

## Mission

The Novartis Institute for Tropical Diseases aims to discover novel treatments and prevention methods for major tropical diseases. In those countries where diseases are endemic, the Novartis Group intends to make treatments readily available and without profit. The discovery technology is state-of-the-art and the scope of the activities range from target discovery through to screen development and compound optimization. The Institute is looking to recruit the best scientists in the world, and as a major center of excellence, will offer exceptional teaching and training opportunities for post-doctoral fellows and graduate students.



## Introduction

Welcome to the Novartis Institute for Tropical Diseases. Today's opening of the Novartis Institute for Tropical Diseases (NITD) is a special highlight for the Novartis Group and for me personally. I am especially pleased that it took less than one year from the announcement of the creation of this center to its realization.

The objective of the NITD is to advance medical research in the area of progressive infectious and parasitic diseases that affect so many people in the developing world. Novartis views this as a long-term endeavor to enhance the discovery of preventative and effective treatments for diseases like tuberculosis and dengue, and ultimately reduce the overall affliction of tropical diseases and improve the prosperity of developing countries.

We believe that investments of this kind need to be undertaken if significant advances towards the treatment and prevention of these diseases are going to be realized. Tropical diseases alone account for approximately 10 % of the global disease burden, but virtually no new medicines are being developed. Tuberculosis and dengue fever remain major, and increasingly prevalent, public health problems around the world, particularly in developing countries, and Novartis is committed to contributing to finding solutions to help deal with them.

I would like to thank the Economic Development Board of Singapore for its outstanding cooperation and its commitment to encourage Biomedical Sciences R&D activities in this country. Singapore is widely

recognized as a regional center of excellence where a modern scientific research center such as this will thrive. Novartis also looks forward to close collaboration with academic centers and other centers of excellence that are already established.

My best wishes for a successful start of the NITD and its mission towards advances in the prevention, education, care, and treatment of tropical diseases. It is only through a new, sustainable model for research in neglected diseases that we can hope to replace the destructive cycle of infectious disease with a more productive cycle of health.

**Mr Daniel Vasella**  
C.E.O. and Chairman  
Novartis AG



## Greetings from the Economic Development Board (EDB)

Research in the biomedical sciences has advanced rapidly in recent years to yield a rich trove of knowledge and technologies.

The Novartis Institute for Tropical Diseases (NITD) is the result of Novartis' long-term commitment to harness these new discoveries for the development of novel therapeutics against tropical diseases. Novartis' decision to base the NITD in Singapore is a testament of our strong research infrastructure, access to a growing pool of international talents and committed government support for the Biomedical Sciences. I am pleased to welcome the NITD into our Biomedical Sciences community and am confident that NITD's presence here will significantly enhance Singapore's biomedical research vibrancy and capabilities.

I also warmly welcome all speakers and delegates of NITD's Inaugural Symposium on Dengue Fever and Tuberculosis. This event offers a unique platform for the world's leading scientists in the field of tropical diseases to learn from one another and be excited by many new ideas and knowledge.

I congratulate the management and staff of NITD and wish all participants an enjoyable and engaging experience at the symposium.

A handwritten signature in black ink, appearing to read 'Philip Yeo', written in a cursive style.

**Mr Philip Yeo**

Co-Chairman, Economic Development Board and  
Chairman, Agency for Science, Technology and Research



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# Programme

9.00 OPENING

## PART 1 - TUBERCULOSIS (CHAIR: MARIA C FREIRE)

- 9.30 - 10.10 'The Immune Response to *Mycobacterium tuberculosis*: Lessons for Rational Vaccine Design' - **Stefan HE Kaufmann**, Max Planck Institute for Infection Biology, Berlin, Germany
- 10.10 - 10.50 'Practical Approaches to Improving the Chemotherapy of Tuberculosis' - **Clifton E Barry**, Laboratory of Host Defenses, Rockville, USA
- 10.50 - 11.15 COFFEE BREAK
- 11.15 - 11.55 'Thinking Downstream to Accelerate the Introduction of New Vaccines for Developing Countries: the Importance of Translational Research' - **John D Clemens**, The International Vaccine Institute, Seoul, South Korea
- 11.55 - 12.35 'Genetic Diversity of *Mycobacterium tuberculosis*' - **Douglas B Young**, Centre for Molecular Microbiology and Infection, Imperial College of Science, London, UK
- 12.35 - 13.05 'How Technology Can Help Overcome Obstacles to TB Control' - **Mark Perkins**, World Health Organization, Geneva, Switzerland
- 13.05 - 14.00 LUNCH BREAK

## PART 2 - DENGUE FEVER (CHAIR: NATTH BHAMARAPRAVATI)

- 14.00 - 14.40 'Dengue/Dengue Hemorrhagic Fever as a Global Public Health Problem in the 21st Century'- **Duane J Gubler**, Centers for Disease Control and Prevention, Fort Collins, USA
- 14.40 - 15.20 'Update on Clinical Dengue'- **Lam Sai Kit**, Department of Medical Microbiology, University of Malaya, Kuala Lumpur, Malaysia
- 15.20 - 16.00 'Breaking the NS3 and NS5 Tango: the Search for Potential Antiviral Targets' - **Subhash G Vasudevan**, James Cook University, Townsville, Australia
- 16.00 - 16.30 COFFEE BREAK
- 16.30 - 17.10 'Dengue Vaccine Safety: Need for Basic Research'- **Scott B Halstead**, Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, USA
- 17.10 - 17.50 'DNDi: a Novel Solution - **Bernand Pécoul**, Access to Medicines Campaign, Medecins Sans Frontieres, Geneva, Switzerland
- 17.50 - 18.30 Key Notes from **Mary A Lansang**, College of Medicine, University of the Philippines, Manila, Philippines
- 18.30 Finish



