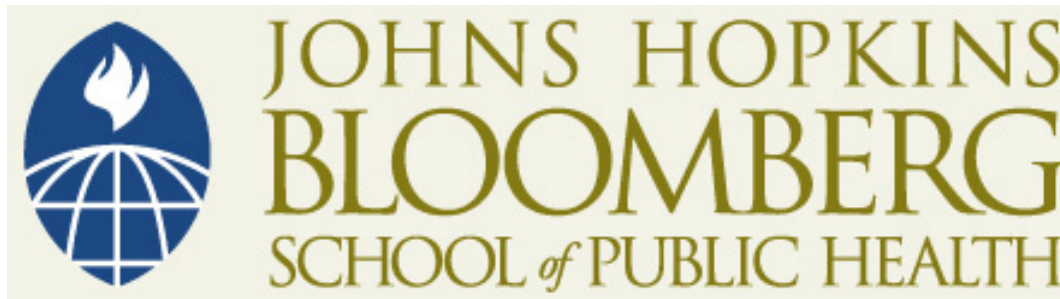


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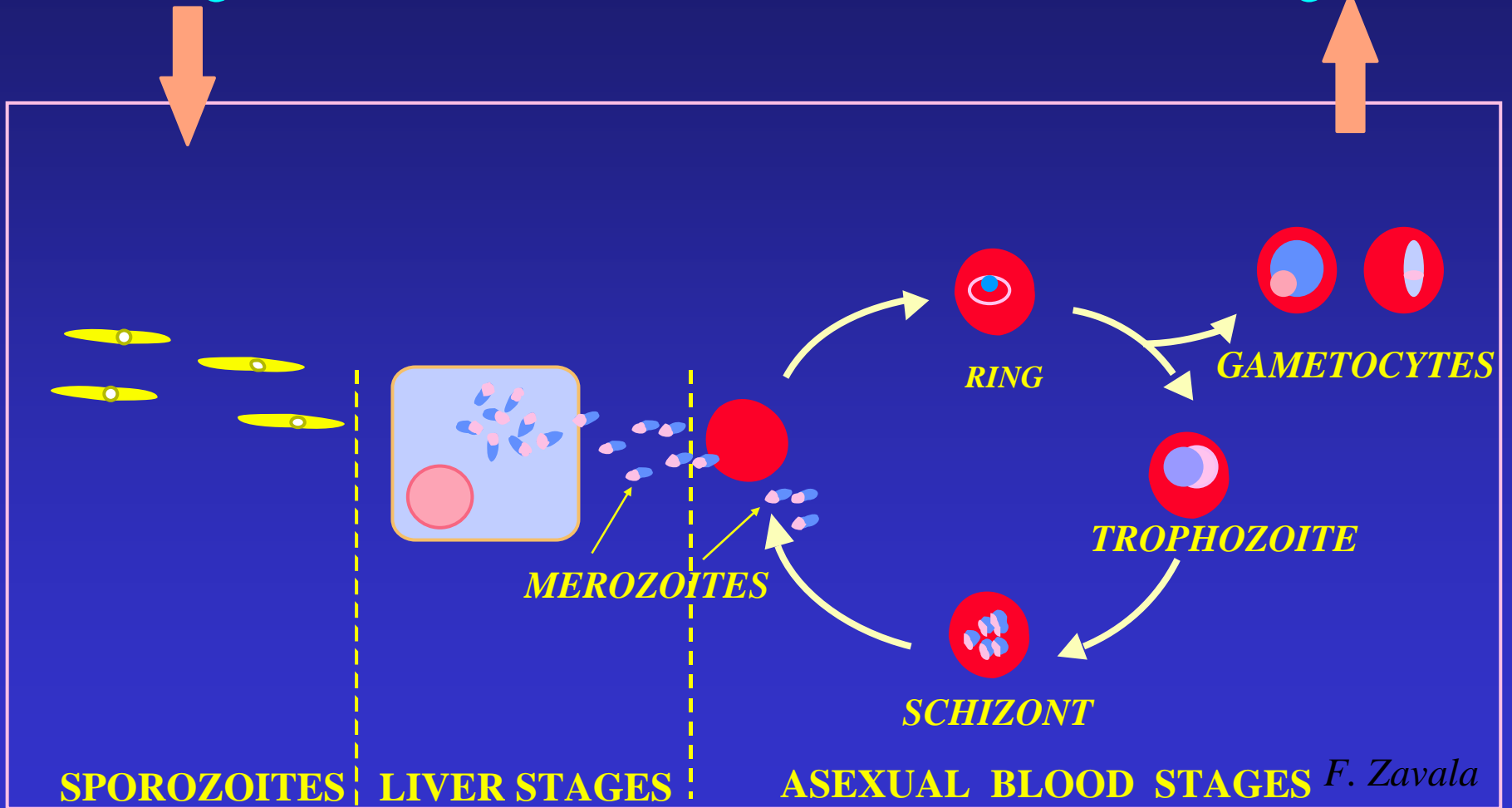
IMMUNITY TO MALARIA

Fidel Zavala

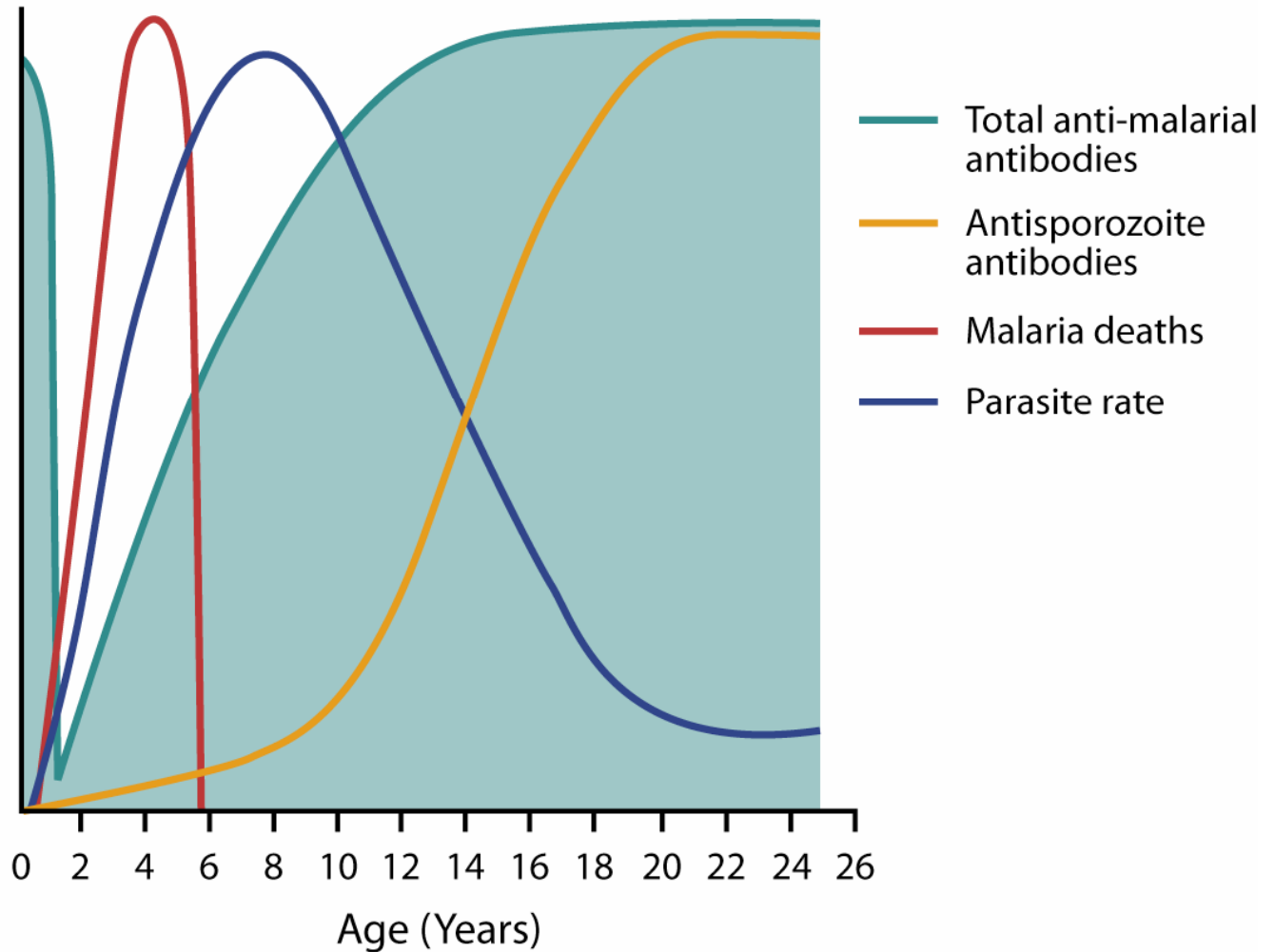
Plasmodium Life Cycle

MOSQUITOES

MOSQUITOES



Age-Related Changes in Anti-Malarial Antibody Levels in Relation to Parasite Rates and Mortality in a West African Population

