SMART IRG
INFECTIOUS DISEASES

Research Projects in the SMART ID IRG
(September 1, 2015)

ID-IRG will tackle some of the major challenges in dengue, malaria and microbial infections with a long term goal to develop vaccines, antibiotics and diagnostics. To achieve these goals, the ID IRG has deployed a two-pronged strategy that combines the power of collaboration between MIT and Singaporean investigators with the synergy of converging life and physical sciences with engineering. Our unique and forward-looking research programs leverage the complementary expertise of MIT and Singaporean investigators with transformative technologies to achieve scientific discovery, translation and entrepreneurship in infectious diseases research.

Dengue Program:
The objectives of the Dengue Program are to develop an effective vaccine and a platform for vaccine development in general. Development of antibody-based therapeutics complements vaccine development.
Group Leaders: *Eng Eong OOI (Duke-NUS Graduate Medical School) and Ram SASISEKHARAN (MIT, Biological Engineering)*

1. **Dengue Vaccine Design**
   This project will apply integrated network and structure approaches to design a universal vaccine capable of inducing potent antibody responses against all four dengue serotypes.

   MIT Investigator(s):
   Ram SASISEKHARAN (Biological Engineering)

   Singapore Investigator(s):
   Eng Eong OOI (Duke-NUS Graduate Medical School)

2. **Dengue Vaccine Formulation and Delivery**
   This project will leverage latest advance of nano and microneedle technologies to formulate dengue vaccine in protein, RNA and DNA format in order to induce most potent antibody responses.

   MIT Investigator(s):
   Paula HAMMOND (Chemistry)

   Singapore Investigator(s):
   Eng Eong OOI (Duke-NUS Graduate Medical School)

3. **Dengue Vaccine Evaluation**
   This project will evaluate the efficacy of dengue vaccines in mice, humanized mice and primates.

   MIT Investigator(s):
   Jianzhu CHEN (Biology)

   Singapore Investigator(s):
   Eng Eong OOI (Duke-NUS Graduate Medical School)
   Sylvie ALONSO (NUS, Microbiology)

4. **Biomarkers of Dengue Infection**
   The focus for this project is discovery and application of biomarkers in the prognosis and intervention of dengue infection and in the evaluation of safety of dengue vaccines.

   MIT Investigator(s):
   Steve TANNENBAUM (Biological Engineering)

   Singapore Investigator(s):
   Choon Nam ONG (NUS, School of Public Health)
   Eng Eong OOI (Duke-NUS Graduate Medical School)

5. **Antibody-based Therapeutics**
   This project aims to test the efficacy of neutralizing antibodies as dengue therapeutics.

   MIT Investigator(s):
   Ram SASISEKHARAN (Biological Engineering)

   Singapore Investigator(s):
   Eng Eong OOI (Duke-NUS Graduate Medical School)

6. **RNA-based Mechanisms in Dengue Pathobiology**
   The RNA genome of dengue virus must undergo a series of chemical modifications to be translated into proteins in cells of the human host. This is accomplished by one of the proteins encoded by the dengue genome – the NS5 RNA methyltransferase and RNA-dependent RNA polymerase. The focus of this project is to characterize the viral and host RNA modifications associated with NS5 and their role in viral pathophysiology, toward the goal of identifying antiviral drug targets.

   MIT Principal Investigator(s):
   Peter DEDON (Biological Engineering)

   Singapore Investigator(s):
   Pei-Yong SHI (Novartis Institute for Tropical Diseases)

Malaria Program:
The objectives of the Malaria Program are to identify targets for vaccine development and advance basic understanding of malaria pathobiology at the molecular and cellular levels for novel therapeutic development.
Group Leaders: *Peter PREISER (NTU, Biological Sciences) and Jianzhu CHEN (MIT, Biology)*

1. **A Platform for Systemic Identification of Effective Vaccine Targets**
   This project aims to develop a platform to systemically identify effective malaria vaccine targets.

   MIT Investigator(s):
   Jianshu CHEN (Biology)

   Singapore Investigator(s):
   Peter PREISER (NTU, Biological Sciences)

2. Humanized Mouse Model of Malaria infection

This project will leverage the novel humanized mouse model of malaria infection to evaluate efficacy of vaccine candidates.

MIT Investigator(s):
Jianzhu CHEN (Biology)

Singapore Investigator(s):
Peter PREISER (NTU, Biological Sciences)

3. Mechanobiology of Malaria Pathogenesis

This project will develop a uniquely comprehensive platform for discovery and elucidation of mechanics-based pathways in malaria pathogenesis with an entirely new perspective on targets for developing malaria therapeutics.

MIT Investigator(s):
Jianshu CAO (Chemistry)
Ming DAO (Material Science and Engineering)

Singapore Investigator(s):
Chwee Teck LIM (NUS, Biological Engineering)
Peter PREISER (NTU, Biological Sciences)

4. RNA-based Mechanisms of Malaria Pathogenesis

This project aim is to develop a broad-based platform for identification of RNA-based mechanisms controlling the malaria life cycle and the pathophysiology of infection that will identify new antibiotic targets and fundamental understanding of microbial pathophysiology and host-pathogen interactions.

