About our Speaker

Name: Dr. Dhanasekaran Shanmugam, Ph.D.

Where does he work

Biochemical Sciences Division, National Chemical Laboratory, Pune.

What does he do

Biological studies and drug discovery in malaria and other tropical infectious disease causing parasites.

Where and what did he study

B.Sc – Biochemistry, PSG College of Arts & Science, Bharathiyar Univ, Coimbatore, India.

M.Sc – Medical Biochemistry, JIPMER, Pondicherry Univ, Pondicherry, India.

Ph.D – Heme Biosynthesis in malaria Parasite, Indian Institute of Science, Bangalore, India.

PDF – Genomic and Molecular Parasitology, Univ. Pennsylvania, Philadelphia, USA.

What are your interests (in your job, and outside):

Job related interests – Actively following current developments in all areas of scientific advancements; teaching and mentoring students; to develop new scientific methodologies.

Other interests – Traveling; Photography; Music

Tropical Infectious Diseases: Biology And Global Impact On Human Health And Economy

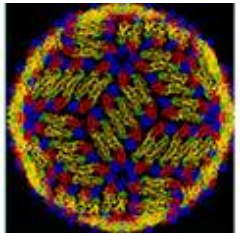
Abstract:

A number of different diseases afflict humans (and animals) living in tropical regions of the world. These diseases include malaria, tuberculosis, leishmaniasis, and filariasis to name a few. In combination, these diseases pose a huge burden in terms of human health and economy. Although latest information from the World Health Organization indicate an overall decline in the incidence of these diseases, the most worrying aspect is the spread of drug resistance, particularly in poverty stricken regions of the world. Moreover, expect for a few pathogens, such as the ones responsible for malaria and tuberculosis, many others have been studied only to a limited extent. The good news, however, is that there is increasing interest among the scientific community in studying the biology of these diseases, and carrying out drug discovery and clinical studies. These efforts, it is hoped, will provide a way to effectively treat, if not eradicate, many of these diseases in the foreseeable future.

This talk will provide an overview of various tropical diseases, discuss the biology of important pathogens, highlight their global impact and address the need for discovering new drugs and vaccines for treating these diseases.

Tropical infectious diseases are caused by a variety of organisms

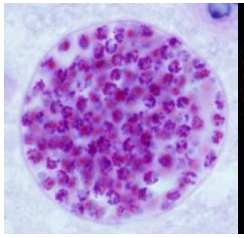
Virus **Dengue**



Bacteria **Tuberculosis**

Leprosy

Malaria



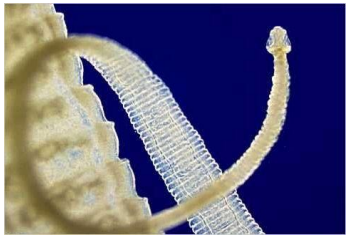
Protozoa **Leishmaniasis**

African trypanosomiasis

Chagas

Worms **Helminths**

Lymphatic filariasis



Onchocerciasis

Schistosomiasis

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

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Global Report for Research on Infectious Diseases of Poverty

Each year infectious diseases kill 3.5 million people – mostly the poor and young children who live in low and middle income countries. Research can change this and bring health to many more people. TDR has brought people and institutions together to identify and advocate for the research priorities that will bring new and innovative approaches and products.

The result is *Global Report for Research on Infectious Diseases of Poverty*, which provides a new cross-disciplinary approach and analysis. It is essential reading for policy-makers, funders and research leaders.

Global Report for Research on Infectious Diseases of Poverty | Community health workers critical for elimination of malaria | A single treatment for visceral leishmaniasis under study | African Network for Drugs and Diagnostics Innovation

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Publications and resources
Publications produced by TDR or in cooperation with others

Malaria
Tuberculosis
Leprosy

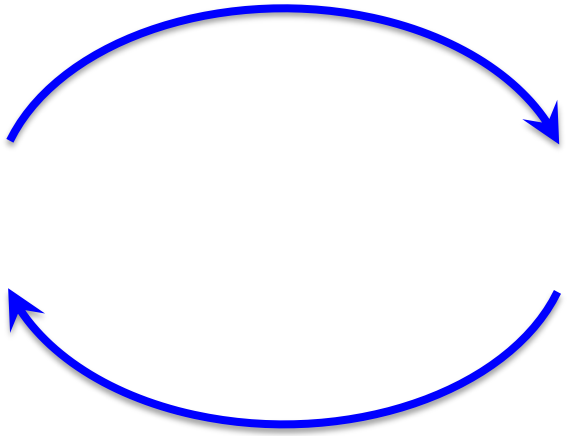
African trypanosomiasis
Chagas
Leishmaniasis

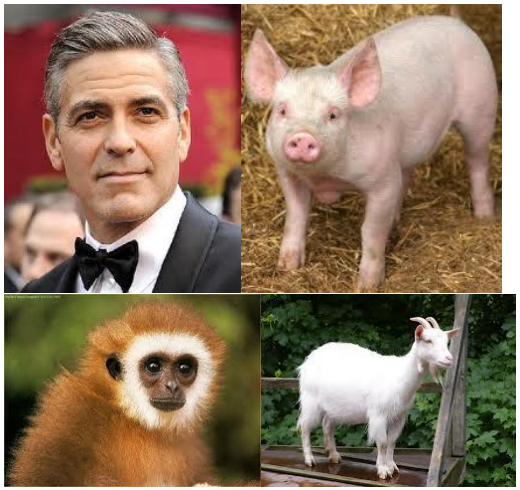
Helminths
Lymphatic filariasis
Onchocerciasis
Schistosomiasis

Pathogens have a some commonalities

Complex Life Cycle

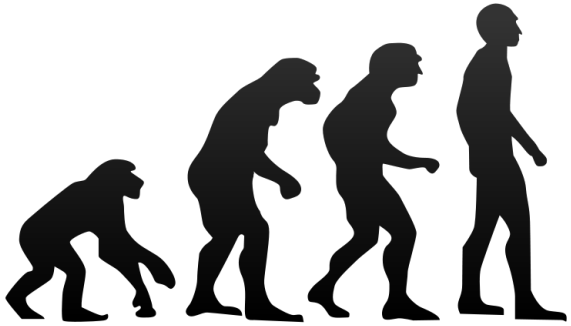
Primary Host (Vector)