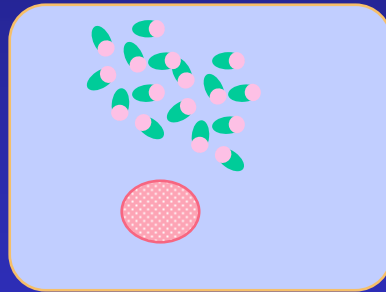


Plasmodium Stages

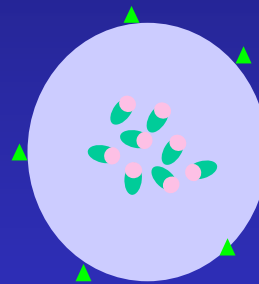
SPOROZOITE
(Serum)



LIVER
(Hepatocytes)



BLOOD
(Erythrocytes)



MEROZOITES
(Serum)



F. Zavala

* LIVE IN DIFFERENT ENVIRONMENTS

* EXPRESS DIFFERENT ANTIGENS

* SUSCEPTIBLE TO DIFFERENT IMMUNE MECHANISMS

Immune Responses to Pre-Erythrocytic States

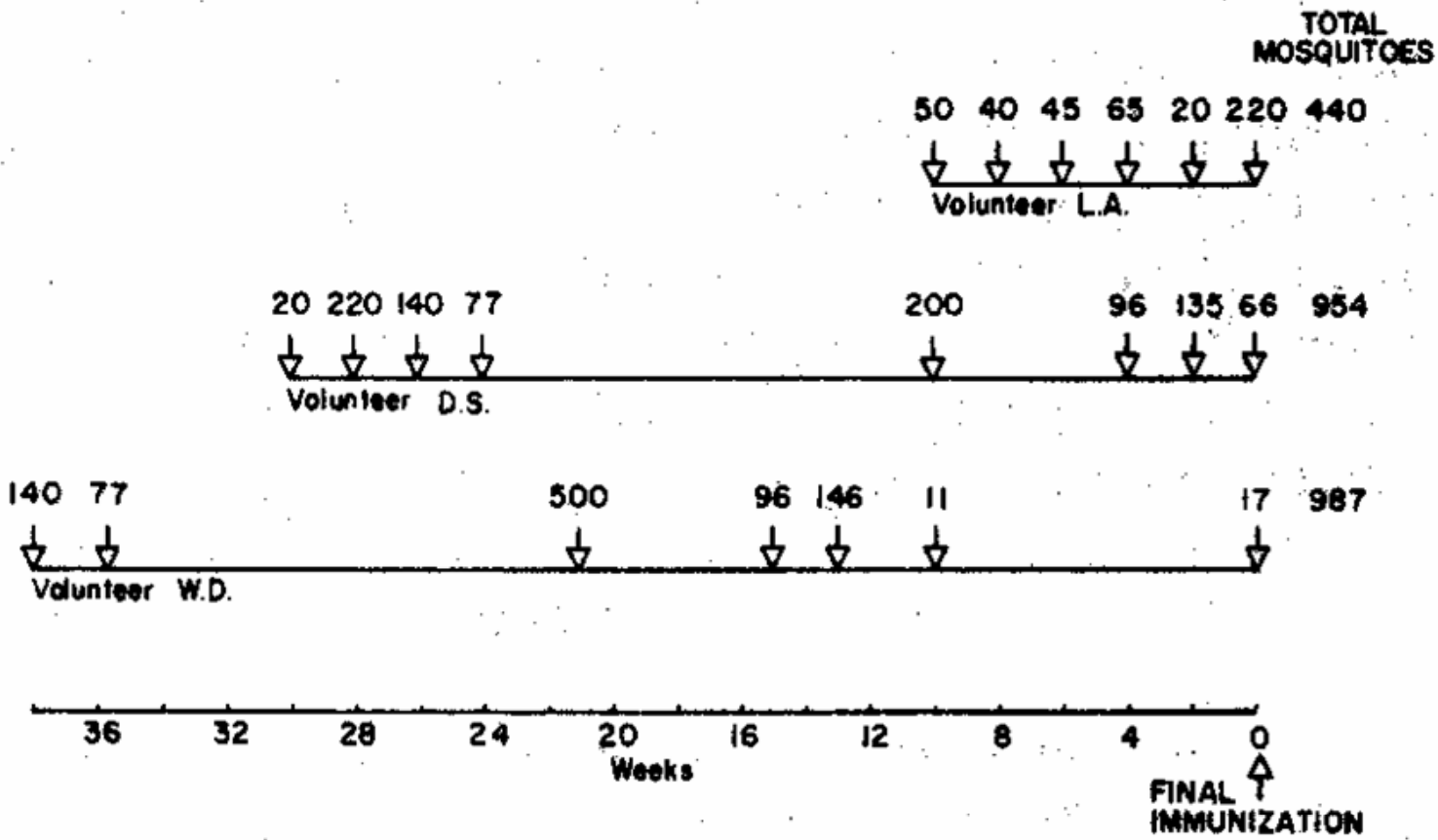


- Mosquitoes inject dozens of sporozoites into the dermis
- Parasites reach the blood and infect hepatocytes

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 *P. falciparum*-Infected Irradiated Mosquitoes



ANTIGENS?

PROTECTIVE IMMUNE MECHANISMS???

Antibodies Abolish Sporozoite Infectivity



Photograph courtesy of Masamichi Aikawa

Antibodies Against The Sporozoite Surface Inhibit

- Parasite Motility
- Hepatocyte Invasion

They can confer sterile immunity...

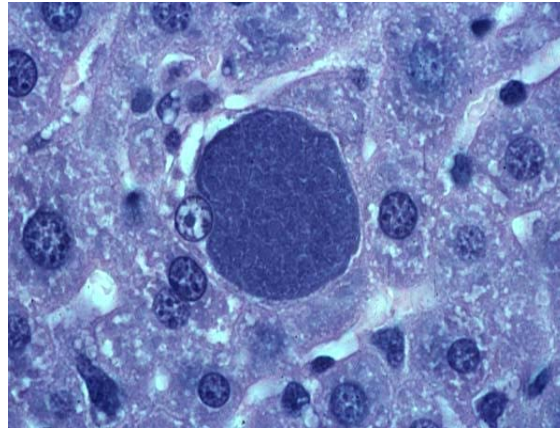
Sterile Protection Against Sporozoite-Induced Infection

- High levels of antibodies
- High binding affinity
- Maintained for a long time

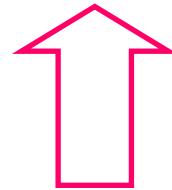
Immunity To Malaria Liver Stages



α, β CD4⁺ T cells

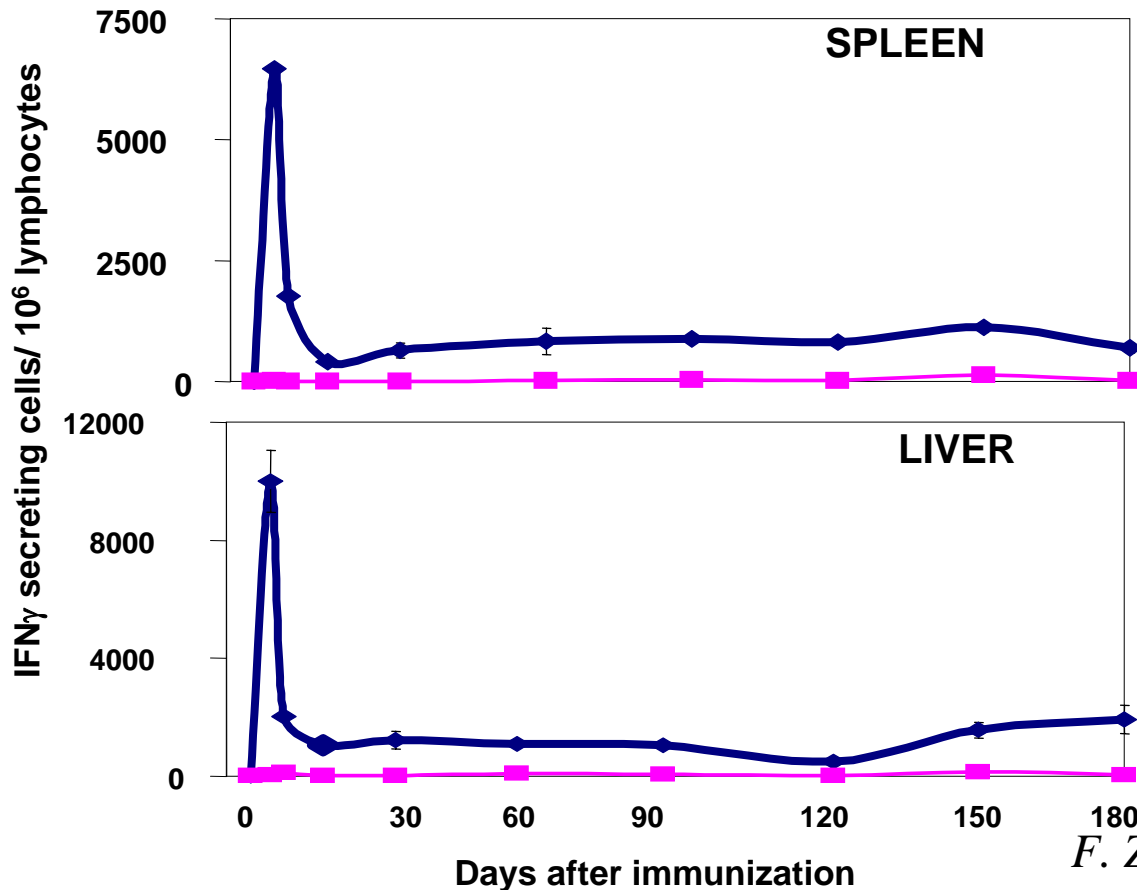


α, β CD8⁺ T cells



$\gamma \delta$ T cells?
NK/NKT cells?

