TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE

TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE

2011 - 12 ANNUAL REPORT

ANNUAL REPORT 2011-12

INTERIM FACILITY - 496, UDYOG VIHAR, PHASE – III, GURGAON

About the Translational Health Science and Technology Institute

The Translational Health Science and Technology Institute (THSTI) was set up in 2009 as an autonomous institute by the Government of India, under the Department of Biotechnology, Ministry of Science and Technology. It is part of a broader cluster of institutes known as the NCR Biotech Science Cluster which houses institutes that offer academic and translational services and links to institutions that offer clinical services. It is an ambitious initiative which hopes to create a unique institutional environment for the conduct of truly multidisciplinary research that translates scientific and technological advancements into medical innovations to improve public health.

THSTI is the country's premier organisation working on translational aspects under three of its specialised centres, namely the Vaccine & Infectious Disease Research Centre (VIDRC), the Pediatric Biology Centre (PBC) and the Centre for Biodesign and Diagnostics (CBD) and two of its extramural centres, namely the Clinical Development Services Agency (CDSA) and the National Biodesign Alliance (NBA).

TABLE OF CONTENTS

REFLECTIONS INTO THE FUTURE II

VISION OF THE VISIONARY IV

MUSINGS FROM DBT NODAL OFFICER FOR THSTI V

INTRODUCTION AND BACKGROUND 1

PILLARS OF THSTI 5

Vaccine and Infectious Disease Research Centre (VIDRC) 7

Pediatric Biology Centre (PBC) 24

Centre for Biodesign and Diagnostics (CBD) 28

Clinical Development Services Agency (CDSA) 31

National Biodesign Alliance (NBA) 35

PUBLICATIONS, SCIENTIFIC EVENTS AND SEMINARS 39

AWARDS AND RECOGNITIONS 45

GOVERNANCE AND ADMINISTRATION 49

STUDENTS AND RESEARCH FELLOWS 57

PROFILES OF FACULTY & SCIENTISTS 61

STAFF WELFARE 67

FINANCIAL STATEMENTS 69

Reflections into the future

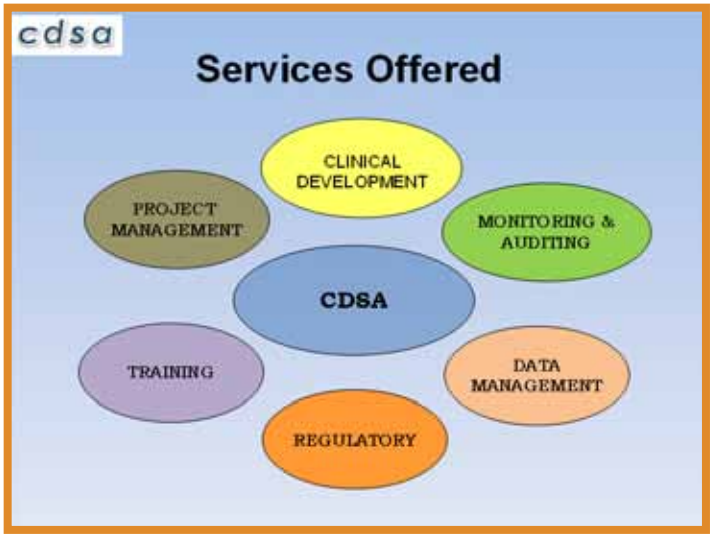
G. Balakrish Nair, Executive Director

THSTI has completed three years since its creation. The Institute is currently functioning from interim facilities in Gurgaon. It is anticipated that the Institute will shift into its new campus in December 2013. The photograph below shows the latest status in construction at the new campus in Faridabad. Three niche centres and two extramural centres are fully functional. The niche centres have begun generating domain specific knowledge through research as evidenced by publications and in one case a diagnostic test kit. All the niche centres now have either Assistant Professors or Scientists recruited and a number of research students working for their doctoral degrees. Recruiting cycles are ongoing and in the next five years the faculty strength is anticipated to double. Several institutions, departments and units have begun collaborating with THSTI niche centres. THSTI has also established the Clinical and Translational Unit in Gurgaon General Hospital and developed a collaborating centre status with the Centre for Health Research and Development, Society of Applied Studies. Two new Centres namely the Centre for Human Microbial Ecology and the Drug Discovery Research Centre are in the process of being established.

THSTI is poised for the next steps of development now. While the research work being performed at THSTI has not assumed the dimension of research programs, the next steps are to develop research programs spanning across Centres. Three such research programs are in the conceptual stages of development. These include Preterm birth to understand the biology of birth, typhoid and rotavirus vaccines and human gut microbiome. Intensive discussions are ongoing to develop these research programs in which different components of the research programs will be addressed by different research groups within and between Centres and with collaborators from other institutes and with International groups. We visualize this as the beginning of functioning as a translational research Institute. International collaborations with University of Turku, International AIDS Vaccine initiative, Osaka University and the appointment of Biotech Chairs have all progressed. THSTI at present is also busy in preparing plans to shift into the new campus and be part of the NCR Biotech Cluster. Being part of the cluster entails collective activities like the development of small animal care facility, primate research centre, the BSL-3 facility and the Advanced Technology Platform.

In the next five years which form part of the 12th Plan of the Government of India, we anticipate that the goals, structure and functions of THSTI will progress vigorously and the process of harnessing the medical benefits of the current revolution in biology will become more apparent. Unlike most other Institutes in India, THSTI is unique and one of its kind and therefore it is charting a path which has not been trodden before in India. The translation of basic biological discoveries into clinical applications involves robust upstream activity in

basic biomedical research and downstream activity that involves premarket clinical trials. In a recent commentary in Science Translational Medicine (July 6th, 2011), Francis Collins, Director, National Institutes of Health, MD, USA, rightly states that "the maximum attrition rates, however, for activities in the translation mode lies in the complex middle zone which has not been subjected to the kind of bold innovation that has characterized other branches of biomedical and clinical sciences". THSTI is making fairly good inroads in the middle zone activities with the development of the CDSA. The range of expertise expected to develop in CDSA is shown in the figure. Complementing CDSA activities is the plans of developing robust translational laboratories which will be different from the research laboratories. The Translational Laboratories will include a range of laboratories developed in the GLP mode to execute laboratory work that are specific to the needs of translation. The next five years should see this functional and available for in house activities and also in a service mode. The National Biodesign Alliance, the other extramural centre, has also made progress with the identification of several partners for joint collaborative work on diagnostics, implants and devices. The NBA Secretariat is housed in the Centre of Biodesign; THSTI is also an alliance partner.



The next five years is crucial for the future of THSTI. We anticipate THSTI developing into a fully functioning national facility that will attract international attention as much interest is already evinced by various stakeholders. The concept of THSTI has appealed industry, academia and other biotech clusters. THSTI researchers will seek to advance the science of translation by identifying bottlenecks in translation of knowledge into therapeutics, diagnostics and treatment development pipelines that may be amenable to various approaches to reduce, remove or bypass bottlenecks. Progress in the education program has also happened. One interesting program that is ongoing in the Glue Grant Scheme which involves THSTI and All India Institute of Medical Sciences (AIIMS). PhD students work with two supervisors, one at AIIMS and the other at THSTI. This is to glue the working ambience and expertise of two different sets of skills. The next five years would require a major boost in the educational activities with the anticipation of the development of a masters program tailored for translational medicine. Many of these activities are in various stages of discussion and development. While many aspects remain to be crystallized, what we are sure of is that THSTI will be different from other Institutes and it is this difference that will determine how successful this Institute will be. THSTI will belong to the future in ways which are being deliberated continuously.

THSTI is the vision of Dr. M.K. Bhan, Secretary of the Department of Biotechnology and in almost all ways we are where we are because of his infectious enthusiasm, enormous energy and thoughtful deliberations all of which have contributed to what THSTI is today. We are indebted to him. We also wish to acknowledge with gratitude the efforts of Dr. T.S. Rao, the DBT nodal officer for THSTI for the continuous help extended.

Vision of The Visionary

Professor M K Bhan

Secretary, Department of Biotechnology, Government of India

Chairman, THSTI Governing Body

After 3 years of its existence the design & direction of the Translational Health Science and Technology Institute continues to be an interesting challenge. The idea underlying THSTI is that available transformative knowledge in biology and its interface with physical, chemical and material science allows for innovative solutions to transform medicine and public health. The need to connect these scientific disciplines with medicine, health and engineering is to orchestrate the creation of transformative biotech tools, product innovations and innovative health care paradigm. This requires an emphasis on disease biology and basic biomedical research, innovation in biotech tools and affordable product profiling as well as innovation landscaping to visualize appealing applications sensitive to cost and context.

Through a lot of creative engagement, the faculty and the governing body arrived at a design of THSTI based on program based centres, extramural entities for advanced translational technology platforms, pre-clinical and clinical centres, incubators, medical connections and strong inter-institutional alliances with medical, engineering and animal science centres. These are at various stages of evolution, and connectivity and collaborativeness continues to be a challenge. It is personally satisfying to see that many Delhi and Faridabad Institutes have really imbibed a cluster concept and the openness to collaborate.

Affordable health care technology creation is a global enterprise and this decade is brilliantly positioned for this mission. THSTI with DBT support has established good relations with institutes and development agencies dedicated to affordable innovation. The challenge now is to engage with translational opportunity for the future molecular design based vaccines, drugs and diagnostics. It is good to see THSTI embark on ambitious programs, such as the human microbiome, biology of pre-mature birth, and novel devices and platforms, in its early stages. These are the roles from which the learning opportunities will grow for the future programs.

THSTI challenge is to create the talent pool and systems to engage with the entire novelty value chain - inspiration for innovation, landscaping and idea profiling, translation, incubation and the product for patient and health care systems. This can only be done by institute whose basic mantra is connectivity and partnership, collaboration rather than competition, technological competency that befits future opportunities for translation, and education that promotes and celebrates innovation. THSTI enjoys science and innovation but its inspiration is better health care for people. The journey has begun, and trial and error will help the institute in its mission, as well as its many collaborators and well-wishers the world over.

Musings from DBT Nodal Officer for THSTI

Dr. T S Rao

Adviser, Department of Biotechnology

Government of India

The idea of possibilities of setting up of Centre for Translational Research in public health was first discussed by Dr. M.K. Bhan, Professor, D/o Paediatrics, AIIMS and Secretary designate of DBT, Govt. of India with me in November, 2003 during the semi annual meeting of rotavirus vaccine development project at Bharat Biotech (I) Ltd. Hyderabad where Dr. Bhan felt a need to establish such centres to facilitate biomedical researchers to translate their innovative research ideas into actual process/product development by bringing together the interdisciplinary groups to work to understand development of technologies to fulfil unmet needs from bedside to bench and bench side to bed.

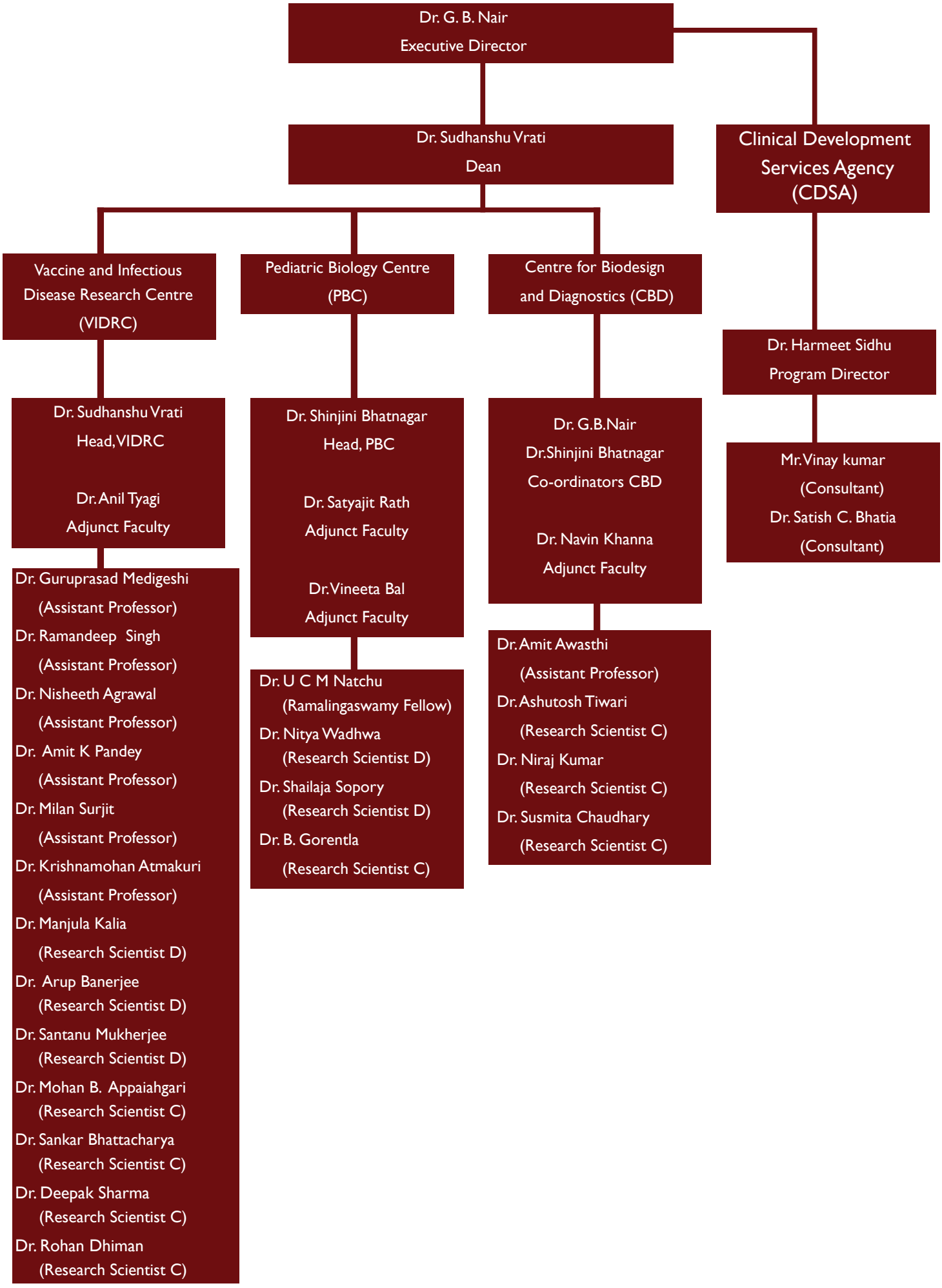
After Dr. Bhan took over as Secretary, DBT in March, 2004, the department made concerted efforts to give shape to this idea through discussions with national and international scientists to establish translational research facility as an independent interdisciplinary technology development and evaluation centre for public health with facilities extended from lab scale development right through promotion of end product for use in health system. It was also envisaged that the centre will facilitate development, process optimization, scale up, evaluation, delivery, commercialization and diffusion of technologies relevant to public health in India, with strong technology support from basic scientists, clinical researchers and technologists including a policy perspective economic analysis and forecasting for technologies with potential for use in public health programmes. It was also planned that the Centre would also provide world class training to physicians in translational and clinical aspects of biotechnology to create a pipeline of talent for the industry and the medical school system. This led to submission of concept document to Planning Commission in November, 2005. Subsequently the Department has taken approval from Expenditure Finance Committee in January 2007 followed by Cabinet approval on 6th Sept. 2007 to establish the "Translational Health Science and Technology Institute (THSTI)" with overall mission to translate science generated knowledge and platform technologies into products for public health system and for defined patient groups and to pursue grand challenges in public health related to affordable technologies through group excellence by initial focus on infectious diseases, to be expanded incrementally to cover chronic life style diseases and translate science generated knowledge and platform technologies into products for public health system for defined patient groups and to respond to opportunities in the market though effective interaction with multiple stake holders including small and medium industries.

As per direction of Cabinet, it was also decided to set up clinical development service agency (CDSA) as an extramural unit of THSTI to provide clinical services and fulfil the Cabinet direction to generate 50% of recurring cost within seven years to provide cost effective high quality services. CDSA has been registered as a Society on 15th July, 2009. Subsequently the Department has also established Vaccine and Infectious Disease Research Centre (VIDRC), Paediatric Biology Centre (PBC) and Centre for Biodesign (CBD) as niche centres of THSTI.

I had a great experience and challenge to create an innovative and unique institute first of its kind in the country to translate innovative ideas to develop by translating health related biotechnologies by acquisition of early leads generated by others, new and improved vaccines, adjuvants, bio-therapeutic products, bio-diagnostics and biomarkers, nutraceuticals, delivery systems for drugs and vaccines and cell based technologies through network of scientific collaboration.

The major challenge of THSTI in my view is networking of scientific collaboration within the NCR Biotech Cluster institutes at Faridabad and Bangalore and outside and continue rapid translation of new scientific knowledge besides attracting international faculty and retaining trained biomedical/basic and physician scientists to carry out translational research and dissemination of knowledge to practice. It is also expected that THSTI to initiate few programmes unique and exclusively to THSTI to fulfil the mission and vision what we (DBT) envisaged in the Union Cabinet approved document in September, 2007. I hope THSTI will work towards fulfilment of these objectives and to become a brand value. Finally i would like to take this opportunity to thank all who helped DBT to create a unique institute through discussions especially weekly meetings on Saturdays.

ORGANOGRAM


Dr. G. B. Nair
Executive Director
Dr. Sudhanshu Vrati
Dean
Clinical Development Services Agency (CDSA)
Vaccine and Infectious Disease Research Centre (VIDRC)
Pediatric Biology Centre (PBC)
Centre for Biodesign and Diagnostics (CBD)
Dr. Harmeet Sidhu
Program Director
Dr. Sudhanshu Vrati
Head, VIDRC
Dr. Anil Tyagi
Adjunct Faculty
Dr. Shinjini Bhatnagar
Head, PBC
Dr. Satyajit Rath
Adjunct Faculty
Dr. Vineeta Bal
Adjunct Faculty
Dr. G.B.Nair
Dr.Shinjini Bhatnagar
Co-ordinators CBD
Dr. Navin Khanna
Adjunct Faculty
Mr.Vinay kumar
(Consultant)
Dr. Satish C. Bhatia
(Consultant)
Dr. Guruprasad Medigeshi
(Assistant Professor)
Dr. Ramandeep Singh
(Assistant Professor)
Dr. Nisheeth Agrawal
(Assistant Professor)
Dr. Amit K Pandey
(Assistant Professor)
Dr. Milan Surjit
(Assistant Professor)
Dr. Krishnamohan Atmakuri
(Assistant Professor)
Dr. Manjula Kalia
(Research Scientist D)
Dr. Arup Banerjee
(Research Scientist D)
Dr. Santanu Mukherjee
(Research Scientist D)
Dr. Mohan B. Appaiahgari
(Research Scientist C)
Dr. Sankar Bhattacharya
(Research Scientist C)
Dr. Deepak Sharma
(Research Scientist C)
Dr. Rohan Dhiman
(Research Scientist C)
Dr. U C M Natchu
(Ramalingaswamy Fellow)
Dr. Nitya Wadhwa
(Research Scientist D)
Dr. Shailaja Sopory
(Research Scientist D)
Dr. B. Gorentla
(Research Scientist C)
Dr. Amit Awasthi
(Assistant Professor)
Dr. Ashutosh Tiwari
(Research Scientist C)
Dr. Niraj Kumar
(Research Scientist C)
Dr. Susmita Chaudhary
(Research Scientist C)

Introduction and Background

1 INTRODUCTION AND BACKGROUND

Translational Health Science and Technology Institute (THSTI) has been conceived at a time when the need for translational research is at an all time high especially in a country like India. Translational research is defined as "the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease (http://grants.jih.gov/grants/ guide/ pa-files/PAR-02-138.html). To accomplish this much felt need in India, THSTI was conceptualized by DBT as an Institute which would deal with all aspects of translational concepts including education and will inspire translational research beyond its own premises.

THSTI will develop around a cluster of niche Centres which form the nucleus of the Institute. These niche centres are stitched together by inter institutional programs with the central theme revolving round bringing science from the bench to the bedside or bedside to bench. Currently three niche centres namely the Vaccine and Infectious Diseases Centre (VIDRC), Pediatric Biology Centre (PBC) and Centre for Biodesign (CBD) are functional. Three more centers namely the Centre for Human Microbial Ecology, Drug Discovery Research Centre (DDRC) and Policy and Forecasting Centre are on the drawing board. The process of developing new centres will follow carefully thought about and debated procedures and will revolve around inter institutional programs; namely maternal and neonatal health and disease, infectious diseases, Biodesign, human microbiome and microbial ecology of the microbiota residing on and in humans and chronic diseases,. The niche centres will have independence of developing collaborative or partnership research proposals with any partners within and outside the country. For instance, the VIDRC has developed collaboration with the International AIDS Vaccine Initiative (IAVI) while the PBC has drawn a memorandum of understanding with the Department of Pediatrics at AIIMS and along with RCB and NBRC with the Gurgoan General Hospital.

Perhaps the most difficult course in the translational process is the implementation of translation. More often than not, discovery faces a cul de sac at the implementation stage of translation. To overcome this, extramural centres have been planned to extend such centres the required autonomy necessary for a translation process. In the long term these centres are anticipated to be self sustaining centres but as a start up the DBT will fund these centres. The extramural centres are envisaged as Independent centres that will manage and facilitate the translation process. While inherently independent the link of the extramural centres will be through the Executive Director of THSTI who will chair its governing and the management committees. Two such extramural centres namely the Clinical Development Services Agency (CDSA) and the National Biodesign Alliance (NBA) are currently operational. The main functions of CDSA is to build up a pool of trained human resources and centres of excellence which would have the wherewithal of performing trials and translational processes of various kinds. The NBA is a multiinstitutional partnership program on Biodesign and *in-vitro* diagnostics, anchored through a coordination secretariat at THSTI, which was initiated by the Department of Biotechnology.

Therefore the philosophy of THSTI is not to plan to do everything within the surrounds of THSTI but to

THSTI Seminar Hall

involve and improve capacity across the country and in the process disseminate the idea and processes of translation.

THSTI will be administered by the Executive Director with the help of three Deans and the heads of centres.

Specifically, THSTI was created through an Expenditure Finance Committee memorandum and with the approval of the Union Cabinet on 6th September, 2008 as a Society registered under the Societies Registration Act XXI of 1860. The society was registered on 15th July 2009 with the Registrar of Societies, Govt. of NCT Delhi vide registration no. S/66271/2009. THSTI started functioning initially from the premises of the National Institute of Immunology (NII) in New Delhi and in January 2010, moved to its rented premises in Gurgaon.

Responsibilities of THSTI's creation and initial start-up were entrusted with the Director, NII to provide administrative and financial support. In August 2010, Dr. Sudhanshu Vrati, a senior scientist at NII, was hired at the level of Dean to provide scientific leadership to the Vaccine and Infectious Disease Research Centre (VIDRC) and Dr. Shinjini Bhatnagar, a senior scientist at AIIMS, was appointed as Professor to lead the Paediatric Biology Centre (PBC). Subsequently, Dr. G. B. Nair, Director NICED, joined as THSTI's Executive Director in October 2011.

The Institute has been functioning independently with the administrative and financial processes having been fully established.