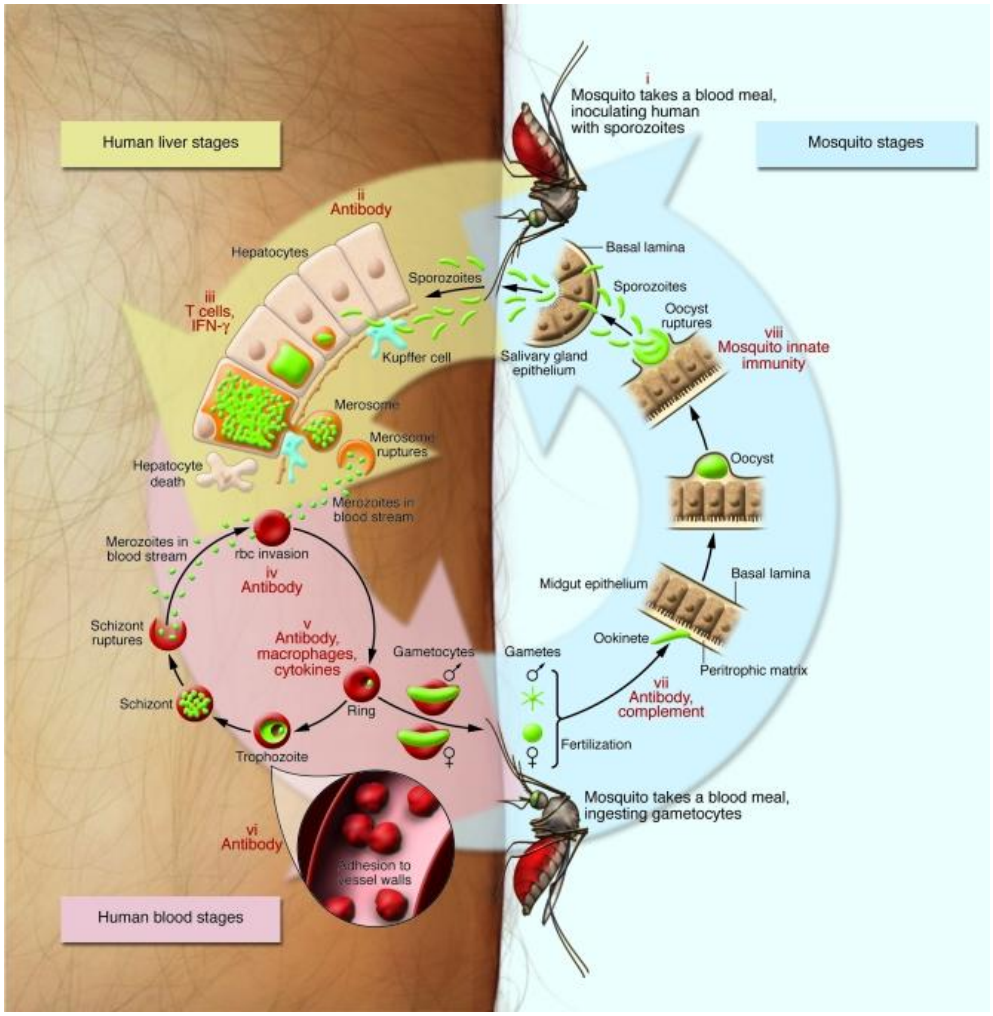
Secondary / Intermediate Host (Disease symptoms)

Very ancient in human association



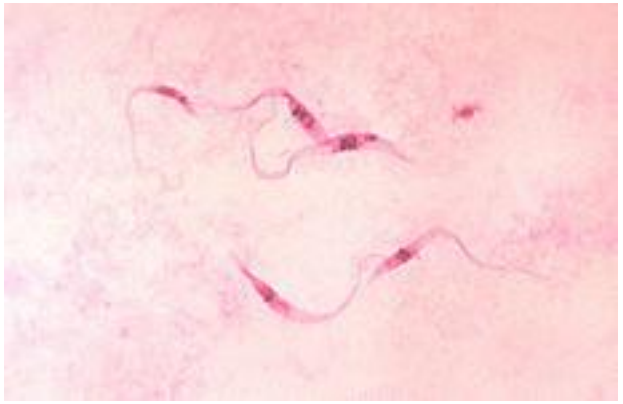
Malaria

Malaria parasite life cycle



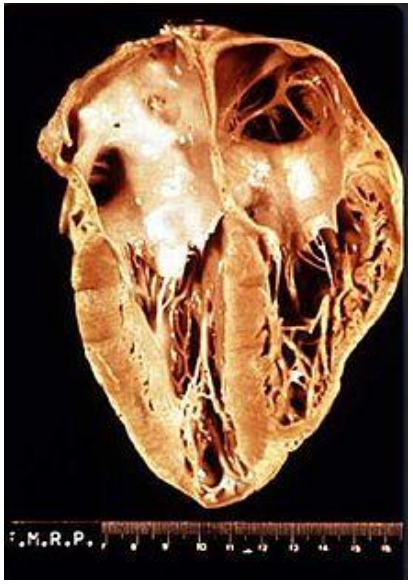
Modified from
J Clin Invest. 2008 Apr;118(4):1266-76.

Chagas disease



Photomicrograph of Giemsa-stained *Trypanosoma cruzi* (CDC)

An acute Chagas disease (Romaña's sign). Source: CDC.)

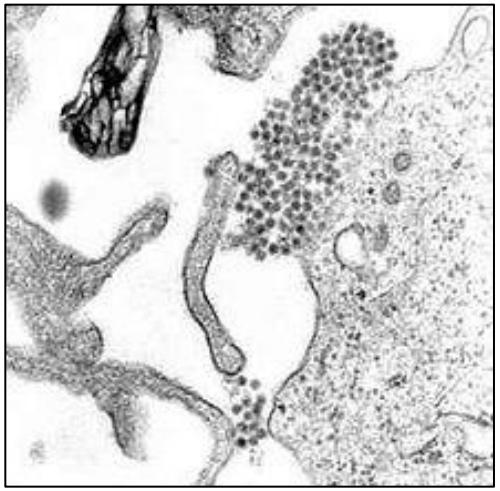


Gross anatomy of a heart in chronic Chagas disease

Source: Wikipedia

Rhodnius prolixus is the principal vector in South American countries.

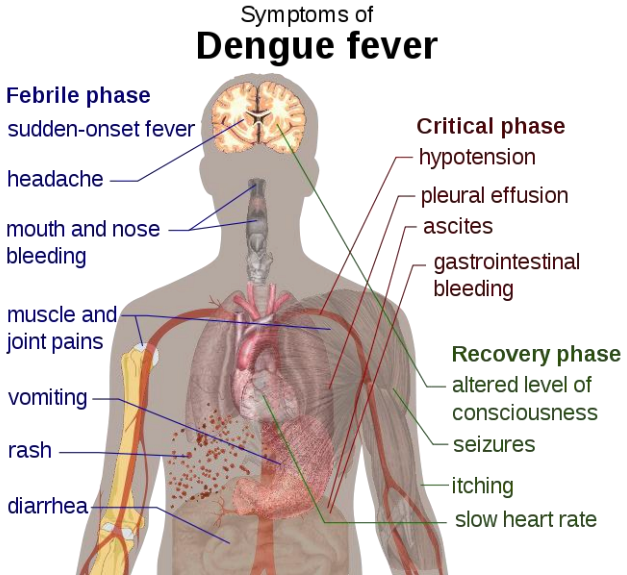
Dengue Fever



A TEM micrograph of dengue virus virions

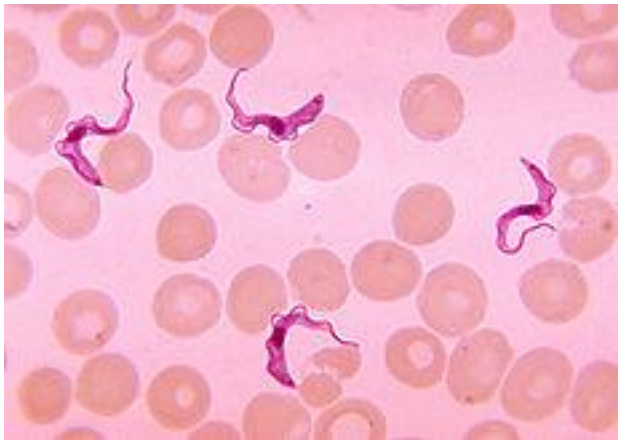
The mosquito *Aedes aegypti*

The typical rash seen in dengue fever



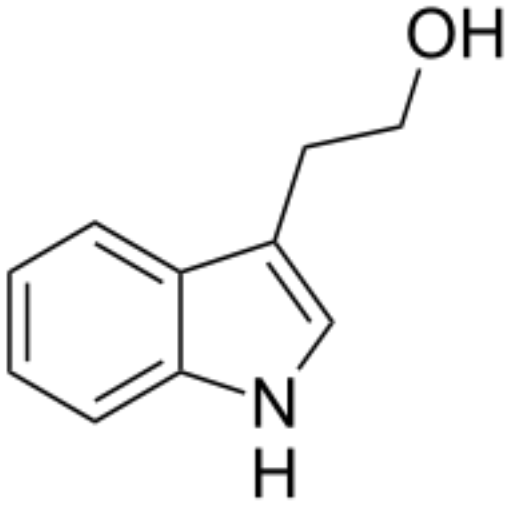
Source: Wikipedia

Sleeping Sickness



Trypanosoma forms in a blood smear.