Persistence of the CD8+ T Cell Response After a Immunization with Sporozoites



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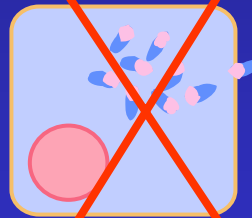
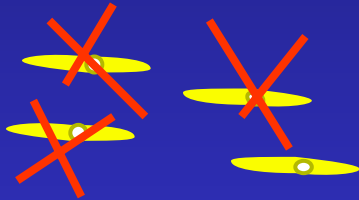
Plasmodium Life Cycle

MOSQUITOES

MOSQUITOES

ANTIBODIES

T-CELLS



MEROZOITES

SPOROZOITES

LIVER STAGES

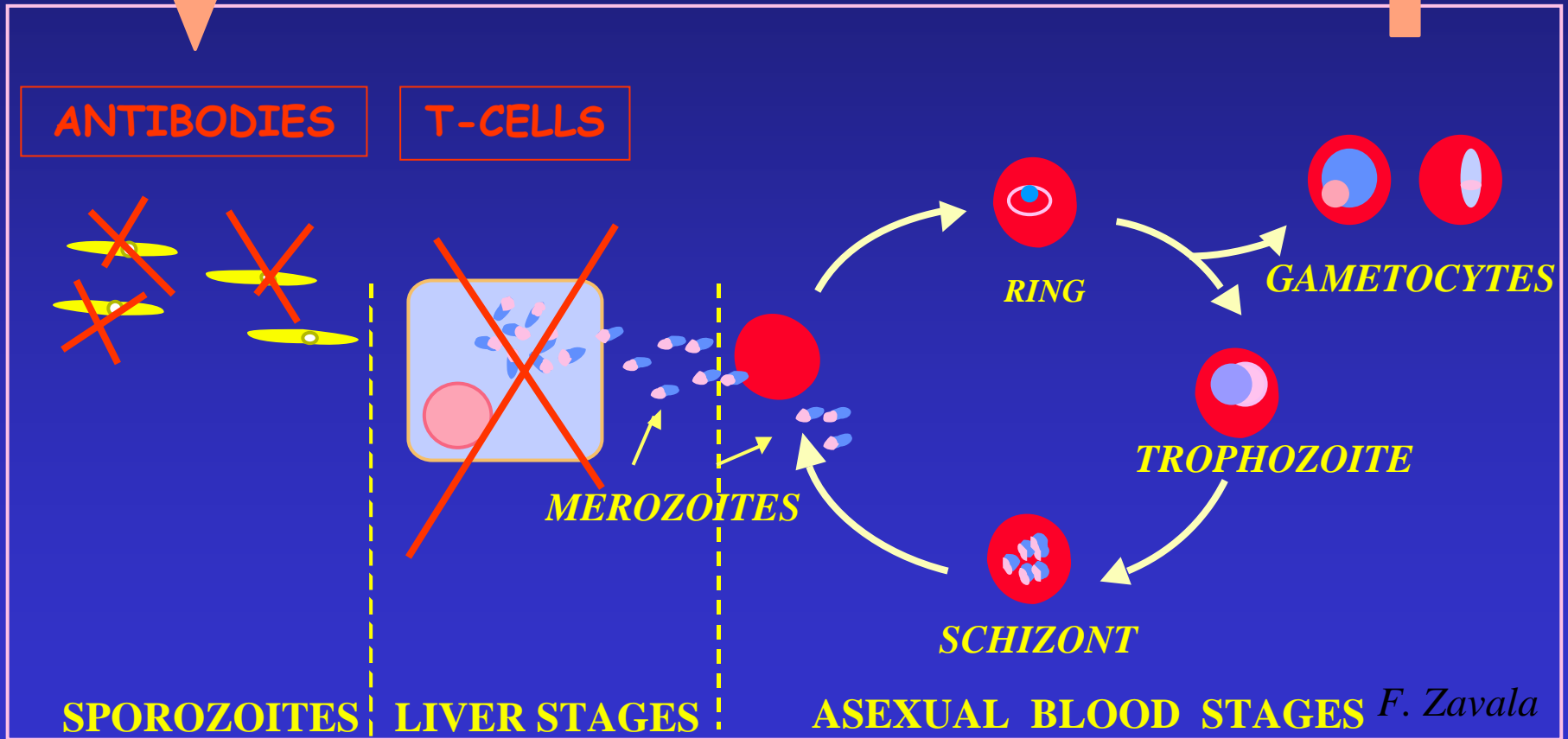
RING

GAMETOCYTES

TROPHOZOITE

SCHIZONT

ASEXUAL BLOOD STAGES *F. Zavala*



Natural Immunity?

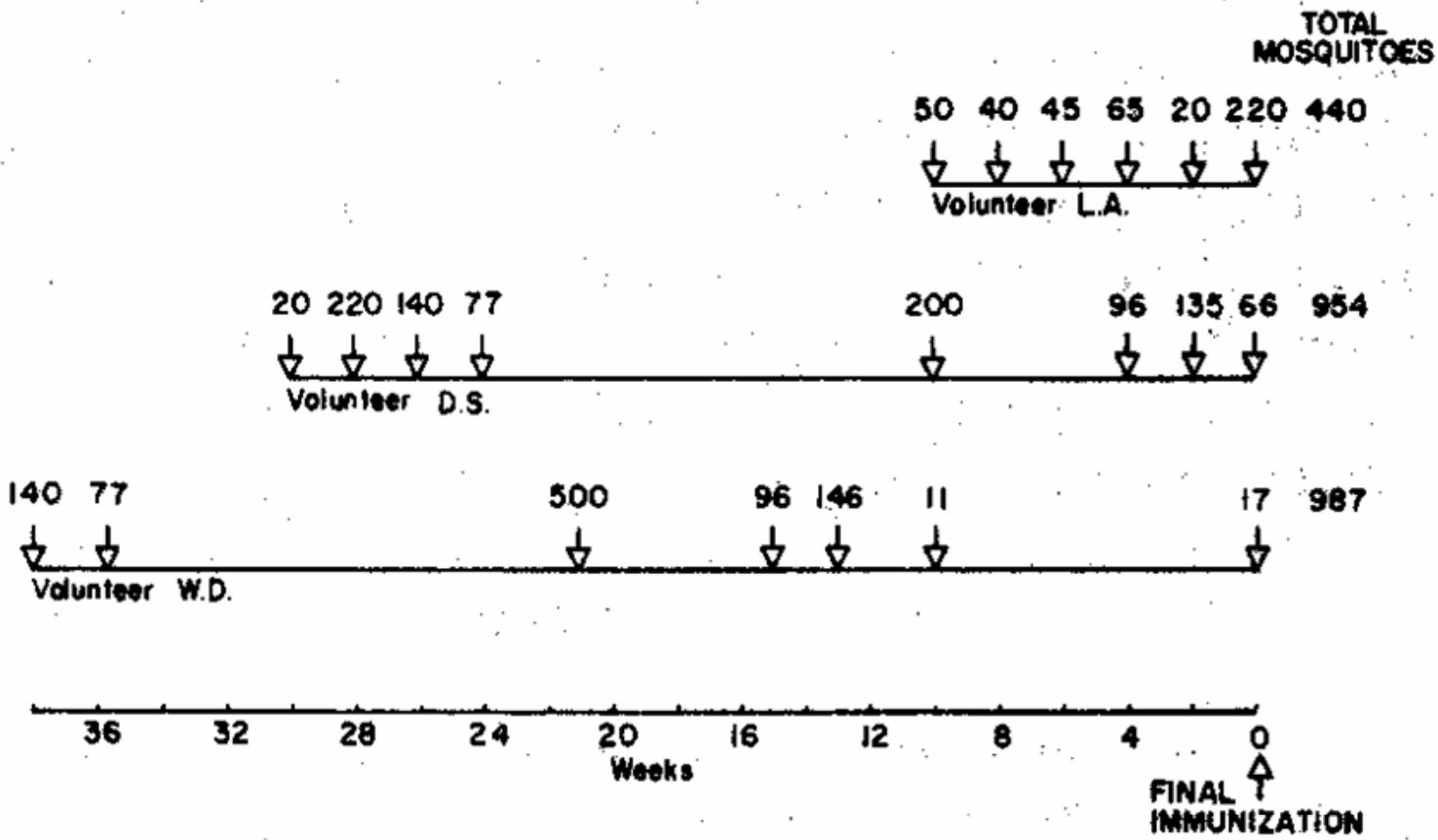
- It is difficult to become immune by natural exposure
- Serum titers from natural infected individuals to sporozoite antigen in IFA is in low hundreds in contrast to immunized individuals with titers in thousands

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.....