1.1 Infrastructure

Permanent Campus of THSTI in Faridabad: The permanent campus of THSTI is coming up in a unique NCR Biotech Science Cluster (BSC) set-up by the Department of Biotechnology (DBT), Government of India in the NCR at Faridabad (Haryana). The other participating constituent partners of the cluster are: Regional Centre of Biotechnology (RCB), National Institute of Immunology (NII), National Institute of Plant Genomic Research (NIPGR) and National Brain Research Centre (NBRC). The development is jointly driven by a fundamental commitment to bring together diverse institutional structures into a synergistic cluster with high value resources and infrastructure, co-ordinated development and optimisation of societal benefits with an intent and purpose for laying down foundation for the rules and bye-laws of the cluster for, inter-alia, research and innovation. Inclusion of a number of other related centres to be co-located at the Cluster is at conceptual stage. The construction contract was awarded to Odeon Construction Pvt. Ltd in July 2011 and is being managed by Engineers India Ltd (EIL) as a Project Management Consultant (PMC). The construction work of laboratory buildings, which is the first phase of the cluster, is in full force and the progress of work is in consonance with the scheduled time lines. The on- going construction of the buildings is expected to be completed before the closure of the financial year 2012-13.

Interim THSTI Laboratories in Gurgaon: The interim Laboratories of THSTI were initially set up at 496, Udyog Vihar Phase III, Gurgaon (NCR) in the year 2009-10. This is a 25,000 sq. ft. space where general laboratory furnishings like laboratory benches, faculty cabins, library, administrative offices, seminar room, cold rooms and cell culture rooms, were structured. Laboratory areas were furnished with deep freezers, -20°C freezers, 4°C refrigerators, liquid nitrogen containers, and other common equipment like PCR machines, gel dryers, speed vac machines, lyophilizer, high-speed centrifuge (floor model) and table-top centrifuges (large and small) for running biology/ biochemistry laboratories.

Additionally, a small clinical data entry, storage and retrieval system has also been set up.

Subsequently, with the expansion of THSTI research activities and requirement of more lab space, two more buildings (of 10,000 sft each) in the vicinity of THSTI's first building have been rented and furnished for research activities as above. Over 100 researchers at various levels are working in these buildings advancing different THSTI scientific programs. A central instrumentation lab was created for high-end expensive equipment such as FACS (analyser and sorter), FPLC, ultracentrifuge, real time PCR machines, confocal microscope, etc. Most of the scientific infrastructure facilities envisaged in the original EFC have been established as per schedule.

THSTI Laboratory and offices under construction at Faridabad

Small animal and primate research facility under construction at Faridabad

PILLARS OF THSTI

THSTI Niche Centres

- Vaccine and Infectious Disease Research Centre (VIDRC)
- Pediatric Biology Centre (PBC)
- Centre for Biodesign and Diagnostics (CBD)

THSTI Extramural Centres

- Clinical Development Services Agency (CDSA)
- National Biodesign Alliance (NBA)

2.1 Vaccine and Infectious Disease Research Centre :

An Overview

Dr. Sudhanshu Vrati

VIDRC Mission: Globally, infectious diseases remain the leading cause of death, but these are particularly damaging for developing economies like ours. In the context of India, the ever-increasing population density, migration of population to urban areas and associated changes in environment and ecology provide fertile ground for emergence of newer infectious agents. Vaccines, anti-virals, novel antibiotics, and antibody-based strategies remain the most cost-effective means to combat the infectious organisms. The scientific mission of the Vaccine and Infectious Disease research Centre (VIDRC) is to study infectious diseases and pathogens to generate translatable knowledge for developing prophylactic and therapeutic measures against diseases prevalent in India.

VIDRC Faculty: The VIDRC has principal investigators at various levels from assistant to full professor and research scientists who work as members of the team led by a principal investigator. The research teams are complemented by post-doctoral fellows, research students and laboratory technicians. The VIDRC scientific manpower is hired through international search and advertising. The following scientists joined VIDRC this year: Dr. Amit Pandey (Assistant Professor), Dr. Krishnamohan Atmakuri (Assistant Professor), Dr. Rohan Dhiman (Research Scientist C), Dr. Milan Surjit (Assistant Professor), Dr. Arup Banerjee (Research Scientist D), Dr. Santanu Mukherjee (Research Scientist D), and Dr. Deepak Sharma (Research Scientist C).

Current Scientific program: Based on their medical importance in the Indian context, the current scientific activities of VIDRC are focused broadly in two areas: viruses that are spread through mosquitos and contaminated drinking water, and tuberculosis (see inset on next page). Both these areas saw further strengthening with new principal investigators joining the VIDRC this year. Dr. Amit Kumar Pandey joined the TB group after several years of a post-doctoral fellowship in Dr. Chris Sassetti's lab at UMASS Medical School, Worcester, where he worked on Mycobacterial transport systems, carbon metabolism in M. tuberculosis and its implication on virulence and latency. Previously he worked at the University of Nebraska-Lincoln where he was involved in identification of mycobacterial genes critical for pathogenesis. The TB group also saw the addition of Dr. Krishnamohan Atmakuri who came with extensive post-doctoral training in bacterial secretion systems and interest in understanding how *M. tuberculosis* utilized its specialized secretion system to promote virulence. Dr. Milan Surjit joined the Virology group having obtained post-doctoral training in Dr. Pierre Chambon's lab in France. He comes with a long experience of working with hepatitis E virus (HEV) and, at VIDRC he wishes to explore biology of this virus further.

The inset here lists various research areas being pursued at VIDRC. In the vaccine development domain, Dr. Sudhanshu Vrati's group continues to be involved with the clinical development of the oral rotavirus vaccine 116E. This vaccine entered Phase

VIDRC Research Domains

Vaccine Development :
Rotavirus 116E vaccine – Phase III trial
JE vaccine – preclinical development
HIV / AIDS – preclinical development

Novel vaccine delivery platforms :
Animal adenoviruses, HPV, BCG

Respiratory infection : Tuberculosis

Enteric infections : Rotavirus, HEV

Mosquito-borne infections : JE, Dengue

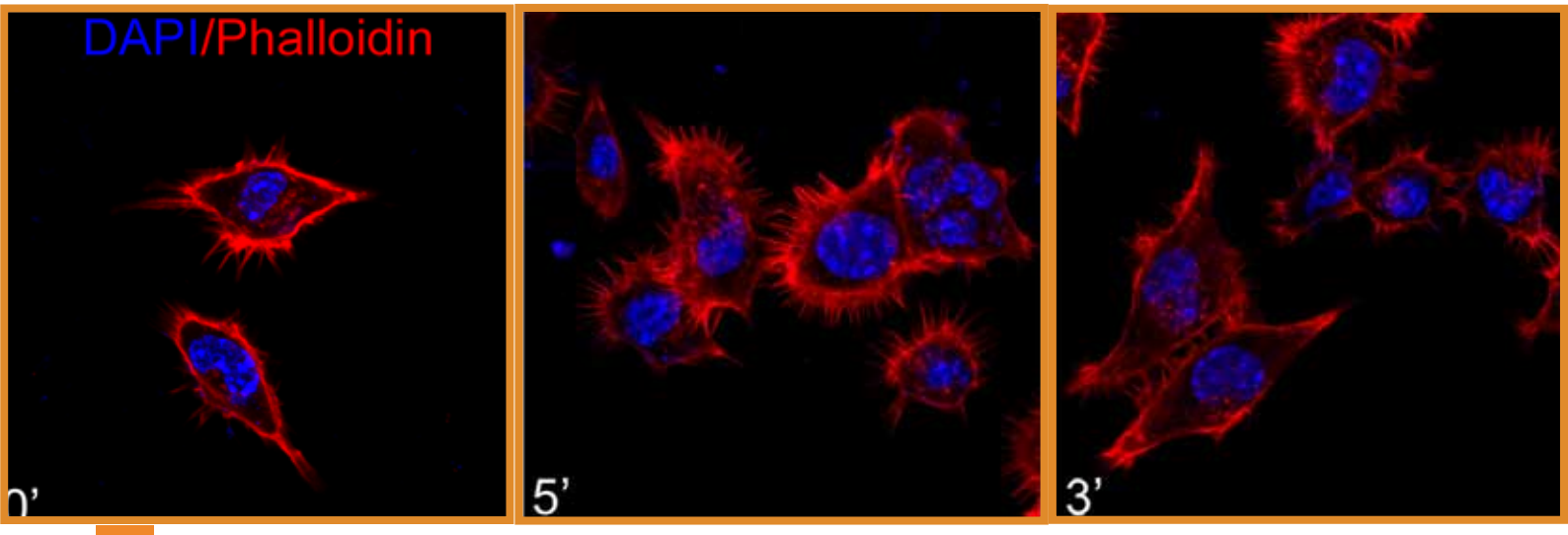
III trial this year and VIDRC is responsible for all laboratory assays. A GLP-compliant laboratory has been established that runs validated assays for the virus antigen detection and genotyping. An assay to determine vaccine immunogenicity is currently under validation. The lab processes and assays have been audited by independent auditors from France and USA. Dr. Vrati's group is also working on improving the DNA vaccine candidate against Japanese encephalitis (JE). This candidate vaccine was previously shown to induce protective immunity in rhesus monkeys.

THSTI has entered into a collaborative agreement with the International AIDS Vaccine Initiative (IAVI) to set us a joint program on HIV vaccine research. On behalf of THSTI, the program is being administered by the VIDRC. The program envisages setting up high throughput methods to identify suitable antigen/s for HIV vaccine design. The laboratory with appropriate infrastructure is being established and a program director and a couple of principal investigators will be hired for the program this year.

In the area of novel vaccine deliver platforms, Dr. Vrati's group is exploring the use of novel animal adenoviruses. The group has isolated adenoviruses from buffalo, chicken and horse. These viruses have been partially characterized at the genome level and those that are able to transduce human cells will be developed into potential vaccine vectors. It may be noted that normal human serum samples did not contain neutralizing activity to these viruses. The group had encouraging results on ovine adenovirus as a potential vaccine vector.

Further progress was made this year to our understanding of the biology of JE and Dengue viruses. It has been established that JE virus (JEV) internalization occurs via a clathrin independent pathway. This pathway however requires dynamin, a large GTPase necessary for pinching of the endocytic vesicle. Additionally, autophagy has been established to be an essential component of JEV life cycle as inhibition of cellular autophagy led to a dramatic block in production of JEV proteins and infectious virus particles. Work on microRNA profiling during JEV infection has identified pathways that may be affected. These include cell cycle, apoptosis, gap and tight junctions, and actin-cytoskeleton regulation. These pathways may be necessary for JEV replication or they may be affected by JEV infection. Similarly, miRNAs have been identified that can potentially target JEV genomic RNA and thereby its replication. Dr. Guruprasad Medigeshi's group has shown modulation of cellular junctions during JEV infection and this compromises the permeability barrier of epithelial and endothelial cells. Disruption of endothelial barriers may have potential implications in the pathogenesis of neurotropic and hemorrhagic viruses such as JEV and Dengue.

Eradication of tuberculosis requires new strategies aimed at targeting non-replicating bacteria that characterize the latent disease. However the physiology and metabolic processes of non-replicating bacteria are poorly understood. The main focus of Dr. Ramandeep Singh's research is to understand the mechanisms of persistence of M. tuberculosis in the presence of anti-tubercular drugs. His group has carried out functional characterization of MazEF toxin-antitoxin (TA) modules at the RNA level. Initial experiments suggest that these TA modules contribute to persistence of M. tuberculosis in vitro. His group has also shown PolyP accumulation under various stress conditions and that PolyP levels might play a role in INH induced persistence in vitro. Dr. Nisheeth Agarwal is studying the role of essential signaling molecules, p-loop GTPases in Mycobacterium. This will not only decipher a new



physiological pathway of Mycobacterium but may also generate novel therapeutic targets. His group is also studying the secretion mechanisms in Mycobacteria that will help identifying the novel drug target and in creating a better vaccine strain.

Human Resource Development: For the young scientists VIDRC has a pre-doctoral, doctoral and post-doctoral training program. During the last year VIDRC provided training to several Master's students who worked for their MSc dissertation with VIDRC faculty. VIDRC also has a PhD program where National Eligibility Test (NET) qualified students are eligible to be considered for the studentship. Presently there are seven PhD students who are working with the VIDRC faculty for their PhD thesis. VIDRC also provides for the VRI awards for post-doctoral work. These are highly competitive awards available to only outstanding young scientists to work towards their post-doctoral training. Currently we have 2 VRI awardees working at VIDRC.

VIDRC Scientific Programs

BIOLOGY OF VIRUSES AND DEVELOPMENT OF NOVEL VACCINES

Principal Investigator: Dr. Sudhanshu Vrati

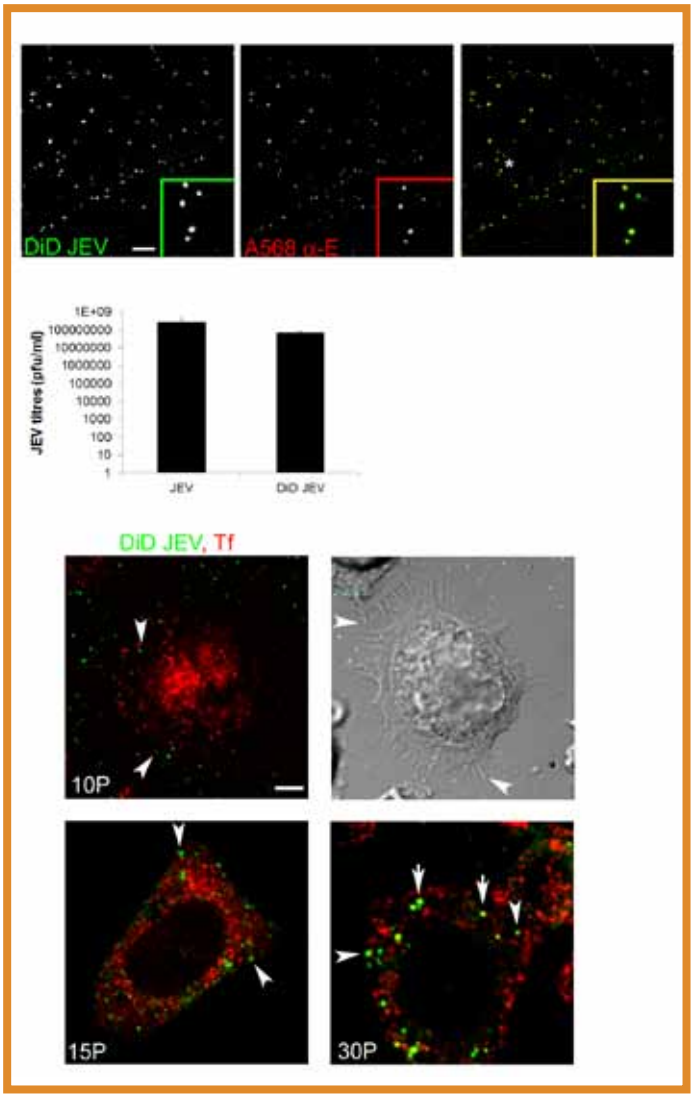
Theme of Research: Study medically important viruses and develop therapeutic and prophylactic interventions against them.

- **Identification of the JEV attachment and receptor system**

  Manjula Kalia, Minu Nain, Sonali Porey Karmakar

Background: Japanese Encephalitis Virus (JEV) continues to remain a serious public health concern in India, China and much of the south-east Asia. There are no specific drugs available to treat the virus infection. Understanding of JEV receptor system will be useful to design molecules to block virus infection. There is very little information available on the nature of the JEV receptor(s) and the molecules involved in virus infection.

Progress: The envelope protein of JEV folds into three structural domains, and it is the third domain (ED3) that mediates the viral attachment to the host cells, and also carries epitopes that elicit neutralizing antibodies. We have expressed and purified the recombinant protein from bacteria and are using it as a tool to find membrane interacting proteins on



cells permissive for JEV infection. The recombinant JEV-ED3 can bind to the surface of Neuro2a cells and can compete for infection by JEV, thus establishing it as a valid tool to explore the JEV receptor. We are currently doing these studies by surface labelling of permissive cells with biotin, purifying the labelled proteins via immobilized NeutrAvidin Gel, and looking for proteins that specifically bind to JEV-ED3. Membrane proteins that specifically interact with JEV-ED3 are resolved on 2D gels and specific proteins/ spots are being analysed by Mass Spectroscopy.

- **Understanding the cellular entry mechanisms of JEV using high-resolution imaging**

  Manjula Kalia, Renu Dhankar

Background: Compared to direct fusion at the plasma membrane, endocytosis is more often the preferred means of viral entry into the target cell. For flaviviruses, the receptor mediated endocytic pathway has been shown to be preferred internalization route, as low pH of the sorting endosome facilitates viral

uncoating and fusion. However, membrane trafficking and virus entry into cells is a very rapidly evolving field and recent studies have demonstrated that a high degree of plasticity exists in eukaryotic cells. Endocytic pathways display extensive cross-talk with respect to molecular players and cargo sorting. For several viruses it has now been shown that often multiple uptake pathways operate simultaneously. JEV uptake into cells is very poorly described till date and JEV internalization has never been visualized.

Progress: We are currently studying JEV uptake into cells in context of the dynamin-dependent clathrin and caveolar endocytic pathways and the dynamin-independent macropinocytotic pathway using fluorescently labelled virus particles and high-resolution imaging. An immunofluorescence based assay to monitor JEV infection in cells has been established. Purified JEV particles are fluorescently labelled with dyes like DiI, DiO, such that the labelled particles retain infectivity. Uptake of fluorescently tagged virus particles in the cells is being tracked with fluorescently labelled ligands of different endocytic pathways. Using a panel of pharmacological inhibitors, dominant negative constructs and RNA inhibition of key endocytic molecules, we have established that JEV internalization occurs via a clathrin independent pathway. This pathway however requires dynamin, a large GTPase necessary for pinching of the endocytic vesicle. The role of the actin and the myosin network of the host cell are being examined in context of the JEV infection process. Imaging studies of virus binding and uptake are being complimented with labelling the cell's actin network. Also the relevance of actin and myosin in establishing JEV infection has been validated using specific inhibitors.

- **Role of autophagy in the JEV infection process**

  Manjula Kalia, Manish Sharma

Background: Autophagy is a cellular process by which cytoplasmic components are sequestered in double-membrane vesicles and degraded to maintain cellular homeostasis. It is also an important component of the innate and adaptive immune response against a variety of viral and bacterial pathogens. Some viruses require components of the autophagocytic machinery for robust replication. We plan to analyse the role of autophagy in the JEV life cycle. This study will provide insights into JEV- host cell interactions.

Progress: We have established that JEV infection leads to induction of autophagy in Neuro2a cells as a normal host response to infection. Autophagy is being monitored in cells by following the conversion of LC3-I to LC3-II (autophagy marker) both by fluorescence microscopy and Western blotting. Autophagy appears to be an essential component of the JEV life-cycle as inhibition of cellular autophagy led to a dramatic block in production of JEV proteins and infectious virus particles. However autophagosomes do not appear to be a site for JEV replication as markers of dsRNA, and newly synthesized JEV proteins like envelope and NS1 do not co-localize with GFP-LC3.

- **Role of micro RNAs in JEV replication and pathogenesis**

  Sanakar Bhattacharya, Arup Banerjee, Deepak Sharma

Background: Studies on the nature and cause of neuronal damage following JEV infection are increasingly pointing towards an unregulated host reaction in the neural tissues. A clear understanding of the host-pathogen interactions during JEV infection would help in the design of novel therapies, not only directed towards limiting the spread of the virus but also limiting the self-inflicted damage of the host through reactions that are elicited by viral infection.

MicroRNAs are emerging as critical regulators of host gene expression and therefore studying the effect of JEV infection on the miRNA pathway might provide critical clues to viral pathogenesis.

Progress: Preliminary high-throughput experiments have indicated significant deregulation of the steady-state level of several host microRNAs in mouse neuronal cells. The pathways which these host microRNAs are predicted to have roles in consist of: cell cycle, apoptosis, gap & tight junction, and regulation of actin-cytoskeleton. Interference with the cell cycle of the host has been shown to be a result of JEV infection. Interestingly, we detected a large number of miRNAs that control the cell cycle to be differentially regulated during JEV infection. Additionally, several cell cycle inhibitors, the transcripts of which are known to be under post-transcriptional regulation, are up-regulated. The studies indicate towards large scale post-transcriptional regulation leading to an arrest of cell-cycle in JEV infected cells.

We are also exploring host microRNAs, if any, that have a potential target site on the JEV genome. MicroRNA microarray on JEV-infected Neuro2a cells has identified microRNAs that were modulated in JEV-infected cells as compared to uninfected cells. These microRNA sequences were then subjected to MicroInspector software in context of JEV whole genome to predict the potential microRNA binding sites. Interestingly, three miRNAs showed probable binding sites on 3'UTR of the JEV genome. However, only 2 miRNA seed sequences perfectly matched with JEV sequence. So far we have verified expression status of one of these miRNAs by real-time TaqMan microRNA assay. Down-regulation of this microRNA was confirmed in both microarrays as well as in Real-time PCR assay. Experimental validation of target region will now be done and its role in JEV replication will be studies.

- **Role of miRNA in regulation of innate immune response during JEV infection**

  Arup Banerjee, Shankar Bhattacharya

Background: JEV is a neurotropic virus, and thus, an effective neuronal innate antiviral response may have bearing on the outcome of infection. The characteristics of the innate immune response are determined in part by the pathogen but can also be influenced by the type of the cell in which the response is generated. Human neuronal cells possess a relatively broad complement of PRR-mediated innate immune

pathways, and that those pathways typically stimulated by viral pathogens via nucleic acid recognition are particularly active. JEV infection is likely to modulate innate immune response by modulating the key target molecules and fine tuning of microRNA expression that can create an environment favourable to viral persistence. Deciphering the signalling target/s will be crucial for understanding the molecular mechanisms of JEV infection, and for the development of potential therapeutic intervention strategies.

Progress: Our initial focus is to examine the role of immune modulatory microRNAs (mir-155, mir-146a) in modulation of innate immune responses. Expression of these miRNAs was measured in neuronal (Neuro2a and CHME3) and non-neuronal (A549) cells. miR-146a was highly expressed in non-neuronal epithelial cells after JEV infection, however, very little change was observed in neuronal cells after JEV infection. On the other hand, miR-155 expression was induced in microglial cells in a time dependant manner after JEV infection. Interestingly, TLR3 expression, IFN-beta and OAS1 expression was significantly induced following JEV infection in both neuronal and non-neuronal cells. JEV is sensed by RIG-I and subsequently induces interferon beta production. Virus can counteract this pathways by modulating mir-146a expression as miR-146a is a negative regulator of RIG-I. As expected, cells treated with Poly(I:C) showed significant reduction in mir-146a expression, however, in JEV infected cells, instead of reduction, mir-146a expression either remain unchanged or increased depending upon cell type. Thus JEV infection modulates miR-146a expression to counteract innate immune pathways. Actual role of these microRNAs on JEV infection will now be studied.

- **Clinical Development of an oral rotavirus vaccine 116E**

  Sharanbasava, Arpita Mishra, Taranjeet Kaur, Mohan Babu Appaiahgari

  (Collaborators: Nita Bhandari and Temsunaro Rongsen–Chandola, SAS, New Delhi; Gagandeep Kang, CMC, Vellore; Ashish Bavdekar, KEM, Pune)

Background: Rotavirus infections are estimated to cause approximately 500,000 deaths annually, predominantly in developing countries. In India, one child in 250 will die from rotavirus diarrhoea and nearly 125,000 rotavirus attributable deaths occur among children under-fives annually. The development and introduction of a rotavirus vaccine, therefore, has been accorded high priority globally. Phase II study conducted in the earlier years established that the 116E oral rotavirus vaccine was highly immunogenic in neonates. These data indicated that the three administrations of 10^4 ffu and 10^5 ffu dosages of the vaccine were safe and the 10^5 ffu dosage of 116E demonstrated a robust immune response after three administrations.