Tsetse fly



Tryptophol

Source: Wikipedia

Leishmaniasis

Cutaneous leishmaniasis Ulcers

Source: Wikipedia

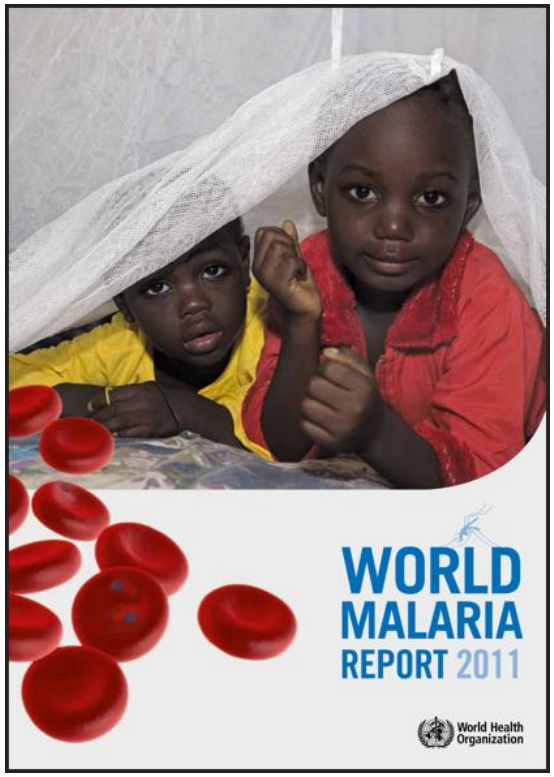
The **BIG 3** Killers!

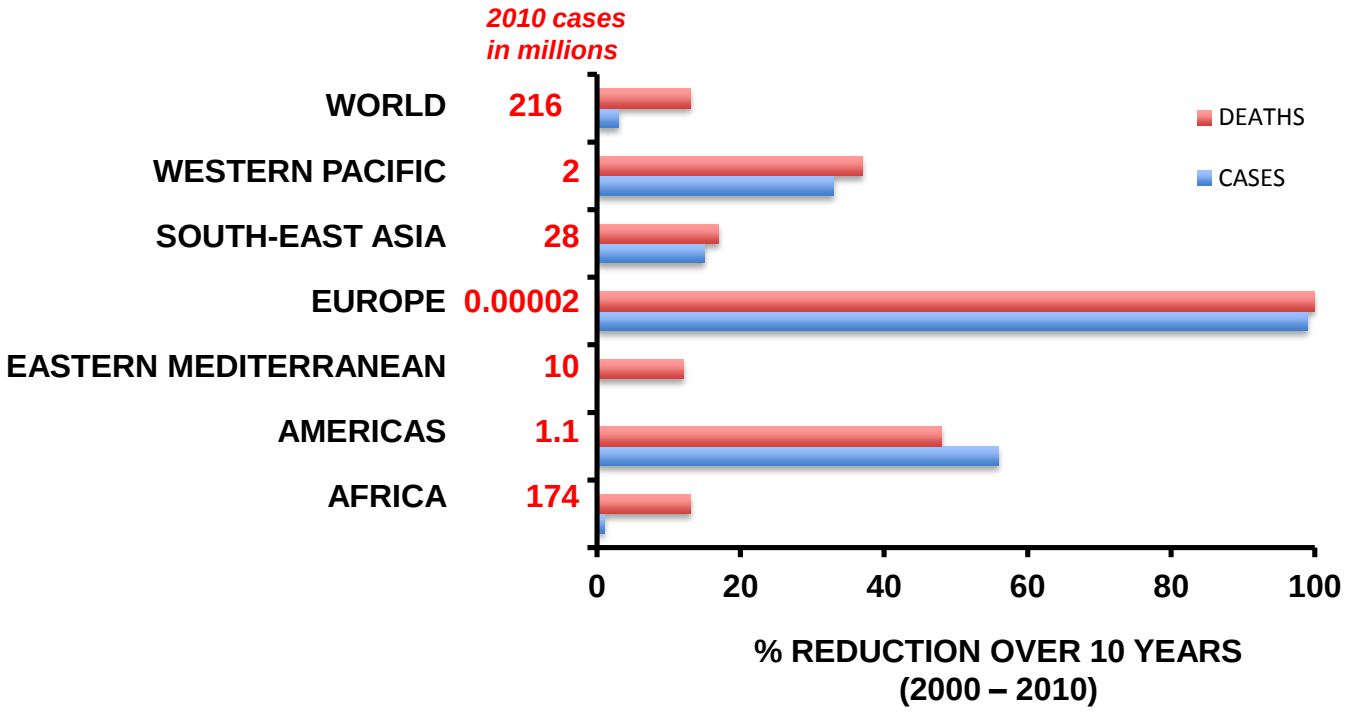
HIV/AIDS

Malaria

Tuberculosis

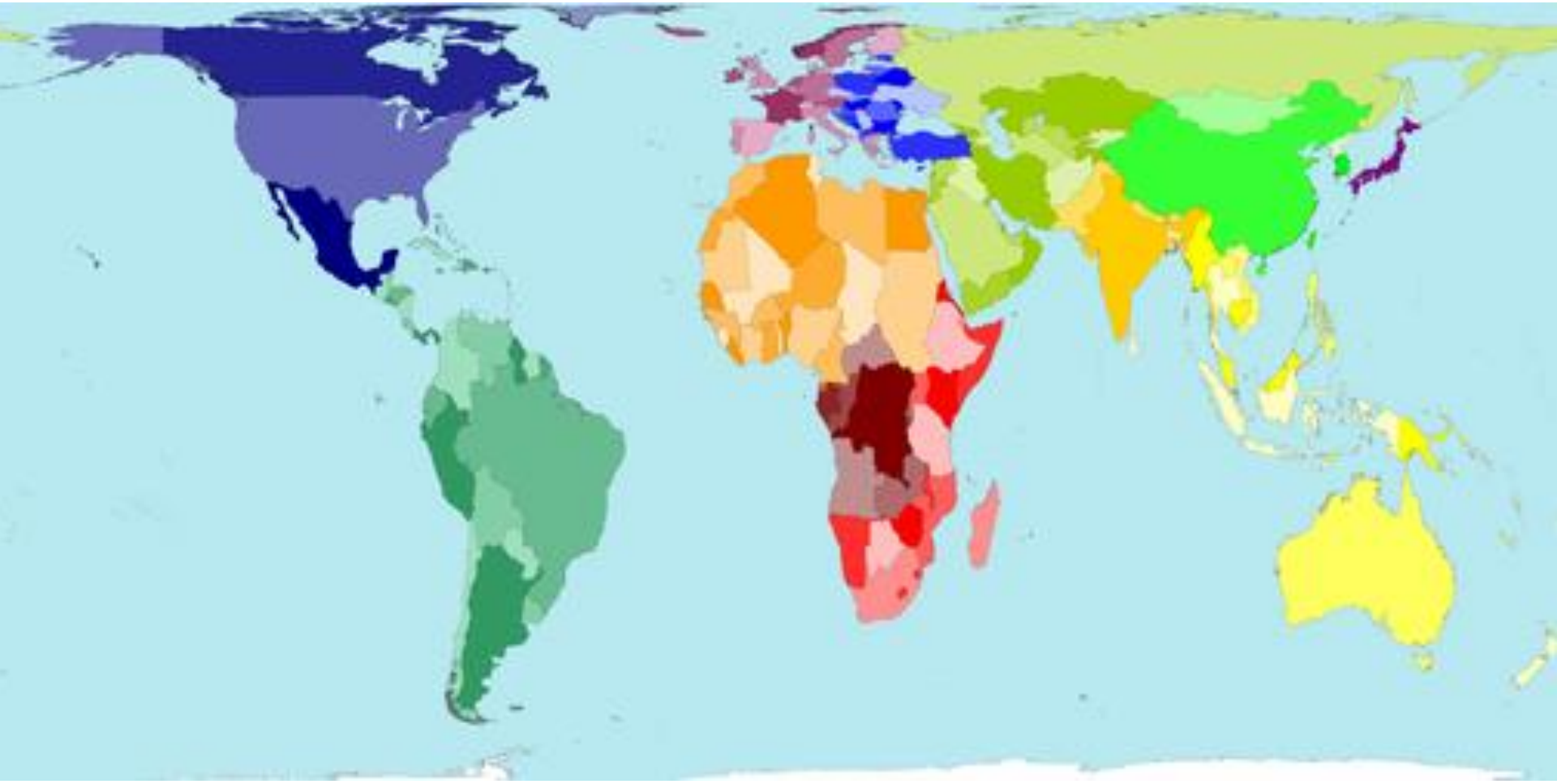
Global malaria scenario over the past decade