MIT Principal Investigator(s):
Peter DEDON (Biological Engineering)

Singapore Investigator(s):
Peter PREISER (NTU, Biological Sciences)

5. Chemical Biology of Malaria Invasion

The objective of this project is to use chemical biology tools to study malaria invasion of human red blood cells for potential therapeutic development. Using small molecules designed to bind to unique protein domains, we have recently shown that an indispensable invasion protein-Merozoite surface protein- 1 (MSP-1) to be a viable target for antimalarial drug development (Chandramohanadas et al., Journal of Infectious Diseases 2014). Next, we would like to dissect the molecular mechanisms through which small molecules inhibit invasion. Using such information, we will design novel chemical scaffolds with better affinity to MSP-1 as anti-malarials. The proposed project will utilize diverse platforms such as chemical biology, proteomics, mechano-biology and medicinal chemistry. Additionally, it will involve in vitro and in vivo testing of invasion inhibitors against various models of malaria, including a humanized mouse model available at SMART.

MIT Principal Investigator(s):
Ming DAO (Material Science and Engineering)

Singapore Investigator(s):
Peter PREISER (NTU, Biological Sciences)
Rajesh Chandramohanadas (SUTD, Engineering Product Development)

6. Mechano-biology of Red Blood Cell Damage and Malaria Infection

Reactive oxygen species (ROS) are ubiquitously produced in all living cells including erythrocytes and play a key role in causing tissue damage associated with ageing and pathological states. Exposure to ROS has been shown to inflict wide-ranging damage to components of the RBCs. Such damage often impedes passage of the altered cells through microcirculation in capillaries, due to impaired morphological and mechanical characteristics. In this project, we mimicked oxidative damage in vitro using ROS-generating scaffolds and investigated changes on erythrocyte morphology, biomechanical properties and cytoskeletal organization at the single cell level (Ameya Sinha et al., In review). The microstructural and mechanical changes observed through micropipette aspiration and AFM imaging suggest their strong correlation with the suitability of the damaged cells to harbor plasmodial parasites, a cause of huge health concern to the developing world. These preliminary results open up a new avenue of research to explore in detail the interplay between bio-physical and biochemical factors related to infection.

MIT Principal Investigator(s):
Ming DAO (Material Science and Engineering)

Singapore Investigator(s):
Chwee Teck LIM (NUS, Biological Engineering)
Rajesh Chandramohanadas (SUTD, Engineering Product Development)

Antibacterial Program:
The objectives of the Antibacterial Program are to discover new target-lead couples against high-priority, multi-drug resistant bacterial pathogens and to advance basic understanding of the pathobiology of mycobacteria and other human pathogens at the molecular and cellular levels for development of novel therapeutics and diagnostics. We approach antibacterial drug discovery along several parallel paths – structure-based drug design, fragment-based screening, high-throughput assays and whole cell phenotypic screens – based on novel technologies and recent mechanistic discoveries in bacterial pathogens.
Group Leaders: *Thomas DICK (NUS, Microbiology) and Peter DEDON (MIT, Biological Engineering)*

1. **Mechanisms of Mycobacterial Persistence in Tuberculosis**
   This project will develop novel technologies to define the basic pathophysiological mechanisms governing mycobacterial infection and latency and to identify new antibiotic targets and diagnostic biomarkers through a fundamental understanding of mycobacterial pathophysiology and host-pathogen interactions.

   MIT Investigator(s):
   Peter DEDON (Biological Engineering)

   Singapore Investigators:
   Sylvie ALONSO (NUS, Microbiology)
   Thomas DICK (NUS, Microbiology)

2. **Whole Cell Penotypic Screening Tools for Mycobacterial Antibiotic Development**
   The mycobacterial cell wall poses a problem for delivery of drugs to intracellular targets. To overcome this pharmacokinetic barrier, this project aims to develop new drug screening tools that take advantage of fluorescence-based phenotypic changes when the drug candidate both enters the cell and reacts with its target.

   MIT Investigator:
   Peter DEDON (Biological Engineering)

   Singapore Co-Investigator:
   Thomas DICK (NUS, Microbiology)

3. **Antibiotic Development Based on Translational Control Mechanisms in Bacteria**
   This project exploits a recently discovered mechanism of translational control of bacterial survival responses to develop novel antibiotics based on rational drug design and high throughput screening.

   MIT Investigator:
   Peter DEDON (Biological Engineering)

   Singapore Investigator:
   Julien LESCAR (NTU, Structural Biology & Biochemistry)

4. Bacterial PK/PD Problems in Drug Resistance and Drug Discovery

This project addresses a new model for bacterial drug resistance and drug activation involving metabolism of drugs and prodrugs within the bacterial cell, including drug- and environmentally-induced up- and down-regulation of metabolic pathways in bacteria.

MIT Investigator:
Peter DEDON (Biological Engineering)

Singapore Investigator:
Thomas DICK (NUS, Microbiology)