## **Dr Maria C FREIRE**

### Biography

Maria Freire is the CEO for Global Alliance for Tuberculosis Drug Development (TB Alliance), a not-for-profit international organization working towards developing anti-tuberculosis drugs that are fast-acting and affordable. Dr Freire was born in Peru and graduated from the Universidad Peruana Cayetano Heredia with a Bachelor of Science before moving to the United States and gaining her Ph.D. in Biophysics at the University of Virginia in 1981. Prior to her position at the TB Alliance, Dr Freire worked for seven years as the Director for the Office of Technology Transfer (OTT) at the National Institute of Health (NIH), during which time she also completed the prestigious Senior Managers Government Program at the John F Kennedy School of Government at Harvard. As part of her role at the OTT, Dr Freire advised the White House and Congress on matters relating to the OTT's role of evaluating, protecting, managing and monitoring all intellectual property arising from the NIH and Food and Drug Administration (FDA). She has received many awards, particularly during her time as the OTT Director, including the distinguished Director's award (1997) as well as Outstanding Performance awards for every year she held this position. Dr Freire remains active on a number of boards and is a regular speaker at a variety of international conferences.



## **Professor Stefan HE KAUFMANN** Biography

Stefan Kaufmann is the Acting Director at the Max-Planck-Institute for Infection Biology where he is also the Founding Director and Member; and Professor at the Charitè Medical Faculty of the Humboldt University, in Berlin. Professor Kaufmann graduated from Johannes Gutenberg University in Mainz, Germany with a Diploma in Biology where he also received his Ph.D in 1977. In 1981 he gained his Habilitation in Microbiology and Immunology at the Free University in Berlin. Professor Kaufmann has held a number of teaching positions at German universities and served extensively on the editorial boards of many scientific publications, most notably as Editor for *Immunobiology*, a position he has held since 1984. Professor Kaufmann regularly acts as Scientific Advisor to the German Research Society and the German Government and also advises international groups such as the World Health Organization (WHO). Professor Kaufmann's research focus is on tuberculosis and immunology, in particular the design of vaccines against tuberculosis, innate immune response and immunity to intracellular bacteria.

## **THE IMMUNE RESPONSE TO *MYCOBACTERIUM TUBERCULOSIS*: LESSONS FOR RATIONAL VACCINE DESIGN**

**Stefan HE Kaufmann**

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A vaccine against tuberculosis has been established by Calmette and Guérin, termed BCG. This vaccine protects newborns from miliary tuberculosis, but fails to prevent the most prevalent form of disease, pulmonary tuberculosis in adults. As a corollary: (i) *Mycobacterium tuberculosis* can be controlled (though not eradicated) by the immune response induced by natural infection, (ii) BCG fails to induce a protective immune response at least in those individuals who are susceptible to tuberculosis. Although it remains to be established whether the immune response evoked by natural infection and by BCG is qualitatively and quantitatively comparable or not, compelling evidence suggests that *M. tuberculosis*-infection fails to prevent reinfection. Animal models aimed at better understanding the immune mechanisms underlying protection and pathogenesis and assessing the efficacy of novel vaccine candidates have to take into account these issues. Acquired immunity against tuberculosis is a T cell-dependent phenomenon. The T cell system comprises distinct populations. The so-called conventional T cells encompass CD4 T cells restricted by MHC class II and CD8 T cells restricted by MHC class I. CD4 T cells are undoubtedly of central importance for acquired resistance against tuberculosis. *M. tuberculosis* preferentially resides in the phagosome. From there its antigens can be introduced to the MHC class II processing machinery. Although *M. tuberculosis* apparently does not egress into the cytosol, its antigens have access to MHC class

processing. Recent findings suggest that *M. tuberculosis* induces apoptotic blebs in macrophages, which are then engulfed by bystander dendritic cells. The dendritic cells process and present the antigenic cargo of the blebs through MHC class I, thus stimulating CD8 T lymphocytes. In addition unconventional T cells also seem to participate in immunity against tuberculosis. These include CD8 T cells restricted by non-classical MHC class Ib molecules, T cells restricted by group I and group II CD1 molecules and  $\gamma\delta$  T cells. CD1 restricted T cells are of particular interest as they recognize glycolipids, which are abundant constituents of the mycobacterial cell wall. Recently the first mycobacterial antigen presented by group II CD1 molecules has been identified as phosphatidylinositol-tetramannoside. Group I CD1 molecules comprise CD1a, b and c, which localize to different intracellular compartments. CD1a/c are preferentially found in early endosomes, whereas CD1b is preferentially localized in the late phagolysosomal vacuole. Macrophages which serve as prime habitats for mycobacteria are virtually devoid of surface expressed group I CD1 molecules. Hence, the question arises how these mycobacterial antigens can be presented. It appears most likely that the apoptosis induced cross-priming of antigens from mycobacteria infected macrophages delivered to bystander dendritic cells can explain this conundrum. What can we learn from these studies for rational vaccine design? Novel vaccination strategies either focus on subunit vaccines including naked DNA-vaccines or viable attenuated vaccines. Subunit vaccination strategies are based on the assumption that one or few antigens suffice for an efficient immune response. Hence, the identification of protective antigens represents an

essential prerequisite for the success of this type of vaccines. Identification of protective antigens is best performed on the global level using transcriptome and proteome approaches. Subunit vaccines come in two forms: Protein/adjuvant formulations or naked DNA constructs. Viable attenuated vaccines are based on the assumption that multiple antigens are required for efficacious protection. Two major strategies are being pursued: Knockout mutants of *M. tuberculosis* and improved recombinant (r)-BCG vaccines. Crippled versions of *M. tuberculosis* should not only be deleted of genes involved in virulence/persistence, but also in genes that manipulate the protective immune response. Improved r-BCG should first be endowed with a higher immunogenicity and second may need a broader antigenic repertoire. Taking advantage of our increasing knowledge about host-pathogen interactions will clearly facilitate rational design of novel vaccines against one of the most frightening threats in the world, tuberculosis.