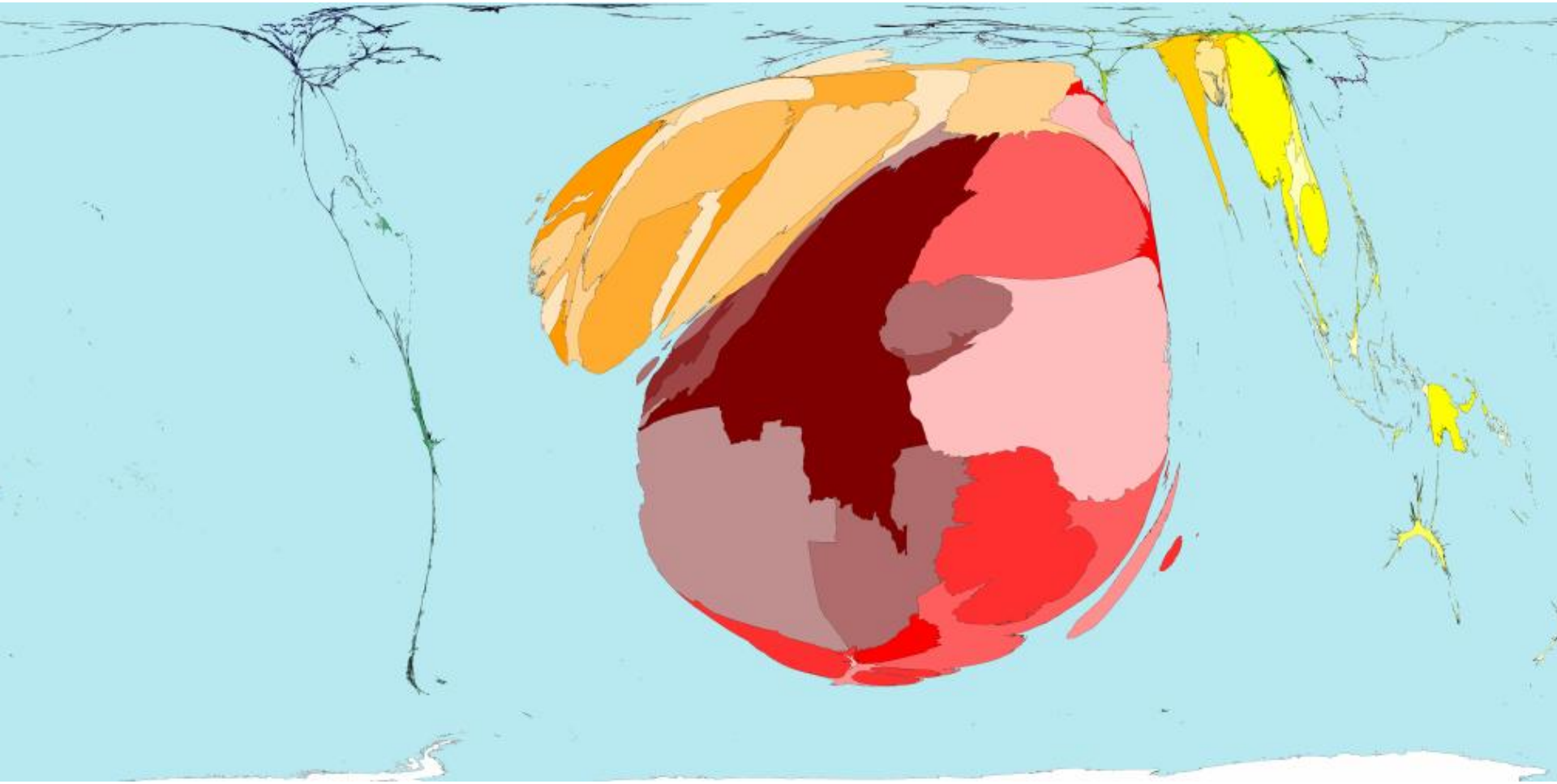


Source: ***World Malaria Report 2011***

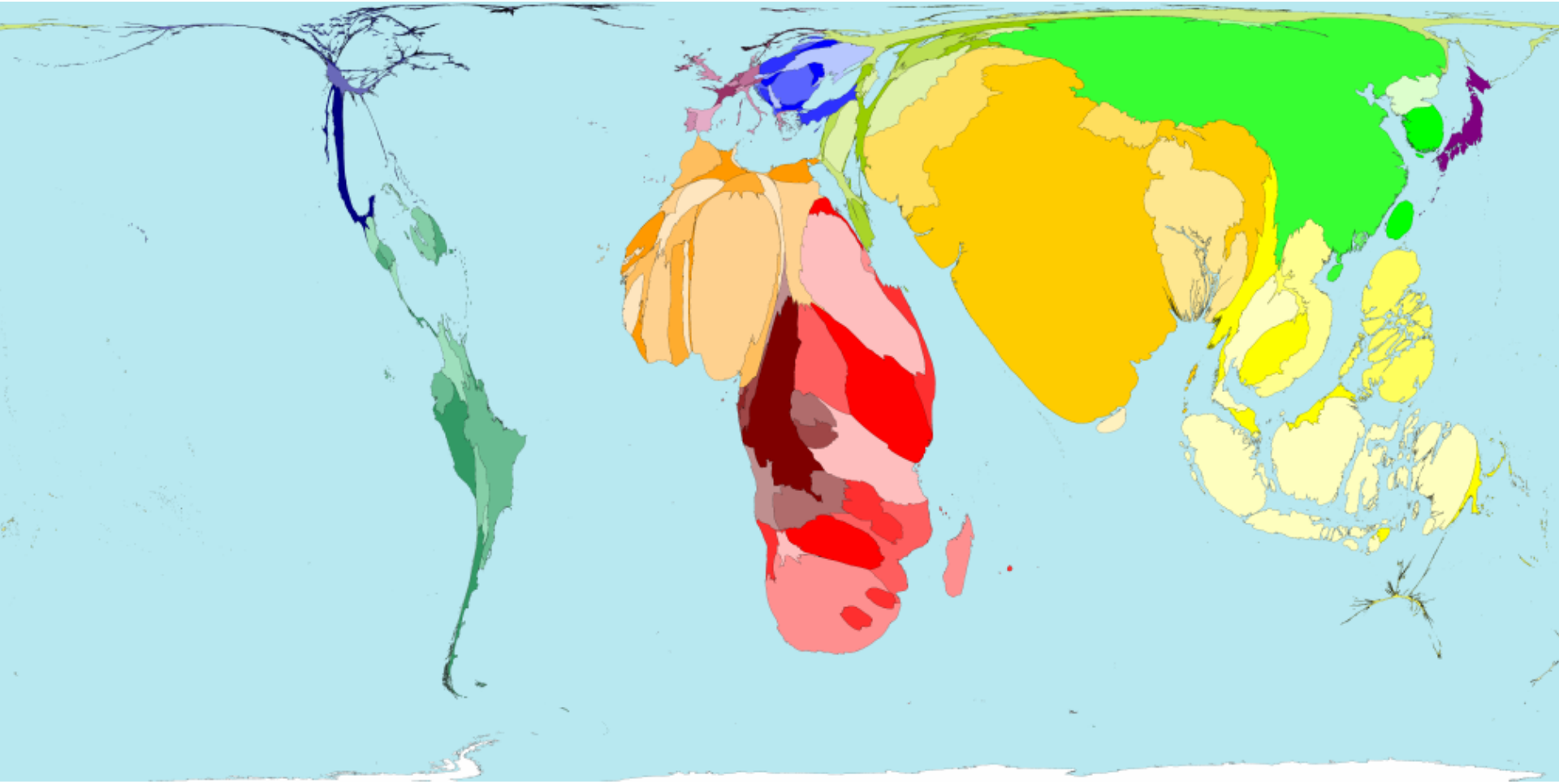