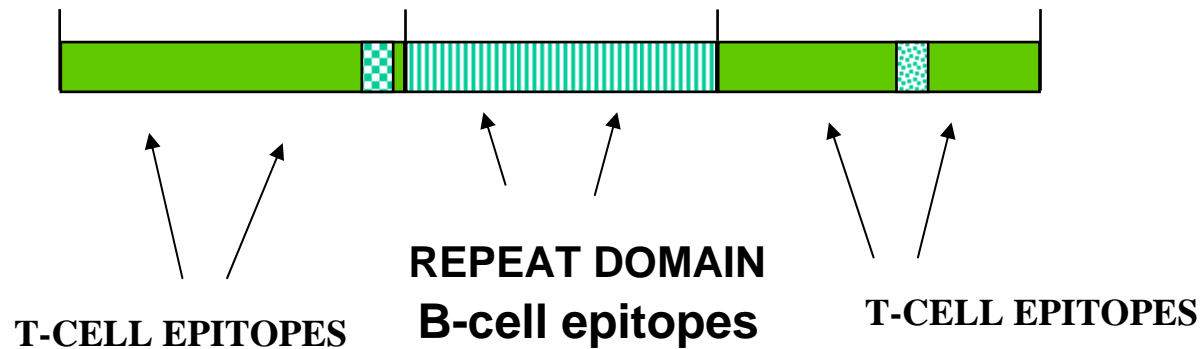
Immunization of Humans with *P. falciparum*-Infected Irradiated Mosquitoes



This is a vaccine but is impractical...

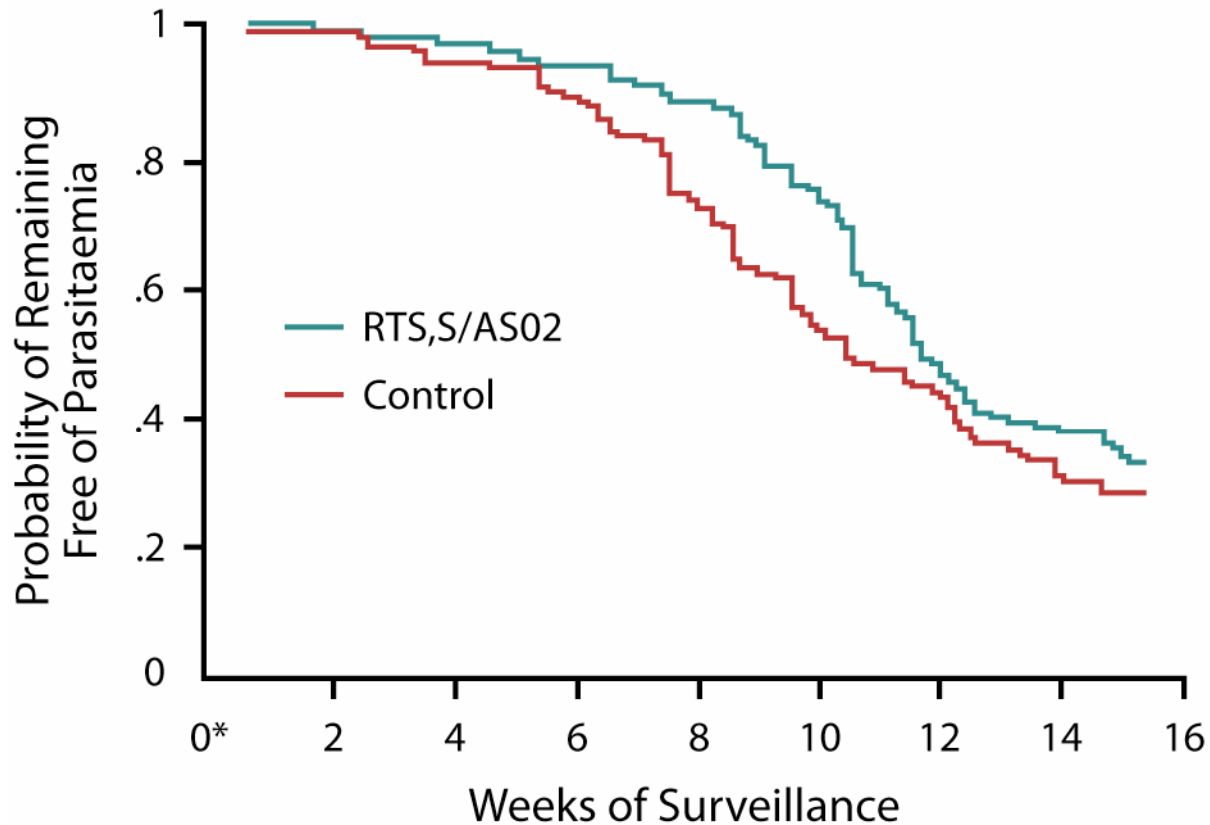
Vaccine Development

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



NUMBER AT RISK	
RTS,S/AS02	Control
131	119
129	118
125	110
118	101
110	82
90	60
58	47
45	33

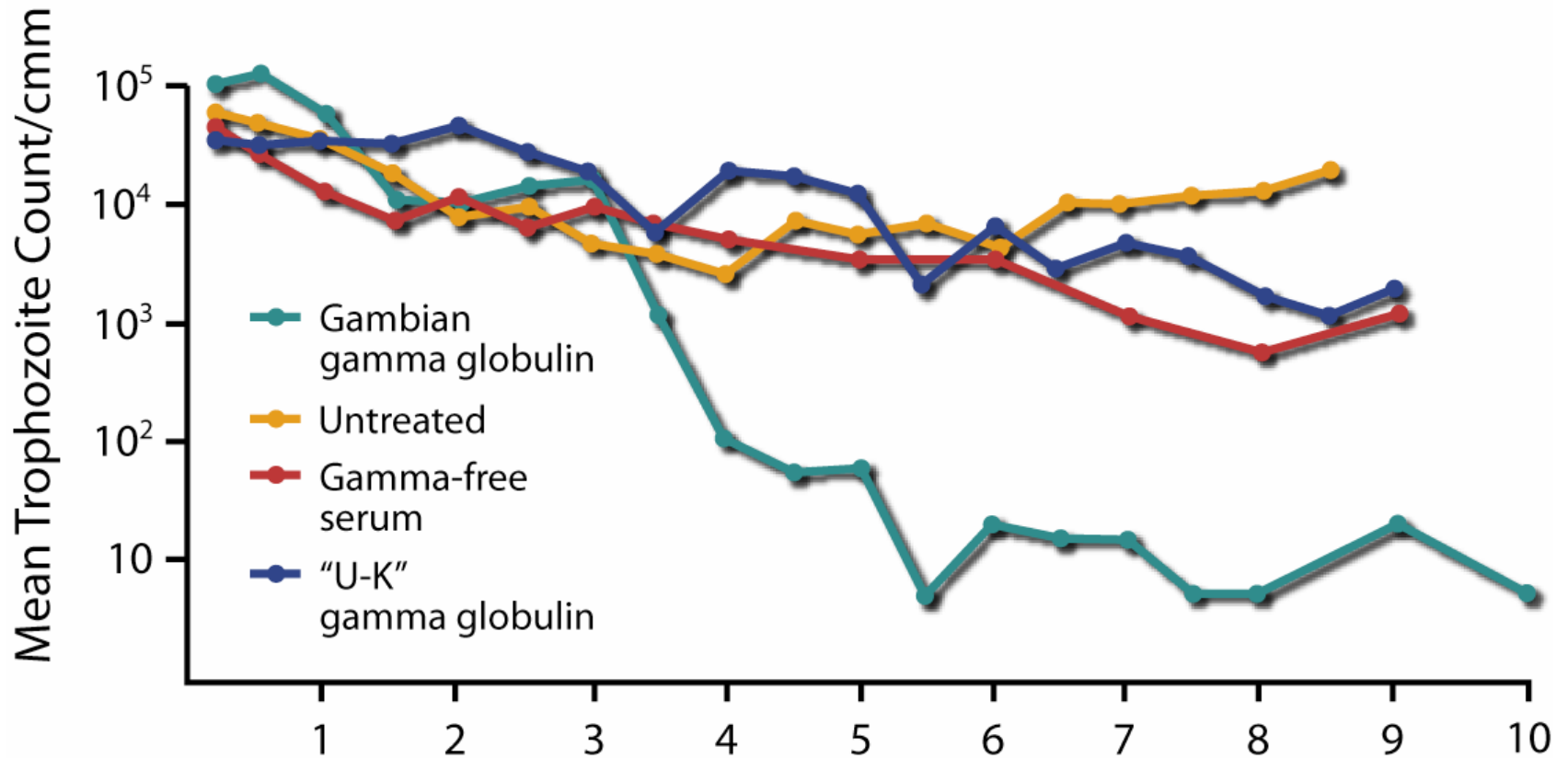
* Week 0 of surveillance began in September, 1998, 14 days after dose 3 of vaccine was administered.

