Keynote Speech to the Joint International Tropical Medicine Meeting 2008 (JITMM 2008), 13-14 October 2008, Imperial Queen's Park Hotel, Bangkok.

Organised by Faculty of Tropical Medicine, Mahidol University

TropMoMe - Tropical Molecular Medicine in the -Omics Era

Yongyuth Yuthavong

BIOTEC, National Science and Technology Development Agency, Thailand

BIOTEC
a member of NSTDA

NSTDA

Tropical Medicine deals with Tropical Diseases

- Malaria
- Trypanosomiasis (African, American)
- Leishmaniasis
- Giardiasis
- Amoebiasis
- Other diarrhoeal diseases
- Helminthic infections
- Respiratory diseases, including TB
- Opportunistic infections from HIV AIDS
- Rabies
- Zoonosis
- Other infectious diseases common in the tropics

Malaria research in Thailand dated back to over 50 years ago …

- 1962 – Prof Khunying Tranakchit Harinasuta's description of chloroquine resistance (TropMed)
- 1950 - Clinical trials with herbal extracts by Prof Ouay Ketusinh at Siriraj Hospital
- 1978 – Prof Bill Trager gave first training outside USA on *P. falciparum* culture (Fac Science, Mahidol Univ). He was later given Prince Mahidol Award.

Prof Chamlong and Khunying Tranakchit

Prof Ouay Ketusinh

Prof Bill Trager

Does tropical medicine include non-infectious diseases?

- Snake bites? Insect stings?
- Genetic conditions (especially in relation to innate immunity, eg. thalassaemia, abnormal haemoglobins)?
- Cancers (especially related to the tropics, eg. cholangiocarcinoma, Burkitt's lymphoma)?
- Chronic diseases/lifestyle diseases (eg. diabetes, obesity, smoking complications)?

Changing Paradigm of Tropical Medicine

- For people from developed countries visiting developing countries (troops, traders, tourists etc.)
- For indigenous population in endemic countries
- For global health
- From treatment to prevention
- From tertiary to primary health care
- **“From Liverpool to ThaiTropMed”**