World Map Land Area



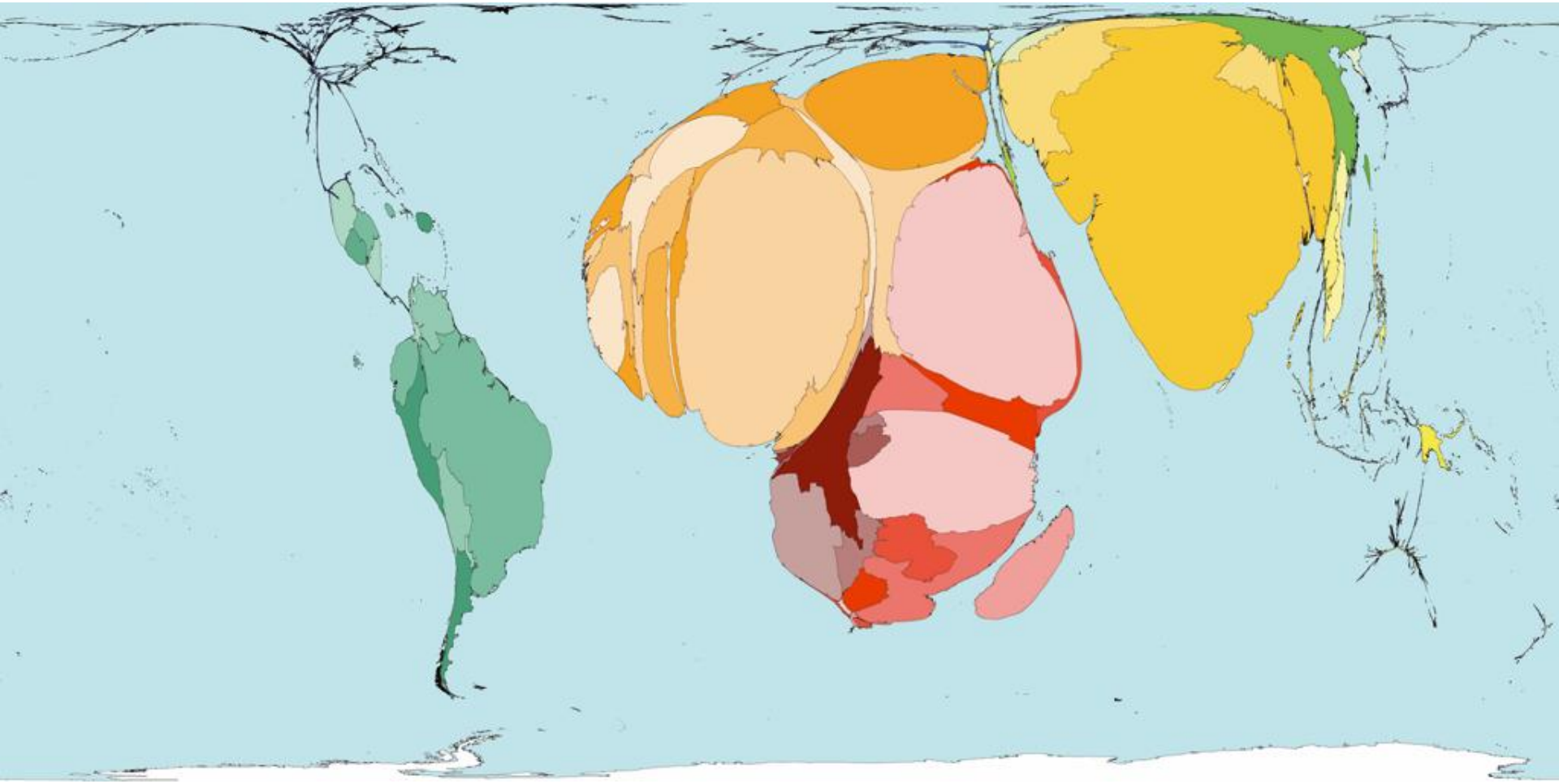
World Wide Malaria Deaths (2003)
(~1 million)