Progress: Phase III efficacy trials of 116E vaccine were initiated this year. This is a randomized, double-blind, placebo-controlled trial with the primary objective of evaluating the efficacy of three doses of ORV 116E, 10^5 ffu, against severe rotavirus gastroenteritis, occurring at least 14 days following the 3rd dose of the test article. Three doses of ORV 116E are being co-administered with routine childhood vaccines (Pentavalent vaccine, OPV) at 6-7 weeks, ≥10 weeks and ≥14 weeks of age. 6800 subjects have been enrolled in three sites - Delhi, Pune (Maharashtra) and Vellore (Tamil Nadu) and will be followed up till the age of 2 years. Multiple trial sites are included to ensure that the vaccine works in different geographical settings in India. Efficacy outcomes are measured through ascertainment and documentation of all episodes of gastroenteritis occurring from enrollment till the age of 2 years. The vaccine immunogenicity will be assessed through a four-fold rise in rotavirus specific serum IgA antibody titers 4 weeks after the third dose in a subset of subjects. Virus shedding will also be assessed on days 0 (prior to administration), 3 and 7 in the "Immunogenicity and Viral Shedding Subset". A GLP-compliant lab with quality controlled processes has been set up with trained manpower. ELISA for the rotavirus antigen in the stool samples and RT-PCR assay for virus genotyping have been validated and are in use. Validation of the IgA assay for the vaccine immunogenicity is ongoing.

- **Development of novel antigen delivery systems**

  Mohan Babu Appaiahgari, Santanu Mukherjee, Arup Banerjee, Rohan Dhiman, Ramandeep Singh, Manpreet Kaur

  (Collaborators: K. Kumanan, MVC, Chennai; B. M. Gulati, NRCE, Hisar; Amarjeet Singh, GADU, Ludhiana; Minakshi, CCSHAU, Hisar, and G. W. Both, BEP, Australia)

Background: Recombinant viruses or virus-like-particles (VLPs) can be exploited for delivering protective antigens or DNA encoding the same. Currently known Adenovirus-based delivery vectors are either IPR-protected or cannot be used in humans due to the presence of pre-existing neutralizing immunity. The aim of the project is to isolate/identify and characterize novel non-human Adenoviruses that can be used for the development of gene/vaccine delivery vectors for human use. We are also exploring the use of human papilloma virus (HPV) VLPs, and BCG for this purpose.

Progress: Adenoviruses from nasal and stool samples from buffalo, horse, and fowls were isolated and partially sequenced to establish their identity. The virus isolates were subjected to "cloning" by two rounds of limiting dilution. Three BAdV isolates could be successfully passaged in MDBK cells and purified by this method. Similarly, one fowl adenovirus and an equine adenovirus isolate could be purified by passaging on QT35 and PS cell lines, respectively. These isolates are being characterized for their ability to infect, replicate and transcribe in human cells. To establish the usefulness of these animal adenoviruses for vaccine delivery to humans, serum samples were tested for neutralizing antibodies to adenoviruses. None of the human sera had antibodies to BAdV serotypes 6, 7 and 8, but they had a range of neutralizing immunity to human adenovirus type 5 (HAd5). Similarly, none of the bovine serum samples had neutralizing immunity to HAd5, but most of them had neutralizing antibodies to all three BAdV serotypes.

In order to test the utility of ovine adenovirus for vaccine delivery, recombinant virus was made (reported last year) that expressed protective antigen (envelope protein) from JEV. Expression of JEV envelope protein by recombinant ovine adenovirus (ROAdV) was demonstrated in Hu911 (human retinal) cell line by immunofluorescence and radio-immunoprecipitation. Ability of ROAdV to induce anti-JEV neutralizing immunity in naïve mice was compared to that of recombinant human adenovirus 5 expressing JEV envelope protein. A 109 PFU/animal dose of ROAdV gave antibody titers similar to those given by 108 PFU/animal of recombinant human adenovirus. The efficacy of anti-JEV immune response generated by ROAdV will be tested by the lethal JEV challenge in the mouse model. We are also exploring the use of BCG as a vaccine vector where JEV envelope protein is being used as a test antigen.

Recombinant L1 and L2 proteins of HPV can be assembled to form VLPs that can package plasmid DNA of ~8kb size. Thus HPV VLPs could be used to deliver DNA vaccines or nucleic acid based antivirals. However, HPV VLPs transduce very few cells of epithelial origin. We are investigating how HPV VLPs could be delivered to various cell types. To this end insertion or replacements could be made of ligand peptides in parts of L1 protein that are exposed. Analysis based on Bioinformatics has predicted loops that may be amenable to modifications. We are attempting to insert a peptide from rabies virus glycoprotein in HPV16 L1 to test if this would then transduce cells of neuronal origin. Other ligands specific to different cells types would subsequently be tested. Similar efforts are being made to modify the fiber protein of Adenovirus 5 for attaining cell specific delivery of DNA.

Publications :

1. Bharati, K. and Vrati, S. (2012) Viral vaccines in India :An overview. Proc. Natl. Acad. Sci. Sect B. Biol. Sci. (In press :DOI 10.1007/s40011-011-0014-9).
2. Anantpadma, M. and Vrati, S. (2011) siRNA mediated suppression of Japanese encephalitis virus replication in cultured cells and mice. Journal of Antimicrobial Chemotherpay 67:444-451.
3. Vashist, S., Bhullar, D., and Vrati, S. (2011) La protein can simultaneously bind to both 3' and 5'-noncoding regions of Japanese encephalitis virus genome. DNA and Cell Biology 30:339-346.

HOST-PATHOGEN INTERACTIONS IN FLAVIVIRUS LIFE-CYCLE

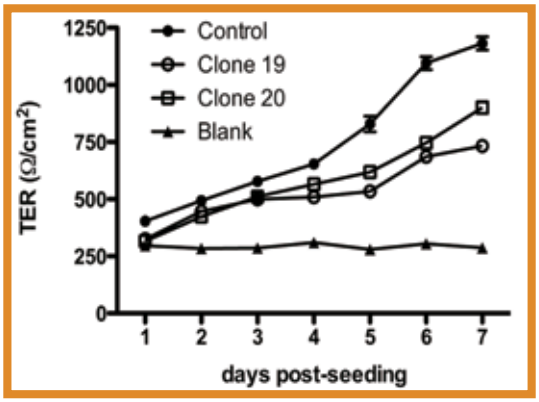
Principal Investigator: Dr. Guruprasad Medigeshi

Research Theme: Molecular mechanism of host-pathogen interactions in mosquito-borne flavivirus infections

- **Role of tyrosine kinases in the life cycle of Japanese encephalitis and dengue virus**

  Rajgokul, K.S., Sharvani and Tanvi Agrawal

Background: Tyrosine kinase (TK) signaling regulates diverse cellular functions such as protein trafficking, cell cycle and angiogenesis. Viruses, being entirely



dependent on host factors for their survival and propagation, have been shown to use TK-mediated signaling pathways at the level of entry, replication, assembly and egress. However, the mechanism of action and the relevance of TK signaling in flavivirus pathogenesis have not been investigated. Identification of TKs that are essential for productive flavivirus infection will provide a better understanding of the host-pathogen interactions.

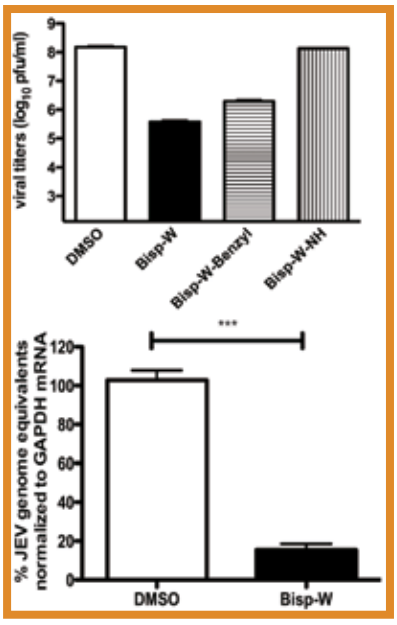
Progress: To identify TKs involved in Japanese encephalitis virus (JEV) replication, Huh7 cells were transfected with TK siRNA library, 48 h post-transfection cells were infected with JEV and supernatants were collected for estimation of viral titers by plaque assays. In our first round of screening, we have identified 6 target genes whose knock-down affected JEV titers by more than 50%. Similarly, for dengue virus (DENV) infection, of the 47 tyrosine kinase genes tested so far we have obtained 6 hits. Surprisingly, the TKs identified in our assays for JEV and DENV are non-overlapping suggesting the involvement of different TKs in the life-cycle of these two viruses. We will complete the screening for DENV and the identified TKs will be further validated by transfection with individual siRNAs and measuring inhibition. Future experiments will focus on characterizing the role of the identified TKs in JEV and DENV life-cycle.

- **Effect of JEV infection on epithelial cell functions**

  Tanvi Agrawal, Rajgokul, K.S. and Sharvani

Background: JEV replication in peripheral organs may play a role in the neuroinvasion of JEV. In this context, epithelial cells of peripheral organs are likely to be susceptible to virus infection and may play an active role in JEV dissemination to the central nervous system.

Progress: We have shown earlier that JEV infection perturbs epithelial barrier function at later stages of infection in polarized epithelial cell culture model. We further discovered that this effect is not mediated by factors such as cytokines or matrix metalloproteinases secreted from the infected cells. Localization of tight junction (TJ) protein claudin-1 was severely perturbed in JEV-infected cells and claudin-1 partially colocalized with JEV in intracellular compartments. The localization of other TJ proteins remained unchanged.



Expression of JEV-capsid alone significantly affected the permeability barrier functions in these cells. We hypothesize that the modulation of TJs by JEV compromises the permeability barrier of epithelial and possibly of endothelial cells and this may lead to viral dissemination into the central nervous system. Further research to confirm this in animal models is in progress.

- **Identification of novel chemical scaffold for developing inhibitors against JEV**

  Rajgokul, K.S., Sharvani and Tanvi Agrawal

Background: The current vaccine against JEV is not easily available in most of the endemic countries and development of effective antivirals to combat recurring JEV infections in India and elsewhere serves as a viable alternative. Our aim is to explore novel chemical scaffolds for antiviral activity against JEV and further develop them to make it suitable for use as therapeutics.

Progress: We had earlier identified bispidine as a scaffold for generating novel anti-virals for JEV. We have now generated improved derivatives and assessed the anti-JEV activity of these amino acid conjugates in Neuro2A cells. At 5µM concentration, the tryptophan conjugate (Bisp-W) was the most potent inhibitor, which reduced the JEV titers in the supernatant by more than 100-fold. The inhibition studies show that bispidine with one Trp and benzyl (Bisp-W-benzyl) decreased JEV infection by hundred-fold but less potent compared to Bisp-W alone. De-protection of terminal Boc groups (Bisp-W-NH) led to complete loss of antiviral activity suggesting that the hydrophobic terminal (Boc) has a role in the inhibition. We found that Bisp-W-treated cells had 90% reduction in the JEV genome levels as compared to DMSO-treated cells confirming the block in viral RNA replication suggesting that Bisp-W is a novel JEV replication inhibitor.

Publication:

Medigeshi, G. R. 2011. Mosquito-borne flaviviruses: overview of viral life-cycle and host-virus interactions. Future Virology 6:1075-1089.

UNDERSTANDING THE BIOLOGY OF HEPATITIS E VIRUS AND DEVELOPMENT OF VACCINE AND DRUGS AGAINST IT

Prinicipal Investigator: Dr. Milan Surjit

Theme of Research: The aim of the lab to study the biology of Hepatitis E virus, and develop novel vaccine and drugs against the virus.

- Establishment of a model expression system to study the life cycle of Hepatitis E Virus (HEV) and application of the secreted virion as a candidate vaccine

  Milan Surjit

Background: Hepatitis E Virus (HEV) causes acute hepatitis in human characterized by jaundice, anorexia, nausea, abdominal pain, malaise, fever and hepatomegaly. In India, it accounts for ~50% of sporadic hepatitis. A recent report also suggests chronic HEV infection in ~60% liver transplantation patients. Neither a model system is available for studying the biology of HEV in the laboratory nor any vaccine or drug is available against HEV.

Proposed research plan: My laboratory is interested in exploring multiple strategies to develop a model system for studying the biology of HEV and developing intervention strategies against it. Precisely, my current research plan involves (a) Development of a DNA based infectious Hepatitis E virus expression system in cultured mammalian cells and test the potential of secreted virions as candidate vaccine

(b) development of a mouse model that mimics HEV infection in human and use this model to characterize the molecular mechanism of HEV pathogenesis and evaluate the protective and therapeutic potential of anti-HEV compounds, (c) Development of a DNA based infectious Hepatitis E virus expression system in Yeast and test the potential of secreted virions as candidate vaccine.

- **Identification of novel therapeutic compounds that inhibit the interaction between Hepatitis E Virus ORF3 protein and TSG 101**

  Milan Surjit

Background: No drug is available against Hepatitis E virus (HEV) induced hepatitis in human. My earlier published report as well as recent reports published by other laboratories has confirmed the essential role of the interaction between HEV ORF3 protein and cellular TSG 101 (Tumor Susceptibility Gene 101) protein in mediating HEV virion release. Therefore, inhibition of this interaction by means of synthetic chemical compounds or peptide-based compounds seems to be an efficient mode of blocking viral spread.

Proposed research plan: It is proposed to screen for (a) novel cell permeable cyclic peptides (b) synthetic chemical compounds that can inhibit HEV ORF3 and TSG 101 interaction, thereby blocking the release of progeny virions. Once such inhibitory peptide(s)/chemical compounds are identified, their efficacy of inhibiting virion release will be assessed in hepatoma cell culture/ Yeast based model of HEV infection. Successful implementation of this project will allow us to develop HEV specific peptide/ chemical compound-based drugs that are effective in controlling HEV associated clinical complications.

- **To explore the molecular mechanisms controlling the release of Hepatitis E virions from infected cells**

  Milan Surjit

Background: As described above, elucidation of the significance of the interaction between HEV ORF3 protein and cellular TSG 101 protein enabled us to attempt at discovering novel therapeutic compounds against HEV. Detailed molecular characterization of the mechanisms controlling the release of HEV virions from infected cells may lead to discovery of additional druggable targets. If successful, multiple compounds can be administered together to improve the therapeutic efficacy.

Proposed research plan: Direct/indirect interacting partners of the HEV ORF2/ORF3 protein will be identified by Yeast two hybrid/cell culture-based pull down assays and mutational studies will be performed to evaluate the importance of this interaction in mediating the release of HEV virions. Synergism or cooperativity between different motifs in mediating HEV virion release will be evaluated. Presence of additional components of the endosomal-sorting pathway in the HEV virus egress complex will be identified. Mechanistic details will be worked out using various biochemical and molecular genetics techniques.

THE BIOLOGY OF MYCOBACTERIUM TUBERCULOSIS INFECTION

Principal Investigator: Dr. Amit Kumar Pandey

Theme of Research: The aim of the lab is to study the mycobacterial pathogenesis.

- **Regulation of cholesterol metabolism in Mycobacterium tuberculosis (Mtb)**

  Amit Kumar Pandey

Proposed Research Plan: We have demonstrated that although Mtb eats cholesterol throughout the infection process, however it becomes essential only during the later chronic stage of infection. The essentiality of cholesterol during the persistent stage of Mtb infection is attributed to the host mediated induction of IFN-gamma. We have confirmed this by demonstrating that the Δmce4 mutant deficient in cholesterol uptake grows poorly inside activated macrophages. In order to further understand the

biology of the cholesterol requirement during persistent stage of Mtb infection Sassetti lab did a transposon capture sequencing (TraCS) based screening of the genes that are required for cholesterol metabolism in Mtb. TraCS, is a modified version of transposon site hybridization (TraSH), which involves deep sequencing instead of microarray. The new version is more robust, informative and statistically more significant. Most of the known cholesterol catabolic pathway genes were underrepresented in the screen. TraCS screening has led to the identification of new interesting metabolic and regulatory pathways required for the utilization of cholesterol. The goal of my study will be to characterize some of these genes that specifically regulate the rate of replication/ metabolism in cholesterol requiring conditions. These regulatory pathways might help us understand the transition of Mtb infection from more acute to persistent stage of Mtb infection leading to latency.

Thus the study has been proposed with the following aims:

1. To characterize genes responsible for regulating cholesterol metabolism thereby regulating the growth and metabolic rate of Mtb.

2. Transcriptional profiling studies of the above mutants, with an aim to identify the regulatory pathways and signaling molecules that regulate these pathways.

- **Genetic requirement of Mycobacterium tuberculosis growth in cholesterol under hypoxia using high-density mutagenesis**

  Amit Kumar Pandey

Proposed Research Plan: Latent tuberculosis, a symptomless form of tuberculosis wherein the infected host acts as an active carrier results in active dissemination of the pathogen. These latent carriers possess a huge challenge for people involved in tuberculosis eradication programs. Extremely long treatment regimen (typically for about 6 months in case of a drug sensitive strain) results in a very high level of non-compliance leading to treatment failure, emergence of multi drug resistance (MDR) and extremely drug resistant (XDR) forms of Mtb. All the above reasons underscore the need to find new and more efficient therapeutics. One of the significant steps in the direction of understanding this phenomenon would be a clear understanding of the in-vivo environment with respect to nutrient available and its effects on Mtb growth rate. We have previously demonstrated the requirement of cholesterol for persistence of Mtb infection. Little is know about the importance of cholesterol

metabolism on Mtb virulence. A better understanding on cholesterol metabolism at the molecular level under a very physiological relevant conditions would definitely help us in designing of better therapeutics. Keeping this in mind the proposal has been designed with the following aims:

1. Generation of a Mycobacterium tuberculosis mariner based transposon library
2. Genetic requirements of Mycobacterium tuberculosis growth in cholesterol under hypoxia
3. Identification and characterization of the critical genes / pathways / regulatory networks

- **Identification of novel scaffold targeting cholesterol catabolic pathways**

  Amit Kumar Pandey

Proposed Research Plan: Targeting critical metabolic pathways has been one of the very under-utilized areas of drug screening in tuberculosis, mainly due to gaps in our knowledge about the nutritional environment inside mycobacterial intracellular niche. We have demonstrated the importance of cholesterol metabolism during the persistence stage of Mtb infection. The focus of the current proposal would be to screen for chemical inhibitors that specifically target these pathways. The long-term goal would be identify novel anti-tubercular drugs that specifically targets "persisters". These novel compounds in combination with the standard frontline antitubercular drugs would significantly enhance the success rate of tuberculosis treatment. The proposal would be designed with the following aims:

1. Development of In-vitro based assay for screening of Mtb cholesterol catabolic pathway inhibitors
2. Molecular and biochemical characterization of the inhibitor
3. In-vitro cell culture and in-vivo animal models validation studies

VIRULENCE SYSTEMS OF MYCOBACTERIUM TUBERCULOSIS

Principal Investigator: Dr. K. Atmakuri

Theme of Research: Targeting Mycobacterium tuberculosis (Mtb) delivery systems and their cognate artillery.

- **Decipher Mtb's artillery and their cognate host molecular targets**

  Krishnamohan Atmakuri and Nishant Sharma

Background: Mycobacterium tuberculosis (Mtb) is predicted to hijack its host by injecting a battery of virulence artillery. To date, this stockpile remains to be identified and the functions deciphered. Lack of temporal and spatial details of Mtb's weaponry and its possible targets severely restricts our efforts/strategies to initiate a coordinated assault on Tuberculosis (TB). To obtain more insights into Mtb's virulence mechanisms and to design superior vaccines and therapeutics against Mtb, it is critical to identify Mtb's stockpile and delineate their host-specific functions and molecular targets.

Proposed Research Plan: By employing novel genetic and proteomic approaches, this project aims at (i) identifying Mtb's protein arsenal, (ii) determining their corresponding host molecular targets and (iii) teasing out the mechanistic functions of their delivery systems. These efforts will also (a) initiate discovery of novel delivery systems, (b) illuminate the molecular details behind the delivery, (c) delineate the

minimal requirements for their effective secretion (d) illuminate host pathways that the secreted artillery target, (e) aid in designing novel therapeutics against pathogen's delivery systems, and (f) identify potential vaccine candidates.

- **Exploring mycobacterial outer membrane vesicle-like structures as novel vaccine delivery system against TB**

  Krishnamohan Atmakuri

Background: Worldwide, TB annually claims two million lives. In immune-competent individuals, while adapting to prolonged persistence, it constantly seeks opportunities to resurge and infect. Classically, though a 6-9 month multi-drug prophylaxis is believed to cure TB and eliminate persistence, non-compliance to the regimen has led to emergence of MDR, XDR and TDR strains. To control this emergence, new vaccines especially in endemic areas become indispensable. Though the current vaccine, Bacillus Calmette Guérin (BCG) can protect children from severe progressive versions of TB, it protects none from pulmonary TB. Neither BCG provides sterilizing immunity nor do antibiotics eliminate Mtb. Thus, there is an urgent need to develop novel TB vaccines that (i) are superior to BCG in mounting rapid and long lasting protective immune responses (at all stages of human life), (ii) prevent latency and/or re-emergence from persistence, and (iii) mount protective response against drug-resistant strains.

Proposed Research Plan: To date, most improvised TB vaccines that have made it to clinical trials are live recombinant BCG, and hence remain incapable of generating the much needed sterilizing immunity to Mtb. Few others are subunit vaccines comprising utmost 1-4 purified antigenic Mtb proteins administered together with an adjuvant. One of the major challenges in a subunit vaccine is the choice of right vaccine candidates that mount protective immune response against all stages of infection. Further, it is unclear if 1-4 vaccine candidates would sufficiently be protective. With no specific and reliable correlates to measure and compare protective immune responses to, none can be sure of the protective ability of any immunogenic candidate until large and expensive clinical trials are undertaken. Since the possibility of protection is significantly better with a combination of several immunogens, one needs to evaluate

the alternate modes of delivering more antigenic candidates especially in their native conformations.

One way to deliver multiple antigens is by exploiting the pathogens's own outer membrane vesicles (OMVs). Mtb produces such structures of size reaching ~10-200 nm. OMVs are proteoliposomes produced naturally and contain pathogenic lipoproteins, outer membrane and periplasmic components. OMVs constitute a unique system in which both the antigens and the delivery vehicle are naturally derived from the pathogen. Furthermore, their ability to strongly stimulate both innate and adaptive host immune responses makes them excellent candidates especially as adjuvants in acellular/multi-subunit vaccine formulations and thus as viable alternates to existing vaccines. Additionally, OMVs circumvent the safety limitations of attenuated and killed organisms that are normally administered as vaccines. Finally, OMVs can be engineered to include several naturally un-incorporated antigens.

Till recently, the main concern with OMVs as vaccine candidate per se has been their heterogeneous composition. However, recent administration of OMVs-based meningococcal vaccine in Europe and USA has culled such apprehensions. In summary, the main objective of this proposal is to make and purify recombinant mycobacterial OMVs that are packed with appropriate Mtb antigens which exhibit superior immunostimulatory properties (in comparison to BCG). Such OMVs will be tested for their ability to protect against Mtb infection. This project would also shed light on OMVs function in Mtb-mediated pathogenesis.

UNDERSTANDING THE MECHANISM OF PROTEIN TRANSLATION AND TRANSLOCATION IN MYCOBACTERIA

Principal Investigator: Dr. Nisheeth Agarwal

Theme of Research: Study essential metabolic pathways in human pathogen Mycobacterium tuberculosis for designing new drug and vaccine against TB.

- **Toward the characterization of multiple P-loop GTPases in mycobacteria**

Nisheeth Agarwal, Madhu Pareek and Eira Choudhary

Background: GTPase superfamily of proteins is universally present in all forms of life, regulating essential cellular pathways such as protein synthesis, cell cycling & differentiation and hormone signaling. A survey of genome sequences of different mycobacterial species reveals the presence of conserved P-loop GTPases namely Era, Obg, EngA, HflX and YchF which have not been characterized and their role has remained obscure in these organisms.