Changing Paradigm of Tropical Medicine

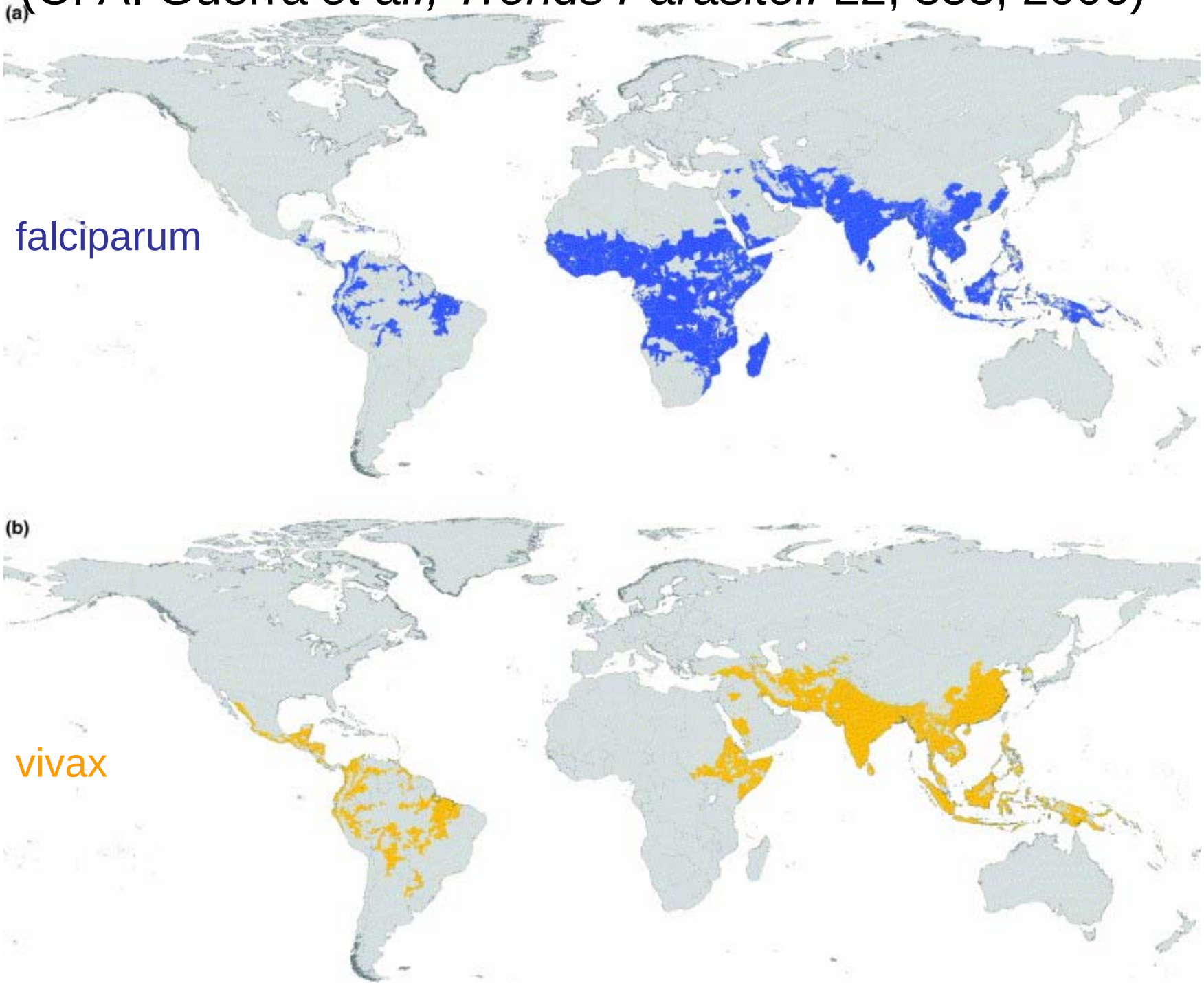
- Climate not the main reason
- Complex socioeconomic/environmental conditions, mixed with medical/scientific aspects of host-pathogen interactions
- **“Geographic Medicine”**
- **Medicine for “Neglected Diseases”**
- **Global Health Medicine**

Malaria is both a Medical/Scientific and Socioeconomic/Environmental Problem

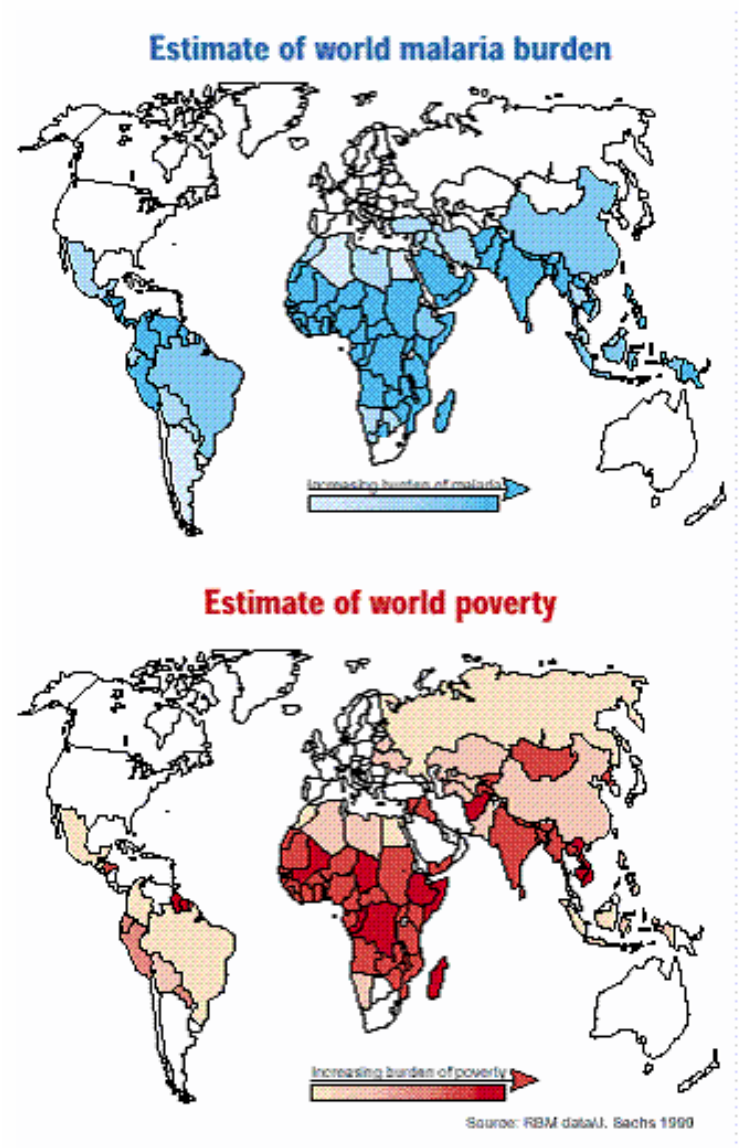
- Medical/Scientific
  - Few effective drugs; widespread drug resistance
  - No vaccine (but a few, eg. RTS,S under development)
  - Host-parasite-vector interaction at genomic level
  - Epidemiology
- Socio-economic-environmental
  - High exposure in endemic areas (home, livelihood)
  - Lack of knowledge on prevention
  - Lack of health infrastructure
  - Poverty

