IMMUNITY TO MALARIA

Fidel Zavala
Plasmodium Life Cycle

MOSQUITOES

SPOROZOITES

LIVER STAGES

MEROZOOTES

ASEXUAL BLOOD STAGES

RING

TROPHOZOITE

SCHIZONT

GAMETOCYTES

F. Zavala
Age-Related Changes in Anti-Malarial Antibody Levels in Relation to Parasite Rates and Mortality in a West African Population
Plasmodium Stages

SPOROZOITE  
(Serum)

LIVER  
(Hepatocytes)

BLOOD  
(Erythrocytes)

MEROZOITES  
(Serum)

* LIVE IN DIFFERENT ENVIRONMENTS
* EXPRESS DIFFERENT ANTIGENS
* SUSCEPTIBLE TO DIFFERENT IMMUNE MECHANISMS

F. Zavala
Immune Responses to Pre-Erythrocytic States
• Mosquitoes inject dozens of sporozoites into the dermis

• Parasites reach the blood and infect hepatocytes
Sporozoite-Induced Immune Response

• Normal exposure to parasites does not induce a response strong enough to protect against infection.
• In experimental immunizations, large immunizing doses are required to achieve protection.
Immunization of Humans with \textit{P. falciparum}-Infected Irradiated Mosquitoes

\textit{ANTIGENS?}
\textit{PROTECTIVE IMMUNE MECHANISMS??}

Bull WHO 1978;57(suppl 1):263
Antibodies Abolish Sporozoite Infectivity

Photograph courtesy of Masamichi Aikawa
Antibodies Against The Sporozoite Surface Inhibit

- Parasite Motility
- Hepatocyte Invasion

*They can confer sterile immunity...*
Sterile Protection Against Sporozoite-Induced Infection

• High levels of antibodies

• High binding affinity

• Maintained for a long time
Immunity To Malaria Liver Stages

\[ \alpha, \beta \text{ CD4}^+ \text{ T cells} \]

\[ \alpha, \beta \text{ CD8}^+ \text{ T cells} \]

\[ \gamma \delta \text{ T cells?} \]
\[ \text{NK/NKT cells?} \]
Persistence of the CD8+ T Cell Response After a Immunization with Sporozoites

F. Zavala
Plasmodium Life Cycle

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ANTIBODIES

T-CELLS

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Natural Immunity?

- It is difficult to become immune by natural exposure

- Serum titers from natural infected individuals to sporozoite antigen in IFA is in low hundreds in contrast to immunized individuals with titers in thousands
Identification Of *P. Falciparum* CD8+ T-Cell Epitopes Recognized By Humans

Specific amino acid residues composing epitopes from CSP, SSP2, EXP1, LSA1, and PfS16 proteins

*But at very low levels.....*
Immunization of Humans with *P. falciparum*-Infected Irradiated Mosquitoes

This is a vaccine but is impractical...

Bull WHO 1978;57(suppl 1):263
Vaccine Development

The CS protein is present in sporozoites and liver stages.

- Induction of specific antibodies
- Induction of anti-liver stage T cells
Probability of Remaining Free of *P. falciparum* Infection During Fifteen Weeks of Surveillance in 1998

*Week 0 of surveillance began in September, 1998, 14 days after dose 3 of vaccine was administered.*

Adapted by CTLT from Bojang et al. Lancet 2001, 358;1927
Immune Responses to Erythrocytic Stages
Passive Transfer of Immunity to *P. falciparum* in Children

- **Gambian gamma globulin**
- **Untreated**
- **Gamma-free serum**
- **“U-K” gamma globulin**

**Mean Trophozoite Count/cm³**

Time (weeks): 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
Early Stages of Red Blood Cell Invasion by the Malaria Merozoite

1. Initial Attachment & Reorientation
   - P. vivax
   - PvRBP-1
   - PvRBP-2
   - Pyoelii
   - Py235?
   - MSP-1 complex?
   - AMA-1?
   - MAEBL?

2. Irreversible Attachment & Junction Formation
   - Secretion of microneme contents (e.g., DBL-EBP)
   - Rhopty discharge
   - High affinity adhesion mediated by DBL-EBP?
   - Inward motion driven by actomyosin motor

3. Parasitophorous Vacuole Formation & Invasion
   - Further rhoptry and microneme discharge
   - Release of dense granule contents (PfSUB-1 & PfSUB-2)
   - Vectorial trafficking, proteolytic processing & shedding of DBL-EBP
   - Proteolytic processing/shedding of MSP-1 complex

Adapted by CTLT from Parasitology Today
Antibodies Inhibit Merozoite Infection of Erythrocytes

F. Zavala
Antigens Of Asexual Blood Stages Recognized By Protective Immune Responses

- Merozoite surface protein-1
- Merozoite surface protein-1 -2
- Dense granule-RESA
- Microneme- EBA-175

- Rhoptry
  - AMA-1, rhoptry-associated protein 1 and 2
  - Rhop-1 and 2

- Red blood cell surface
  - PfEMP-1
  - Pf332
  - Rosettin
Immunization with Merozoite surface antigen protected monkeys from death during course of infection of *Plasmodium falciparum* (FUP strain) in vaccinated monkeys (*Aotus trivirgatus*)
Monocyte-Antibody Mediated Inhibition of Parasite Growth

F. Zavala
“Knobs” In \textit{P. Falciparum} Infected Erythrocyte

D. Sullivan
P. falciparum Cytoadherence

Adapted by CTLT from Cooke, Wahlgren and Coppel, 2000, Parasitology Today, 16, 416-420.
Extensive Antigen Polymorphism in Malaria Parasites

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Immune Responses to Sexual Stages
Plasmodium Life Cycle

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Developmental Stages of the Malaria Parasite in the Mosquito Midgut

<table>
<thead>
<tr>
<th>Gametocytes</th>
<th>Gametes</th>
<th>Zygote</th>
<th>Ookinetes</th>
<th>Oocyst</th>
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</thead>
</table>

Potential Target Antigens for Transmission Blocking Vaccine

- Pfs2400
- Pfs230
- Pfs48/45
- Pfg27/25
- Pfs25
- Pfs28
- Chitinase
- Mosquito Protease
TBV Concept

Immunize people

Antibodies picked up by the mosquito during blood feed will stop parasite’s development in the mosquito

(NON-INFECTIOUS MOSQUITOES)

No further Malaria Transmission
Immunopathology
Anti-Parasite Immune Responses May....

* Abolish parasite development

* Attenuate parasite infection

* Be ineffectual or irrelevant

* Exacerbate disease
CEREBRAL MALARIA: PATHOGENESIS

- Infected RBC
- Malaria "toxins" (GPI?)
- Macrophages?
- T-cells?
- HYPOGLYCEMIA
- METABOLIC ACIDOSIS
- CYTOKINES: LT, TNF-α, IFN-γ...
- ENDOTHELIAL CELLS
  - ↑ adhesion molecules
  - ↑ nitric oxide?

SEVERE MALARIA

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Severe Malaria

_CEREBRAL MALARIA:_
confusion, stupor, delirium, convulsions, paralysis, coma…
Cerebral Malaria: Obstruction Of Small Capillaries By Parasitized Erythrocytes

**Sequestration of Trophozoites and Schizonts**

CDC/Dr. Melvin
Anemia

- Erythrocyte destruction
  - Release of parasites
  - Phagocytosis

- Dyserythropoiesis
  - TNF-α
  - INF-γ
Vaccine Targets

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ALL STAGES...
Immunity Against Malaria

PARTIAL:
- Attenuates Infection

STERILE:
- Abolishes Infection