Based on the conserved occurrence of P-loop GTPases in different mycobacterial species, we hypothesize their involvement in essential metabolic pathways. We aimed at investigating the role of multiple P-loop GTPases in the biology of mycobacteria to explore this class of proteins as novel drug targets. We planned the following strategies:

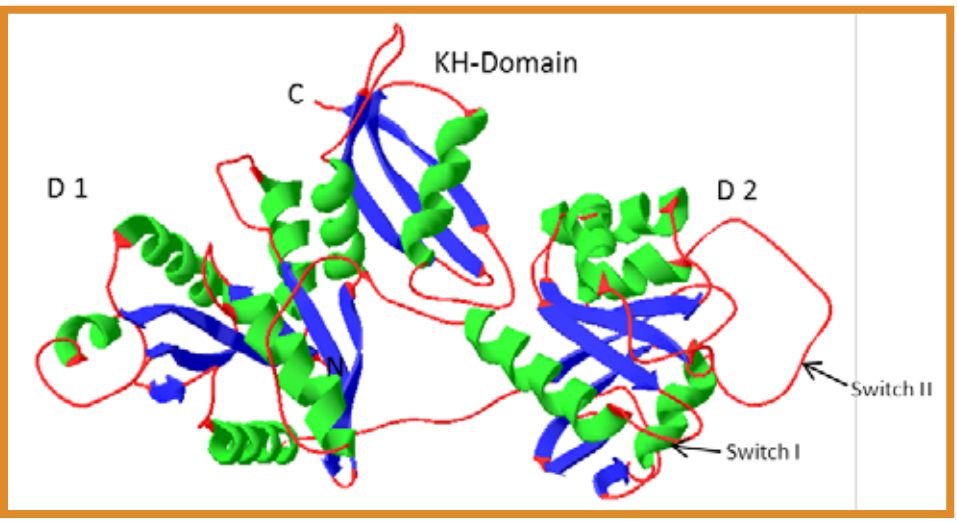
1. Cloning, expression and purification of P-loop GTPases of pathogenic and non-pathogenic mycobacteria and their biochemical characterization.

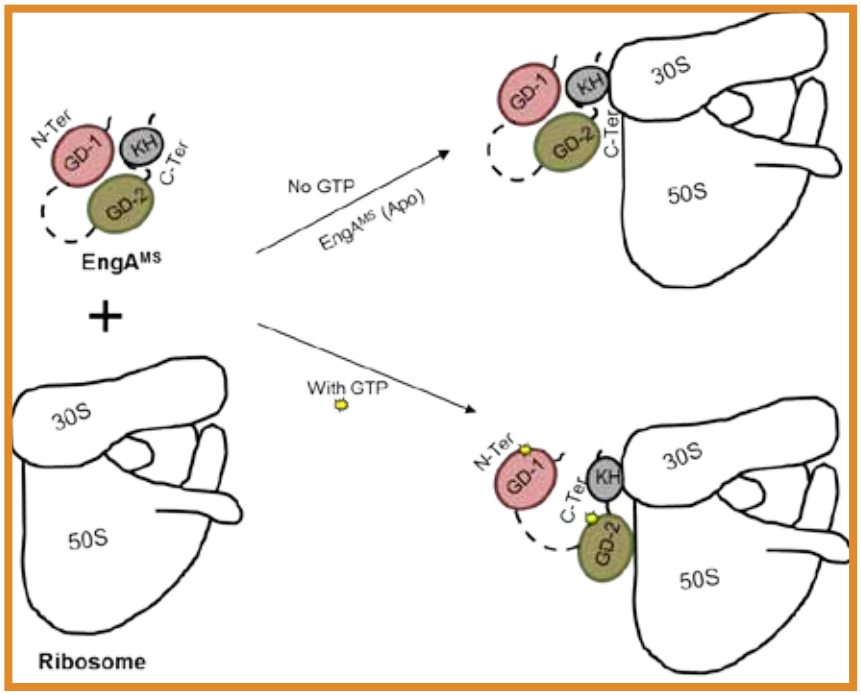
2. Deletion/downregulation of P-loop GTPases in Mycobacterium smegmatis, a surrogate host of the pathogen M. tuberculosis, and their effect on mycobacterial physiology.

3. Identification of interacting partners of mycobacterial GTPases.

Progress: To achieve our goals, we cloned, expressed and purified these GTPases from recombinant E. coli and subjected the purified proteins to in vitro GTPase assay. Our studies showed that all proteins except MSMEG_5222 hydrolyse GTP. Inability of MSMEG_5222 to hydrolyse GTP is not surprising, as it lacks GTP-recognition motif. Subsequently, we constructed a GTPase knockdown strain of each of these GTPases of M. smegmatis and studied the effect of downregulation of each of these GTPases on global gene expression profiles of M. smegmatis by microarray. Interestingly our microarray results indicated that MSMEG_2736 and MSMEG_3738 primarily regulate expression of a common set of genes. A thorough analysis indicates that both MSMEG_2736 and MSMEG_3738 commonly regulate 22 genes out of which 10 genes encode hypothetical proteins. Out of remaining 12 genes, two are involved in protein synthesis, transport and fatty acid biosynthesis respectively. Similarly, both MSMEG_4493 and MSMEG_4623 regulate 62 common genes, as mentioned in figure 2, some of which are extremely important for mycobacteria.

Further, we performed a detailed characterization of one of the five GTPases namely EngA of M. smegmatis encoded by gene MSMEG_3738. Amino acid sequence alignment and phylogenetic analysis suggest that MSMEG_3738 (termed as EngAMS) is highly conserved in mycobacteria. Homology modelling of $EngA^{MS}$ reveals a cloverleaf structure comprising of alpha/beta fold typical to EngA family of GTPases. Interestingly, the EngAMS protein is co-eluted with 16S and 23S ribosomal RNA during purification and exhibits association with 30S, 50S and 70S ribosomal subunits. Further studies demonstrate that GTP is essential for interaction of EngAMS with 50S subunit of ribosome and specifically C-terminal domains of EngAMS are required to facilitate this interaction. Moreover, EngAMS devoid of N-terminal region interacts well with 50S even in the absence of GTP, indicating a regulatory role of the N-terminal domain in





EngAMS-50S interaction. Knocking down the expression of EngAMS indicates that EngA regulates protein biosynthesis, and is thus indispensable for in vitro growth of mycobacteria.

- **Characterization of mycobacterial protein translocation and secretion machinery**

  Preeti Thakur and Nisheeth Agarwal

Background: The virulence and sustenance of any pathogen is largely influenced by membrane composition. Also, the host-pathogen interaction is governed by the unique organization of several factors on the envelope which are in-turn regulated by specific protein translocases. In M. tuberculosis there are two protein export pathways: the conserved general secretion pathway and the Tat pathway. The general secretion pathway involves SecA, Y, E, G, D, and F multi-protein complexes which targets unfolded proteins. On the contrary the Tat pathway is involved in the secretion of folded proteins which usually have a twin Arg residues in folded conformation and one or more positively charged residues as a sec-avoidance signal.

Another pathway which is known in several bacterial species for protein insertion is the YidC–dependent pathway. This pathway works both in a Sec translocase-dependent and independent manner. Sequence analysis of different mycobacterial species reveals that YidC is highly conserved in mycobacteria. The transposon insertion mutagenesis studies further suggest that YidC is essential in mycobacteria. However, there is no published information available about the role of this important translocase in mycobacteria. Hence, we propose to characterize the role of YidC in mycobacteria.

Progress: In order to characterize the role of YidC in mycobacteria we first attempted to analyse the expression pattern of YidC by RT-PCR. M. bovis BCG was cultured at 37°C in 7H9 broth medium and cells were collected at different growth stages. For RT-PCR based expression analysis of yidC, total RNA was extracted from bacterial cells and cDNA was synthesized from mRNA by using reverse transcriptase. The level of expression of yidC was obtained after normalization to the values of a housekeeping gene, sigA. We did not observe any significant difference in yidC mRNA transcript levels over a period of 20 days, thus suggesting that yidC is expressed constitutively in M. bovis BCG.

Next, to establish whether YidC of M. bovis BCG plays any role in protein translocation we first sought to determine whether it establishes any interaction with Sec–machinery. We utilized BacterioMatchTM two-hybrid system (Agilent Technologies) to study specific interaction of YidC with SecD, SecF, and SecY. The yidC gene of M. Bovis BCG was PCR amplified and the BCG_0027 ORF was subsequently cloned in a vector, pBT (Agilent Technologies) to generate bait clone pBT-yidC. Similarly target genes secD, secF, secDF and secY were PCR amplified and subsequently cloned in target vector, pTRG, resulting in target cloness pTRG-secD, pTRG-secF, pTRG-secDF, and pTRG-secY, respectively. To study the interaction of YidC with each of the target proteins, the BacterioMatch II Validation Reporter Competent Cells were co-transformed with pBT-yidC and each of the target clones and interaction was analysed according to the manufacturer's specifications (Agilent Technologies). Our results show that YidC interacts specifically with SecY, SecD and SecF, and intensity of interaction is increased when both SecD and SecF are present together to interact with YidC. These observations thus suggest that YidC of mycobacterium could be involved in protein translocation in Sec-dependent manner

BIOLOGY OF MYCOBACTERIUM TUBERCULOSIS AND VALIDATION OF NEWER DRUG TARGET PATHWAYS

Principal Investigator: Dr. Ramandeep Singh

Theme of Research: Understanding persistence mechanism of M. tuberculosis and validation of new drug target pathways to combat tuberculosis

- **To understand the mechanism of drug-induced persistence of M. tuberculosis**

  Mamta Singh, Garima Arora, Saqib Kidwai and Prabhakar Tiwari

Background: Tuberculosis kills an annual 2 million people globally and an estimated one-third of world population is infected with latent tuberculosis, 10% of them have a risk for developing active TB disease. Eradication of this dreaded disease requires new strategies aimed at targeting non-replicating bacteria that characterize the latent disease. However the physiology and metabolic processes of non-replicating bacteria are poorly understood. It has been hypothesized that these bacilli are metabolically inactive due to orchestrated shutdown of microbial metabolism in response to hypoxic, nitrosative and nutrient stress and that these persistent bacilli are drug tolerant. There is very little information available on the metabolic pathways that enable the bacteria to persist in the host and in the lab we are focusing on understanding the role of Toxin-antitoxin modules and stringent response pathways in drug induced persistence of M. tuberculosis.

Progress: The genome of M. tuberculosis encodes for several TA modules. We have biochemically characterized MazEF family of TA modules. We have shown that 3 such family of proteins are bonafide TA modules and these proteins interact with each other. Since RNA cleaving toxins have been reported to be upregulated under various stress conditions such as nutritional starvation or antibiotic stress, we have shown that these toxins are differentially regulated under various stress conditions that mycobacteria encounter in the host by RT-PCR analysis. Transcriptional profiling of bacteria overexpressing these toxins revealed that genes that are differentially regulated were also similarly regulated in nutritionally starved cells, thereby suggesting these toxins might act as regulators, shutting down the bacterial metabolism under various stress conditions thereby leading to metabolically less active (dormant) bacteria, which are able to persist in the presence of various drugs. In order to understand the role of these MazF toxins in survival of M. tuberculosis under various stress conditions, we have generated single mutant strains of M. tuberculosis devoid of ribonuclease activity associated with MazF toxins. We are currently doing experiments that would decipher the role of these toxins in the survival of M. tuberculosis under various stress conditions and in drug induced persistence.

We have also biochemically characterized the enzyme involved in polyphosphate metabolism in M. tuberculosis. Inorganic polyphosphate (PolyP) has been shown to accumulate under various stress conditions and proposed to play a role of a stress manager. The presence of enzymes involved in PolyP metabolism in various bacterial pathogens coupled with their absence in humans suggests that they may be excellent bacterial drug targets. We have also standardised an ATP based PolyP quantification assay and observed ~10-20 fold more accumulation of PolyP in stationary phase cultures in comparison to levels of PolyP in early-log phase. We also observed that exposure of bacteria to various drugs leads to approximately 10-20 fold increase in PolyP levels as compared to untreated cells. Nealry 10-20 fold PolyP accumulation was also observed upon exposure to certain stresses such as acidic, oxidative, nitrosative and nutritional stress. We have also generated strain of M. tuberculosis devoid of polyphosphate accumulation. The mutant strain was observed to be defective (~ 7- fold) for survival in nitrosative stress when compared to the survival of wild type

strain upon exposure to nitrosative stress. We also observed that reduction in PolyP levels markedly reduced the levels of persistence in the presence of isoniazid and levofloxacin. Our future experiments include evaluating the role of PPK-1 in survival of M. tuberculosis in Wayne Model of non-replicative persistence and guinea pigs.

- **Screening of synthetic compounds for anti-mycobacterial activity and identification of novel mycobacterial drug target pathways**

  Saqib Kidwai

Background: Due to emergence of MDR-XDR-TB strains, there is always a need to identify scaffolds with potent anti-tubercular activity. To identify such scaffolds, we are performing whole cell based assays for activity using M. bovis BCG as a model system.

Progress: We have screened small synthetic libraries for activity against replicative mycobacteria. We have screened nearly 4,000 compounds for activity against aerobically growing M. bovis BCG. Out of these 4,000 compounds, we have shortlisted ~40 compounds which are active at a concentration <10μM. All these 40 compounds were evaluated for their anti-mycobacterial activity against three strains of mycobacterium; M. Smegmatis; M. bovis BCG and M. tuberculosis. Interestingly most of the short-listed compounds were more active against slow growing mycobacterium (M. bovis BCG and M. tuberculosis) than fast growing mycobacterium (M. Smegmatis), thereby, suggesting these molecules target a pathway which might be specific for slow growing species of M. tuberculosis. Some of the compounds tested were atleast as active as some of the current first-line TB drugs such as Ethambutol and Isoniazid. Next, we have also performed cytotoxicity assays for these 40 active compounds in THP-1 cell line using LDH release based assay system and 18 of these compounds were found to be non-cytotoxic even at concentration 100μM. Our initial experiments suggest that most of the compounds selected have bactericidal mode of killing as seen from reduced ATP levels in cells exposed to drugs at a concentration of 2x, 1x MIC99. We are evaluating these compounds for activity against intracellular bacteria and non-replicative bacteria. Once we have identified few active scaffolds both against replicative and non-replicative bacteria, we would like to evaluate their efficacy in mouse model of tuberculosis.

Dr. Shinjini Bhatnagar

2.2 Pediatric Biology Centre (PBC)

The Pediatric Biology Centre has been set up with the purpose of bridging the gap between classical clinical and population epidemiology unconnected to molecular causality on one hand and the more recent mechanistic biology insulated from community health problems on the other hand. The elucidation of causal biological processes that result in individual and public health consequences will critically contribute to hypotheses building for classical epidemiological research in these areas resulting in sustainable solutions for communities.

Focus Areas

- Immunobiology of perinatal period and early infancy
- Nutritional regulation of immunity and infection
- Biology of specific pediatric diseases; pathobiology of pediatric renal disease
- Programme on biology of birth with specific reference to prematurity and intrauterine growth retardation
- Biology of sepsis and its clinical applications

Most of the research carried out in PBC has been developed as domain programmes in keeping with the immediate objectives stated in the initial proposal and are at various stages of development and execution. Some of the work carried out in the above mentioned focus areas during the year, is enumerated below.

Immunobiology of perinatal period and early infancy

The rationale for this core programme is to understand development and maturation of immune system in perinatal period and early infancy to identify dysfunctional states and their significance. In India, more than a quarter of the one million neonatal deaths are attributed to serious bacterial infections such as pneumonia, sepsis and meningitis. The immune system in neonates is quantitatively and qualitatively distinct. A void in understanding of infectious diseases and immunology in newborns and young infants has been a lack of clear characterisation of development and maturation of immune system in this period.

PBC aims to create rich datasets with a large number of immune system readouts and clinical correlates/ covariates. The team at PBC has initiated a cross-sectional study for immunophenotypic characterisation of cord blood, in full-term appropriate- and small-for-gestational age neonates; is examining the status of immune system maturation in a situation of intrauterine growth retardation and evaluating other potential modifiers of the immune system maturation and development.

Nutritional regulation of immunity and infection

- Summary of trial on usefulness of zinc in serious bacterial infections and future plans: PBC investigators evaluated the efficacy of giving oral zinc for treatment of sepsis in young infants in reducing treatment failure and time to recovery from hospital. The study done across three tertiary hospitals in Delhi showed that giving zinc caused 40% reduction in treatment failure in infants 7 days to 4 months of age and 43% reduction in mortality (Bhatnagar et al, Lancet, 2012). These results need to be validated in a large multi-centre, perhaps multi-country, study, which PBC now intends to plan and undertake. An immunological analysis of sepsis and zinc was done as an additional objective in this study. The results of this study are being discussed to form the basis of understanding biology of sepsis in neonates and young infants.
- Role of vitamin D as a modulator of immune responses to vaccines: Evaluation of vitamin D as a modulator of mucosal priming following cutaneous delivery of vaccines (in collaboration with NII)

has been done, in which initial results indicate that mice challenged with antigen have better primary and memory antibody response when also injected with vitamin D 24h prior to immunisation.

This work further substantiates the rationale for the proposed work on human infants to examine if Vitamin D supplementation can improve immune responses to vaccines administered in early infancy – 'Nutrivac-D Trial'. The study design of placebo controlled trial on newborns at Gurgaon General Hospital I will randomize 900 subjects to 400 IU of Vitamin D or placebo to evaluate seroconversion to OPV & Hepatitis B and response to tuberculin skin test as outcomes. Because OPV is meant to trigger mucosal immunity, Hepatitis B humoral immunity, BCG primarily cell mediated immunity to offer protection, these vaccines were chosen. Follow-up of study subjects will take place at study hospital immunisation clinics and homes of subjects.

Paediatric renal disease biology: A small focus on pediatric renal disease biology has been generated in PBC as a result of collegial interactions between interested PBC faculty members and senior professors at AIIMS, New Delhi There are globally significant potential outcomes, and PBC's approach to the problem is unique.

- **Molecular mechanisms of minimal change disease:** Role of CD80: Nephrotic syndrome (NS) is a common chronic disease in children characterised by heavy proteinuria. The most common being minimal change disease (MCD), accounting for 80-90% cases in <10 years and 50% in children >10 years. Besides proteinuria, NS is characterised by hypoalbuminemia, hyperlipidemia and edema and is perceived to be a T-cell disorder with a circulating factor playing a major role in massive proteinuria.

  The purpose of this initiative is to understand the mechanism of CD80 mediated proteinuria at the level of cellular and molecular changes in the kidney podocyte (highly differentiated, specialized epithelial cells). The immune co-stimulatory molecule, CD80, is expressed on both immunocytes and renal podocytes during human NS and mouse models of NS-like proteinuria, and CD80 expression appears essential for disease in the mouse model. The project is supported through a grant under Bio-CARe scheme for three years (2012-15). The study will look at the effect of artificially increasing CD80 levels in podocyte cell lines with the aim of addressing changes in expression and localisation of various podocyte specific protein and signaling at the podocyte slit diaphragm (specialized adherens junction) in presence of CD80. Podocyte cell line cultures have been established and conditions have been standardized to successfully differentiate them in culture. Podocyte cell lines (2 mouse and 1 human) have been characterised by looking at expression of all slit diaphragm proteins under conditions of differentiation, by RT-PCR and western blot analysis. Cell lines stably expressing CD80 have been generated. Different domains of CD80 have been expressed as GST fusion proteins for pull down assays to fish for CD80 interacting proteins from podocyte cell lines and work is in progress towards this.

  Moreover transgenic mice over expressing CD80 under a constitutive promoter and specifically in podocytes will be generated in collaboration with Dr. Satyajit Rath at National Institute of Immunology (NII) to see if it can be used as a model for CD80 mediated proteinuria, which is seen in MCD.

- **Immunity and inflammation in kidney diseases with special focus on India-specific problems, including haemolytic-uraemic syndrome (HUS):** Atypical HUS (aHUS), a disorder of complement regulation is a lot more frequent in India than in Europe,

and while only 6-10% European aHUS patients have autoantibodies to an important complement regulator, factor H, data suggests that frequency of anti-factor H autoantibodies in Indian pediatric aHUS patients is as high as 60-70%, along with far higher titres of auto antibodies. Since occurrence of these autoantibodies is associated with a deletion of genes encoding some complement factor H related (CFHR) proteins, ethnic variations may be relevant. The project is intended to confirm preliminary data, to characterise auto antibody response in terms of magnitude, isotype and affinity and to determine proportion of patients with CFHR deletions. This study is being conducted in collaboration with AIIMS and NII.

- **Cytokine balance of CD4 T cell activation: implications for minimal change nephrotic syndrome and other diseases:** The rationale behind the study, namely, the hypothesis that genetic and/or environment-mediated variation in intrinsic tendencies of CD4 T cells to generate inflammatory cytokines such as interferon-gamma and allergogenic cytokines such as interleukin-4 is a factor in determining susceptibility to a range of inflammatory and allergic diseases. Mouse experiments as well as ongoing optimisationefforts for activation and priming of human naive CD4 T cells from adult volunteers, as well as results from efforts to characterise cytokine balance in memory CD4 T cell compartment have been done. Blood samples from NS patients are being collected, their clinical course monitored and both memory CD4 T cell cytokine properties and intrinsic T cell polarisation properties are being examined. CD4 T cells from patients at the first episode of NS are particularly interesting in this context. This study is also being conducted in collaboration with AIIMS and NII.

Innovative Technology Development Approaches

- Diagnostic test for Celiac disease: A rapid diagnostic test for diagnosis of celiac disease (CD) is being developed. In-house point of care immunochromatographic and ELISA tests designed to detect antibodies (*Ig*A or *Ig*A+*Ig*M+*Ig*G) in human blood or serum/plasma against human recombinant tissue transglutaminase are being developed in a collaborative project between AIIMS, International Centre for Genetic Engineering & Biotechnology (ICGEB) and PBC. The industrial partner is J. Mitra, Pvt Ltd. Both tests

use a human recombinant tissue transglutaminase (tTG) as a capture antigen. The evaluation of prototype is under progress at AIIMS and PBC.

- **Evaluation of a micronutrient mix for children with severe acute malnutrition:** PBC in partnership with CDSA and three tertiary pediatric hospitals in India will conduct an acceptability study for a micronutrient mixture for children with severe acute malnutrition (SAM). This mixture has been prepared by BIBCOL (a public sector enterprise) in collaboration with PBC scientists following WHO guidelines. The relevant regulatory permissions are being taken before the study is initiated.

Stable Clinical Partners for human clinical research

- In order to fulfill the mission of conducting large translational programs there is a need to have stable clinical partners. These partnerships will create models of implementable clinical research in hospitals and the community. PBC has established a stable clinical partnership program with the Department of Pediatrics at AIIMS through the DBT Glue Grant scheme for linking basic and clinical science departments in inter-institutional linkages. This partnership has established a multidisciplinary research hub spanning the two institutions that will aim to comprehensively understand the cellular-molecular patterns of the causal mechanisms of child health and disease, and search for innovative solutions. A number of collaborative proposals with the department have been conceived that are being executed through this partnership programme.

  Another stable clinical partnership program has been established with the Gurgaon General Hospital, Haryana in collaboration with National Brain Research Centre (NBRC) and the Regional Centre of Biotechnology (RCB) through the DBT Glue Grant scheme. The partnership will create a model of 'grassroots' level implementable clinical research in hospitals and the community that can be conducted outside of tertiary academic medical centers. It will facilitate scientists at PBC to regularly interact with clinicians at the clinical centre and identify problem areas and needs that could act as seeds for translational research programs.