## **Dr Clifton E BARRY** Biography

Clifton Barry is Section Chief and Senior Investigator of the Tuberculosis Research Section at the Laboratory of Host Defenses, a division of the National Institute of Health (NIH). Since graduating with a Bachelor of Science (Chemistry and Mathematics) at the University of Arizona, Dr Barry obtained his Masters (Organic Chemistry) followed by his Ph.D. (Organic and Biorganic Chemistry) at the prestigious Cornell University in New York. Dr Barry's specialist research area is microbiology, in particular research on *Mycobacterium tuberculosis*. His research projects include investigating the biochemical pathways and processes unique to the tubercle bacillus; understanding existing antitubercular therapies' modes of action; and developing novel antitubercular therapies using combinatorial chemical and genomic approaches. Dr Barry tours frequently to speak about his research and findings at universities and conferences, both in the US and abroad. Notable recipients of his presentations include Harvard Medical School, John-Hopkins Medical School, University of Cape Town, Kyoto University, American Thoracic Society Annual Meeting and The Global Alliance for Tuberculosis Drug Development meeting. Dr Barry is also currently acting as advisor to TB Alliance and the World Health Organization (WHO).

## PRACTICAL APPROACHES TO IMPROVING THE CHEMOTHERAPY OF TUBERCULOSIS

**Clifton E Barry**

Laboratory of Host Defenses, NIAID, NIH,  
12441 Parklawn Dr., Rockville, MD 20852, USA

Antituberculosis chemotherapy currently consists of a six month regimen of four antibiotics: two months of intensive treatment with isoniazid, rifampicin, pyrazinamide and ethambutol followed by four months of continuation therapy with isoniazid and rifampicin. Even following this ideal regimen, as many as 5% of patients will ultimately relapse with active disease. In practice, the logistical constraints of ensuring that patients comply with such extended drug regimens is overwhelming and despite widespread application of directly observed therapy programs, compliance is poor and drug-resistance is increasingly common.

Of the four primary antibiotics used in tuberculosis (TB) therapy, three have potent *in vitro* activity against actively growing bacteria and the combination of these three *in vitro* at doses achievable in serum sterilizes a bacterial culture in a few days. Nonetheless, patients often fail to completely clear viable bacteria from their sputum even after two months of therapy. Understanding this differential activity of these drugs *in vivo* is essential if the duration of therapy is to be shortened. The fourth drug, pyrazinamide, illustrates the dilemma. Pyrazinamide has no activity against *in vitro* bacterial cultures yet in human clinical trials it has been shown to drastically reduce the percentage of patients who ultimately fail therapy and relapse with disease. The precise

Abstract by C. E. Barry continued..

molecular target for pyrazinamide remains uncertain yet the addition of this agent allowed TB therapy to be shortened from eight months to six months. Clearly the target for pyrazinamide is essential uniquely to bacteria in the context of an active infection. Pyrazinamide would never be identified by designing drugs for classical essential targets.

These observations have led us to consider two hypotheses to begin to develop a framework for logically improving current therapeutic approaches for TB. The first hypothesis is that the fundamental physiology of the bacteria, or a sub-population of the bacteria, in a patient presenting with active TB is inherently different from that of an *in vitro* actively growing culture. There is substantial data to substantiate this proposition and to suggest that *in vivo* grown bacteria are phenotypically resistant to many agents potent against *in vitro* grown organisms. The phenomenon can be replicated in animal models of infection. Conventional assessment of antitubercular activity involves initiating therapy shortly after infection of mice with TB. At the time when efficacy is typically assessed the bacteria *in vivo* are actively growing, and highly sensitive to conventional therapy. TB patients, however, do not present with disease at this stage of disease. Instead they present with a chronic condition, usually after extensive pulmonary damage and at a time when the immune system has largely controlled bacterial replication. Mice also develop a chronic infection after six weeks of uncontrolled replication. Typically this infection is stable after several months in the absence of immunosuppression and bacterial numbers do not change until the mouse succumbs from old age.

Treatment of such persistently infected mice reveals a phenotypic drug susceptibility and resistance pattern strikingly similar to that observed in infected humans. We have developed moderate throughput assays for identifying enzymatic targets and assessing compound activities in this model. We have also discovered that immunomodulation of such persistently infected mice dramatically affects the *in vivo* drug susceptibilities of the organisms.

The second hypothesis for the differential drug susceptibility *in vivo* is that the physical microenvironment of the bacteria limits exposure of the organism to the drug. Typical lesions in patients are composed of highly calcified tissue masses and granulomas that are often neither well-oxygenated nor well exposed to blood-borne agents. The precise micropharmacokinetic environment of the organism may mean that the actual concentration of drug at the interior of these granuloma structures is quite low. We have developed aerosol formulations of several front-line and second-line agents and an animal model for aerogenic infection and therapy. Aerosol administration of some agents with extensive tissue penetration and bioavailability (such as isoniazid) has no overall impact on efficacy in this model. However, reformulation of some agents with poor tissue penetration and bioavailability dramatically improves their potency and improves therapeutic outcome. In addition, systemic exposure is markedly reduced following aerosol delivery, reducing the likelihood of toxicity.

## **Professor John D CLEMENS** Biography

John Clemens is the Director of the International Vaccine Institute (IVI) in Seoul, Korea, a non-profit international institute established by the United Nations in 1997 to promote the health of children in developing countries through the development, introduction and use of new vaccines. Professor Clemens began his five-year term on 1 July 1999, during which time he has a leave of absence from his position as Chief of the Epidemiology branch at the National Institute of Child Health and Human Development (NICHD), a division within the National Institute of Health (NIH). He also has a continuing appointment as an Adjunct Professor at Johns Hopkins University. Professor Clemens is a graduate of Stanford University and Yale School of Medicine, and an international expert on vaccine evaluation in developing countries. Professor Clemens has successfully undertaken his numerous vaccine research projects in countries which include Bangladesh, India, Indonesia, and Vietnam. He has been a long-term advisor to WHO and is Director of the WHO Collaborating Center for Clinical Evaluation of Vaccines in Developing Countries. Professor Clemens has published numerous articles on the development of vaccines and is an expert both on vaccines against enteric infections and on methodological approaches for vaccine evaluations. He has pioneered methods for the conceptualization, design, implementation, and evaluation of effectiveness trials of new vaccines.

