NOVARTIS

## Dengue Unit

The global burden of dengue has grown dramatically in recent decades, and is currently classified as a re-emerging infectious disease. Dengue and dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) occur in more than 100 countries, with more than 2.5 billion people at risk and an estimated 50 million to 100 million infections per year. The major disease burden is found in Southeast Asia and the western Pacific, with increased reporting of dengue in the Americas. There is currently no treatment for dengue, only supportive care. DHF/DSS is a leading cause of hospital admissions and death among children in most Asian countries. The strain put on countries' healthcare systems during a dengue epidemic can be quite staggering, both financially and with respect to resources, especially in developing countries. Dengue epidemics are often well publicized in the press and have the attention of governments and ministries of health because of the burden on the health resources and the economy.

The increasing number of dengue epidemics in endemic countries within the tropical/subtropical regions of the world may be due to new virulent strains or higher rate of secondary dengue infections. Both situations can lead to increased viremia and this has been directly correlated with severe dengue diseases (DHF and DSS). By comparison, patients suffering from classical dengue fever appear to have a lower viral load[1]. Leading from this observation, our strategy is to find medicines that reduce the viral load so that morbidity and mortality associated with dengue will be lowered and this will then lead to a lower rate of transmission of the virus. We will:

- Identify small molecules that can interfere with viral replication either by blocking essential virus/host membrane fusion, preventing polyprotein processing or inhibiting RNA replication (i.e., to find dengue virus inhibitors that bind directly to viral targets such as the NS3 protease and helicase, NS5 polymerase and methyltransferase, or the replication complexes);
- Test dengue inhibitors for their action on homologous targets in other important human-disease-causing-flaviviruses such as West Nile Virus, Japanese Encephalitis Virus, Yellow Fever Virus or Tick Borne Encephalitis Virus in a platform approach to identify pan-flavivirus inhibitors;
- Discover and validate nonimmune host targets that permit viral replication or are directly required for replication, and assess their responsiveness to treatment through extensive use of new technologies available both within Novartis (Functional Genomics Area) and other partner institutions (e.g., Genome Institute of Singapore).

The Dengue Unit is staffed with nearly 24 scientists to achieve the above goals together with the scientists from Chemistry and Pharmacology Units. Specifically the dengue unit scientists will carry out *in vitro* assays using cloned enzymes/proteins, cell-based assays with infectious virus and/or replicons (non-infectious), animal models for viremia, structural studies of targets, biomarker

[1] Libraty et al. Journal of Infectious Diseases 2002; 185: 1213-21.

identification as well as contribute, together with an international network of partners (including members of the Singapore Dengue Consortium), to a better understanding of dengue pathogenesis in patients through carefully planned prospective studies.

## Singapore Dengue Consortium

The Singapore Dengue Consortium was first established in 2003 and consisted of six healthcare and research companies who have joined forces to study mosquito-borne diseases. Membership of the consortium was expanded to eleven healthcare and research companies in 2007.

The intention of the consortium is to explore ways to better understand and manage dengue infection and ultimately minimize the incidence of dengue in Singapore. Consortium members will be able to leverage each other's strengths and capabilities in terms of clinical management, laboratory diagnosis and viral research in order to accelerate the diagnosis of dengue, determine the serotype of dengue as well as its full genome sequence, and understand what role the genes of dengue virus play in causing the different types of dengue diseases with different severity.