International workshop

- INDO-US Workshop on Measuring Human Immune Responses, THSTI, Gurgaon 31st October, 2011 – 2ndNovember, 2011

People behind the initiative

Drs Shinjini Bhatnagar, Uma Chandra Mouli Natchu, Nitya Wadhwa and Shailaja Sopory are Principal Investigators on a number of research projects described above. Drs Vineeta Bal and Satyajit Rath are adjunct faculty in PBC and have been integrally involved with all the research activities. They were the coordinators of PBC before Dr Shinjini Bhatnagar. Dr. Balachandra K. Gorentla has recently joined the centre. Other members in the team include Dr Deepak Rathore (Research Associate) and Bhavya Khullar (Ph.D student).

2.3 Centre for Biodesign & Diagnostics (CBD)

Development of novel diagnostic tools and medical devices for risk assessment, early detection and management of the disease are crucial for improving clinical care. These will help in disease prevention and appropriate therapy at an early stage, leading to improved outcomes and reduction of treatment cost. Over 80 percent implants and medical devices are imported today and are accessible to only a limited few due to their high cost and lack of appropriate health insurance coverage.

The Centre for Biodesign and Diagnostics aims to transform this field by creating a novel medical technology enterprise in India for affordable health care. This will be done through a "bio-design process" for development of in-vitro diagnostics and medical devices, which essentially utilizes feedback from clinical-care settings to innovate or improve existing designs. Its primary mission is to promote science and application related to affordable implants, devices, in-vitro diagnostics and imaging. The program will also promote an effective translational route of basic findings ultimately into routine applications of major importance, with particular focus on the public good. This is proposed through a multidisciplinary approach, combining new biomarkers, novel technological concepts and clinical expertise.

Centre for Biodesign at THSTI recognizes the need to provide an organizational structure, ecosystem and governance process that ensures long-term sustainability and scope for growth for a new cadre of professionals who work at the interface of biology, engineering and medical sciences. These processes and facilities will be readily accessible to support a collaborative model of working, public-private partnership and entrepreneurship development through a multi-disciplinary approach.

Programs

The Centre's research work since its inception till date has been largely in the area of in-vitro diagnostics and medical implants and devices.

In-vitro Diagnostics: Major areas of research in the field of in-vitro diagnostics includes protein and antibody engineering, detection technologies and concepts, nucleic acid diagnostics, new clinical markers, de-centralized diagnostics (point-of-care), bio-organic chemistry diagnostic technologies, bio-affinity test concepts and systems, micro-fluidics, multiplexing, miniaturization, and development of reporter alternatives.

Current and Ongoing Activities

Rapid, simple and sensitive test modules for multiplex testing of infectious disease in blood banks:

The program aims to develop an affordable robust, rapid, simple and sensitive test technology/system for multiplex testing of infectious diseases in blood banks. An in-house Time Resolved Fluorescence (TRF) immunoassay has already been developed as a single diagnostic intermediate for detecting respective antibodies in infected human serum samples. Each individual assay has been evaluated using commercially available and well-characterized serum panels from British Biocell International (BBI). The immunoassay is able to detect HIV and HCV infection from diverse geographical locations, with high specificity and sensitivity.

An in-house HBsAg TRF) immunoassay is also being developed using two purified MAbs. Furthermore, individual TRF immunoassays based on r-Bio-HIV-MEP and r-Bio-HCV-MEP and HBsAg TRF immunoassays has been combined to develop a multiplexed TRF immunoassay for the simultaneous detection of one or more of the following analytes in human serum samples from the same well, namely, anti-HIV antibody, anti-HCV antibody and HBsAg. The multiplex assay has been evaluated with commercially available and well-characterized viral co-infection performance panel from BBI. The objective of multiplexing was successful as all the samples that were positive by individual in-house TRF immunoassays were also detected by the TRF multiplexed assay.

The 'know-how' of the design and production of the novel r-HIV-MEP has been transferred to a leading diagnostics manufacturing company in India.

Developing a Rapid Test for Diagnosis of Celiac Disease (CD):

The patent for the diagnostic kit has been filed. This is being done in partnership with ICGEB, AIIMS and PBC.

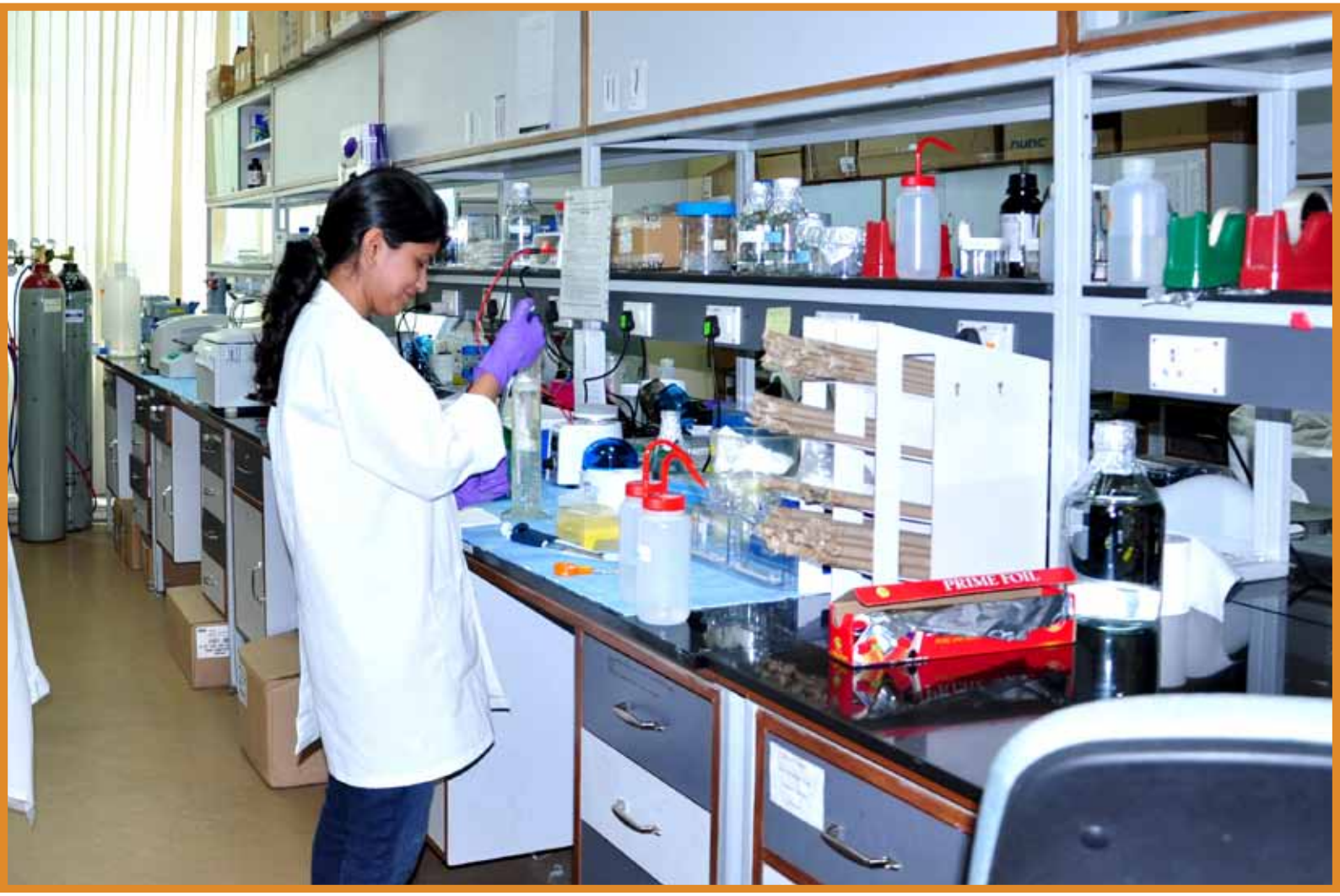
Novel sample processing for the simple and rapid diagnosis of TB, MDR-TB and XDR-TB:

TB is a public health problem of immense proportions in a large number of countries worldwide, particularly India. A low-cost rapid and accurate diagnostic test for TB remains an unmet need and challenge, ever since the smear microscopy test was developed. The aim is to work towards improving the safety and performance of existing direct smear microscopy test for TB diagnosis. A rapid PCR-based method for TB, for Multi-Drug-Resistant Tuberculosis (MDR-TB) and Xtensively Drug-Resistant Tuberculosis (XDR-TB) diagnosis using DNA extracted from the stained slides/filters used in smear microscopy. A novel bio-safe processing solution will be used to process sputum samples and to enhance the sensitivity of sputum smear microscopy in simple laboratory settings. Molecular-DST using PCR and Sloppy Molecular Beacons (SMBs) for detection of rifampicin resistance and fluoroquinolone resistance targeting rpoB and gyrA will be used for MDR-TB and XDR-TB diagnosis. The assays will be performed on DNA isolated from microscopy slides without culturing the bacteria. Therefore an open indigenous system for TB diagnosis comprising of smear microscopy, MDR-TB and XDR-TB detection is proposed..

Future Research Plans:

Development of human recombinant antibody library platform:

Construction of a human combinatorial synthetic antibody library, will use the best-represented heavy and light chain variable region genes of human antibody repertoire with synthetic CDR cassettes. This antibody library would be an ideal technology platform for rapid screening of antigens for specific binders and serve as a national facility. It will be based on human immunoglobulin sequences, suited for the therapeutic antibody segment in the largest growing sector in the area of recombinant protein therapeutics. This will provide a common resource for any subsequent efforts in this direction.



Multi-analyte Assay for Acute Coronary Syndrome Diagnostics:

Multiple pairs of high affinity antibodies against validated and new acute coronary syndrome (ACS) biomarkers will be developed along with a multiplex diagnostic cardiac panel through this project. This diagnostic tool will help detect the disease with improved sensitivity and specificity as well as have a predictive value for the occurrence of the disease.

Diagnostic Assay for KIM-1: Human Urinary Renal Dysfunction Biomarker:

The project aims to develop an assay to detect urinary levels of Kidney Injury Molecule-1(KIM-1), which serves as a non-invasive sensitive, reproducible, and potentially high-throughput method to detect early kidney injury. KIM-1 is widely recognized as an excellent tool in pre-clinical studies to monitor acute kidney tubular toxicity, by identifying adverse reactive drugs, vaccines and therapeutic agents in drug development.

Identification of Novel Protein Biomarkers for Early Diagnosis of Pregnant Women at Risk for Preterm Birth:

In this research proposal, an attempt is being made to use proteomics-based approach to identify novel protein biomarkers for early-diagnosis of women at risk for preterm birth. Proteomics enables identification and quantification of peptides/proteins in wide variety of individual biological samples and hence has been used to identify potential protein biomarkers for diagnostic and therapeutic development for various diseases, such as cancer and diabetes. This is being done in collaboration with RCB.

People behind the initiative

Dr. GB Nair, Dr. Navin Khanna (ICGEB and Adjunct Professor at THSTI) and Prof. Shinjini Bhatnagar are the Centre coordinators and principal investigators of the Centre. Dr. Ashutosh Tiwari, Dr. Niraj Kumar and Dr. Susmita Chaudhury are Research Investigators of the ongoing research projects. Dr. Sagarika Haldar, is an Innovation Awardee working on the TB diagnostic project. More innovation awardees and PhD students will be joining the centre in the next few months.

2.4 Clinical Development Services Agency (CDSA)

CDSA's Mission: To develop a cadre of investigators of global standard in regulatory product evaluations through training programmes; create support for biotech product evaluations; and provide training in clinical trials.

CDSA was launched in 2010 as an extramural unit of THSTI. It was created to facilitate development of affordable healthcare products for public health diseases. Registered as an autonomous, not-for-profit research society by the Registrar of Societies, Delhi, under the Societies Registration Act XXI of 1860, it aims to develop an eco-system for training and learning. By building clinical trial capacity in India through its Centers of Excellence (CoE), it will strengthen clinical research and conduct training programmes; monitor public health trials for GCP compliance and work with public sector institutions and small and medium enterprises (SME) to develop innovative technologies into medical products.

By providing a supportive and focused environment to host world class clinical translation through a collaborative network of clinical investigators and premier research institutions, CDSA will tend enterprises, particularly SMEs involved in new technology innovation. This will help facilitate translation of scientific know-how into viable products for public health diseases like malaria, TB and dengue, among others.

CDSA has a simple governance structure. Led by a high-powered Governing Body, it has 12 members including the Programme Director who acts as Member Secretary. Special committees will be appointed to direct and supervise different areas of work. The operational oversight of CDSA is provided by an Executive Management Committee (EMC) that comprises of experts in training, product development, organisational development among others.

Partners

A partnership between CDSA, the Bill & Melinda Gates Foundation (BMGF) and the National Institutes of Health, USA ensures availability of an experienced international faculty to conduct initial clinical training along with trainers drawn from premier clinical research institutions in the country. PATH provides project management and logistical support for the BMGF initiative.

Focus Areas

- Training: Provide comprehensive training in clinical trials methodology to enhance capability and capacity
- Clinical Trial Services: Strengthen infrastructure at specialised trial centres; monitor clinical trials for quality; provide select centralised services to support conduct of clinical trials as per international standards; and provide a peer review and consensus forum for formulation of national healthcare policies.

Programmes and Activities

In the area of training, the following activities were conducted in 2011-12:

CDSA's Clinical Investigator Development Programme (CIDP): The objective of CIDP is to develop and enhance clinical research capacity in India at par with international standards through a comprehensive training programme that aims to create a pool of professionals capable of conducting high quality clinical research and trials for epidemiological studies, community outreach and regulatory approvals.

CDSA-supported training has been rolled out in partnership with leading institutions that conduct clinical trials in India. The programme establishes a training resource, tailored to the needs of research personnel at clinical research sites across the country, to bring about an adept acquisition of skills required for design and conduct of clinical trials in accordance with national and international guidelines.

Role of Training

- Supports capacity building for clinical research and Phase I to III development of public health products such as drugs, vaccines, biologics, medical devices and/or healthcare technologies in alliance with the Indian industry
- Increases partnership of CoEs
- Trains key trainers to sustain clinical training programmes in the geographical regions where they are located.
- Increases bandwidth to cover research professionals from other institutions
- Develops self-sustaining certificates and post-graduate degree programmes in translational and clinical research in collaboration with THSTI and Regional Centre for Biotechnology (RCB).

As part of training activities, CDSA holds a number of general courses and advanced workshops. The modules developed through these courses and workshops will feed into the one-year Clinical Research Training Certificate and a two-year post-graduate degree programme in Clinical and Translational Research to be conducted by THSTI and RCB

General courses: These courses will cover different aspects of clinical research like clinical trial design, ethics, data management and biostatistics, safety reporting, regulatory compliance and quality management. Designed as two-day training programmes, they will be conducted by national and international faculty from leading clinical research institutions such as CMC, Vellore, KEM, Pune, KEM, Mumbai, NICED, Kolkata and PGI, Chandigarh. Some of the courses that will be conducted include:

- General courses in New Delhi in July, 2011: The two-day programme covered Regulatory Affairs, Ethics, Pharmacovigilance, Clinical Quality Management, Clinical Trial Management Strategies and Best Practices; Training Methods and Best Practices.
- General course in Chennai in December, 2011: The six-day programme covered the themes of Clinical Development, Safety Reporting, Clinical Trial Management, Statistical Methods in clinical research, Ethics in conduct of clinical trials, Regulatory Affairs and Quality Control and Quality Assurance in Clinical Trials.

Other programmes that were held during 2011-12 included 'Ethical issues and regulation of human subjects research' on September, 2012 in CMC, Vellore and 'Discovery and Development of Biopharmaceuticals' in January, 2012 in Goa/Mumbai.

Upcoming programmes

- Preparing and conducting regulatory trials, March, 2013 in TBD
- Design and evaluation of diagnostics and biomarkers in 2013 in TBD
- Population-based clinical trials in 2013 in TBD
- Course on Principles and Practice of Clinical Research in New Delhi, October, 2012: The six-day programme will be conducted jointly by the National Institutes of Health (NIH) Clinical Centre and Office of AIDS Research & Fogarty International Center, USA.
- Clinical trial design and statistical methods in July, Vellore: A 5-day advanced level workshop will be held in CMC, Vellore. A workshop on vaccinology was also conducted in September, 2012 in CMC, Vellore.
- Advanced workshops: In-depth advanced workshops will be conducted on specialised topics relevant to the overall needs of the investigators, therapeutic area and training programme. These will be conducted in partnership with CoEs and other premier research institutions with the help of expert course coordinators drawn from national and international institutions

Establishing a consortium of Centers of Excellence:

CDSA is in the process of identifying select institutions and organisations that have been conducting clinical trials to form a consortium. This will provide high quality clinical trial related services. Applications have been invited from suitable organisations through advertisement for selecting the CoE. The process should be completed by end 2012.

"There is acute shortage of institutions conducting Phase III trials in India. CDSA will identify and support institutions and help them focus on early/late phases of trials and improve their infrastructure, leadership, skilled personnel and governance models."

Managing clinical trials: An alliance was formed among Departments of Health Research (DHR) and Biotechnology (DBT) and Ministry of Health and Family Welfare, Government of India to support research to generate evidence for development of practical and scalable regimens to medically rehabilitate children suffering from SAM without serious complications at home/community level and/or at peripheral inpatient facilities. The Steering Committee of the programme is chaired by Dr MK Bhan. The technical component is monitored by the Technical Advisory Group. Three research projects have been initiated in the first phase.

Activities planned under the SAM programme

As a secretariat for the SAM programme and coordinates meetings of the Steering Committee and TAG and implements their decisions

CDSA is responsible for commissioning, monitoring and quality assurance of various clinical research projects as pertinent to objectives of the programme.

Data Safety Monitoring Board(s) for the various projects.

A consultative peer review process to discuss and evaluate evidence generated through various projects of the programm to aid formulation of a national policy on community management of SAM

Future Plans

The range of expertise expected to develop in CDSA in the coming months is depicted in the figure below. Complementing its activities are plans that include development of robust translational laboratories which will be different from the research laboratories.

By 2014, the CDSA-COE collaboration aims to enhance development of research personnel; development of infrastructure, systems and processes; acquire and dispense technical expertise; participate in development of clinical products; and seek national and international funding.

Additional functions of data management, monitoring and auditing, setting up of regulatory mechanisms and project management would be taken up in a phased manner. Its two core areas of training and clinical development would be further strengthened.

CDSA TEAM

Dr. Harmeet Sidhu

Program Director, CDSA

Dr. Sidhu is working as the Program Director of Clinical Development Services Agency (CDSA), an extramural unit of THSTI. She started her career in academics as lecturer in Biochemistry at Punjab University and then as assistant professor in Biochemistry at PGIMER, Chandigarh. In 1995 she moved to USA and worked her way to senior management positions in Biotech Industry. Dr. Sidhu brings forth a tremendous amount of experience in the field of clinical trials and clinical development regulations. She has over 15 years of experience in the Biotech industry and has played a crucial role in the development of new biologic drugs from discovery/ infancy through preclinical and clinical phases and all the way to commercialization.

Dr. Satish Bhatia, Ph.D

Consultant, CDSA

Dr Bhatia has over 30 years of international experience in pharmaceutical R&D. He was associated with Ciba-Geigy (Novartis) for 17 years in their R&D labs in Switzerland, India and USA. While in India, he was an integral part of the team from early discovery through proof-of-concept clinical trials at Ciba-Geigy's research centre in Mumbai specialising in tropical diseases. In New Jersey, USA he was a core member of 'Other Therapeutic Areas' group dealing with cancer and metabolic diseases, and Business Development Cell for in-licensing of new molecules. On his return from the US in 1995, he served the Indian pharmaceutical industry by establishing a GCP centre of excellence in clinical pharmacology and pharmacokinetics at the Ranbaxy R&D laboratories in Gurgaon, and then, two start-up CROs – Wellquest (now Piramal Clinical Research) in Mumbai and Fortis Clinical Research Ltd in Faridabad. Following his PhD in Biochemistry from the University of Delhi, Dr Bhatia held faculty positions at the University of Geneva in Switzerland. His interests include clinical and preclinical drug development, pharmacokinetics, GLP/GCP-based bioanalytics and proof-of-concept clinical trials, quality assurance, business development and mentoring.

Mr. Vinay Kumar

Consultant, CDSA

Vinay Kumar holds an MBA and M.Phil degree. He has been closely associated with training and performance improvement initiatives in global health for the past 15 years. He was the Regional Specialist in Performance Improvement at International Training in Health (Intrah) of University of North Carolina at Chapel Hill and led several initiatives to successful completion in Yemen, Oman, Bangladesh, India and Indonesia. Until recently, he was India Operations Director for PATH and contributed to its exponential growth and diversified donor base.

2.5 National Biodesign Alliance (NBA)

Mission: To promote an effective translational route of basic findings into routine applications of major importance using a multidisciplinary approach.

The National Biodesign Alliance (NBA) is a multi-institutional partnership program on Biodesign and *in-vitro* diagnostics, anchored through a coordination secretariat at THSTI, which was initiated by the Department of Biotechnology (DBT), Government of India on September 24, 2010.

It is a network of biologists, engineers, clinicians and medical technology experts who work to promote an effective route for translation of basic findings into routine applications of major clinical importance in India using a multidisciplinary approach. It is proposed to be done by combining new biomarkers, novel technological concepts and clinical expertise.

Partners

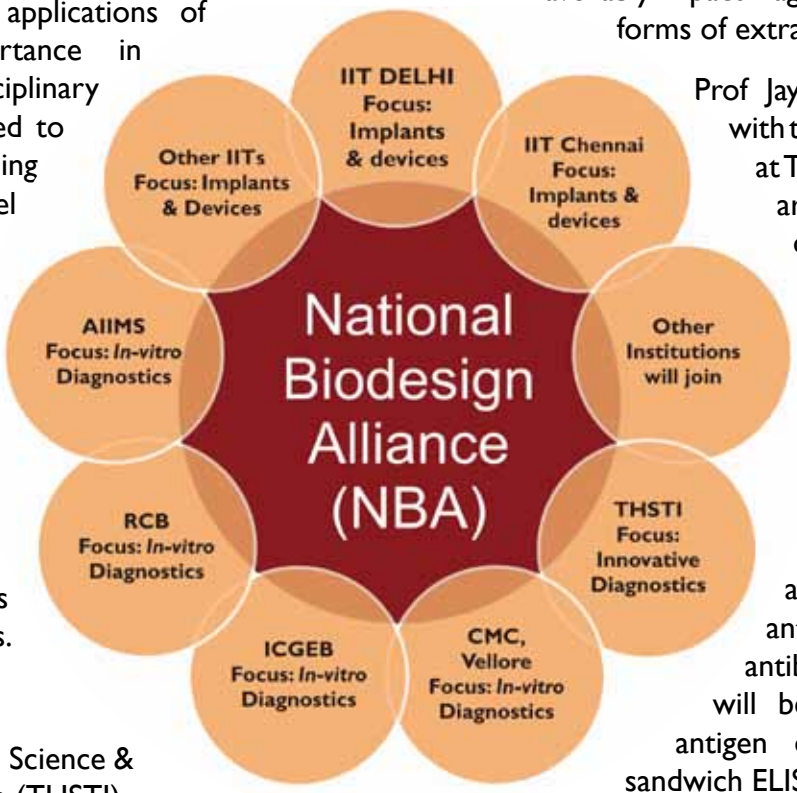
The objectives of the alliance are met with the help of national and international partnerships that support its various initiatives and programs.