World Distribution of Falciparum and Vivax Malaria, 2005

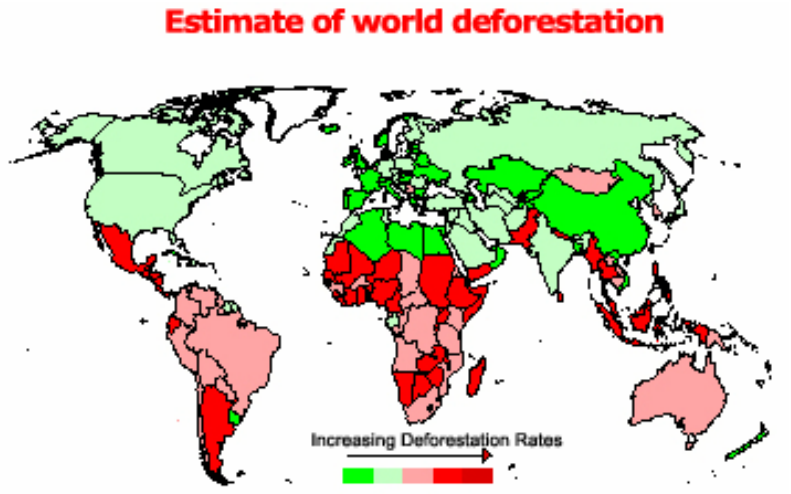
(C. A. Guerra *et al., Trends Parasitol.* 22, 353, 2006)