Adapted by CTLT from Bojang et al. Lancet 2001, 358;1927

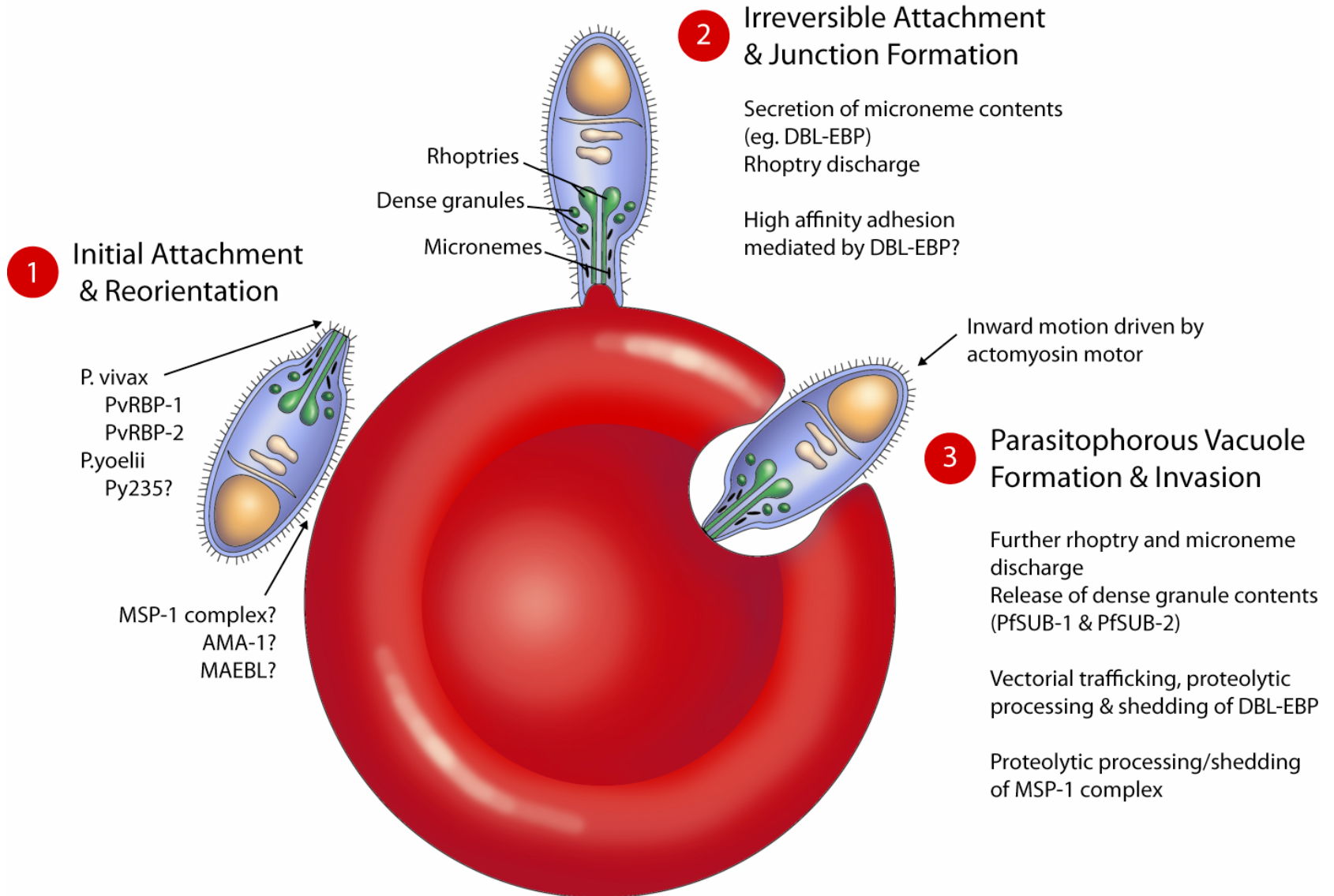


Immune Responses to Erythrocytic Stages

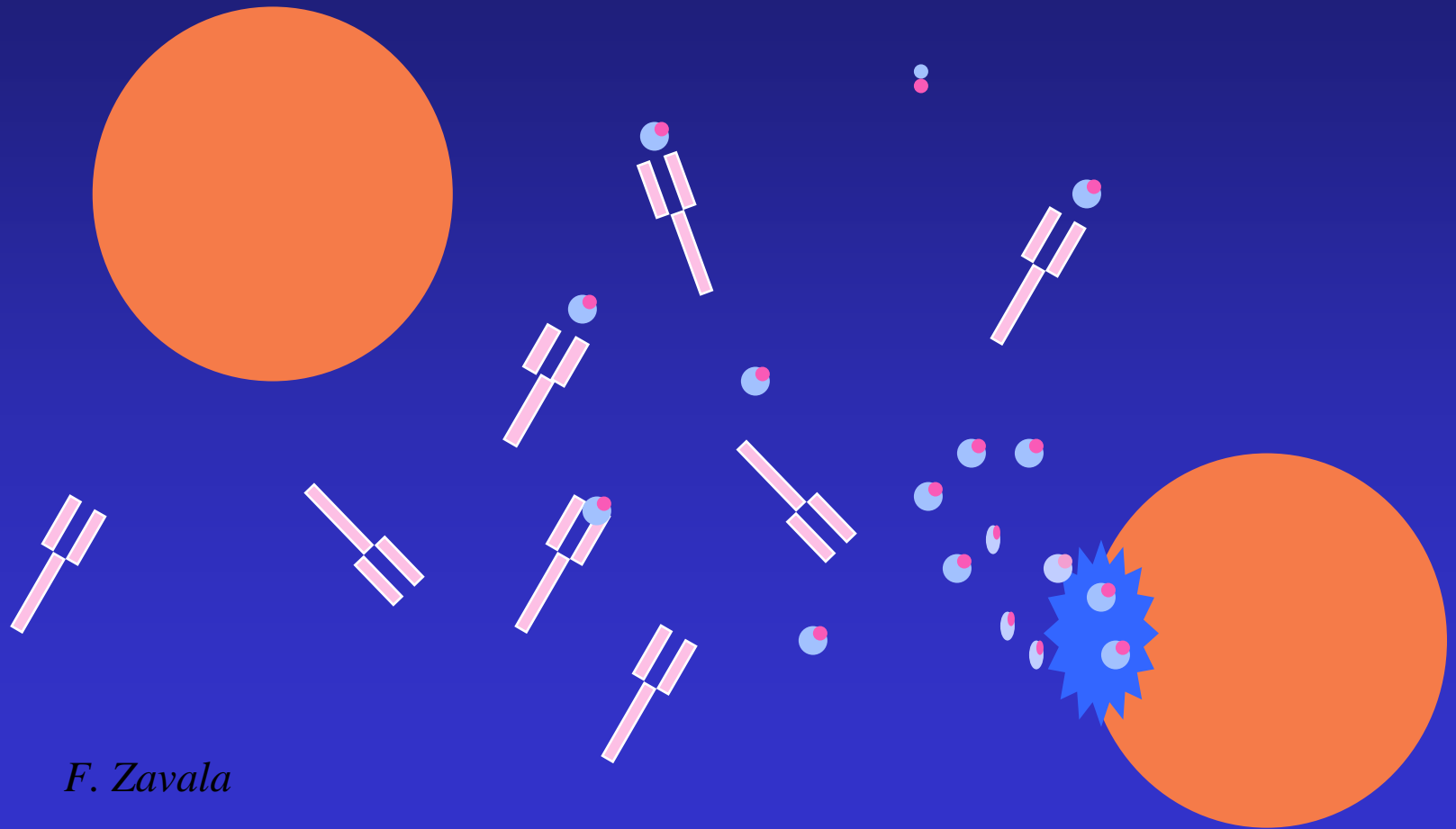
Passive Transfer of Immunity to *P. falciparum* in Children



Early Stages of Red Blood Cell Invasion by the Malaria Merozoite



Antibodies Inhibit Merozoite Infection of Erythrocytes



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Antigens Of Asexual Blood Stages Recognized By Protective Immune Responses