National Partners

- Translational Health Science & Technology Institute (THSTI),
- Regional Centre for Biotechnology (RCB),
- International Centre for Genetic Engineering and Biotechnology (ICGEB),
- All India Institute of Medical Sciences (AIIMS),
- Indian Institute of Technology (IIT) Delhi,
- IIT Chennai
- Christian Medical College (CMC) Vellore

International Partner

- University of Turku (UT), Finland



Programs

Rapid Diagnostic Test for Tuberculosis Meningitis:

"TB is one of the world's most pressing public health problems with a global prevalence of 14 million cases with 1.68 million deaths with India accounting for a fifth of the global burden"

WHO report, 2009

A pilot mode collaborative study between AIIMS and RML Hospital, New Delhi suggested that the detection of *Mycobacterium tuberculosis* antigen in pediatric CSF samples could provide value addition to the existing TBM diagnostic paradigm. The results further implied that diagnostic tests based on antigen detection would favorably impact diagnosis of TBM and other forms of extra-pulmonary disease.

Prof Jaya Tyagi (AIIMS) along with the innovation awardees at THSTI mentored by her, are developing these diagnostic tests and antigen detection reagents by preparing selected recombinant *M. tuberculosis* antigens, their corresponding high affinity monoclonal antibodies (capture antibody) and polyclonal antibodies (detection antibody). These reagents will be used for preparing antigen detection systems in sandwich ELISA and lateral flow test formats. In the next phase of research, these tests will be applied to the diagnosis of other extra-pulmonary forms of TB using a variety of sample fluids such as aspirates from joints, lymph node, pleural effusion, ascites etc. Collaborations will be established with an industry partner for up scaling and commercialization.

The project aims to develop an open indigenous system for TB diagnosis comprising of smear microscopy, MDR-TB and XDR-TB detection which will improve the safety and performance of existing direct smear microscopy test for TB diagnosis. A rapid detection method for TB will also be developed for Multi-Drug-Resistant Tuberculosis (MDR-TB) and Xtensively Drug-Resistant Tuberculosis (XDR-TB)

University of Turku Delegation meeting with National Biodesign Alliance

using DNA extracted from the stained slides/filters used in smear microscopy.

Development of a Rapid Diagnostic Kit for Chikungunya:

The epidemiology and disease burden of Chikungunya remain largely undetermined, partially due to lack of an appropriate diagnostic test other than RT-PCR/ Real-time. A simple, rapid and affordable point of care diagnostic test for early detection of chikungunya antigen in the serum/plasma of patients is required.

Dr. Pratima Ray (AIIMS) and her team have started working towards developing a diagnostic kit which will select the best suitable target (antigen) for early diagnosis of chikungunya fever, and have initiated development of reagent intermediates for developing a micro-ELISA test for detecting viral antigens in the serum/plasma of patients. The kits will be evaluated with a panel of clinically defined chikungunya infected sera/plasma.

DXPhone – Mobile Phone Diagnostic Platform:

Diabetes is the one of the leading causes of death around the world. In India alone, there are nearly 50 million diabetic patients, a number that is expected to rise to 80 million by 2030, according to the World Health Organization. Thus, there is a large unmet clinical need to provide an affordable, simple and easily accessible glucose monitoring solution to patients and physicians.

Mr. Sidhant Jena (Jana care) and his team along with Prof. Nikhil Tandon (AIIMS) are developing a sensor platform - DXPhone that turns any camera phone into a glucose monitor. The platform comprises of two components - a colorimetric test strip for blood glucose and a software application that uses the phone's camera to analyze the test strip. Additionally, the software application can provide automated decision support and transmit data to remote specialists, enabling millions of field health workers to screen and manage diabetes in even the most remote communities.

This platform is substantially cheaper as it utilizes colorimetric glucose strips which cost less than Rs.2.5 each compared to current electrochemical strips which sell for > $0.50 each in the market.

International Collaborations Add Value: University of Turku (UT)

A formal MoU was signed by THSTI on behalf of the NBA and UT under the DBT Indo-Finnish program on January 28, 2011 in order to establish a program of cooperation between the UT and NBA for collaborating in research, innovation, higher education, training and capacity building in the area of diagnostics related to human health. Turku is an

internationally recognized stronghold in research on *in-vitro* diagnostic technologies. The Diagnostics Program within the framework of Bio-City Turku is actively engaged in the development and coordination of higher education of researchers in this field. It promotes interactions within the research community and in segments of Finnish biotechnological industry involved with innovation.

Research collaborations:

Indo-Finnish Postdoctoral Fellows:

In order to create a sizable pool of researchers who specialize in development of diagnostics in India, the Department of Biotechnology has instituted 5 postdoctoral fellowships for training in various Finnish Institutes for a period of two years. The program will be evaluated for success before it is expanded further. The process of selection for re-entry of few of these fellows into the mainstream is being thought through by the Alliance, to enable them to not only establish laboratories in partnering institutions and industry but also act as trainers for developing similar capacity within the country.

Sandwich Ph.D. program between the NBA and University of Turku:

A sandwich Ph.D. program between the NBA and University of Turku is in the process of being discussed. The Ph.D. students of the Indian partner institutions of NBA, who choose to work on problems under already sanctioned Indo-Finnish projects will have an option of training at University of Turku for a period not exceeding three months. Similar training will also be made available for Finnish students working in Indo-Finnish projects to work in India for a similar duration. This exchange will initiate a relationship between the "diagnostics community" of the two countries, with better understanding of each other's needs, processes and expertise.

People behind the diagnostic initiative

Collaborating Principal Investigators include Dr. Navin Khanna, ICGEB, New Delhi; Dr. Jaya Tyagi, , AIIMS, New Delhi; Dr. Pratima Ray, AIIMS, New Delhi; Dr. Gagandeep Kang, CMC, Vellore; Dr. Nikhil Tandon, AIIMS, New Delhi; Dr. Vinod Paul, AIIMS, New Delhi, Dr Shinjini Bhatnagar, THSTI

The team also includes a nominee of each partner of the Alliance, an Adviser and a representative of DBT.

Coordination Secretariat: Dr. Shinjini Bhatnagar, THSTI and Dr. Navin Khanna (ICGEB and Adjunct Professor, THSTI).

2.6 Forthcoming centres

In addition to the existing 3 niche centers, 3 more niche centers have been conceptualized and are in the process of being established. The proposals for these centers are being examined by the DBT. The brief of these centers are given below:

Centre for Human Microbial Ecology

The vision of Center for Human Microbial Ecology (CHME) is to understand the dynamics of human microbiome and its influence on various clinical outcomes such as prematurity, malnourishment and response to vaccinations. Its aim is to harness the human microbiome for providing knowledge-based solutions for public health. The mission of CHME is to create a multi-disciplinary research center designed to conduct basic, clinical and translational research on the role of the human microbiome in health and disease.

Drug Discovery Research Centre

The Drug Discovery Research Centre (DDRC) is proposed as a multi-disciplinary research centre that will integrate basic with translational research in the field of drug discovery. The overall mission of the centre will be to combine multiple disciplines in order to generate a robust and versatile pipeline for drug discovery research. This will also include capabilities for analysing large-scale data in order to identify the most promising targets for further drug development.

In a broad sense, the DDRC will function as a technology-intensive base that can spur the human health-related research activity in the country. That is, at one level, it will facilitate on-going programs in different laboratories by providing the via media for translating early leads, either at the level of target identification or preliminary biological activity, into candidate drugs. This it will achieve by providing platforms and expertise for target/activity validation, in silico inhibitor design, high-content screening, structure-activity optimization of lead molecules, chemical synthesis of template structures, and pharmacological evaluation of the lead compounds. In addition, the DDRC will also actively collaborate with ongoing research programs related to public health (especially those at THSTI) in order to translate the findings into possible strategies for chemotherapy. Thus, data obtained from such studies could be further refined at DDRC by experiments at the cellular level.

Policy and Forecasting Centre

In India major use and diffusion of health interventions are handicapped due to various reasons such as lack of economic analysis and sustainable financing

mechanisms, lack of appropriately managed technology transfer units, lack of guidelines on appropriate heat-stability profile of product and appropriate allocation of cold chain space and lack of properly coordinated demand generation activities for developed technologies. To address these issues it is proposed to establish a Policy & forecasting centre at THSTI. It is already in existence as a unit of DBT but it is proposed to be transferred to THSTI since it more appropriately suits its mandate. The centre in the proposed structure is likely to have three functions:-

i. Intelligent Ideas for innovation:

ii. Exploring strategies where there are opportunities but implementations is not happening.

iii. Technology diffusion and technology demand creation.

PUBLICATIONS, SCIENTIFIC EVENTS AND SEMINARS

3.1 Publications

1. Bharati, K. and Vrati, S. (2012) Viral vaccines in India: An overview. Proc. Natl. Acad. Sci. Sect B. Biol. Sci. (In press :DOI10.1007/s40011-011-0014-9).
2. Anantpadma, M. and Vrati, S. (2011) siRNA mediated suppression of Japanese encephalitis virus replication in cultured cells and mice. Journal of Antimicrobial Chemotherpay 67:444-451.
3. Vashist, S., Bhullar, D., and Vrati, S. (2011) La protein can simultaneously bind to both 3' and 5'-noncoding regions of Japanese encephalitis virus genome. DNA and Cell Biology 30:339-346.
4. Medigeshi GR. Mosquito-borne flaviviruses: overview of viral life-cycle and host-virus interactions. Future Virology 2011 2011/09/01;6(9):1075-89.
5. Sudha VB, Ganesan S, Pazhani GP, Ramamurthy T, Nair GB, Venkatasubramanian P. 2012. Storing drinking-water in copper pots kills contaminating diarrhoeagenic bacteria. J Health PopulNutr. 30(1):17-21.
6. Sarkar BL, Kanungo S, Nair GB. 2012. How endemic is cholera in India?Indian J Med Res.135:246-8.
7. Hajela N, Nair GB, Abraham P, Ganguly NK. 2012. Health impact of probiotics – visionand opportunities.Gut Pathog. 4(1):1.
8. Naha A, Pazhani GP, Ganguly M, Ghosh S, Ramamurthy T, Nandy RK, Nair GB, Takeda Y, Mukhopadhyay AK. 2012. Development and evaluation of a PCR assay for tracking the emergence and dissemination of Haitian variant ctxB in Vibrio cholerae O1 strains isolated from Kolkata. India. J ClinMicrobiol. 50(5):1733-6.
9. Nahar S, Sultana M, Naser MN, Nair GB, Watanabe H, Ohnishi M, Yamamoto S, Endtz H, Cravioto A, Sack RB, Hasan NA, Sadique A, Huq A, Colwell RR, Alam M. 2011. Role of Shrimp Chitin in the Ecology of Toxigenic Vibrio cholerae and Cholera Transmission. Front Microbiol. 2:260.E.Pub Jan 4.
10. Sinha A, Sengupta S, Guin S, Dutta S, Ghosh S, Mukherjee P, Mukhopadhyay AK, Ramamurthy T, Takeda Y, Kurakawa T, Nomoto K, Nair GB, Nandy RK. 2011. Culture-independent real-time PCR reveals extensive polymicrobial infections in hospitalized diarrhoea cases in Kolkata, India. ClinMicrobiol Infect. doi: 10.1111/j.1469-0691.2011.03746.x.
11. Clemens J, Shin S, Sur D, Nair GB, Holmgren J. 2011. New-generation vaccines against cholera. Nat Rev GastroenterolHepatol. 8(12):701-10. doi: 10.1038/nrgastro.2011.174.
12. Sur D, Kanungo S, Sah B, Manna B, Ali M, Paisley AM, Niyogi SK, Park JK, Sarkar B, Puri MK, Kim DR, Deen JL, Holmgren J, Carbis R, Rao R, Nguyen TV, Han SH, Attridge S, Donner A, Ganguly NK, Bhattacharya SK, Nair GB, Clemens JD, Lopez AL. 2011. Efficacy of a low-cost, inactivated whole-cell oral cholera vaccine: results from 3 years of follow-up of a randomised, controlled trial. PLoSNegl Trop Dis. 5(10):e1289.
13. Bhatnagar S, Wadhwa N, Aneja S, Lodha R, Kabra SK, Natchu UC, Sommerfelt H, Dutta AK, Chandra J, Rath B, Sharma M, Sharma VK, Kumari M and Strand TA. Zinc as adjunct treatment in infants aged between 7 and 120 days with probable serious bacterial infection: a randomised, double-blind, placebo-controlled trial (accepted for publication by Lancet)
14. Wadhwa N, UCM Natchu, Sommerfelt H, Strand TA, Kapoor V, Saini S, Kainth UPS and Bhatnagar S. Oral rehydration solution is a poor vehicle for zinc in the treatment of acute childhood diarrhea. J Pediatr Gastroenterol Nutr. 2011 Aug; 53(2):161-7.
15. Gulani A, Bhatnagar S, Sachdev HP. Neonatal zinc supplementation for prevention of mortality and morbidity in breastfed low birth weight infants: systematic review of randomized controlled trials. Indian Pediatr. 2011 Feb 7;48(2):111-7.
16. Yadav P, Das P, Mirdha BR, Gupta SD, Bhatnagar S, Pandey RM, Makharia GK. Current spectrum of malabsorption syndrome in adults in India. Indian J Gastroenterol. 2011 Feb;30(1):22-8.
17. KN Beeesabathuni, UC Natchu. Production and Distribution of a Therapeutic Nutritional Product for Severe Acute Malnutrition in India: Opportunities and Challenges. Indian Pediatr 2010 Aug 7;47(8):702-6.
18. Goldie SJ, Sweet S, Carvalho N, Natchu UC, Hu D. Alternative strategies to reduce maternal mortality in India: a cost-effectiveness analysis. PLoS Med. 2010 Apr 20;7(4):e1000264

19. Lee Y*, Awasthi A *, Nir Yosef, Francisco Quintana, Sheng Xiao, Sharon Kunder, Aviv Regev Sobel R, Kuchroo VK. Induction and molecular signature of pathogenic TH 17 cells. Nature. Immunology. [Shared first and senior author]. 2012 Oct;13(10):991-9.

20. Kuchroo VK, Awasthi A. Emerging new roles of Th17 cells. European Journal of Immunology. 2012 Sep;42(9):2211-4.

3.2 Scientific Events

1. Vaccines : Discovery to Translational

An international symposium on 'Vaccines: From Discovery to Translation' was organized from November 14-17 at The Claridges, Surajkund, Faridabad to bring together world-leading experts to debate the many-sided correlations between vaccines, medicine and society at the dawn of the third millennium. The symposium offered a unique platform for very high level discussion in basic science discovery, product development, market introduction, and adoption into immunization programs so that collaborative opportunities may be explored and exploited.

There were nearly 20 international experts and as many Indian experts of international repute who made presentations. All known experts in the world on vaccine related science were present at the symposium that became the 'go to' scientific event at the global scale. The participants (about 150) included scientists, academicians, science administrators, parliamentarians, civil servants and research students. The symposium successfully took advantage of the collective experience, good practices and research tools that various stakeholders and initiatives around the world apply in order to protect people of all ages as a safe and friendly "life insurance" from a multitude of diseases reaching far beyond classic childhood vaccines. It encouraged the participation of all the disparate fields of vaccinology in both its human and veterinary domains in order to facilitate valuable cross-fertilization of ideas and approaches among researchers often narrowly focused on their specific diseases or methods.

The symposium was organized by the Department of Biotechnology (DBT), Ministry of Science & Technology, Government of India under its new initiatives – Vaccine Grand Challenge Program (VGCP), Vaccine and Infectious Diseases Research Centre (VIDRC), Pediatric Biology Centre, Clinical Development Services Agency (CDSA) and International AIDS Vaccine Initiative (IAVI).

2. Measuring Human Immune Responses

An Indo –US workshop on "Measuring Human Immune Responses" was organised in Delhi between Oct 31 – Nov 02, 2011. The overarching objective of the workshop was to introduce and nucleate intensive and rigorous immunological analyses in studies of human infectious and immunological disease and vaccine trails in India. It is now widely accepted that failures of many current vaccines, and difficulties in implementing rational approaches to immunological therapy, are often because of a poor definition of immune biomarkers for vaccine efficacy and disease outcome. In fact, the understanding of the human immune response remains rudimentary, and although much has been learned from studies of experimental models, particularly mice, it is becoming increasingly clear that many conclusions reached from these models cannot be extrapolated to humans.

In order to address these problems , the workshop had three specific goals :-

1. To discuss cutting –edge technology for studying human immune responses and for bio-informatic analyses.
2. To develop ways of transferring the technology from the US to selected institutions in India.
3. To establish scientific collaborations between biomedical research institutions in the US and India, focused on human immunological analyses.

The workshop was organized by PBC, Dr. Satyajit Rath from the National Institute of Immunology, Delhi and Dr Gagandeep Kang from CMC, Vellore along with Professors Abul Abbas and Rafi Ahmed from UCSF and Emory, and Dr. Satyajit Rath from the National Institute of Immunology, Delhi.

3.3 Meetings and Seminars

SEMINAR TITLE	SPEAKER
Nano-Scale Device for Diagnostic Application: Fabrication, Characterisation and Detection	Dr. Nirankar N. Mishra, CAMBR University of Idaho,Post Falls, ID USA
Imaging Protein Activity in Living Cells: Src Kinases at the Leading Edge	Dr. Akash Gulyani, Department of Pharmacology University of North Carolina, Chapel Hill
Present/Future Research Activities Towards Developing Point of Care Diagnostic Assays for Pathogen Detection	Dr. Seema Nara Department of Applied Message
Approaches to Treat Neuropathic Pain disorders using Behavioural & Controlled Drug Release Systems	Dr. Sahadev Shankarappa, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology and Department of Anesthesiology (MIT), Children's Hospital Boston, Harvard Medical School
Disorders of Haemoglobin Metabolism: Leishmaniasis and Sickle Cell Disease	Dr. Nitin Patel, University of Genetic Medicine, Keck School of Medicine University of Southern California, CA
Integrating Mobile DNA Elements exploiting Xer (IMEXs): Mechanisms of Acquisition and Dissemination	Dr. Bhabatosh Das, Centre de Genetique Moleculaire (CNRS) France
Emerging Molecular Signatures in Inflammation: Special Focus on Obstructive Respiratory Diseases	Dr. Saheli Chowdhury, Departments of Respiratory Medicine and Experimental Immunology, Academic Medical Centre, Amsterdam.
Novel Recombinant Designer Proteins for Differential Diagnosis of Infectious Diseases	Dr. Gaurav Batra, Department of Biotechnology, University of Turku, Finland.
Next Generation Diagnostics of Bacterial Infections and Comprehensive Drug Susceptibility Testing for M. tb	Dr. Soumitesh Charkavorty, Division of Infectious Diseases,New Jersey medical School, UMDNJ, NJ, USA.
Microbiota in Health and Disease; A High Resolution Picture of a Complex Interaction	Dr. Ateequr Rehman, Department of Environmental Health Sciences, University Medical Centre, Freiburg, Germany
Coronary Artery Disease and Atherosclerosis in Indians	Dr. Bhanu Duggal Cardiology, GMC &Sir JJ group of Hospitals, Mumbai
Neural Engineering & Rehabilitation for Stroke/Spinal Cord Injury Patients	Dr. Sukanta Kumar Sabut, Assistant Prof, Electronics Engineering, KIIT Univ, Odisha
Sensors For Biotechnology: Our Approach	Dr. Ida Tiwari, Assistant Professor, Dept of Chemistry, BHU, Varnasi
Regulation of Claudin-1 Mediated Colon Tumor Progression and Metastasis	Dr. Ashok Sharma, Vanderbilt Medical Center Vanderbilt University, Nashville, TN,USA
Next Generation Diagnostic Assay Concepts	Dr. Sheikh Mohd. Talha, Department of Biotechnology, University of Turku (DBUT), Finland
Dual Functional Role of Histone Methyltransferase G9a in Regulating Gene Expression Program in Adult Erythroid Cells	Dr. Chandra Prakash Chaturvedi, Ottawa Health Research Institute, Ottawa
Challenges in Setting up a GMP Compliant Facility for Investigational Medicinal Products - An Academic Perspective	Dr. Eugene R Arulmuthu, Operations & Manufacturing Manager, Gene Therapy Group, UCL, London
Integrated Mobile Health (mobile health) Intervention for HIV & Depression	Dr. Mona Duggal, Associate Research Scientist in Dept of medicine, Yale University, New Haven, CT, USA
Antibody Engineering : One Stop Shop for Improved Diagnosis and Effective Therapy	Dr. Ashutosh Tiwari, Centre for Biodesign, THSTI, Gurgaon
FlowJo - A Flow Cytometry Data Analysis Software	Dr. Hemant Agrawal, Application Scientist
Technical Presentation on "Cell – IQ Live Cell Imaging System"	Mr. Kevin McCormack, International Sales Manager, Chip- Man Technologies, Finland
Systematic Discovery of Protein Networks using Computational Proteomics	Dr. Sudipto Saha, Center for Proteomics and Bioinformatics, School of Medicine, Case Western Reserve University Cleveland, OHIO USA

SEMINAR TITLE	SPEAKER
New Class of Adjuvants to Promote and Polarise Immunity in Lymph Nodes	Dr. Ashley St. John, Program in Emerging Infectious Diseases, Duke- National University of Singapore, Singapore
Macaque Models to Study HIV Clade C Pathogenesis and Vaccine Development	Dr. Siddappa Nagadenahalli, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA
Deep Sequencing	Roche
Horror Autotoxicus: T Cell Receptor Recognition of Self and Foreign Antigens	Dr. Dhruv Sethi, Dana-Farber Cancer Institute Harvard Medical School Boston, MA (USA)
Nano-Engineered Tools for Cell Therapy and Tissue Engineering	Dr. Parijat Bhatnagar, Research Engineer / Visiting Scientist at MD Anderson Cancer Centre & The Methodist Hospital Research Institute, Houston, TX (USA)
Oxygen and Cell-competition Drives Cancer and Cardiovascular Diseases: A Therapeutic Approach	Dr. Rajan Gogna, Dorothy M Davis Heart and Lung Research institute
The RAGE axis: Novel Structural and Molecular Insights and Key Regulations in Chronic Inflammations and Tumorigenesis	Vivek Rai, PhD, Department of Medicine, New York University Medical Center
Altering Immune Response to Balance Immunity and Immunopathology upon Virus Infection	Dr. Sharvan Sehrawat, Whitehead Institute for Biomedical Research
Building Foundations of New Biology	Pawan K Dhar, PhD, Director, Centre for Systems and Synthetic Biology
Autophagy in host defense: Role of p62 in TLR4 signaling	Srinivasa M. Srinivasula Ph.D. , National Cancer Institute, Bethesda MD 20892
Photocontrol of protein activity in a single cell of a live organism	Dr. Deepak Kumar Sinha, Laboratoire de Physique Statistique, Ecole Normale Supérieure, Paris
Role of Broad Neutralizing antibodies in HIV-1 Vaccine Design	Dr. Sanjay K. Phogat, Ph.D., Associate Director, IAVI, AIDS Vaccine Design and Development Lab, Brooklyn, New York
Cancer Nanomedicine: A Translational Story	Dr. Shiladitya Sengupta, Co-Chair, Center for Regenerative Medicine, Brigham and Women's Hospital.
Regulation of Mycobacterium tuberculosis replication and proliferation	Dr. Murty Madiraju, Professor at University of Texas Health Center at Tyler, Texas (USA)
Molecular Evolution at different time scale	Dr. Anchal Vishnoi,
Surface Engineering of Biomedical Polymers for Biocompatibility and Tissue Regeneration	Dr. Anand Khandwekar, Department of Bioengineering, Massachusetts Institute of Technology, Cambridge, MA, USA
Deciphering the molecular interplay of cell proliferation using Drosophila	Dr. Pallavi Kshetrapal, Harvard Medical School
CD8+T Cell effector functions in viral infections	Dr. Suneetha, Hannover Medical School, Hannover, Germany
Construction and Evaluation of Novel Recombinant BCG Vaccines	Dr. Velmurugan Kamalakannan
Translational Sciences and Clinical Application	Prof. Ashok Venkitaraman, MRC Cambridge, UK
Consequences of the natural propensity of HIV-1 and Leishmania to target Monocytic lineage	Dr. Ravendra Garg, Vaccine Infectious Disease organization, University of Saskatchewan, Saskatoon, SK, Canada
From Gene Discovery to Therapy: Translational Research in Myotonic Muscular Dystrophy	Prof. Mani S. Mahadevan, Medical Director, Molecular Diagnostics Lab, UVA Health System, Associate Director, Cytogenetics Lab, UVA-Health System, Department of Pathology, University of Virginia
Interplay between HIV/AIDS and Drug Use: A tale of miR-125b	Chandravanu (CV) Dash, Ph.D., Assistant Professor, Center for AIDS Health Disparities Research
Dynamic Tissue Models for Probing Pathophysiological Responses of Liver and Skin	Dr. Rohit Jindal, Research Associate, Rutgers The State University of New Jersey, Piscataway, NJ 08854