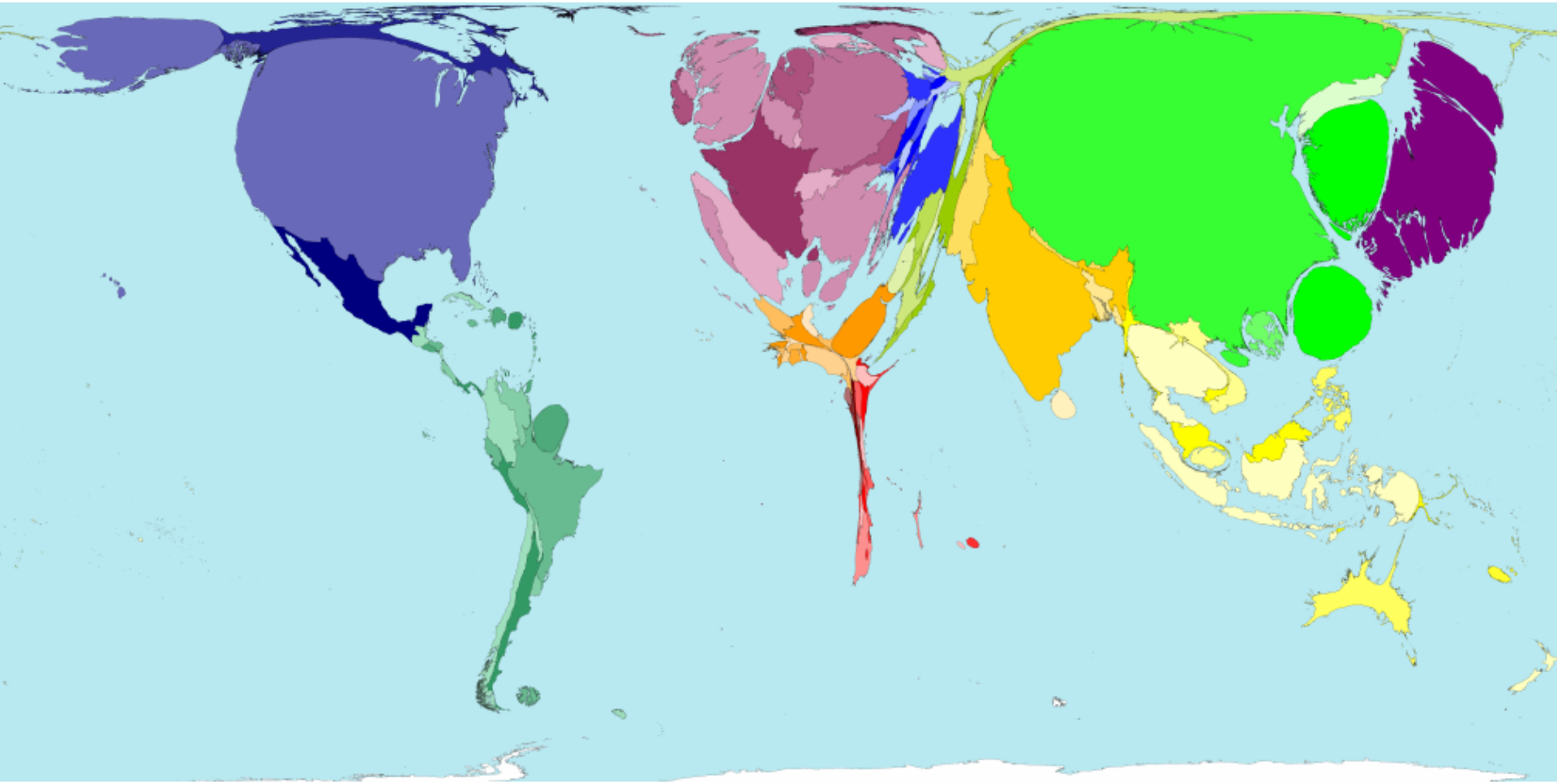
World Wide Tuberculosis cases (2003)
(~9 million)



World Wide Local Tropical Diseases Death



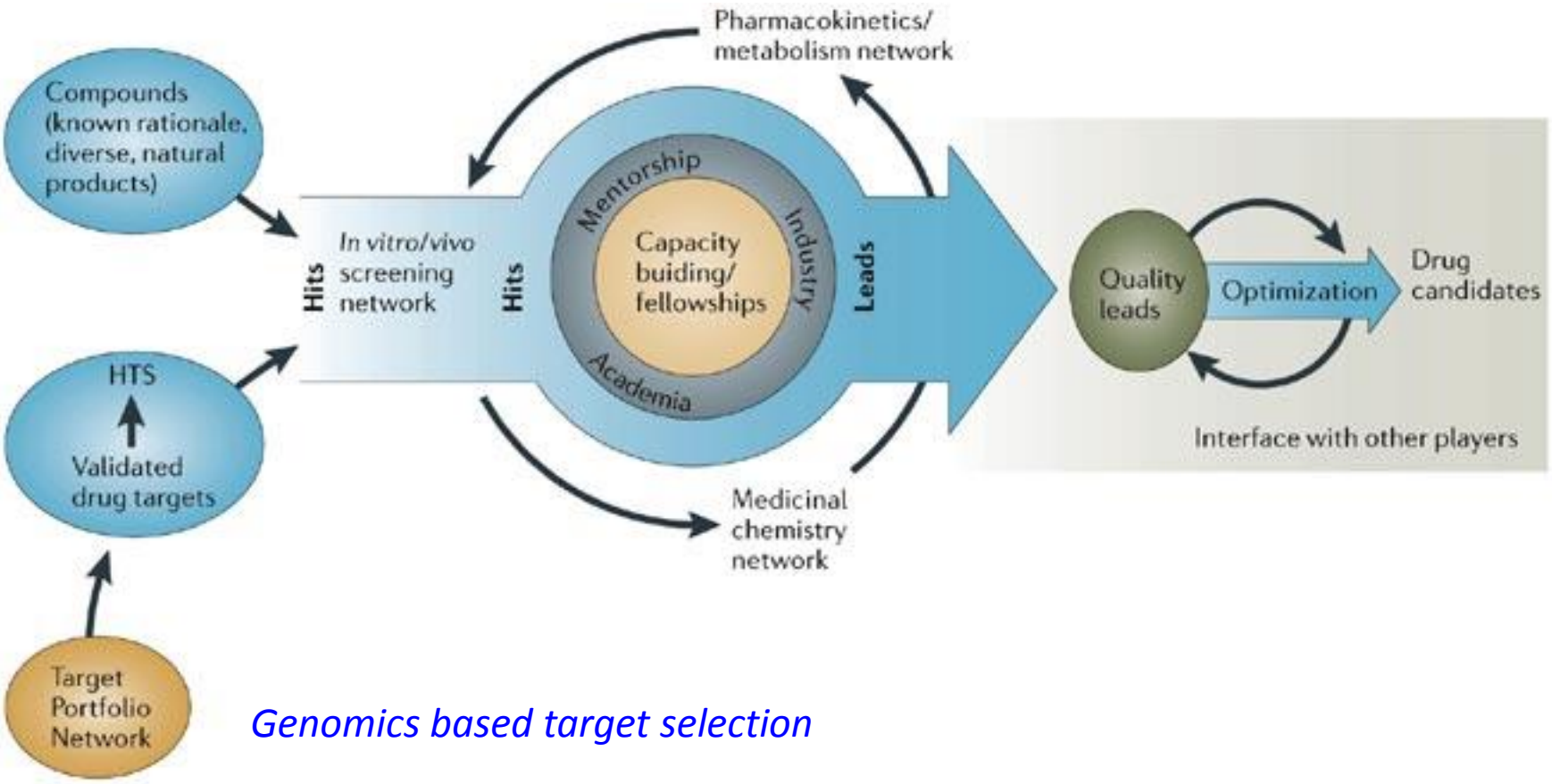
Projected World Wide Absolute Wealth Distribution in 2015



Available treatments for major tropical diseases

Disease	Drugs in current use
Chagas Disease	Benznidazole; Nifurtimox
African Trypanosomiasis (Sleeping Sickness)	Pentamidine; Suramin; Eflornithine; Melarsoprol; Nifurtimox.
Dengue	No specific drug or vaccine
Leishmaniasis	meglumine antimoniate (Glucantime) and sodium stibogluconate (Pentostam); Miltefosine; paromomycin
Malaria	Chloroquine, amodiaquine, lumefantrine, mefloquine or sulfadoxine/pyrimethamine, artemisinin.
Tuberculosis	Isoniazid, rifampicin, pyrazinamide and ethambutol

