



**MMS Bulletin #92**

*Vernachlässigte Krankheiten*

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***Drug Discovery for Neglected Diseases***

**The Novartis Institute for Tropical Diseases  
NITD**

Von Paul Herrling und Frauke Fischer

*The Novartis Institute for Tropical Diseases (NITD) is the result of a public-private partnership initiative with the Economic Development Board of Singapore. The institute held its inaugural symposium in January 2003 and will work to advance research on tropical diseases. Initially, the NITD will focus on Dengue fever and Tuberculosis research thus addressing two of the most threatening tropical diseases on the increase worldwide.*

According to the World Health Organization, infectious diseases carry 10 percent of the global disease burden with many diseases being on the increase. Traditionally, many tropical diseases have been neglected in the past. Research effort to understand these diseases mechanistically, has not been high in many cases. With the NITD, Novartis intends to contribute to the understanding of tropical diseases as well as to the development of drugs to effectively treat these diseases. The mission of the NITD is to make treatments readily available and without profit in those developing countries where these diseases are endemic.

The NITD is currently located in the Singapore Science Park II, and will soon move to its new facilities in the Biopolis@one-north area. Since October 2003, Alex Matter, former head of the Novartis Oncology Disease Area at Novartis Institutes for Biomedical Research, has been heading the institute. The NITD will employ 70 associates and up to 30 students and postdoctoral fellows.

The NITD will perform basic and conceptual research to identify targets, develop screening assays, and work on synthesis and optimization of compounds up to readiness for clinical testing. Furthermore, the institute aims at becoming a center of training on drug discovery for young scientist from all over the world. The NITD hopes to establish a research network with tropical disease institutes worldwide. The institute is currently involved in several partnerships with third-party organizations, that are committed to reducing the overall affliction of infectious diseases on a global scale.

The NITD is one of the three Corporate Research Institutes of Novartis that are overseen by Paul Herrling. The other two institutes are the Genomics Institute of the Novartis Research Foundation (GNF) in La Jolla, and the Friedrich Miescher Institute (FMI) in Basel. The NITD will closely collaborate with all other Novartis Research Institutes and leverage their expertise in basic research, assay development, and drug discovery science.

## A Focus on Dengue Fever

Dengue Fever is a viral disease, which is transmitted by a mosquito called *Aedes aegypti* and occurs mostly in the tropics. Dengue virus belongs to the family of Flaviviridae and exists in four closely related, but distinct serotypes named DEN-1, DEN-2, DEN-3, and DEN-4. Infection with one of the serotypes does not provide immunity to viruses of the other three serotypes.

A typical Dengue infection starts with severe flu-like symptoms, that are accompanied by severe headache, muscle and joint pain (the disease is also called "breakbone-fever"), and rash.

Dengue haemorrhagic fever (DHF) and Dengue haemorrhagic shock (DHS) are potentially lethal complications. Both can occur after sequential infection with different serotypes. DHF usually begins with a sudden rise in temperature. Patients develop haemorrhagic symptoms, enlargement of the liver, and circulatory problems. In severe cases, the patient's condition may suddenly deteriorate. Circulatory failure develops, the patient may rapidly go into a critical state of shock (DHS), and die within 12-24 hours.

The case-fatality rate of DHF in most countries is about 5%; most fatal cases are among children and young adults. In a number of Asian countries, DHF has become the leading cause of hospitalization and death.

Dengue fever is globally on the increase. During the past 30 years, Dengue has grown dramatically and 2500 million people - which accounts for more than 40% of the world population - are now at risk from Dengue. The disease is endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific. Western Pacific and South-east Asia are most seriously affected. Before 1970 only nine countries had experienced DHF epidemics, a number that had increased more than four-fold by 1995. The WHO currently estimates there may be 50 million cases of Dengue infection worldwide every year.

It is not only the number of patient cases that is threatening, but also the number of sudden outbreaks that are occurring as well as the spreading of the disease to new areas. For instance in Brazil, there were over 390 000 cases including more than 670 cases of DHF reported in 2001 only. Dengue fever cases have frequently been reported from the south of Texas within the last 20 years. Northern Mexico suffered from Dengue epidemics in the recent decades.

Additionally, increased global travel leads to the distribution of Dengue vectors and thus viruses. It is very likely, that a number of cases go unreported each year because surveillance in many countries is passive, and relies on physicians to recognize the disease.

Currently, there is no specific treatment for Dengue available. There are a number of efforts to develop vaccines for the prevention of Dengue. However, development of vaccines against different viral serotypes could pose some difficulties. Protection against one or two serotypes might increase the risk of a more serious disease after infection with a third serotype. There are, however, efforts to develop vaccines against all four serotypes of Dengue. Those treatments may become available within several years.

At the NITD, scientists aim to develop small molecular compounds for the treatment of acute cases of Dengue and DHF. There are a number of different approaches which can be taken to stop the virus, once it has entered a patient, from infecting other cells of the body. For example, the attachment and uptake of the virus into a cell is regulated by a number of host proteins. Blocking the uptake by the host receptor, or inhibiting the unpacking of the viral information when it docks to the host cell and tries to import its genetic information into the cell, could potentially be a way of keeping the viral infection under control. Another strategy for attacking the virus could be to inhibit the translation and poly-protein processing of the virus, once it has entered the host cell. This process is important for the virus, since it activates a number of viral tools, which are essential in order to be able to reproduce in the host cell. In order to infect other cells by exporting its information to them, the virus needs to produce a copy of its genome. There are a number of viral enzymes involved in the process, which could potentially be targeted with a drug. Finally, once the virus has duplicated its genetic information, there are a number of processes involved in the packaging and export of this information from the host cell in order to infect other cells.

There are still a large number of open questions along the sequence of Dengue infection. With the Institute for Tropical Diseases in Singapore, Novartis wants to contribute to the understanding and ultimately to the fight against tropical diseases such as Dengue.

*\*Authors: Frauke Fischer, Scientific Assistant to Head of Corporate Research, and Paul Herrling, Head of Corporate Research, Novartis International AG, Basel, Switzerland. Contact: frauke.fischer@group.novartis.com.*

## **Kontakt**

### **Deutschschweiz**

Medicus Mundi Schweiz  
Murbacherstrasse 34  
CH-4056 Basel  
Tel. +41 61 383 18 10  
info@medicusmundi.ch

### **Suisse romande**

Medicus Mundi Suisse  
Rue de Varembé I  
CH-1202 Genève  
Tél. +41 22 920 08 08  
contact@medicusmundi.ch

### **Bankverbindung**

Basler Kantonalbank, Aeschen, 4002 Basel  
Medicus Mundi Schweiz, 4056 Basel  
IBAN: CH40 0077 0016 0516 9903 5  
BIC: BKBBCHBBXXX