AWARDS AND RECOGNITIONS

4 AWARDS AND RECOGNITIONS

Name	Awards
Dr. G B Nair	Elected to the National Academy of Sciences, Bangalore, India (2012) Elected to the Membership of the German National Academy of Sciences Leopoldina (2011)
Dr. Sudhanshu Vrati	Australian Alumni Excellence Award 2011
Dr. Shinjini Bhatnagar	Shri. Har Bhagwan Kumar Oration by the Nutrition Sub Chapter of the Indian Academy of Pediatrics at the 49th National Conference of the Indian Academy of Pediatrics
Dr. Amit Kumar Pandey	Ramalingaswamy Fellowship

Name	Lectures Delivered / Other Recognitions
Dr. G. B. Nair	Delivered the Eighth Prof. V. Ramalingaswami-Professor Frederick C. Robbins Lecture entitled "Cholera vaccines - where do we stand?" under zaegis of Indo-US Vaccine Action Programme on 4th November, 2011 in New Delhi Delivered a special lecture on "THSTI Perspective" on 23rd, November, 2011 at the Indo-Spanish workshop on Health and Medical Research in New Delhi from November. Delivered a talk on "Probiotics and Diarrhea in Low- and Middle- income countries" conducted by Yakult India Microbiota and Probiotic Science Foundation, on 10th December, 2011 at Mumbai. Delivered a special session talk titled, "Are enteric pathogens a part of the microbiota of the impoverished gut" at the 46th US –Japan Cooperative Medical Science Programme Cholera and other Bacterial Enteric Infections Conference in Kolkata on 13th December, 2011. Delivered a special invited lecture entitled "In pursuit of the intercontinental transmission of cholera: Origin and spread of cholera in Haiti" at the Asian-African Research Forum on Emerging and Reemerging infections 2012 in Kobe, Japan on 11th January, 2012. Delivered the invited talk entitled "The inside story of the impoverished gut" at the 4th Madras Diabetes Research Foundation on 5th February, 2012 at Chennai. Delivered a special lecture entitled "Rapid diagnosis of cholera, a new tool to assist surveillance" at the JST-DST Workshop on "Biomedical Research", TWIns, Waseda University, Tokyo from 28th February-3rd March, 2012. Delivered a special lecture on "Variant EL Tor Vibrio cholerae01: Resurrection of severe cholera" at the 85th Annual meeting of Japanese Society of Bateriologyin Nagasaki, Japan on 29th March, 2012. Delivered a luncheon session lecture entitled "Role of Lactobacillus casei strain Shirota in preventing acute diarrhea in Indian children- Community based randomised double blind placebo controlled field trail in an urban slum of Kolkata, India " at the 85th Annual meeting of Japanese Society of Bateriology in Nagasaki, Japan on 28th March, 2012.

Name	Lectures Delivered / Other Recognitions
Dr. Sudhanshu Vrati	Delivered lecture at School of Biotechnology, Jawaharlal Nehru University, New Delhi [April 2011] Delivered lecture at Young Investigators' Meet, Boston, USA [Oct 2011] Delivered lecture at University of Calcutta, Kolkata [Oct 2011] Delivered lecture at Jamia Hamdard, New Delhi [Nov 2011] Delivered lecture at Annual Conference of the Association of Microbiologists of India, Chandigarh [Nov 2011] Delivered lecture at Vaccines: From Discovery to Translation, Faridabad [Nov 2011] Delivered lecture at Indo-French Seminar on novel vaccines, Hyderabad [Feb 2012] Delivered lecture at Annual Conference of the Biotech Society of India, New Delhi [Feb 2012]
Dr. Shinjini Bhatnagar	Delivered lecture on issues of randomization and blinding in clinical trials [April 2011] : Workshop on Clinical Biostatistics in SGPGI Chacha Nehru Bal Chikitsalaya: Delivered lecture on Serological diagnosis of celiac disease [May 2011] : CME on Celiac disease Delivered lecture on Clinical Research methods in surgical trials [Aug 2011] : Scientific Program Pediatric Surgery Delhi Chapter Delivered lecture on Evidence for use of zinc in treatment of diarrhea [September 2011] : Gates and WHO meeting for the "Zinc suppliers Delivered lecture on Interventions to Reduce Severity and Duration of Childhood Diarrhea-from Evidence to Policy" [Oct 2011] : Harvard School of Public Health, Frontiers in Global Health Seminars Delivered lecture on Translational research opportunities in Pediatric gastroenterology [Nov 2011] : 21st Annual Conference of Pediatric Gastroenterology, Gurgaon Delivered lecture at Yakult India Microbiota and Probiotic Science Foundation Probiotic Symposium "Health impact of Probiotics – Vision and Opportunities" –Evidence for use of probiotics in health [Dec 2011] Member of the expert committee on treatment of diarrhoea [Jan 2012] : 49th National Conference of the Indian Academy of Pediatrics, Gurgaon:
Dr. Nitya Wadhwa	Selected for a short term course on 'Experimental Epidemiology' conducted by the Centre for International Health, University of Bergen, Norway

Dr. G. B. Nair unfurls the flag on Independence Day at THSTI

Prof. M. K. Bhan hoisting the tricolor at the Republic Day celebrations at THSTI

GOVERNANCE AND ADMINISTRATION

5 GOVERNING STRUCTURE

THSTI is registered as a society headed by an eminent scientist. A Governing Body (headed by the Secretary, DBT), Finance Committee (also headed by Secretary, DBT) and the Institute Management Committee (headed by the Executive Director, THSTI) are responsible for administering all activities of the institute.

Following are the composition of these committees.

THSTI Society			
S.No.	Name	Affiliation	Position
1	Dr. G. Padmanaban	Distinguished Professor, IISc, Bangalore	President
2	Prof. M.K. Bhan	Secretary, DBT	Member, Ex-officio
3	Dr. Chandrima Shaha	Director, NII	Member, Ex-officio
4	Dr. V. M. Katoch	Secretary, DHR and DG, ICMR	Member, Ex-officio
5	Prof. Ashok Jhunjhunwala	Professor - IIT Madras	Member
6	Dr. B. Ravindran	Director, Institute of Life Sciences, Bhubaneshwar	Member
7	Dr. J. Gowrishankar	Director , Centre for DNA Fingerprinting & Diagnostic, Hyderabad	Member
8	Dr. G.C. Mishra	Former Director, National Centre for Cell Sciences	Member
9	Dr. M. Radhakrishna Pillai	Director, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram	Member
10	Dr. G. B. Nair	Executive Director, THSTI	Member, Ex-officio
11	Ms. Anuradha Mitra	JS & FA, DBT	Member, Ex-officio
12	Dr. T. S. Rao	Advisor, DBT	Member Secretary, Ex-officio

Governing Body			
S.No.	Name	Affiliation	Position
1	Prof. M. K. Bhan	Secretary, DBT	Chairman, Ex-officio
2	Dr. V. M. Katoch	Secretary, DHR and DG, ICMR	Member, Ex-officio
3	Dr. T. S. Rao	Advisor, DBT	Member, Ex-officio
4	Dr. Dinakar M. Salunke	Executive Director, RCB	Member, Ex-officio
5	Ms. Anuradha Mitra	JS & FA , DBT	Member, Ex-officio
6	Dr. P. N. Tandon	President , NBRC, Manesar	Member
7	Dr. G. Padmanaban	NASI-Chair/Distinguished Professor, IISc, Bangalore	Member
8	Dr. Subrata Sinha	Director, NBRC, Manesar	Member
9	Dr. Balram Bhargava	Professor, AIIMS, New Delhi	Member
10	Dr. K. Srinath Reddy	President, PHFI	Member
11	Dr. K. VijayRaghavan	Director, NCBS and inStem, Bangalore	Member
12	Dr. M. S. Ananth	Former Director, IIT Madras	Member
13	Dr. T.S. Balganesh	Distinguished Scientist and Head of OSDD, CSIR	Member
14	Dr. S.K. Biswas	Professor, Department of Electrical Engineering, IISc, Bangalore	Member
15	Dr. Ashutosh Sharma	Institute Chair Professor, IIT Kanpur	Member
16	Dr. Sudhanshu Vrati	Dean, THSTI	Member, Ex-officio
17	Dr. Shinjini Bhatnagar	Professor, THSTI	Member, Ex-officio
18	Dr. G. B. Nair	Executive Director, THSTI	Member Secretary, Ex-officio

Finance Committee			
S.No.	Name	Affiliation	Position
1	Prof. M. K. Bhan	Secretary, DBT	Chairman, Ex-officio
2	Ms. Anuradha Mitra	JS & FA, DBT	Member, Ex-officio
3	Dr. T. S. Rao	Advisor, DBT	Member, Ex-officio
4	Dr. G. B. Nair	Executive Director, THSTI	Member, Ex-officio
5	Dr. Sudhanshu Vrati	Dean, THSTI	Member, Ex-officio
6	Mr. Chandrabhan Yadav	Administrative Officer (F & A), THSTI	Non-Member Secretary and Convener

Institute Management Committee			
S.No.	Name	Affiliation	Position
1	Dr. G. B. Nair	Executive Director, THSTI	Chairperson
2	Dr. Sudhanshu Vrati	Dean, THSTI	Member
3	Dr. Shinjini Bhatnagar	Professor, PBC, THSTI	Member
4	Dr. Harmeet Sidhu	Program Director– CDSA	Member
5	Dr. Guruprasad Medigeshi	Assistant Professor	Member
6	Mr. Chandrabhan Yadav	AO (F&A), THSTI	Co-opted Member
7	Dr. Satyajit Rath	Staff Scientist , NII	Co-opted Member
8	Mr. M.V. Santo	AO and Head, Administration, THSTI	Co-opted Member and Secretary

6 Officers and Staff

Scientific		
S.No.	Employee Name	Designation
1	Dr. G. B.Nair	Executive Director
2	Dr. Sudhanshu Vrati	Dean
3	Dr. Shinjini Bhatnagar	Professor
4	Dr. Guruprasad R. Medigeshi	Assistant Professor
5	Dr. Ramandeep Singh	Assistant Professor
6	Dr. Nisheeth Agarwal	Assistant Professor
7	Dr. Amit Kumar Pandey	Assistant Professor
8	Dr. Krishnamohan Atmakuri	Assistant Professor
9	Dr. Milan Surjit	Assistant Professor
10	Dr. Amit Awasthi	Assistant Professor
11	Dr. Uma Chandra Mouli Natchu	Ramalingaswamy Fellow
12	Dr. Manjula Kalia	Research Scientist D
13	Dr. Shailaja Sopory	Research Scientist D
14	Dr. Santanu Mukherjee	Research Scientist D
15	Dr. Arup Banerjee	Research Scientist D
16	Dr. Nitya Wadhwa	Research Scientist D (Clinical Investigator)
17	Dr. M. B. Appaiahgari	Research Scientist C
18	Dr. Sankar Bhattacharya	Research Scientist C
19	Dr. Deepak Sharma	Research Scientist C
20	Dr. Rohan Dhiman	Research Scientist C
21	Dr.Bala Chandra K. Gorentla	Research Scientist C
22	Dr. Ashutosh Tiwari	Research Scientist C
23	Dr. Niraj Kumar	Research Scientist C
24	Dr. Susmita Chaudhuri	Research Scientist C (P)
25	Dr. Reeta Singh	Research Officer (P)
26	Dr. Amit Kumar	Research Officer (P)
27	Dr. Sagarika Haldar	Innovation Awardee
28	Dr. Prabhakar Tiwari	Research Associate (P)
29	Dr. Deepak Kumar Rathore	Research Associate (P)
30	Dr. Tanvi Agarwal	VRI Awardee
31	Dr. Vikas Sood	VRI Awardee
32	Ms. Renu	Senior Research Fellow
33	Mr. Saugata Roy	Senior Research Fellow
34	Ms. Siddhika Pareek	Senior Research Fellow
35	Dr. Ravi Verma Anbazhagan	Senior Research Fellow (P)
36	Ms. Mandeep Kumari Puran Chand	Senior Research Fellow (P)
37	Ms. Mamta Singh	Junior Research Fellow
38	Ms. Deepa Nair	Junior Research Fellow (P)
39	Ms. Saimah Raza	Junior Research Fellow (P)
40	Ms. Sharvani	Junior Research Fellow (P)
41	Mr. Rajgokul K.S.	Junior Research Fellow (P)

Scientific		
S.No.	Employee Name	Designation
42	Ms. Garima Arora	Junior Research Fellow (P)
43	Ms. Preeti Thakur	PhD Student
44	Ms. Bhavya Khullar	PhD Student
45	Ms. Minu Nain	PhD Student
46	Mr. Manish Sharma	PhD Student
47	Mr. Nishant Sharma	PhD Student
48	Ms. Rinki Kumar	PhD Student
49	Mr. Amar Pratap Singh	PhD Student
50	Mr. S. Chandru	PhD Student
51	Mr. Shayan Sarkar	PhD Student
52	Mr. Amit Bhardwaj	PhD Student

Technical		
S.No.	Employee Name	Designation
1	Mr. G. R. Agarwal	Instrumentation Engineer
2	Mr. Vishal Gupta	Sr. Technical Officer
3	Dr. Madhu Pareek	Technical Officer-I
4	Ms. Sonali P. Karmakar	Technical Officer-I
5	Mr. Saqib Kidwai	Technical Officer-I
6	Dr. Manpreet Kaur	Vaccine Technologist
7	Ms. Arpita Mishra	Assistant Vaccine Technologist
8	Mr. Sharanabasava	Assistant Vaccine Technologist
9	Ms. Taranjeet Kaur	Assistant Vaccine Technologist
10	Ms. Shilpa Chopra	Data Entry Operator
11	Mr. Mukesh Juyal	Data Entry Operator
12	Mr. Gaurav Singh	Technical Assistant
13	Mr. Uttam kumar Saini	Technical Assistant
14	Mr. Dharmendra Sharma	Programmer
15	Ms. Taruna Sharma	Programmer
16	Mr. Imran Khan	Lab-Technician
17	Mr. T.M. Rao	Lab-Technician
18	Mr. Manoj Mahato	Technician-II
19	Mr. Shri Chand Pandeya	Technician-II
20	Ms. Sonia Joshi	Data Entry Operator (P)
21	Mr. Raj Kumar Tanwar	Data Entry Operator (P)
22	Mr. Lokesh Singh Chandolia	Lab-Technician (P)
23	Mr. Ranjeet Rai	Lab-Technician (P)
24	Mr. Ashish Tyagi	Lab-Technician (P)
25	Mr. Suresh Kumar	Lab-Technician (P)
26	Mr. Vijay	Lab-Technician (P)
27	Mr. Rakesh Kumar	Lab-Technician (P)
28	Mr. Ranjeet Kumar	Technician II (P)
29	Mr. Praveen Kumar Nagar	Technician II (P)

Technical		
S.No.	Employee Name	Designation
30	Mr. Brij Mohan	Technician II (P)
31	Mr. Ashok Saini	Technician II (P)
32	Mr. Ashok Kumar	Technician II (P)
33	Mr. Dinesh Kumar	Technician II (P)
34	Ms. Deeksha Garg	Technician II (P)
35	Ms. Preeti Koli	Technical Assistant (P)
36	Mr. Ajay Kumar	Technical Assistant (P)
37	Ms. Krishna Kumari	Nurse (P)
38	Ms. Madhu Singh	Nurse (P)
39	Ms. Pooja Shishodia	Nurse (P)
40	Ms. Sujata	Nurse (P)
41	Ms. Manisha Kumari	Nurse (P)
42	Ms. Suman Rawat	Nurse (P)
43	Ms. Sherin Yohannan	Nurse (P)
44	Ms. J. Madhumalini	Nurse (P)
45	Ms. Susmita	Nurse (P)
46	Ms. M. Sumathi	Nurse (P)

Administrative		
S.No.	Employee Name	Designation
1	Mr. M.V. Santo	Administrative Officer
2	Mr. C. B. Yadav	Administrative Officer
3	Mr. J. N. Mishra	Administrative Officer
4	Mr. Mohd. Shahid	Section officer
5	Mr. Deepak Joshi	Section officer
6	Ms. Jyoti Sinha	Management Assistant
7	Mr. Rajesh Kumar	Management Assistant
8	Mr. Arif Saifi	Management Assistant (P)

STUDENTS AND RESEARCH FELLOWS

Students and Research Fellows

Students form an integral component of any vibrant academic community – youthful minds constantly probing with questions keep the faculty on their toes. Mentoring junior and senior research fellows, master's trainees and postdoctoral fellows takes many forms at THSTI. A formal session of course work takes place in the first semester of the year with courses covering a range of topics from clinical research and laboratory techniques to product development. These sessions are often interactive with student led discussion being the mainstay; students review seminal articles from leading journals in immunology and infectious diseases. Faculty from a number of universities is invited to take guest lectures during these courses. Students visit hospitals like the All India Institute of Medical Sciences to get first hand exposure of diseases and conditions they are conducting research on and to get a flavor of clinical research.

In addition, centres and divisions conduct weekly lab meetings and journal clubs that encourage students and fellows to independently review scientific literature, keep abreast of current advances as well as present their progress and solicit critical appraisal and mentorship.

Life for a student is not all work and no play – most recreation at THSTI is student led and organized with active support from the administration. The annual picnic and foundation day were put together mainly by students – conceiving games, compering the events and lending youthful exuberance. Without their constant inquiry, infectious enthusiasm and zest a day at THSTI wouldn't be nearly half as inspiring.

PhD Students and Fellows		
S.No.	Name	Position
1	Ms. Renu	Senior Research Fellow
2	Mr. Saugata Roy	Senior Research Fellow
3	Ms. Siddhika Pareek	Senior Research Fellow
4	Dr. Ravi Verma Anbazhagan	Senior Research Fellow
5	Ms. Mandeep Kumari Puran Chand	Senior Research Fellow
6	Ms. Mamta Singh	Junior Research Fellow
7	Ms. Deepa Nair	Junior Research Fellow
8	Ms. Saimah Raza	Junior Research Fellow
9	Ms. Sharvani	Junior Research Fellow
10	Mr. Rajgokul K.S.	Junior Research Fellow
11	Ms. Garima Arora	Junior Research Fellow
12	Ms. Preeti Thakur	PhD Student
13	Ms. Bhavya Khullar	PhD Student
14	Ms. Minu Nain	PhD Student
15	Mr. Manish Sharma	PhD Student
16	Mr. Nishant Sharma	PhD Student
17	Ms. Rinki Kumar	PhD Student
18	Mr. Amar Pratap Singh	PhD Student
19	Mr. S. Chandru	PhD Student
20	Mr. Shayan Sarkar	PhD Student

PROFILES OF FACULTY & SCIENTISTS

7 PROFILES OF FACULTY & SCIENTISTS

Dr. G. B. Nair

Executive Director

Dr. Balakrish Nair graduated from Madras University in 1975, gained his Masters in Marine Biology in 1977 from Annamalai University and acquired the Degree of PhD from Annamalai University in 1982 specializing in Marine Microbiology of seafood borne diarrhea pathogens. His post-doctoral research involved stints at the Department of Infectious Diseases Research, National Children's Medical Research Center, Tokyo, at the Department of Microbiology, Kyoto University, Japan, at the Department of International Health, Johns Hopkins University and at the Laboratory Centre for Disease Control, Ottawa, Canada. Dr. Nair works on enteric pathogens with particular emphasis on Vibrio cholerae, the causative agent of the disease cholera. Under his supervision, 29 students have obtained their doctoral degrees. He is the author of over 450 research papers in the area of Clinical Microbiology, Molecular Epidemiology and Molecular Pathogenesis of enteric bacteria. Dr. Nair's current interests are on the Human Microbiome with special focus on gut microbiota and microbe-based therapies.

Dr. Sudhanshu Vrati

Dean

Dr.Vrati did his M.Sc in Microbiology from G. B. Pant University of Agriculture and Technology in Pantnagar, DIIT in Biochemical Engineering from Indian Institute of Technology Delhi and PhD in Biochemistry from the Australian National University in Canberra. He did his postdoctoral research at CSIRO Molecular Sciences in Sydney. His present research interest lies in the area of RNA virus replication and vaccine development. His group at the VIDRC focuses on key aspects of the JEV life-cycle like receptor binding and entry mechanisms, molecular mechanisms of virus replication, assembly and egress. Besides, his is involved in the clinical development of an oral rotavirus vaccine.

Dr. Shinjini Bhatnagar

Professor

Professor Shinjini Bhatnagar did her MBBS from Lady Hardinge Medical College, post graduation in Pediatrics and PhD from All India Institute of Medical Sciences (AIIMS), New Delhi. As a Senior Research Scientist and Pediatric Gastroenterologist at the Centre for Diarrheal Diseases and Nutrition Research, Department of Pediatrics, AIIMS, she conducted hypothesis driven studies that evaluated interventions directed at host responses in morbidity related to infections. Her research was primarily to facilitate evidence based recommendations in child health for global and national policy; algorithm for treatment of persistent diarrhea, low osmolarity oral rehydration salts solution and zinc in treatment of diarrhea, pneumonia and serious bacterial infections. The predominant direction of current research of her group is to conduct hypothesis driven and hypothesis generating studies that will facilitate development of knowledge based interventions and public health tools for child health.The broad focus is in the domain of molecular mechanistic causality of neonatal and infant infections particularly with reference to host responses and the potential interventions. Another research focus is to develop diagnostics and low cost health products for childhood diseases. One such test that is being developed is for the diagnosis of Celiac disease.

Dr. Guruprasad R Medigeshi

Assistant Professor

Dr. Medigeshi did his M.Sc. in Biotechnology from the University of Mysore and Ph.D. from Georg-August University Goettingen in Germany where he studied protein trafficking pathways in the context of lysosomal disorders. His post-doctoral training was at the Oregon Health and Science University, Portland, USA where he investigated host-pathogen interactions in West Nile virus life-cycle. At THSTI,

his laboratory primarily focuses on the: i) biology of mosquito-borne flaviviruses with specific focus on understanding the role of host factors involved in pathogenesis and viral dissemination and ii) establishing assays for various stages of viral life-cycle for antiviral drug discovery.

Dr. Ramandeep Singh

Assistant Professor

Dr Singh did his B.Sc, M.Sc and Ph.D in Biochemistry from the Department of Biochemistry in New Delhi. He did his Postdoctoral Fellowship from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA. His work at THSTI currently involves research in the area of tuberculosis. The initial focus of his lab is to understand and validate metabolic pathways that enable mycobacteria to survive in stressful conditions that include characterisation of MazF toxins of Mycobacterium tuberculosis; identification and characterisation of biochemical pathways involved in regeneration of reduced co-factors in low-oxygen conditions; and identification of novel drug targets for M. tuberculosis.