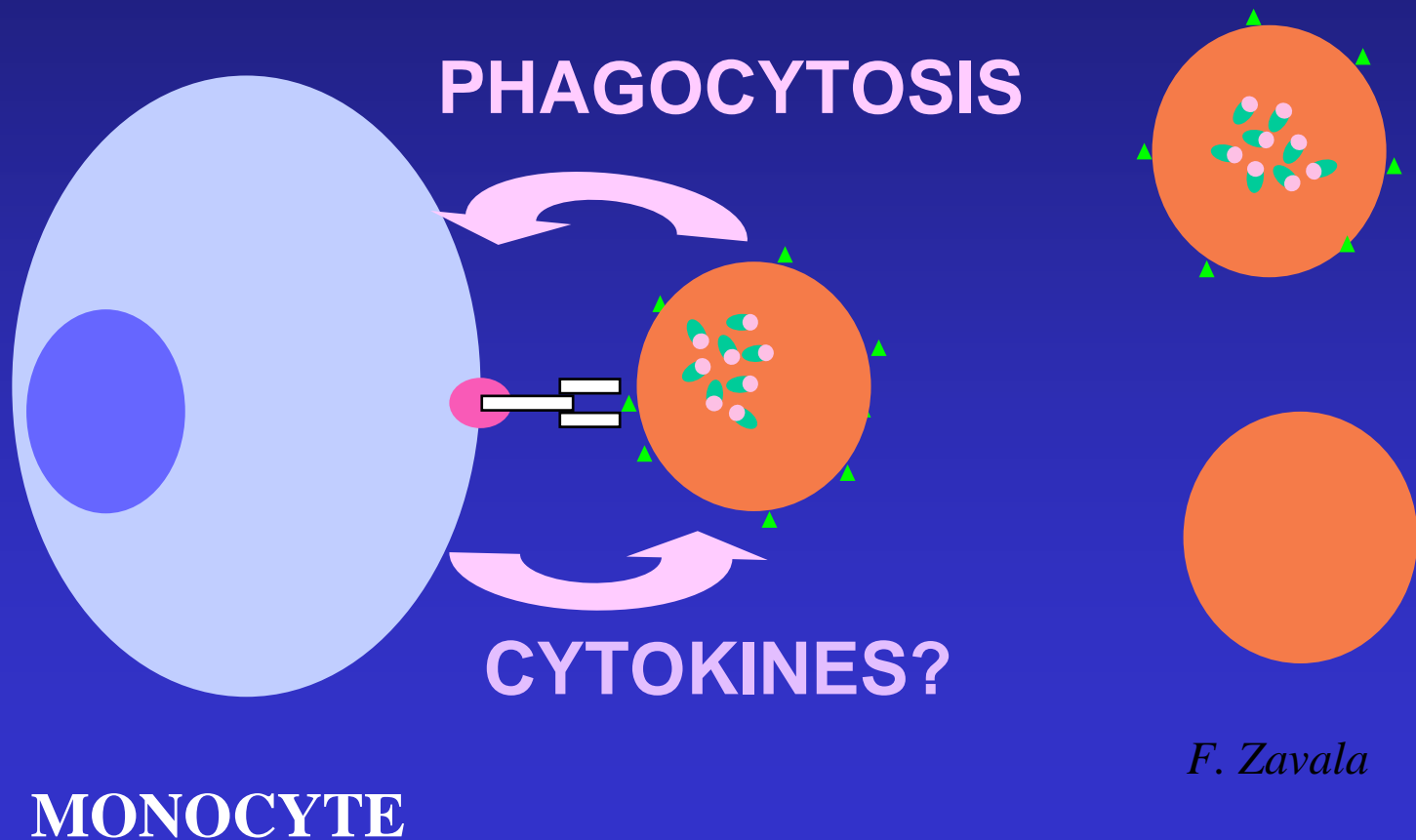
- Merozoite surface protein-1
- Merozoite surface protein-1 -2
- Dense granule-RESA
- Microneme- EBA-175

- 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



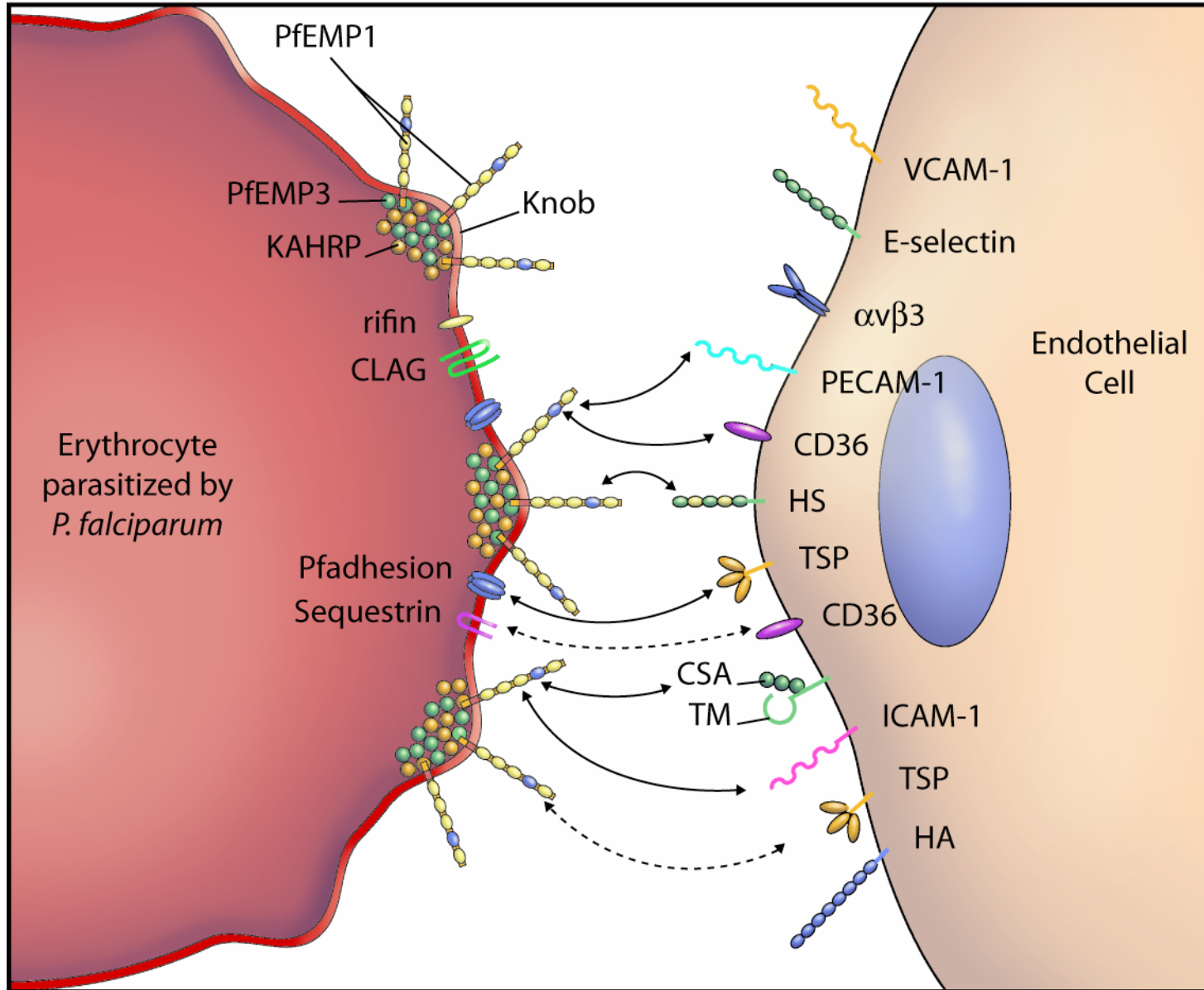
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“Knobs” In *P. Falciparum* Infected Erythrocyte