## **THINKING DOWNSTREAM TO ACCELERATE THE INTRODUCTION OF NEW VACCINES FOR DEVELOPING COUNTRIES: THE IMPORTANCE OF TRANSLATIONAL RESEARCH**

**John D Clemens**

International Vaccine Institute, Kwanak, Seoul, Korea 151-600

The world is in the midst of a revolution in vaccinology, which is yielding a wide diversity of new approaches to vaccines and an increasing number of vaccines against multiple disease targets. Despite this abundance of potential riches for public health, the movement of new and improved vaccines into the public health programs of developing countries has been painfully slow. This is despite the fact that many recently developed and licensed vaccines, such as those against meningitis and pneumonia, address major public health problems in developing countries.

Much has been written about the financial and political forces that have impeded the movement of new vaccines into public health programs for the poor. Less well appreciated is fact that standard paradigms of clinical research on vaccines often fail to provide the entire spectrum of evidence needed to convince donors and policymakers, both at the international and national levels, of the benefits and feasibility of introducing new vaccines.

Some of the limitations with the standard clinical paradigm stem from the fact that it usually focuses on demonstrating the safety and efficacy of new vaccines in industrialized countries, since these countries provide the most important commercial markets for vaccines once they are licensed. According to this paradigm, vaccines are evaluated in developing countries only at a much later date, if at all, leading to significant delays in introducing vaccines into these settings. Moreover,

many vaccines have proved to be less protective in populations living in developing countries than in those residing in industrialized countries. These delays in testing and North-South gradients in vaccine protection have led to calls for parallel, simultaneous testing of new vaccines in industrialized and developing settings, a strategy that is currently being used for vaccine candidates against rotavirus and HIV.

Unfortunately, even when such parallel programs of clinical evaluation are undertaken in the developed and developing world, they may still not yield the evidence needed to persuade donors and policymakers about the public health value of introducing a vaccine into developing countries. The restricted populations, idealized conditions, and narrow focus on 'hard' biological outcomes of conventional vaccine efficacy trials may leave doubts about vaccine performance under realistic conditions, in the wide spectrum of persons who are likely to receive the vaccine in practice, and against syndromic outcomes of concern to public health policy. Moreover, conventional, pre-licensure clinical evaluations, even in developing countries, rarely provide information on the realistic costs and cost-effectiveness of introducing the vaccine, nor about the programmatic feasibility and acceptability of vaccine introduction in public health programs. Thus, even when the trials are completed in developing countries, doubts may remain that impede the introduction of vaccines into public health programs.

While some of these deficiencies in conventional vaccine evaluations can be overcome by designing vaccine trials with more attention to

the public health perspective, often this will not be sufficient to provide persuasive evidence about the need for, value of, and feasibility of introducing a new vaccine into public health practice. These persisting deficiencies lead to the argument for a new agenda of *translational research* to generate the multi-faceted evidence needed to facilitate the rational introduction of new vaccines into developing country public health programs.

What types of research are needed to ‘translate’ a promising new vaccine into public health practice in developing countries? An inventory of such studies was provided by the experience of the Hepatitis B Task Force, mounted in the 1980s to surmount the barriers hindering introduction of hepatitis B vaccine, licensed in the U.S. and Europe, into the programs of developing countries. These studies include: 1) assessments of local disease burden; 2) demonstration projects of using the vaccine in real-life public health programs; 3) analyses of the economic consequences of vaccine introduction; 4) assessments of the perceptions of the importance of the target disease for the vaccine, the usefulness of current, non-vaccine control measures, and the need for vaccination; and 5) policy research to assess potential channels of vaccine introduction, as well as feasible, transparent, and sustainable mechanisms for financing the purchase and delivery of the new vaccine. As such, translational research is distinct from and complementary to pre-licensure trials of vaccines, even those undertaken in developing countries.

While the current focus of research on new vaccines against tuberculosis

is understandably on surmounting the biological challenges of creating safe and protective vaccine candidates, experience with the introduction of other new-generation vaccines into developing countries underscores the importance, even at a relatively early stage of vaccine development, of undertaking translational research to answer key policy questions about the ultimate deployment of these new vaccines in public health practice. These studies should assess the actual burden of disease; policymaker and public perceptions of the disease burden and the relation of these perceptions to the actual disease burden; the appropriate targeting of a new vaccine to groups at risk; the likely demand for a new vaccine in both the private and public sectors; the characteristics of a new vaccine that would make it acceptable and programmatically feasible; alternative channels for introducing a new vaccine into public health programs; and the likely economic consequences of using a new vaccine and the manner in which purchase of the vaccine would be financed.

## **Professor Douglas B YOUNG** Biography

Douglas Young is the Fleming Professor of Medical Microbiology and co-founder of the recently established Centre for Molecular Microbiology and Infection (CMMI) at the Imperial College in London. Professor Young graduated with a degree in biochemistry from Edinburgh University and, after completing a doctorate at Oxford, has spent his research career in Bombay, Seattle and London. He has had a long-term interest in mycobacterial diseases and his research focuses on the mechanisms that are responsible for controlling mycobacterial growth during its initial infection; mycobacterial survival within the host; and the design of improved drugs to ensure mycobacterial elimination. Professor Young was chairman of the World Health Organization (WHO) steering committee responsible for coordination of research on the immunology of leprosy and tuberculosis (TB) from 1992 to 1998, and is currently Chairman of the Stop TB Working Group on Vaccine Development.

## GENETIC DIVERSITY OF *MYCOBACTERIUM TUBERCULOSIS*

**Douglas B Young**

Center for Medical Microbiology and Infection,  
Imperial College, London UK

Over the last decade molecular epidemiology has made a major contribution to investigation of local patterns of tuberculosis transmission. With the introduction of comparative genomics there is an opportunity to expand such studies to investigate the global dissemination of *Mycobacterium tuberculosis* and to begin to understand the evolutionary forces that have shaped this highly successful pathogen.

