Global causes of death

- 52.2 million deaths
- 17.3 million deaths caused by infectious and parasitic diseases

33% infectious and parasitic diseases
29% circulatory diseases
12% cancer
6% respiratory diseases
7% perinatal conditions
13% other
Antibiotics
Vaccines
Old strategies against infectious diseases no longer work

- Globalization of risk
- Drug resistance
- Few new drugs
- New diseases

- New solutions
  - Need for effective vaccines and drugs
  - Sustainable distribution
Globalization of Risk
The spread of SARS May 2003
Emergence of resistance to antimalarial drugs

- Chloroquine: 16 years
- Fansidar: 6 years
- Mefloquine: 4 years
- Atovaquone: 6 months
Only 1% of new drugs developed are for neglected diseases.

1393 New chemical entities

Tropical diseases

Tuberculosis
A Major New Health Threat?
Tuberculosis
The Impact of Tuberculosis

- TB rates rising worldwide
- Most common cause of death in HIV is TB
- ~1/3 of the world’s population is infected
- 8 million new cases each year, 2 million deaths
- Drug resistance rates are rapidly rising
Malaria Life Cycle

Meiosis happens in the mosquito.

Mosquitos often only bite once.

Outcrossing therefore requires multiply-infected hosts.
Some Good News:
Recent Origin of Epidemic Malaria

Malaria: A “giant with feet of clay”?

Distribution of falciparum malaria

Distribution of sickle-cell anemia
1638 Jesuit Bernabé Cobo used a preparation of bark from certain tree to cure the Countess Dona Ana de Chincon (wife of the Viceroy of Peru) of malaria. The tree was named cinchona in her honor, and the preparation became known as “Jesuit bark.”

Might he have escaped death from malaria had his physicians dared to use the “Jesuit bark”?

Quinine 1820

Chloroquin

Oliver Cromwell (1599-1658)
Malaria in the United States—1970s

Red River
Mississippi River
Ohio River
Atlantic Coast
Chesapeake Bay

Transportation
Sanitation
Nutrition
We now have all 3 genomes involved in the malaria cycle
A genome-wide map of diversity in

**Plasmodium falciparum**

*Nature Genetics 39, 113-119; 2007*

Harvard School of Public Health
Dyann Wirth, Sarah Volkman, Johanna Daily, Amanda Lukens, Dan Milner, Manoj Duraisingh, Nira Mahesh, David Rosen

The Broad Institute of MIT and Harvard
Eric Lander, Pardis Sabeti, Steve Schaffner

Genome Analysis: Bruce Birren, Nicole Stange-Thomann, Joanne Zainoun

Microbial Sequence Analysis: James Galagan, Dave DeCaprio, Dan Neafsey, Alan Derr, Michael Koehrsen, Tim Ledlie, Danny Park

Genome Assembly: David Jaffe, Evan Mauceli, Sante Gnerre

Infectious Disease Initiative: Roger Wiegand, Joseph Cortese, Rachel Daniels

Harvard University: Dan Hartl

Cheikh Anta Diop University: Souleymane Mboup, Ousmane Sarr, Douda Ndiene, Omar Ndir
Genetic Diversity and Geography
SNP Discovery

8X Coverage—Dd2 + HB3
1.25X Coverage—12 Strains
Targeted PCR—16 Strains

Discovery of 96,351 SNPs
47% of SNPs have MAF of <5%

~112 K SNPs Discovered

Broad + NIH + Sanger
~112 K SNP = 1 per 213 bp
Population Genetics

Su et al, Microbes and Infection (2003)
Nucleotide Diversity Correlates Strongly With Gene Function

Molecules associated with the cell surface are highly polymorphic compared to molecules involved in basic cell metabolism.
Distribution of Gene Diversity

Antigens Have Extremely High Diversity
Drug Resistance
Single origin
Multiple origins
Selective Sweeps Detectable

Drug-Sensitive

Drug-Resistant

BEFORE

Drug-Sensitive

AFTER

Drug-Resistant

SNP diversity

Position on chromosome 7 (kb)

pfcrt

CQ Resistant

CQ Sensitive

Drug Resistance locus
A Genome-Wide Map of Genetic Diversity in *P. falciparum*

Discovery of ~112K SNPs ~1 SNP Per 213 bp

Molecular Barcode Uniquely Identifies Parasite

DNA Barcode = 24 Common SNPs

Molecular Barcode for Parasite Identification

Parasitemia Time

Same Parasite Recrudescence

Application to Drug or Vaccine Failure

A Genome-Wide Map of Genetic Diversity in *P. falciparum*

Determine Population Structure

Identify Drug Resistance Loci

Follow Vaccine Trial “Break Through” Parasites

Molecular Barcode Uniquely Identifies Parasite
Developing a Malaria Haplotype Map
Malaria Community

• Study malaria population biology in natural setting working with endemic scientists

• Workshop in Dakar Senegal on Malaria Genomics held December 2006
Genome sequence of Plasmodium falciparum (30 Mb)...........2002
Genome sequence of Anopheles gambiae (280 Mb)...............2002
Finished human genome sequence (3000 Mb).........................2003
Roles in Drug Development
Many partners combine for success

- **Novel Target Discovery**
- **Compound Screening**
- **Lead Selection & Optimization**
- **Preclinical Development**
- **Clinical Trials & Approval**

- **MMV**
- **Genzyme**
- **Broad**
- **Outsourced providers**

Target discovery primarily conducted by Broad and UW with Genzyme input
Screening conducted by both Broad & Genzyme
Both organizations to support lead selection and optimization
Genzyme to support or manage preclinical development
MMV to provide clinical trial management

**Legend:**
- Green: Dedicated Efforts
- Yellow: Support Efforts
- Red: Minimal Involvement
DAPI *P. falciparum* Growth Assay

1. Transfer compounds
2. 384-well plate containing medium
3. Add parasites
4. Incubate at 37 °C (72 h)
5. Detect stained parasite DNA
6. Imaging-based analysis
7. Plate reader

Baniecki, M.L.
Distribution of Identified Screening Positives

Drug Discovery

3D7 CQ(S), MQ(S), PY(S)

HB3 CQ(S), MQ(S), PY(R)

Honduras

Dd2 CQ(R), MQ(R), PY(R)

Indochina

104

25

4

42

1

1

4
Multi-Dimensional Screening

A. Live/Dead Assay: MDR
B. Human Cytotoxicity
C. Erythrocyte Lysis
D. PfHSP90
E. PfDHODH
F. PfHDAC
G. Heme Polymerization

Adapted from: Ramanathan et al. (2005) PNAS 102 5992-5997
Once we were very close; we can get there again.
A Major New Health Threat?
Influenza Pandemics in 20\textsuperscript{th} Century

1918: “Spanish Flu”
A(H1N1)
20-100 million deaths

1957: “Asian Flu”
A(H2N2)
1-4 million deaths

1968: “Hong Kong Flu”
A(H3N2)
1-4 million deaths

Credit: US National Museum of Health and Medicine
Mechanisms of Influenza Virus Antigenic "Shift"
Current Strategy against H5N1
Access to world experts nearby