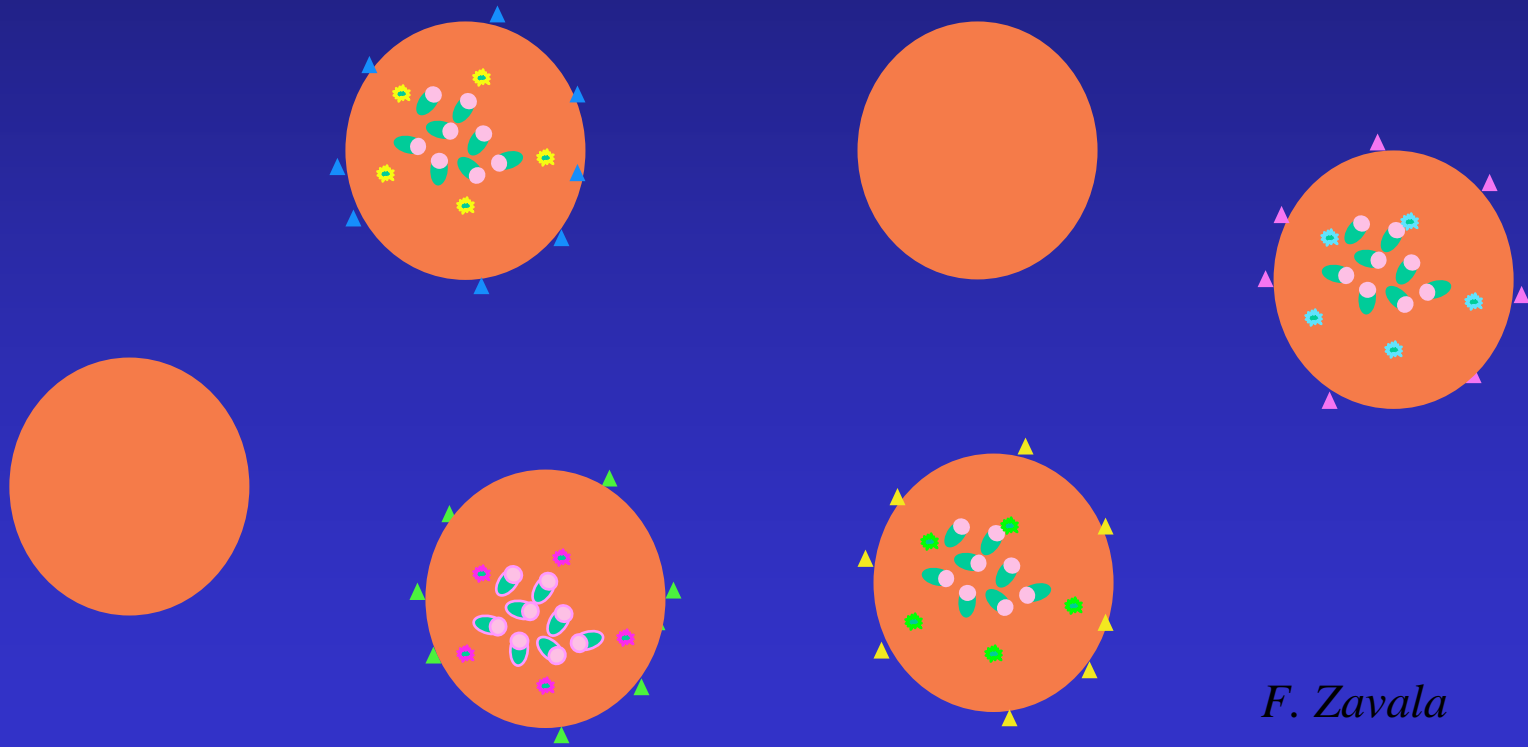


D. Sullivan

P. falciparum Cytoadherence



Extensive Antigen Polymorphism in Malaria Parasites



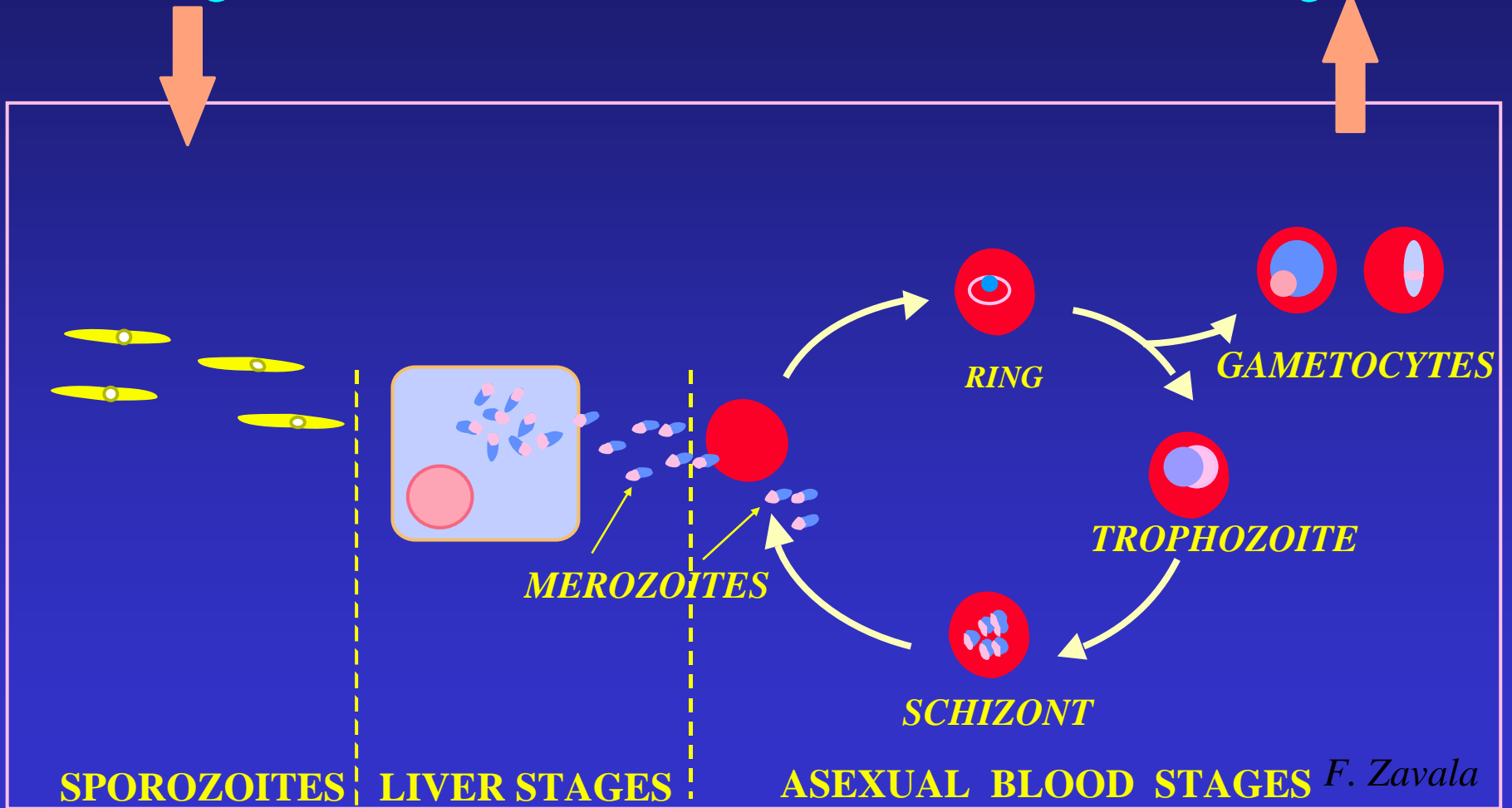
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Immune Responses to Sexual Stages

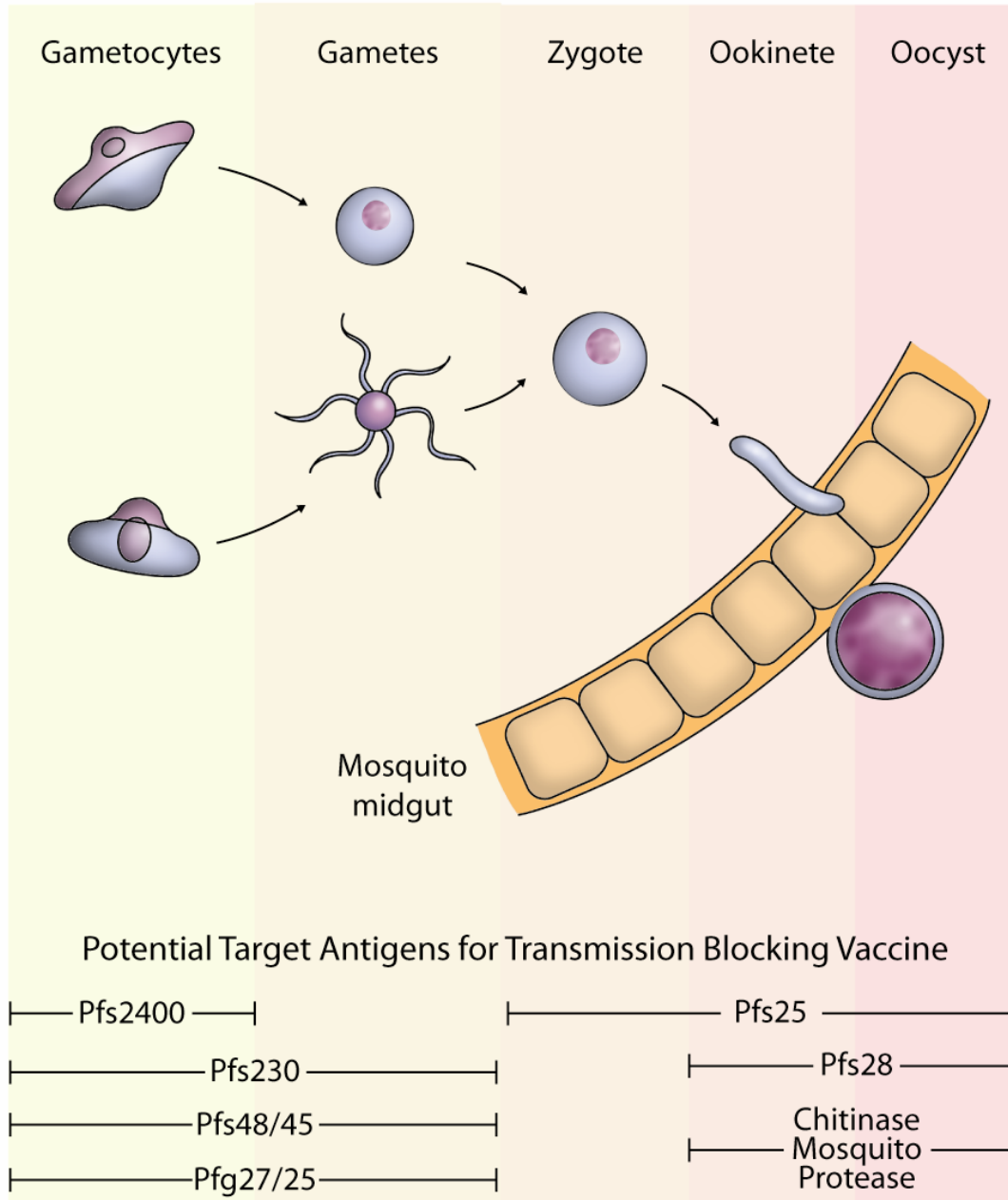
Plasmodium Life Cycle

MOSQUITOES

MOSQUITOES



Developmental Stages of the Malaria Parasite in the Mosquito Midgut



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

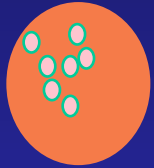
Immunopathology

Anti-Parasite Immune Responses May....