Socioeconomic/Environmental Aspects of Malaria

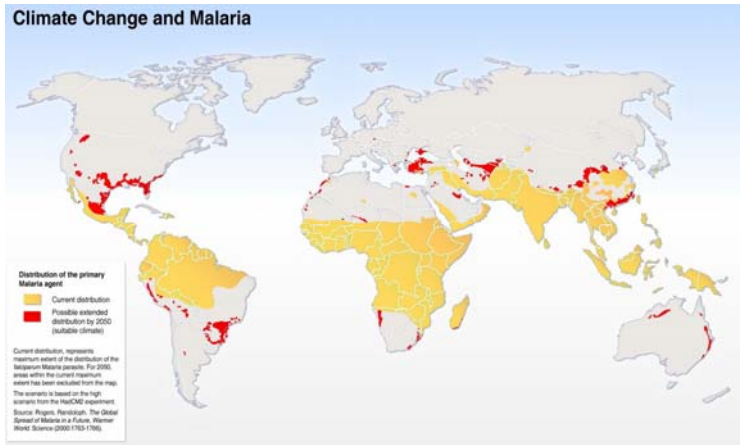


WHO, 2001



FAO, 2001

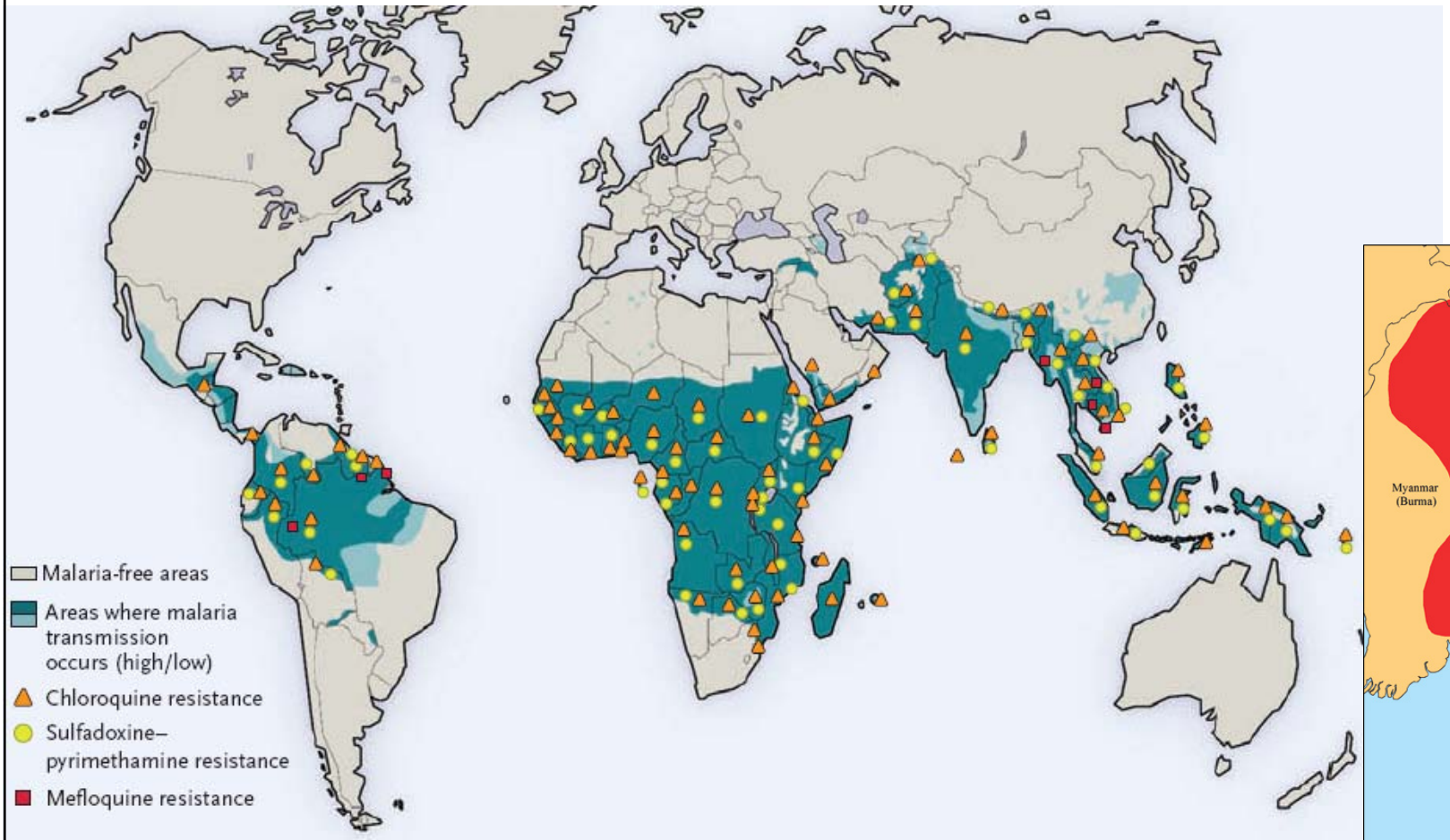
Malaria in 2050, climate change scenario

