Malaria - a serious problem

243 million cases / 863,000 deaths in 2008

Only matched by HIV (2.1 mill. deaths (2007)) and TB (1.6 mill. deaths (2005))

Most victims are children under the age of 5 in sub-Saharan Africa

Source: WHO
Malaria

- Caused by a parasite of the genus *Plasmodium*, mainly:
  - *Plasmodium falciparum* (Africa)
  - *Plasmodium vivax* (Asia and America)

- Transferred to humans by a mosquito of the genus *Anopheles*

- Drug resistance is a major problem for treatment

Sources: WHO and Centers for Disease Control and Prevention (CDC)
Prevention

Source: WHO
Malaria - Life cycle

Sources: Miller, Nature, 2002 and CDC
Infected Red Blood Cells

Source: scienceblogs.com
Malaria - immunological targets

Pre-erythrocytic stage (CSP, SSP2 and LSA1)

Merozoite RBC-invasion (MSP1 and AMA1)

Vector transmission antigens

iRBC adherence (PfEMP-1)

Sources: Miller, Nature, 2002 and Malaria Vaccine Initiative (MVI)
Pathogenicity

PfEMP1

HA

CSA

Placenta

Placental malaria

TSP

ICAM-1

ELAM-1

P-Sel.

VCAM-1

Microvascular adhesion

Brain

Cerebral malaria

Source: Miller, Nature, 2002
Pathogenicity

PfEMP1

CR1
HS-like GAGs, IgM, blood group A

CD36

CD36

Rosetting

Clumping

Dendritic cell

Source: Miller, Nature, 2002
Blood stage parasites

Vascular endothelium
Blood stage parasites

Vascular endothelium

PfEMP1
Blood stage parasites

Vascular endothelium

PfEMP1
Blood stage parasites

- Spleen
- Vascular endothelium
- PfEMP1
PfEMP1 variant antibodies

Antigenic distinct waves of parasitaemia

Source: Miller, Nature, 2002
PfEMP1 variant antibodies

- Encoded by the *var* gene family

- The *Plasmodium falciparum* genome contains ~60 copies of the *var* gene

- Extremely diverse

Source: Miller, Nature, 2002
PfEMP1 domain structure

Plasmodium falciparum erythrocyte membrane protein - PfEMP1

Domain structure: DBL-1α, CIDR1, DBL-2β, DBL-3γ, DBL-4δ, CIDR2, ATS

Exon-1: Multi-adhesive, semi-conserved headstructure
Exon-2: TMDomain

DBL domains are described by the position of the domain on the particular var gene (DBL1-5) and the greek letter identifies the homology type group.

DBL = Duffy Binding Like domain - polymorphic
CIDR = Cysteine Rich Inter domain Region - polymorphic
ATS = Acidic Terminal Segment

Highly polymorphic interdomain region
Conserved cytoplasmic domain

var genes:
- Dd2var-1: DBL-1α, CIDR1, DBL-2β, DBL-3γ, DBL-4δ, CIDR2, ATS
- MCvar-1: DBL-1α, CIDR1, DBL-2β, CIDR2, DBL-3γ, DBL-4δ, ATS
- ItvarA4: DBL-1α, CIDR1, DBL-2β, DBL-3δ, CIDR2, DBL-4γ, DBL-5β, ATS

Source: Adapted from Wahlgren et al (sites.huji.ac.il/malaria/maps/PfEMP1.html)
Pregnancy associated malaria (PAM)

- Maternal anaemia and death (~10,000 cases/year in Africa)
- Perinatal deaths (~200,000 cases/year in Africa)
- Spontaneous abortion
- Stillbirth
- Premature delivery
- In some endemic regions, 40% of all newborns have low birth weight caused by PAM

Sources: Greenwood BM (2005), WHO
Pregnancy associated malaria (PAM)

- Caused by PfEMP1 binding to CSA in placenta

- PfEMP1 variant: VAR2CSA

Source: Miller, Nature, 2002
PfEMP1: VAR2CSA

- Upregulated in iRBC adhering to CSA and in placental isolates
- Highly conserved between falciparum strains compared to most other var genes (nucleotide sequence diversity is 10-30%)