Genetic diversity is seen in variations in patterns of insertion elements, differing copy numbers of tandem repeat sequences, single nucleotide polymorphisms, and gene deletions. The limited pattern of diversity in comparison with other bacteria suggests that the strains comprising the *M. tuberculosis* complex have evolved from a common ancestor perhaps within the last 15-20,000 years. Analysis of genetic diversity amongst present day isolates, together with amplification of ancient DNA from archaeological samples, can be used to build up a picture of the evolution of tuberculosis in humans and other mammals. In addition to the phylogenetic interest, analysis of genetic diversity provides a means of identifying biological properties underlying strain-specific differences in host tropism, and perhaps contributing to differences in clinical manifestation and transmission of human tuberculosis.

Viewing tuberculosis from the perspective of evolutionary biology may generate novel insights that are relevant to the design of rational strategies for control of disease both locally and at a global level.



## **Dr Mark Daniel PERKINS** Biography

Mark Perkins is the Diagnostics Manager of Communicable Diseases Research at the World Health Organization (WHO) and Manager of the Special Programme on Research and Training in Tropical Diseases in Geneva, Switzerland. Dr Perkins graduated from the University of Texas Southwestern Medical School at Dallas in 1984 and completed his internship and residency in Medicine and Pediatrics. In 1988, he was a Medical Staff Fellow at the National Institutes of Health's (NIH) Laboratory of Infectious Diseases, and he remained working in this area of disease for the next five years at various US hospitals. Dr Perkins was Assistant Professor of Medicine and Pathology at Duke University Medical Center whilst he concurrently held positions in Brazil as Co-Director of the Infectious Diseases Unit and Director of the Reference Mycobacteriology Laboratory at the Federal University of Esp rito Santo in Vit ria. In 1998, Dr Perkins moved to Switzerland to work for WHO as Medical Officer for the Global Tuberculosis Programme before assuming his current position in 1999. Dr Perkins holds five American Board Certifications, including the Board of Tropical Medicine and Hygiene.

## **HOW TECHNOLOGY CAN HELP OVERCOME OBSTACLES TO TB CONTROL**

**Mark Perkins**

Special Programme for Research and Training in Tropical Diseases  
World Health Organization, 1211 Geneva 27, Switzerland

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## **Professor Natth BHAMARAPRAVATI** Biography

Natth Bhamarapravati is Chairman for the National Research Council for Medical Science in Thailand, as well as a member of the National AIDS Commission and Chairman of its Subcommittee for HIV Vaccine Trials. He gained his medical degree from Siriraj Hospital in Bangkok before moving to the US and becoming a Doctor of Science (Pathology) at the University of Pennsylvania. Professor Bhamarapravati worked for two years as a Pathologist for the US Armed Forces in Washington before returning to Siriraj Hospital in Thailand to research and teach. In 1968, he became Professor of Pathology and founding Chairman of Mahidol University's new second medical school at the Ramathibodi Hospital in Bangkok whilst concurrently holding several positions at the University, including Dean of the Faculty of Graduate Studies. Professor Bhamarapravati became President of Mahidol University in 1979, a position he held for 13 years. Professor Bhamarapravati has served on numerous committees for WHO, including Chairman of the Steering Committee for Dengue Fever Vaccine Development, and regularly acts as an advisor to the Thai government. He has received many awards, amongst which include awards from the Thai Government, the World Health Organization (WHO) as well as the prestigious Pasteur Medal (1995). Professor Bhamarapravati research interest is in the pathology and immunopathology of Dengue Haemorrhagic Fever (DHF) and the development of a live-attenuated vaccine which is currently undergoing clinical development.

## **Professor Duane J GUBLER** Biography

Duane Gubler is the Director of the Division for Vector-borne Infectious Diseases at the Centers for Disease Control and Prevention in the US and also acts as Adjunct Professor at both John Hopkins University and Colorado State University. He received his Bachelor of Science (Entomology and Zoology) at Utah State University, and his Masters of Science (Parasitology) at the University of Hawaii. In 1969, he became a Doctor of Science (Pathobiology and Tropical Disease Ecology) at the John Hopkins University School of Hygiene and Public Health and continued his research into tropical medicine in Baltimore and then Hawaii. In 1975, Professor Gubler moved to Indonesia where he was Head of the Virology Department for the US Naval Medical Research Unit 2 for four years, before moving back to the US to research and teach further. Professor Gubler then spent nine years in Puerto Rico, where he was Director of the San Juan Laboratories, and Chief of the Dengue Branch of the Division of Vector-Borne Viral Diseases, whilst concurrently acting as Professor Ad Honorum at the University of Puerto Rico. In 1988, Professor Gubler returned to the US to assume his current positions in Fort Collins. His work focuses on the epidemiology of dengue fever. Throughout his career, Professor Gubler has consulted and lectured in the US and abroad, including to numerous government bodies and the World Health Organization (WHO). Amongst his numerous awards, Professor Gubler has been honoured with US Public Health Service Medals and Outstanding Alumni Awards for Science and Research at The John Hopkins University School.

## DENGUE/DENGUE HEMORRHAGIC FEVER AS A GLOBAL PUBLIC HEALTH PROBLEM IN THE 21<sup>ST</sup> CENTURY

**Duane J Gubler**

Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, CO 80522

Dengue fever and dengue hemorrhagic fever are caused by infection with dengue viruses, which are members of the family *Flaviviridae*, genus *Flavivirus*. Other members of this virus family include yellow fever, West Nile, Japanese encephalitis, tick-borne encephalitis and hepatitis C. There are four dengue viruses, called DEN-1, DEN-2, DEN-3 and DEN-4. These four dengue serotypes are closely related antigenically and cross-react in serologic tests, but there is no cross-protective immunity. Infection with a particular dengue virus provides life-long protective immunity to that serotype. All four dengue viruses cause a similar illness in humans ranging from mild, non-specific viral syndrome to severe and fatal dengue hemorrhagic fever. They also have the same epidemiology, being maintained in large tropical urban centers in a mosquito-human-mosquito transmission cycle. *Aedes aegypti* is the principal urban mosquito vector. This species is highly domesticated and prefers to live with humans in their houses, feeding almost exclusively on humans. Its blood-feeding behavior makes *Ae. aegypti* a highly efficient epidemic vector for dengue viruses.