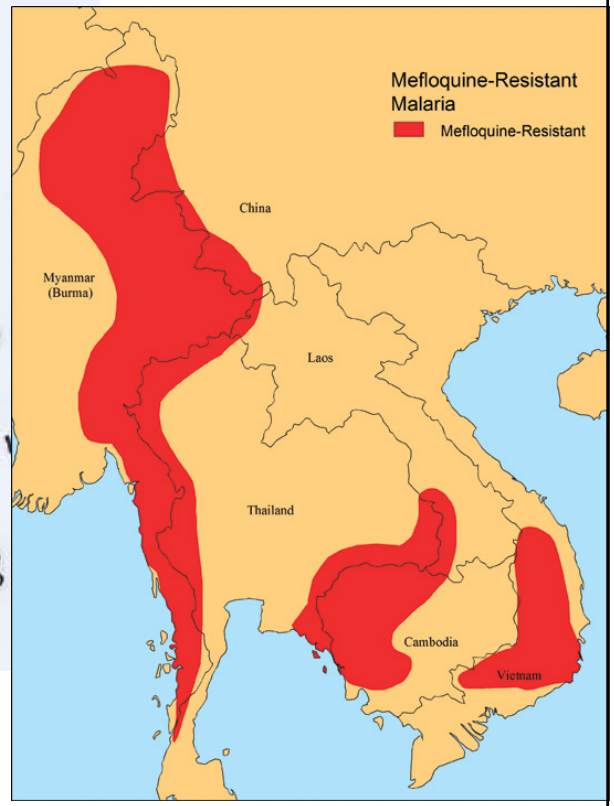


UNEP, 2005

Distribution of Antimalarial Resistance

S. Okie, NEJM 358, 2425, 2008: Data from WHO 2007





CDC Health Information for International Travel 2008

Changing Paradigm of Tropical Medicine

- More biomolecular components
  - Disease process (molecular pathology), prevention and intervention (molecular immunology, pharmacology, diagnostics)
  - Gene-gene and gene-environment interactions (host-parasite-vector interactions)
  - Molecular epidemiology (eg. markers for disease susceptibility and resistance)
- **Tropical Molecular Medicine**

Roots of the “Omics” Era
(http://omics.org)

- New word derived from “chromosome” (chromo=colour, soma=body), or “-ome” (totality, wholeness, completeness)
- Genome as the first –ome
- Genomics as the first -omic science
  - covering complete gene sequences, functions and interactions,
  - combining biology with informatics
  - revealing complexity of molecular biology, rooted in genes and bioinformatics

The Major “Omics”

Genomics category
Arenayomics (RNAomics) category
Transcriptomics category
Proteomics category
Ligandomics category
Glycomics
Expressomics category
Chromatinomics
Regulomics
Cytomics

Cryobionomics
Interactomics
Phenomics category
Psychogenomics
Functomics category
Textomics category
Transgenomics
Vaccinomics
Integromics
Sociomics
Otheromics

TropMoMe:
Tropical Molecular Medicine

- Total approach to tropical medicine
- Emphasis on molecular basis of health and disease
- Complex interactions of host, pathogen, vectors and other health/disease factors (nutrition, climate etc.) taken into consideration
- Socioeconomic/environmental aspects covered

Tropmomics (or Motromics) is an Omic Science

- Tropmomics: Science concerning Tropical Molecular Medicine
- Motromics: Science concerning Molecular Tropical Medicine
- Covers tropical medicine in complex totality
  - Molecular level
  - Cellular and tissue levels
  - Organism level
  - Epidemiological/environmental level
  - Socioeconomic level

Example of Tropmomics: Selective Sweep of Chloroquine and Pyrimethamine Resistance in Malaria

- Origins of resistance: multiple or single?
- Epidemiological data over the years indicated single origin around SE Asia
- Same or similar sets of mutations in PfCRT (for chloroquine resistance) and DHFR (for pyrimethamine resistance)
- Analysis of SNP (single nucleotide polymorphisms), microsatellites, indels (insertions/deletions) of *P. falciparum* DNA indicates selective sweep of resistance genes