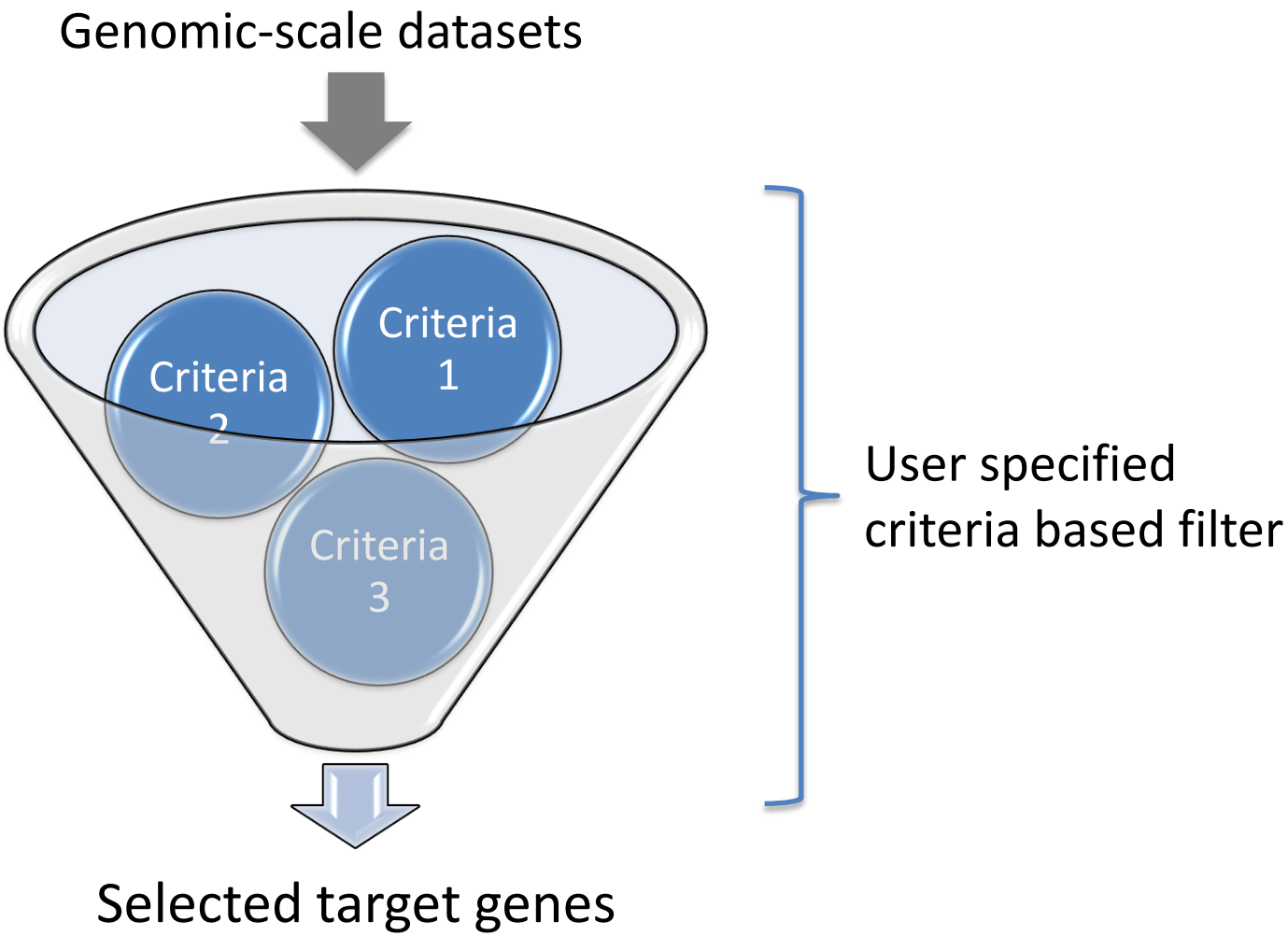
An innovative lead discovery strategy for tropical diseases

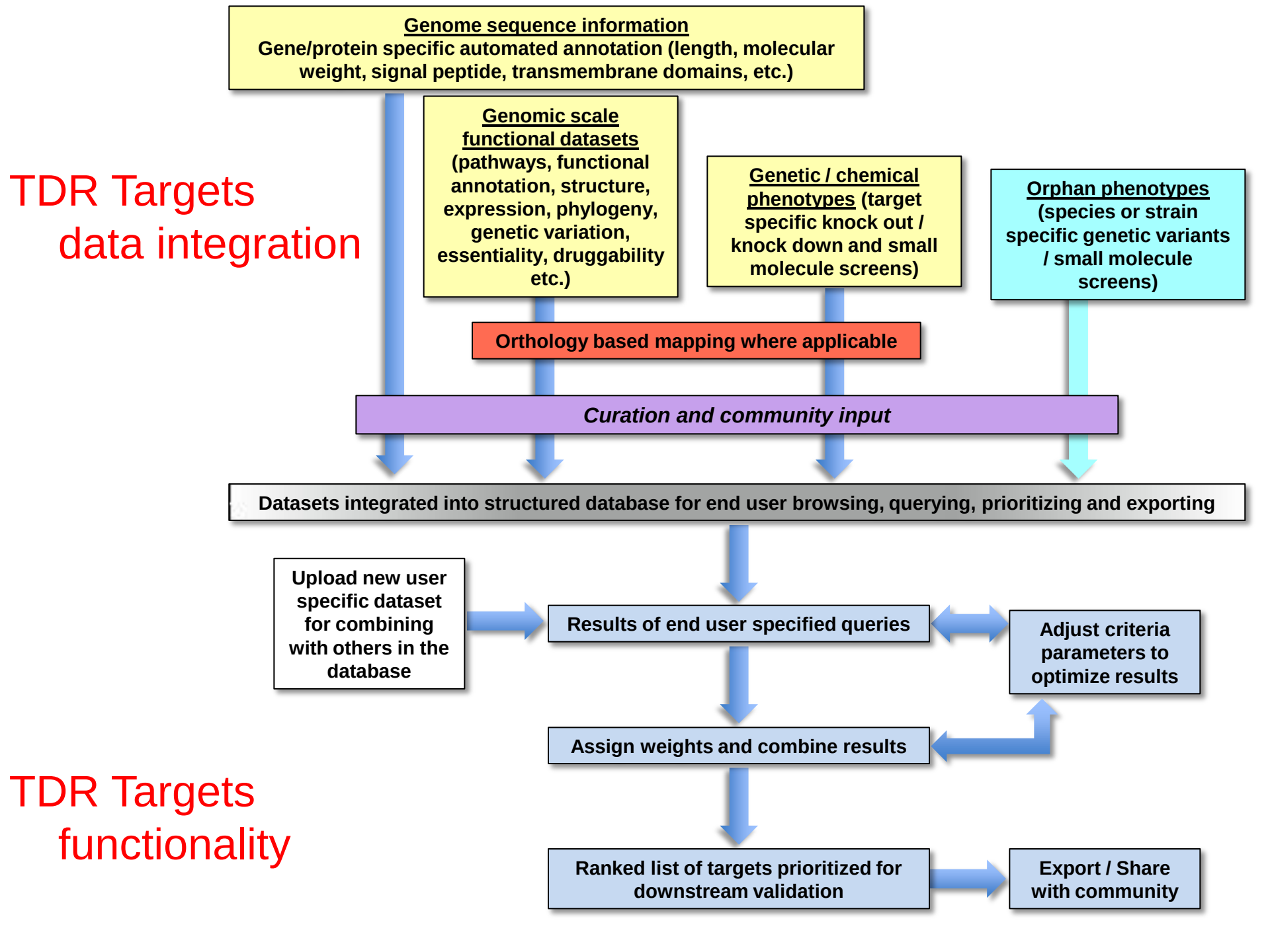


Genomics based target selection

Solomon Nwaka and Alan Hudson
Nature Rev Drug Disc, 2006, 5, 941

Target search strategy implemented in TDR Targets database




TDR Targets
data integration
Genome sequence information
Gene/protein specific automated annotation (length, molecular weight, signal peptide, transmembrane domains, etc.)
Genomic scale functional datasets (pathways, functional annotation, structure, expression, phylogeny, genetic variation, essentiality, druggability etc.)
Genetic / chemical phenotypes (target specific knock out / knock down and small molecule screens)
Orphan phenotypes (species or strain specific genetic variants / small molecule screens)
Orthology based mapping where applicable
Curation and community input
Datasets integrated into structured database for end user browsing, querying, prioritizing and exporting
TDR Targets
functionality
Upload new user specific dataset for combining with others in the database
Results of end user specified queries
Adjust criteria parameters to optimize results
Assign weights and combine results
Ranked list of targets prioritized for downstream validation
Export / Share with community