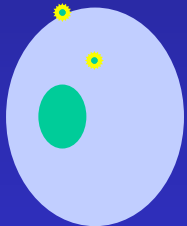
- * **Abolish** parasite development
- * **Attenuate** parasite infection
- * **Be ineffectual** or irrelevant
- * **Exacerbate** disease

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**

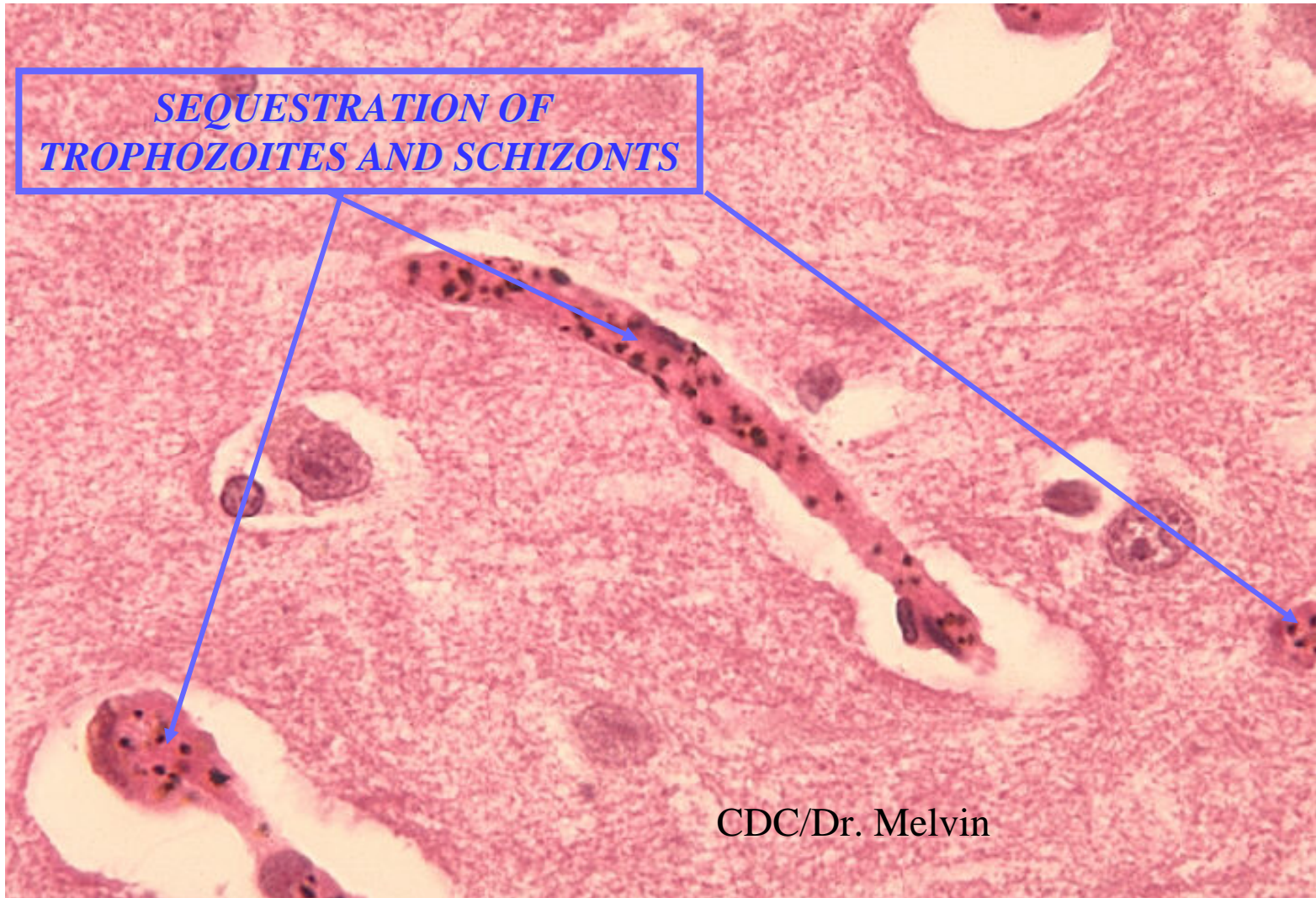
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Severe Malaria

CEREBRAL MALARIA:

confusion, stupor, delirium,
convulsions, paralysis, coma...

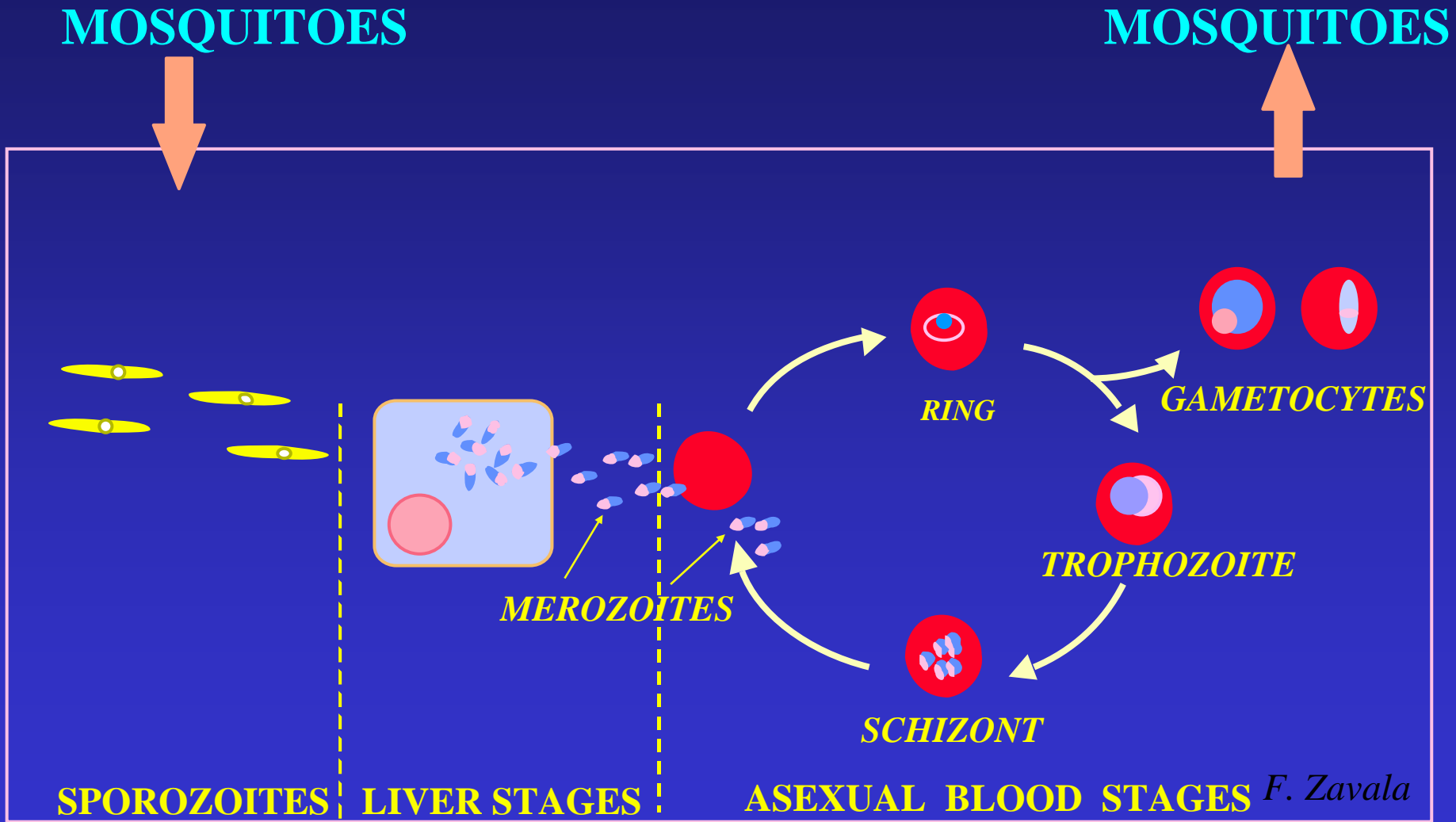
Cerebral Malaria: Obstruction Of Small Capillaries By Parasitized Erythrocytes



Anemia

- Erythrocyte destruction
 - Release of parasites
 - Phagocytosis
- Dyserythropoiesis
 - TNF- α
 - INF- γ

Vaccine Targets



ALL STAGES...

Immunity Against Malaria

PARTIAL

**Attenuates
Infection**

STERILE

**Abolishes
Infection**