See eg. SK Volkman *et al. Nature Genet* 2007, 39, 113-119

Example of Tropmomics: Identification of a Key Drug Target of Scistosomoma

(AN Kuntz *et al., PLoS Med* 2007, 4, e206)

- Schistosoma must survive in aerobic environment by evading reactive oxygen species
- Eukaryotes normally have thioredoxin (Tx) reductase and glutathione reductase (GR)
- Schistosomes have thioredoxin glutathione reductase (TGR) instead
- RNA interference (RNAi) showed that TGR is essential, and can be differentially inhibited
- High-throughput screening yielded oxadiazoles as new drug leads

Example of Tropmomics: Molecular Vaccines against Hookworm

(E. Devaney, *PLoS Med* 2005, 2, e327)

- Hookworms secrete anticoagulant and proteases which digest haemoglobin and other serum proteins
- Specific proteins which can elicit host antibody response, hence starving the parasites
- Human Hookworm Vaccine Initiative (HHVI) is developing vaccines from such hookworm proteins expressed in yeast (*Pischia pastoris*)

Research article

Open Access

Burkholderia pseudomallei genome plasticity associated with genomic island variation

Sarinna Tumapa[1], Matthew TG Holden[2], Mongkol Vesaratchavest[1], Vanaporn Wuthiekanun[1], Direk Limmathurotsakul[1], Wirongrong Chierakul[1], Edward J Feil[3], Bart J Currie[4], Nicholas PJ Day[1,5], William C Nierman[6,7] and Sharon J Peacock*[1,5]

Address: [1]Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, [2]The Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK, [3]Department of Biology and Biochemistry, University of Bath, UK, [4]Menzies School of Health Research, Charles Darwin University, Darwin, Australia, [5]Center for Clinical Vaccinology and Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Churchill Hospital, Oxford, UK, [6]J. Craig Venter Institute, Rockville, Maryland 20850, USA and [7]The George Washington University School of Medicine, Department of Biochemistry and Molecular Biology, Washington DC 20037, USA

Email: Sarinna Tumapa - jay@tropmedres.ac; Matthew TG Holden - mh3@sanger.ac.uk; Mongkol Vesaratchavest - mongkol@tropmedres.ac; Vanaporn Wuthiekanun - lek@tropmedres.ac; Direk Limmathurotsakul - direk@tropmedres.ac; Wirongrong Chierakul - kae@tropmedres.ac; Edward J Feil - e.feil@bath.ac.uk; Bart J Currie - Bart.Currie@menzies.edu.au; Nicholas PJ Day - nickd@tropmedres.ac; William C Nierman - wnierman@jcvi.org; Sharon J Peacock* - sharon@tropmedres.ac

* Corresponding author

Published: 25 April 2008

BMC Genomics 2008, 9:190 doi:10.1186/1471-2164-9-190

Received: 1 October 2007

Accepted: 25 April 2008

nature medicine 9, 921 (2003)

Original antigenic sin and apoptosis in the pathogenesis of dengue hemorrhagic fever

Juthathip Mongkolsapaya[1,2,7], Wanwisa Dejnirattisai[2,7], Xiao-ning Xu[1], Sirijitt Vasanawathana[3], Nattaya Tangthawornchaikul[4], Aroonrung Chairunsri[2], Siraporn Sawasdivorn[6], Thaneeya Duangchinda[1], Tao Dong[1], Sarah Rowland-Jones[1,5], Pa-thai Yenchitsomanus[2], Andrew McMichael[1], Prida Malasit[2,4] & Gavin Screaton[1,5]

Dengue virus presents a growing threat to public health in the developing world. Four major serotypes of dengue virus have been characterized, and epidemiological evidence shows that dengue hemorrhagic fever (DHF), the more serious manifestation of the disease, occurs more frequently upon reinfection with a second serotype. We have studied dengue virus–specific T-cell responses in Thai children. During acute infection, few dengue-responsive $CD8^+$ T cells were recovered; most of those present showed an activated phenotype and were undergoing programmed cell death. Many dengue-specific T cells were of low affinity for the infecting virus and showed higher affinity for other, probably previously encountered strains. Profound T-cell activation and death may contribute to the systemic disturbances leading to DHF, and original antigenic sin in the T-cell responses may suppress or delay viral elimination, leading to higher viral loads and increased immunopathology.