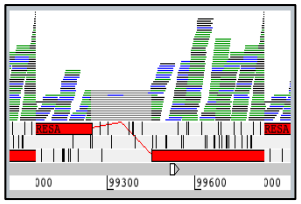
Parasite genomics and drug discovery

*Availability of genome info for many parasites and host species, has enabled **comparative genomics** studies, which has greatly facilitated understanding of parasite biology, host parasite interactions and drug discovery.*

P. falciparum (2002)

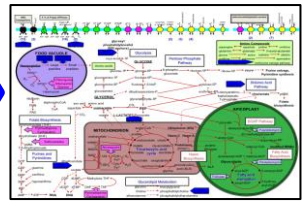
P. Vivax
P. knowlesi
(2008)

genome sequencing & annotation

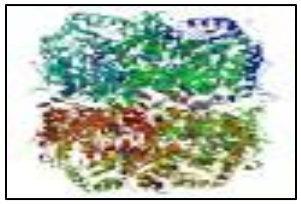


Comparative genomics using dedicated databases

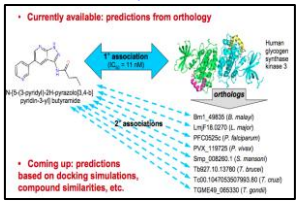
Mapping parasite metabolic pathways



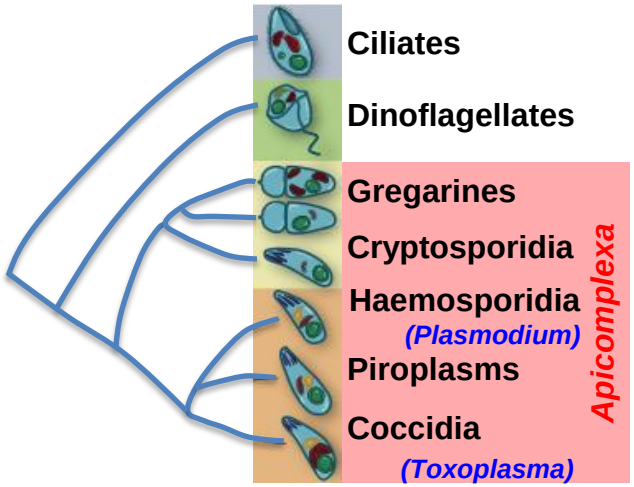
Parasite specific metabolic enzymes as drug targets



In silico approaches for linking potential targets with novel chemical inhibitors



Genomics reveals similarities between malaria and other related parasites such as Toxoplasma gondii, a useful model organism

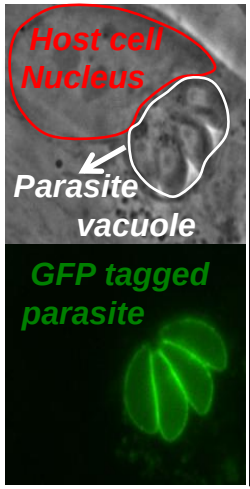


*The close phylogenetic relation, similar cellular architecture, and conserved molecular processes among apicomplexa makes T. gondii a useful model organism, especially for **metabolic studies**.*

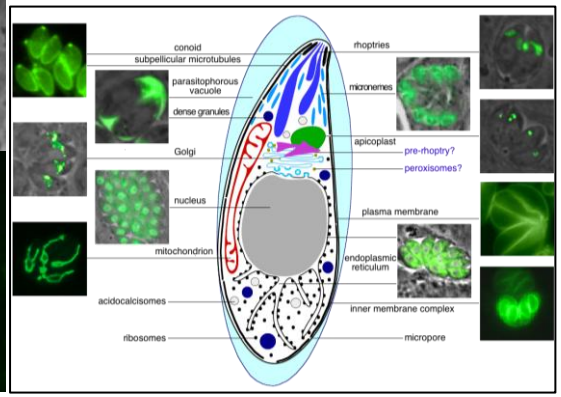
*In addition to the malaria parasite, **Dr. Dhanaekaran Shanmugam's** group will conduct studies on T. gondii and other important human pathogens*

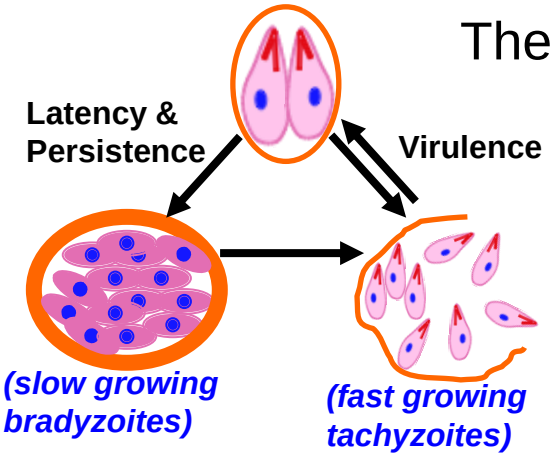
Genetic, metabolic and cell biological studies using T. gondii

Ease of genetic manipulation and availability of convenient animal models makes *T. gondii* a useful laboratory organism



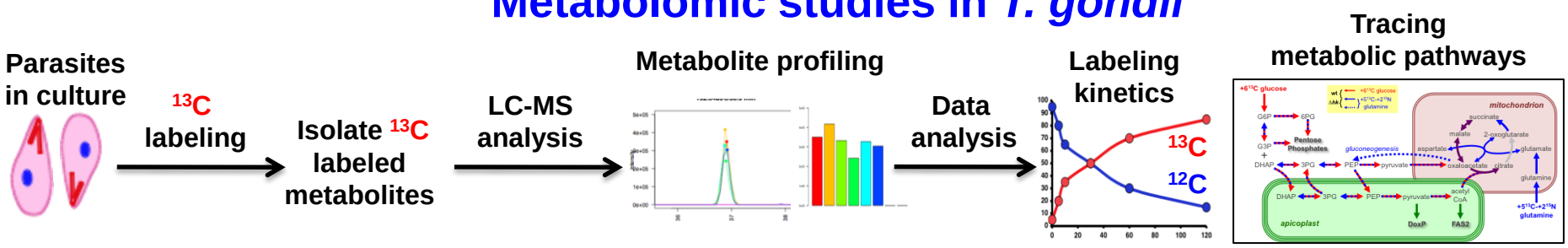
T. gondii cell biology informs Plasmodium studies





The ***in vivo* biology** of *T. gondii* provides insights into the mechanisms by which parasites persist in host and avoid their defense.

Metabolomic studies in *T. gondii*



Dr. Dhanasekaran Shanmgam's lab will carry out extensive metabolomics studies to dissect unique aspects of carbon and energy metabolism in *T. gondii*. Such studies have already helped identify a genetic mutant that will facilitate identifying chemical inhibitors of oxidative phoshorylation and ATP synthesis in parasites.

The apicomplexan central carbon metabolism