Dengue fever is a very old disease, but during World War II, a global pandemic of dengue fever began in southeast Asia. The principal mosquito vector, *Ae. aegypti*, was widely dispersed with war materials

and occurred in high population densities at the same time the dengue viruses were being spread by infected soldiers. At the end of the war, much of the region was hyperendemic (the co-circulation of multiple virus serotypes), and these conditions were propagated during the economic boom that occurred in the years following the war. The first epidemic of the severe form of disease, dengue hemorrhagic fever, occurred in Manila, Philippines in 1953. In the 1970s, epidemic dengue/dengue hemorrhagic fever began to spread geographically, with intensified global transmission in the tropics in the last two decades of the 20<sup>th</sup> century. At the beginning of the 21<sup>st</sup> century, over half of the world's population lives in areas at risk, and epidemic dengue/dengue hemorrhagic fever is the second (after malaria) most important vector-borne tropical disease in the world. It is one of the most important causes of morbidity and mortality among children in many southeast Asian countries. Each year there are an estimated 50-100 million cases of dengue fever and several hundred thousand cases of dengue hemorrhagic fever, depending on epidemic activity. The average case fatality rate for dengue hemorrhagic fever is 5%. The World Health Organization estimates that over 100 countries are endemic for dengue fever and 60 countries have endemic dengue hemorrhagic fever in 2002.

The factors responsible for this dramatic global resurgence of epidemic dengue fever and the emergence of dengue hemorrhagic fever are not well understood. However, certain demographic and societal changes have occurred, primarily unprecedented population growth in the urban centers of tropical developing countries, and the dramatic increase in

the movement of people via modern transportation, that have allowed most tropical urban centers to become hyperendemic. This appears to be the most important risk factor associated with the emergence of dengue hemorrhagic fever in a city or country. These aspects will be discussed along with prospects for prevention and control using vaccines versus mosquito control.

## Professor Sai Kit LAM Biography

Lam Sai Kit is Head of the Department of Medical Microbiology at the University of Malaya and Senior Consultant Virologist at the University Hospital, in Malaysia. Professor Lam gained his tertiary education in Australia: his Bachelor of Science at the University of Western Australia, followed by a Masters of Science at the University of Queensland, and a Ph.D. from the Australian National University in 1966. Since this time, apart from a two year stint working as a Scientist at the World Health Organization (WHO) in Geneva, Professor Lam has dedicated his entire career to researching and lecturing at the University of Malaya. He has Fellowships in four countries: Malaysia, China, the UK and the US, and is a member of numerous advisory committees for public health programmes. Professor Lam regularly collaborates with WHO, and acts as Director for the WHO National Influenza Centre, WHO National Centre for Rapid Viral Diagnosis and WHO Collaborating Centre for Arbovirus Reference and Research. Professor Lam's research area is tropical viruses, particularly enterovirus 71, Nipah and dengue virus, for which he has received many awards, including the Prince Mahidol Award in 2001 and the Charles C Shepherd Science award for his Nipah virus article in *Science*.

## UPDATE ON CLINICAL DENGUE

### Professor Sai Kit Lam

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Since the publication of the second edition of WHO Dengue Haemorrhagic Fever in 1997, there have been recent developments in the diagnosis, treatment, prevention and control of dengue haemorrhagic fever (DHF) which necessitates a review.

The clinical events leading to DHF and Dengue Shock Syndrome (DSS) have been well documented. However, the possibility of the virus being able to cause unusual clinical manifestations has surfaced in several studies. Vertical transmission has been reported and this should alert us to the possibility of foetal wastage in late pregnancy. There have also been increasing reports of neurological manifestations in severe dengue and this phenomenon deserves further study.

The main pathophysiological abnormality seen in DHF/DSS is an acute increase in vascular permeability leading to loss of plasma from the vascular compartment with consequent hypovolaemia. Treatment of shock is based on fluid resuscitation ranging from dextran, gelatin, lactated Ringer's and physiological saline. There is the growing practice of anticipatory administration of platelet concentrates to prevent haemorrhage. Recent findings in Vietnam have indicated that the use of normal saline in fluid resuscitation is not only effective but reduces cost. The frequent use of platelet concentrates may not be justified. With a better understanding of the pathophysiology of DHF/DSS and the role

played by immune mediators, the question is raised whether antiviral therapy such as interferon-alpha may have a role to play in clinical management.

The management of DHF and DSS is aided by the differential diagnosis of the infection. Although serological diagnosis is still the mainstay of diagnosis, it has a number of drawbacks that make it an unsatisfactory tool. The application of the polymerase chain reaction (PCR) is only now becoming a serious contender for rapid diagnosis however many in-house assays are not standardized and this may give rise to false results. Commercial PCR assays are making an appearance and may become an important supplement to existing tests.

The failure of mosquito control in the prevention of dengue outbreak is an accepted fact. At best, the impact is only transient. However, this has not deterred research into more novel methods of vector control. Several groups are working on the genetic manipulation of vectors as a potential approach for control of vector-borne diseases.

The progress towards a dengue vaccine has been protracted. The development of the live attenuated vaccine in Thailand has already taken 20 years and it has yet to reach the stage where clinical trials have been completed. Other candidate vaccines based on the formation of live-attenuated chimeric viruses are reaching the stage of clinical trials in humans. The setting up of the Pediatric Dengue Vaccine Initiative in Seoul, Korea, will undoubtedly push forward the dengue vaccine programme, a move applauded by endemic countries.