Characteristics of Tropmomics

- Significant “tropical” health/medicine problems
- Requires knowledge of local context
- Transdisciplinary approach
- International collaboration
- In short, the heart of JITMM!

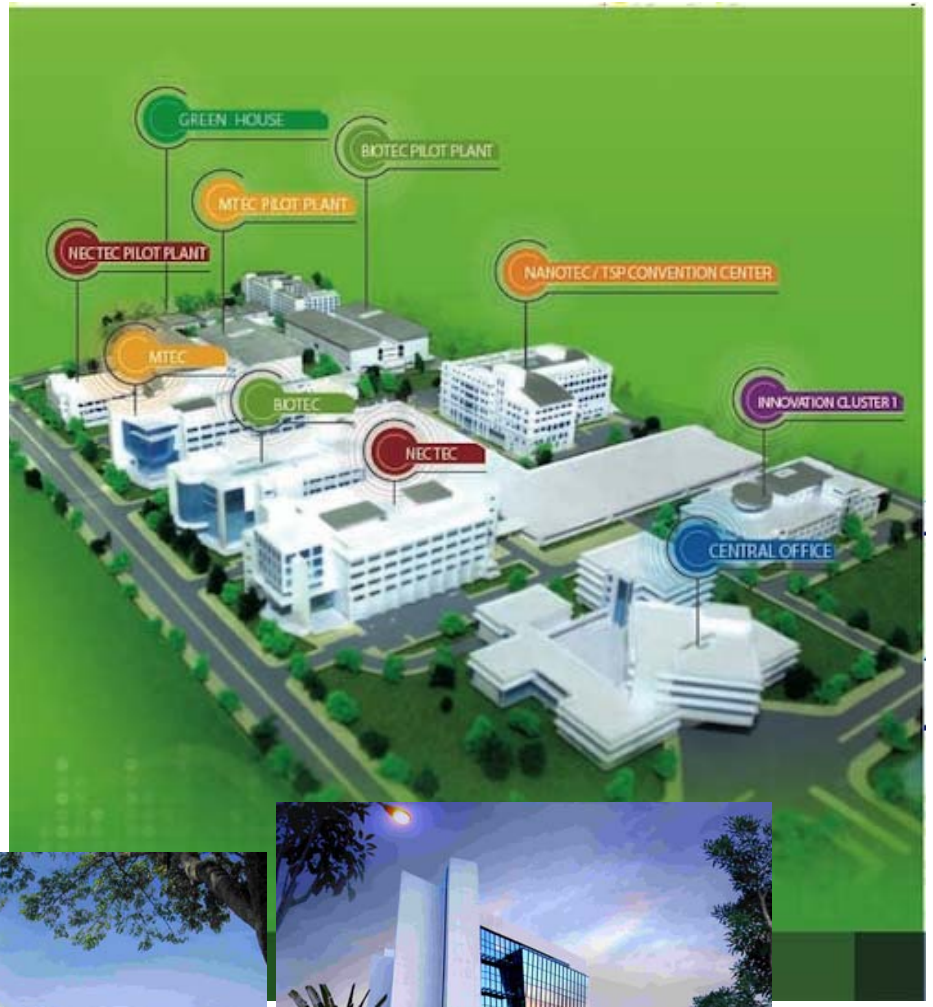
Potentials for Tropmomics

- Development of chemical genomics for new drug development
- Contribution of genomics to molecular immunology (genes in host-parasite interaction)
- “Barcoding” of genes for
  - susceptibility or resistance of individuals to tropical diseases
  - virulence, drug resistance etc. of disease pathogens

Potentials for Tropmomics

- Development of molecular diagnostics, drugs and vaccines
- Molecular epidemiology and pharmacogenomics of tropical diseases
- Basis for disease prevention and clinical care
  - Present (mostly infectious and acute diseases)
  - Future (covering also non-infectious and chronic diseases)

Thailand Science Park



BIOTEC
a member of NSTDA

NSTDA