-mediated or other responses?
- Can MHC Class II restricted effectors affect sporozoite or ELF-infected hepatocytes?
  - Upon viral infection or inflammation hepatocytes express MHC Class II (sporozoites, ELF?)
  - Plenty of professional APCs in the liver; CSP shedding during sporozoïte gliding through liver sinusoids: alternative antigen presentation possibilities
- Arguments supportive of an important role in response to RTS, S:
  - Role of the inclusion of T-cell epitopes containing C-terminal flanking region in addition to the repeat region
  - Role of the particulate structure of the antigen construct
  - Role of adjuvants
  - Associations in vaccine efficacy studies
An improved vaccine against *P falciparum*

- Prime boost immunization with different vaccine constructs targeting the same antigens: avenue to strengthen / broaden immune responses

- Prime with Ad35.CS (Crucell), boost with RTS,S/AS01

- Ad35.CS: Ad35 genome with E1 and E3 regions deleted. Replication-incompetent. Incorporates the full length CS gene. Schematic representation of the CS:
Ad35 CS x RTS,S/AS01 Prime-Boost

Proof of principle in NHP

- Ad35.CS x RTS,S/AS01: superior CD4 T cell responses re RTS,S/AS01 alone
- No Ag-specific CD8 T cell responses detected
Ad35.CS x RTS,S/AS01 prime boost: proof of concept Phase I/IIa sporozoite challenge study

- Target: 50% increase in vaccine efficacy with prime boost compared to RTS,S/AS01 alone

- R,DB,C trial in malaria-naïve American adults 3 IM immunizations 0-1-2 months schedule. Total sample size (N=168 outside infectivity controls)

- Study groups: ARR, RRR, infectivity controls for each challenge day

- Pf sporozoite challenge 3 weeks after vaccination

- Translational research: Systems Biology endpoints.

- Futility analysis after 1/3 of the total cohort, pre-defined stopping criteria if target 50% increase in vaccine efficacy (ARR vs RRR) can be excluded
Lessons and key questions

- Robustness of the sporozoite challenge model
  - control of exposure and highly specific endpoint
  - allows dissection of protective mechanisms
  - should support down selection of vaccine candidates before field trials
  - answer key vaccinology questions beyond malaria?

- Need for the right immune response against the right antigen. Two avenues for strengthening RTS,S/AS01
  - strengthen anti-CS immune response
    - what evidence supporting CS as a good target for liver stage cell mediated immunity?
  - combine antigens
    - need to demonstrate the value of each antigen individually
    - careful consideration of multiple hurdles: vaccine development complexity, ultimate implementation logistic questions
Acknowledgments

- GSK: Rip Ballou, Joe Cohen, Yannick Vanloubbeek, Gerald Voss, Danielle Morelle, Erik Jongert, Amanda Leach, Marc Lievens
- MVI: Rich Welrzin, Ashley Birkett, Didier Leboulleux, Cynthia Lee, Ulli Wille- Reece
- WRAIR: Chris Ockenhouse, Jason Regules, Donna Tosh, Ann Stewart
- Crucell: Maria Grazia-Pau, Jerry Sadoff, Jenny Hendriks, Isabella Versteegh
- University Maryland: Kirsten Lyke, Matthew Laurens
- NIH: Steve Rosenthal. NIAID/DMID supplied Ad35.CS.01
- Emory University: Bali Pulendran
- Seattle Biomedical Research Institute: Alan Aderem
- All partners in the RTS,S project
- Study volunteers and communities