## **Dr Subhash G VASUDEVAN** Biography

Subhash Vasudevan is a Reader in Biochemistry and Molecular Biology at James Cook University in Townsville, Australia, where he joined as a lecturer in 1993. He obtained his Bachelor of Science with Honours from La Trobe University, Melbourne in 1985, and was awarded a scholarship from The Australian National University (ANU) to complete his Ph.D. at the John Curtin School of Medical Research. In 1989, Dr Vasudevan moved to Germany to take up the position of Postdoctoral Fellow at the Max Planck Institute of Biophysics in Frankfurt before returning to Australia for a further Postdoctoral Fellow position at the ANU's Research School of Chemistry. Dr Vasudevan's research focuses on the understanding of molecular mechanisms that are required for dengue virus replication and the development of novel antiviral strategies based on the prevention of critical molecular interactions that are essential for the normal viral life cycle.

## **BREAKING THE NS3 AND NS5 TANGO: THE SEARCH FOR POTENTIAL ANTIVIRAL TARGETS**

**Subhash G Vasudevan**

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Dengue virus is a member of the *Flaviviridae* family, which includes members of the family associated with human diseases such as yellow fever, Japanese encephalitis, West Nile Virus fever and Hepatitis C. The family members are small, enveloped, single-stranded (ss), positive polarity RNA viruses. There are four serotypes of dengue virus, Den 1-4.

The ~11 kb ss (+) RNA genome of the dengue virus acts directly as a template for the synthesis of the virus proteins. A single translation initiation site leads to production of a precursor polyprotein that is arranged NH<sup>3+</sup>-C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5-COO-. Host signal peptidases and viral proteinases co- and post-translationally process the polyprotein into at least 10 viral proteins: the three structural proteins C, prM and E that form the virion particle, and the seven non-structural proteins, NS1 to NS5, that function in the virus life cycle. The untranslated terminal regions account for less than 5% of the genome, and complementary elements in these regions form stem-loop structures and cyclization motifs that are important for the synthesis of new RNA. In flavivirus genome replication a dsRNA known as the replicative form (RF) is the recycling template for the synthesis of new plus strand RNA and the replication occurs at membrane associated replicase complexes (RC) localised in the perinuclear region

of infected cells. The RC has been extensively characterised in several flaviviruses and includes NS1, NS2A, NS3, NS4A, and NS5 and possibly some cellular proteins. However, the replication of the RNA requires the concerted action of two virus encoded multidomain non-structural proteins, NS3 (helicase) and NS5 (RNA-dependent RNA polymerase - RdRP).

NS5, the largest of the ten flavivirus proteins at 104kDa (900 amino acid residues), is a multidomain protein with at least two domains that contain enzyme activities that are crucial for the replicative cycle of the virus. The N-terminal region is associated with the RNA capping reaction that puts a cap 1 structure ( $^7\text{MeG}^5\text{-ppp}^5\text{-N}^{\text{Me}}$ ) on the plus strand RNA genome and the C-terminal contains the eight highly conserved sequence motifs (I to VIII) that have been recognised in many RdRPs and includes the tripeptide 'GDD' found in all polymerases (POL).

NS3 is composed of 618 amino acids and is the helicase involved in an unwinding step during replication of the virus genome. The N-terminal one-third (167 amino acid residues) has the characteristic serine protease domain that requires NS2B for cleaving the polyprotein at NS2A-NS2B, NS2B-NS3, NS3-NS4A and NS4B-NS5 junctions. The remainder of NS3 forms the helicase domain which consists of nucleotide binding, nucleotide triphosphatase (NTPase) and RNA binding motifs.

Our work has focussed on the interactions of NS5 with the NS3 and also cellular nuclear transport proteins, importin  $\alpha$  and importin  $\beta$  as

heterodimeric complex and importin  $\beta$  on its own. Using a number of different techniques we have located NS5 residues 320 to 405 as being critical for the various protein interactions. Within this region a highly conserved 20 amino acid signature is postulated to be the NS3 binding site. The talk will focus on the structure and function of the interacting regions of NS5 and NS3 as an attractive potential target for a broad-acting antiviral agent against flaviviruses that utilise the same replicative mechanism as Dengue.

## **Professor Scott B HALSTEAD**

### Biography

Scott Halstead is Adjunct Professor at the Department of Preventive Medicine and Biometrics, a division of the Uniformed Services University of the Health Sciences in Bethesda, US. Professor Halstead gained his Bachelor of Arts from Yale University before graduating from medical school at Columbia University in 1955. After two years training in Internal Medicine, he was drafted into the U.S. Army Medical Corps, where he served for eleven years at virology research laboratories in Japan, Thailand and the US. He was Professor and Chair to the Department of Medical Microbiology and Tropical Medicine at the University of Hawaii School of Medicine for 15 years before moving to New York to work at the Rockefeller Foundation where he served successively as Associate, Deputy and Acting Director of the Health Sciences Division between 1983 and 1995. Professor Halstead has been involved in numerous health development policies and projects, including co-founding the Children's Vaccine Initiative in 1990 and coordinating the International Clinical Epidemiology Network from 1983 until 1995. He has acted as a Consultant to the World Health Organization (WHO) for over thirty years and continues to act as Consultant to the Health Equity Program for Rockefeller Foundation as well as acting as Senior Advisor to the Pediatric Dengue Vaccine Initiative in South Korea. Amongst his numerous awards, Professor Halstead has an honorary Doctorate of Science from Mahidol University in Malaysia and is a recipient of the RM Taylor Medal. Professor Halstead is a world leader on epidemiology and the pathogenesis of arboviral infections.

## DENGUE VACCINE SAFETY: NEED FOR BASIC RESEARCH

**Scott B Halstead**

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Dengue viruses cause a wide spectrum of diseases from dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), to dengue fever and un-differentiated febrile illnesses. The four dengue viruses are unique among human pathogens in that naturally acquired dengue immunity can modify disease in two directions, lessened or increased severity. While many genetic as well as acquired human factors affect the severity of dengue virus infections the most important of these is the dual role of IgG<sub>1</sub> dengue antibodies. Infection control by dengue antibodies appear to derive from two attributes of the dengue virus group: 1) four types have evolved from a common ancestor resulting in viruses with many common antigens but sufficient critical structural difference(s) to permit sequential infections, and 2) dengue viruses have a tropism for and ability to replicate in cells of the mononuclear phagocyte system. These cells support antibody-dependent enhanced infection (ADE). Many epidemiological studies provide the background evidence supporting ADE as a biologically plausible hypothesis. More details on host and viral factors that control dengue infection, on the growth of dengue viruses in mononuclear phagocytes, dengue ADE in humans and ADE *in vivo* and *in vitro* involving viruses from a wide spectrum of taxons and many species of animals can be found in published references and reviews (see References).

ADE places an unusual burden on dengue vaccine developers because primary or secondary vaccine failure in individuals who live in or subsequently visit dengue-endemic areas may lead to break-through infections and enhanced dengue disease. The goal of dengue vaccines, therefore, must be to raise life-long protection against disease produced by all four dengue viruses, optimally following a single immunization. Vaccine safety must be demonstrated in human efficacy trials. But it will be important also to be able to identify a successfully immunized individual using an *in vitro* test. Current understanding concerning *in vivo* protection against dengue infection by antibodies is sound epidemiologically, but, there has been little organized research on protection by antibodies. The literature on dengue viral neutralization by antibodies is comprised largely of *in vitro* observations on common laboratory cell systems. Mechanisms of antibody protection are known only for viruses other than dengue. There have been no systematic studies on the natural history of dengue antibody responses in humans following initial or heterotypic infections. A critical unknown is the identity of the cells that support human dengue infection and their relative contribution to disease. The absence of such data limits what is known about biologically relevant receptors for attachment, entry and replication of dengue viruses in human cells. A targeted research effort will be essential to achieve insights on protective immunity and design safe dengue vaccines.

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## **Dr Bernard PÉCOUL**

### Biography

Bernard Pécoul is the Executive Director of the Access to Essential Medicines Campaign for Médecins Sans Frontières (MSF), the France-based Nobel Peace Prize winning medical humanitarian organization that provides emergency medical assistance to more than 80 countries. Dr Pécoul received his medical degree from the University of Clermont Ferrand, France in 1983, and his Masters of Public Health from Tulane University in the US. Dr Pécoul first joined MSF as a volunteer physician in 1983 in Honduras, where he provided healthcare to refugees from El Salvador, Nicaragua, and Guatemala; and then in Thailand and Malaysia, managing public health projects for refugees from Vietnam, Burma, and Laos. In 1988, became Director of Research and Training at Epicentre, MSF's new sister epidemiological research center in Paris, which he also co-founded. From 1991, Dr Pécoul led the French section of MSF as Executive Director, where he oversaw one hundred field projects in 40 countries, before taking on his current position. Dr Pécoul is an international speaker for MSF, raising awareness and lobbying for its support and also the people requiring its medical aid.

## **DNDi: A NOVEL SOLUTION**

### **Bernard Pécoul**

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In recent years, awareness of the absence of effective treatments for neglected diseases has been growing. Intensive lobbying has called for a change in the status quo and different organisations have been created to stimulate research and development and produce health tools adapted to the needs of developing countries. However, these have not been adapted to the specific problems encountered for the most neglected diseases such as leishmaniasis, human African trypanosomiasis, and Chagas disease, rampant in these countries.

The 'Drugs for Neglected Diseases Initiative' (DNDi), the brainchild of Médecins sans Frontières, seeks to address these problems and find a way to meet the need for research and development (R&D) of new field-adapted, effective, and affordable drugs for neglected diseases. The idea is to harness the accumulated knowledge and cutting edge science and technology, collaborate with organizations and governments to develop critically needed drugs for these diseases, and ensure that these are suited for and accessible to the poorer patients of the world.

The DNDi's main objective is to develop and make available drugs for patients suffering from neglected diseases on a not-for-profit basis. It will achieve this by building a needs-driven portfolio of short, medium, and long-term R&D projects, raising awareness about the issue, and building R&D capacity in countries where these diseases are endemic. The initiative aims to foster collaboration both amongst developing

countries and between developing and developed countries. Its design is a blend of centralized management to give it a clear project-specific focus, and decentralized operations that mimic modern drug companies. The model relies heavily on support from the public sector with contributions from the private sector, DNDi's founders, and the general public.

It is only through global collaboration between developed and developing nations that the DNDi can reduce the disparities that exist between drugs and diseases, prioritizing need over profitability.

## **Professor Mary Ann D LANSANG** Biography

Mary Ann Lansang is Executive Director of International Clinical Epidemiology Network (INCLEN) Trust International, an independent, non-profit organisation that works to help clinicians and other scientists obtain the knowledge and tools to improve the health of people in the developing world, and is based in the Philippines. Professor Lansang is also Professor of the Department of Clinical Epidemiology and Infectious Diseases at the University of the Philippines' College of Medicine, where she has taught since 1984. Professor Lansang grew up in Baguio City in the Philippines where she completed a Bachelor of Science in Psychology at St Louis University. She then moved to the University of Manila where she completed a Medical Degree in 1978. Whilst Professor Lansang was Head of the Clinical Epidemiology Unit at the University of the Philippines, she completed her Masters Degree in Clinical Epidemiology from the University of Newcastle in Australia. Amongst other notable positions, she worked for ten years at the Research Institute for Tropical Diseases in Muntlupa City as Consultant, Assistant Director and Head of the Department of Epidemiology and Biostatistics. Professor Lansang's area of interest and research is infectious and tropical diseases, particularly vaccine-preventable diseases such as tuberculosis. Professor Lansang also regularly acts as an advisor both internationally and locally, in particular to the World Health Organization (WHO) and their special programme on Research and Training in Tropical Diseases and the WHO Initiative on Vaccine Research.