Dr. Nisheeth Agarwal

Assistant Professor

Dr Agarwal did his M.Sc in Biotechnology from Banaras Hindu University and his Ph.D in Biochemistry from the University of Delhi. He went on to do his Postdoctoral Fellowship from the Centre for Tuberculosis Research at the Johns Hopkins University in Baltimore, USA. His present research interest lies in regulation of gene expression and pathogenesis of Mycobacterium tuberculosis, drug designing, and development of a new TB vaccine.

Dr. Amit Kumar Pandey

Assistant Professor

Dr. Pandey is a veterinarian by training. He did his bachelors in Veterinary Sciences from Orissa Veterinary College, Bhubaneswar, Orissa, and Masters in Animal Biotechnology from National Dairy Research Institute (NDRI) Karnal, Haryana. After completing his PhD from Indian Veterinary Research Institute (IVRI), Izatnagar Bareilly India, Dr Pandey did postdoctoral stints at University of Nebraska-Lincoln, Nebraska, USA and University of Massachusetts Medical School, Worcester, Massachusetts, USA. Dr. Pandey's long-term research interest is to contribute towards a better understanding of mycobacterial pathogenesis. Currently, the lab is trying to understand the regulation of cholesterol metabolism in Mycobacterium tuberculosis and its implications on mycobacterial persistence.

Dr. Krishnamohan Atmakuri

Assistant Professor

Dr. Atmakuri did his PhD in biotechnology from Madurai Kamraj University in TamilNadu followed by Postdoctoral research from the Department of Microbiology and Molecular Genetics, UT Medical School, University of Texas Health Science Centre, Houston, USA and thereafter in the Department of Immunology and Infectious Diseases, Harvard School of Public Health, Harvard University, Boston, USA. The focus of his research is on Mycobacterial pathogenesis and host-pathogen interactions. His research interest lies in the following areas-

- Understanding Mycobacterium tuberculosis-mediated pathogenesis by deciphering pathogen's artillery, their targets and host-specific functions
- Investigating Mycobacterium tuberculosis delivery systems and their exploitation for superior therapeutics and vaccine development

Dr. Milan Surjit

Assistant Professor

Dr. Surjit holds a Masters degree in Zoology from Banaras Hindu University. He did his PhD in Molecular Biology (Virology) from the International Centre for Genetic Engineering and Biotechnology in New Delhi

and Postdoctoral Research in Functional Genomics and Cancer from Strasbourg, France.

At THSTI, his research interest lies in understanding the biology of Hepatitis E virus and development of vaccine and drugs against it.

Dr. Amit Awasthi

Assistant Professor

Dr Awasthi did his M.Sc. in Biotechnology from Jiwaji University Gwalior and PhD in Immunology from National Centre for Cell Science, Pune. He did his postdoctoral training from Brigham and Women's Hospital and Harvard Medical School, Boston, MA. Dr. Awasthi was appointed as Junior faculty at Harvard Medical School, Boston, USA before he joined as Assistant Professor at Translational Health Science and Technology Institute, Gurgaon. His present research interest lies in the area of understanding the interplay between effector and regulatory T cells in IBD and gut infections.

Dr. Manjula Kalia

Research Scientist-D

Dr Kalia holds a B.Sc in Botany (Hons.) from Hindu College in Delhi University. She did her M.Sc. in Biotechnology from M.S. University.

Her interest in THSTI lies in studying host-pathogen interactions with respect to JEV and the supporting cellular mechanisms. Her research focused on the identification of JEV attachment and receptor system on neuronal and non-neuronal cells using a combination of molecular biology and proteomic strategies. The study provides insights into how viruses drive formation of endocytic vesicles by binding to their specific receptors to gain productive infection

Dr. Shailaja Sopory

Research Scientist –D

Dr. Sopory is a graduate from the Indian Institute of Science, Bangalore. She did her post-doctoral training at Oregon Health Science University, Portland. Her interest lies in the area of cellular signaling. During her post doctoral training, she looked at activation, regulation and establishment of morphogen gradient by Bone morphgenetic protein 4 (BMP4) and its drosophila ortholog, decapentaphlegic using Xenopus and Drosophila as model system. At PBC she is trying to understand the signaling pathways in the podocyte (specialized kidney epithelial cells) which are perturbed under specific conditions of injury to these cells leading to minimal change nephrotic syndrome in children. She is also involved in other projects aimed at understanding the development of the neonatal immune system and susceptibility to diseases during the early stages of life.

Dr. Santanu Mukherjee

Research Scientist-D

Dr. Mukherjee did his M. V. Sc. in Biotechnology from Indian Veterinary Research Institute, Izatnagar (U.P.), India and Ph. D from the Hebrew University of Jerusalem, Israel. His research interest lies in Virus assembly and packaging; virus-like particles based vaccine and delivery system; virus-host interactions (towards anti-viral drug development).

Dr. Arup Banerjee

Research Scientist-D

Dr Banerjee did his B.Sc in Chemistry and M.Sc in Biochemistry from the University of Calcutta in India. He did his Ph.D in Science from the Jadavpur University, also in Kolkata.

His research interest in THSTI lies in studying the role of micro RNAs in innate immune response and pathogenesis during viral infection.

Dr. Nitya Wadhwa

Research Scientist-D

(Clinical Investigator)

Dr Wadhwa is a scientist with an MD in Pediatrics. After spending a decade in clinical pediatric practice and neonatology, she joined clinical research at AIIMS where she supervised the conduct of five randomised controlled trials, one surveillance study and one study on validation of a diagnostic test. She has conducted hypothesis driven studies that evaluated interventions directed at several commonly occurring infections in children in India.

At PBC, she is a Clinical Investigator, supervising a multicentre cross-sectional study as Principal Investigator. She is involved in the preparation and implementation of a large randomised controlled trial that aims to determine efficacy of Vitamin D supplementation on vaccine responses in infants.

Dr. M.B. Appaiahgari

Research Scientist-C

Dr Appaiahgri did his M.Sc. in Virology, Shri Venkateswara University in Tirupati. He did his Ph.D from the Jamia Hamdard University, Delhi.

His current research interest in THSTI lies in the area of identification and characterisation of novel viruses for the development of gene/vaccine delivery vectors; understanding the biology of Flaviviruses; and investigating various vaccine/therapeutic approaches against medically important Flaviviruses.

Dr. Sankar Bhattacharya

Research Scientist-C

Dr. Bhattacharya did M. Sc. from the Department of Botany, University of Calcutta, West Bengal and Ph.D from the department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore, Karnataka. His research interest lies in studying host-pathogen interactions with respect to Japanese encephalitis virus.

Dr. Deepak Sharma

Research Scientist-C

Dr. Sharma did his B.Sc.(Hons.) Human Biology, M. Biotechnology and Ph.D. from All India Institute of Medical Sciences (AIIMS), one of the premier institutes in India. His research interest lies in the field of Bioinformatics wherein he would like to address diverse biologically relevant questions, such as role of small RNAs in viral pathogenesis, comprehensive analysis of metagenomic sequences, dissection of regulatory pathways/networks and ensemble motif prediction. In addition, he is also interested to use the combined arsenal of computational and molecular tools to break into the armor of M. tuberculosis.

Dr. Rohan Dhiman

Research Scientist-C

Dr. Rohan Dhiman did his B.Sc. (Hons. School) and M. Sc. (Hons. School) from deptt. of Botany, Panjab University, Chandigarh. He did his Ph.D. in cell biology and Immunology from Institute of Microbial Technology, Chandigarh wherein he studied the effect of virulent and avirulent mycobacteria on TNF-□ signaling of macrophages. He went on to do his post-doc from University of Texas Health Science Center at Tyler, Texas, USA where he studied the role of NK cells, monocyte heterogeneity and T regulatory cells in tuberculosis. His research interest in THSTI lies in studying the differential regulation of adaptive and innate immune responses by virulent and avirulent mycobacteria.

Dr. Balachandra K. Gorentla

Research Scientist-C

Dr. Balachandra K. Gorentla received PhD from department of Biochemistry & Molecular

Biology, University of North Dakota, USA. He had postdoctoral training in immune signaling & function and development of immunotherapies for food allergies from Duke University Medical Center, North Carolina, USA. His current research interests are focused towards understanding the role of vitamins in immune modulation and signal transduction mechanisms/pathways of immune system.

Dr. Ashutosh Tiwari

Research Scientist-C

Dr. Tiwari did his MSc in Biochemistry from CSJM University in Kanpur, and PhD in Biochemistry from All India Institute of Medical Sciences, New Delhi. He did his postdoctoral research in All India Institute of Medical Sciences, New Delhi and Wayne State University, Michigan, USA. His present research interest lies in the area of protein engineering technologies for designing new class of scaffolds and synthetic antibodies for therapeutics and diagnostics use. His group at the CBD focuses on generating novel antibody binders for various pathogens for improved diagnosis and effective therapy using phage display in conjunction with high-throughput screening and sequencing. He is also interested in the molecular mechanisms underlying maturation of antibody and autoantibody responses, with emphasis on somatic hyper mutation (SHM) and class switch DNA recombination (CSR) of the immunoglobulin genes in B-lymphocytes.

Dr. Niraj Kumar

Research Scientist-C

Dr. Kumar did his M.Sc. in Biotechnology from Indian Institute of Technology, Roorkee (IIT,R), Uttaranchal, India and Ph.D. in Biotechnology from National Institute for Cellular Biotechnology (NICB), Dublin, Ireland. He did his post-doctoral research at NICB and Institute of Applied Microbiology (IAM), Vienna, Austria. His primary research focus is towards Novel Biomarker Discovery and Diagnostics Development for various human diseases. He is also interested in cell line development for improved recombinant rotein production for therapeutic and/or diagnostic purposes.

Dr. Susmita Chaudhuri

Research Scientist-C

Dr. Susmita Chaudhuri did her M.Sc. in Zoology with specialization in Microbiology from Calcutta University and PhD in Microbiology from National Institute of Cholera and Enteric Diseases, Kolkata. She did her postdoctoral research in Medical Microbiology and Immunology from University of Alberta, Canada. During her stint in the biopharmaceutical industry, she worked in the R&D of Panacea Biotec Ltd. in Delhi, on therapeutic protein development. Her present research interest focuses on biomarker discovery and validation and diagnostic development for cardiovascular diseases and infectious diseases.

Dr. Uma Chandra Mouli Natchu

Ramalingaswamy Fellow

Mouli started with an MBBS and an MD in Pediatrics from the All India Institute of Medical Sciences (AIIMS). After practicing pediatrics for 3 years subsequently and spending a year doing clinical research at AIIMS, he left to the Harvard School of Public Health (HSPH) for an MPH in Quantitative Methods and research in Nutritional Epidemiology. He has worked on micronutrient supplementation for maternal and child health while at AIIMS and HSPH. His group, as part of the Pediatric Biology Centre, attempts to explore issues of nutrition in pregnancy and childhood with a multidisciplinary approach that involves fundamental biology, clinical research and public health perspectives and methods. The group currently focuses on Vitamin D as a nutrient that plays a major role in susceptibility to infectious morbidity and mortality. His group attempts to link clinical research exercises with fundamental biological experiments to efficiently nest these issues in well-executed clinical trials and cohort studies. They also conduct secondary analyses of open source data or from collaborators to generate or 'test' hypotheses in the area of nutrition that can be further explored by other approaches.

STAFF WELFARE

8 STAFF WELFARE

THSTI accords staff development and employee welfare as valuable tenets in its evolution process. An equal opportunity employer, it does not discriminate on grounds of age, gender, colour, race, ethnicity, language, caste, creed, economic or social status or disability.

Providing ample freedom to its researchers, it respects the need for individual space. From having a well designed physical environment to a straight-forward linear organisational structure, team leaders and departmental heads are easily accessible.

The Institute also has a sensitive Complaints Committee that looks into any issues that employees may have, relating to sexual harassment, discrimination, exploitation or any other problem.

While still in its nascent stage, the Human Resource Team is trying to create a fair opportunity for leisure, fun and informal activity amongst teams, across departments and with families, to ensure more intermixing as also to create a greater sense of belonging to the organisation.

Taking out time from its scientific routine, the Institute organised a family get together with all faculty, scientists, officers and staff on 29th January 2012. The employees of the Regional Centre for Biotechnology also joined the function with their family members. The function was held in a lush green farm house in Bijwasan, New Delhi. The transport facilities from different pick-up points were arranged to facilitate people reaching the site.

Families intermingled and children particularly had a wonderful time participating in activities like cricket, volleyball, basketball, lawn-tennis, musical chairs and, drawing competitions. There were games for adults too. Apart from a sumptuous meal, there were exciting prizes to be won.

FINANCIAL STATEMENTS

9 FINANCIAL STATEMENTS

9.1 AUDITOR'S REPORT

We have audited the attached Balance Sheet of Translational Health Science and Technology Institute, 496, Udyog Vihar Phase-III, Gurgaon - 122016 as on 31st March 2012. The annexed Income and Expenditure Account and Receipts and Payments Account for the year ended on that date with the books of accounts and vouchers maintained by the Institute and report is as under:

1. That the Institute's Balance Sheet, Income and Expenditure Account & Receipt and Payment Account are in agreement with the books of accounts.

2. We conducted our audit in accordance with auditing standards generally accepted in India. Those Standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amount and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by the management, as well as evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

3. Subject to Accounting Policies and Notes on Accounts as per Schedule-24, in our opinion and to the best of our information and according to the explanations given to us, the said accounts give a true and fair view:

i) In the case of Balance Sheet of the State of Affairs of the Institute as at 31st March, 2012

ii) In the case of Income and Expenditure Account of the excess of Expenditure over Income during the ended on that date.

For Mehra & Sistani

Chartered Accountants

(Sanjiv Rai Mehra)

Partner

Membership No. 80402

Firm Regn. No.000409N

Place: New Delhi

Date: 27th September 2012

TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE

BALANCE SHEET AS AT 31ST MARCH, 2012

Amount (In Rs.)

LIABILITIES	**Schedule**	**Current Year**	**Previous Year**
Corpus / Capital Fund	1	513,529,291	72,713,417
Reserves and Surplus	2	114,586,598	19,940,066
Earmarked/Endowment Funds	3	-	-
Secured Loans and Borrowings	4	-	-
Unsecured Loans and Borrowings	5	-	-
Deferred Credit Liabilities	6	-	-
Current Liabilities and Provisions	7	73,687,955	76,429,061
TOTAL		**701,803,844**	**169,082,544**
ASSETS			
Fixed Assets	8	588,245,045	14,196,580
Investment From Earmarked/Endowment Funds	9	-	-
Investment - Others	10	-	-
Current Assets. Loans, Advances etc.	11	113,558,799	154,885,964
Miscellaneous Expenditure (to the extent not written off or adjusted)		-	-
TOTAL		**701,803,844**	**169,082,544**
SIGNIFICANT ACCOUNTING POLICIES AND NOTES ON ACCOUNTS	24		
CONTINGENT LIABILITIES	-		

Schedules 1 to 24 form an integral parts of Accounts

As per our separate Report
of even date attached
For Mehra & Sistani
Chartered Accountants

C. B. YADAV	**DR. SUDHANSHU VRATI**	**Dr.G.B. NAIR**	**SANJIV RAI MEHRA**
(ADMINISTRATIVE OFFICER-F&A)	**(DEAN)**	**(EXCECUTIVE DIRECTOR)**	**(PARTNER)**
			M No.80402

Place: Gurgaon

Date: 24/09/2012

TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE

INCOME AND EXPENDITURE ACCOUNT FOR THE YEAR ENDED 31st MARCH, 2012

Amount (in Rs.)

INCOME	**Schedule**	**Current Year**	**Previous Year**
Income from Sales/ Services	12	-	-
Grants/Subsides	13	38,403,000	71,784,835
Fees/Subscriptions	14	-	-
Income from Investments	15	-	-
Income from Royalty, Publication etc.	16	-	-
Interest Earned	17	12,059,730	1,163,950
Other Income	18	4,646,282	77,996
Increase/(Decrease) in stock of Finished goods and works in progress	19	-	-
Deferred Income-Fixed Assets		48,932,359	3,207,111
TOTAL (A)		**104,041,371**	**76,233,892**
EXPENDITURE			
Establishment Expenses	20	16,785,016	11,950,060
Other Administrative Expenses etc.	21	41,865,136	41,136,655
Expenditure on Grants , Subsidies etc.	22	-	-
Interest	23	-	-
Depreciation (Net Total at the year-end-corresponding to Schedule 8)		48,932,359	3,207,111
Prior period Adjustment A/c (ANN-A)		-	-
TOTAL(B)		**107,582,511**	**56,293,826**
Balance being excess of Expenditure Over Income (A-B)		**(3,541,140)**	**19,940,066**
Transfer to special Reserve(Specify each)		-	-
Transfer to /from General Reserve		(3,541,140)	19,940,066
BALANCE BEING SURPLUS (DEFICIT) CARRIED TO CORPUS/CAPITAL FUND		**-**	**-**
SIGNIFICANT ACCOUNTING POLICIES AND NOTES ON ACCOUNTS	24		
CONTINGENT LIABILITIES	-		

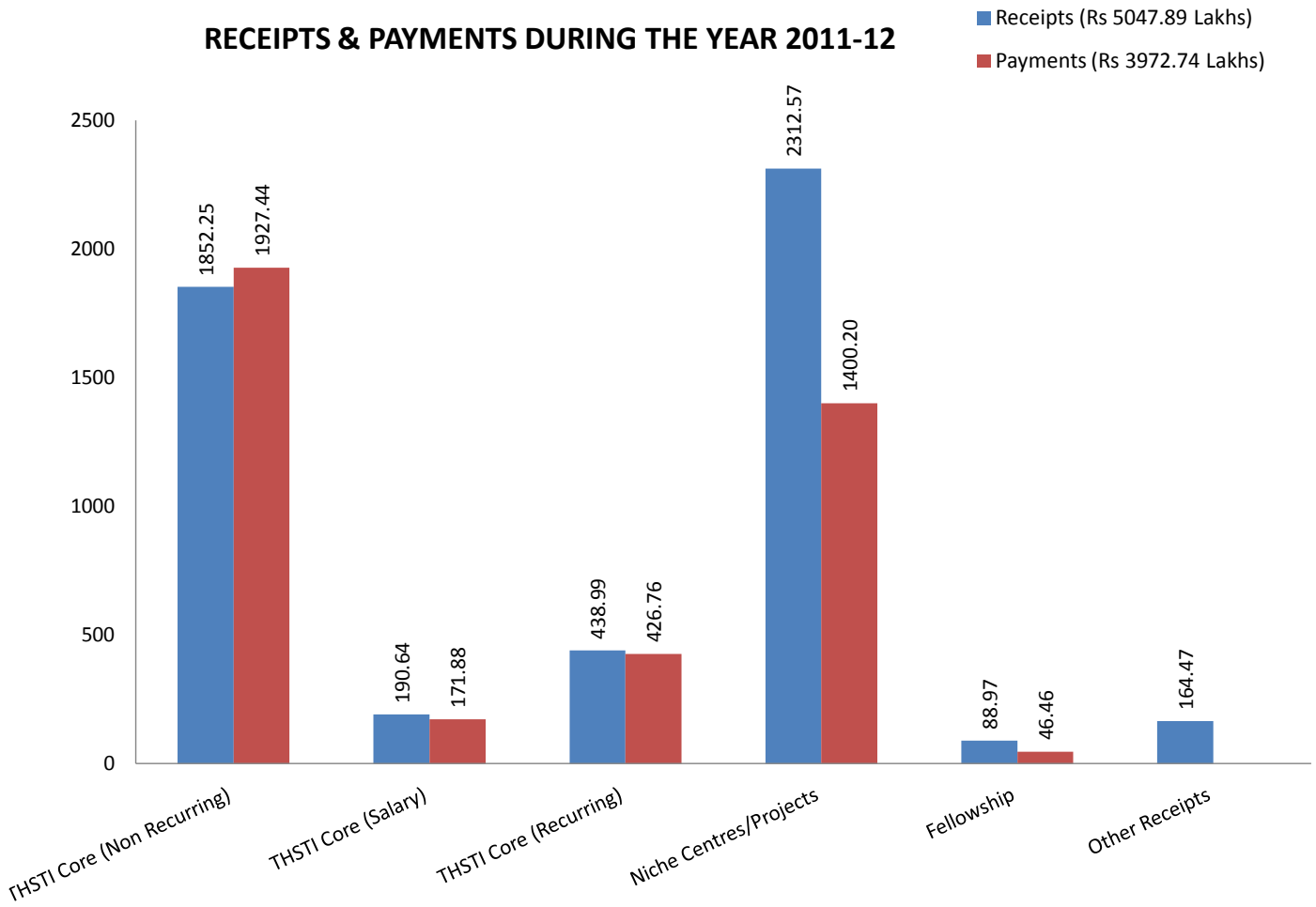
Schedules 1 to 24 form an integral parts of Accounts

As per our separate Report of even date attached
For Mehra & Sistani
Chartered Accountants

C. B. YADAV	**DR. SUDHANSHU VRATI**	**Dr.G.B. NAIR**	**SANJIV RAI MEHRA**
(ADMINISTRATIVE OFFICER-F&A)	**(DEAN)**	**(EXCECUTIVE DIRECTOR)**	**(PARTNER)**

Place: Gurgaon

Date: 24/09/2012


RECEIPTS & PAYMENTS DURING THE YEAR 2011-12
Receipts (Rs 5047.89 Lakhs)
Payments (Rs 3972.74 Lakhs)
2500
2000
1500
1000
500
0
1852.25
1927.44
190.64
171.88
438.99
426.76
2312.57
1400.20
88.97
46.46
164.47
THSTI Core (Non Recurring)
THSTI Core (Salary)
THSTI Core (Recurring)
Niche Centres/Projects
Fellowship
Other Receipts

9.2 AUDITOR'S REPORT

We have audited the attached Balance Sheet of the Clinical Development Service Agency, 470, Udyog Vihar Phase-III, Gurgaon - 122016 as on 31st March 2012. The annexed Income and Expenditure Account and Receipts and Payments Account (AABAC 0442Q) for the year ended on that date with the books of accounts and vouchers maintained by the Institute and report are as under:

1. That the Institute's Balance Sheet, Income and Expenditure Account & Receipt and Payment Account are in agreement with the books of accounts.

2. We conducted our audit in accordance with auditing standards generally accepted in India. Those Standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amount and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by the management, as well as evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

3. Subject to Accounting Policies and Notes on Account as per Schedule-24, in our opinion and to the best of our information and according to the explanations given to us, the said accounts give a true and fair view:

i) In the case of Balance Sheet of the State of Affairs of the Institute as at 31st March, 2012

ii) In the case of Income and Expenditure Account of the excess of Income over expenditure during the ended on that date.

For Mehra & Sistani

Chartered Accountants

(Sanjiv Rai Mehra)

Partner

Membership No. 80402

Firm Regn. No.000409N

Place: New Delhi

Date: 27th September, 2012

CLINICAL DEVELOPMENT SERVICES AGENCY

BALANCE SHEET AS AT 31ST MARCH, 2012

Amount (In Rs.)

LIABILITIES	**Schedule**	**Current Year**	**Previous Year**
Corpus / Capital Fund	1	15,108,158	
Reserves and Surplus	2	(8,556,831)	
Earmarked/Endowment Funds	3	-	
Secured Loans and Borrowings	4	-	
Unsecured Loans and Borrowings	5	-	
Deferred Credit Liabilities	6	-	
Current Liabilities and Provisions	7	2,012,559	
TOTAL		**8,563,886**	
ASSETS			
Fixed Assets	8	2,739,963	
Investment From Earmarked/Endowment Funds	9	-	
Investment - Others	10	-	
Current Assets. Loans, Advances etc.	11	5,823,923	
Miscellaneous Expenditure (to the extent not written off or adjusted)		-	
TOTAL		**8,563,886**	
SIGNIFICANT ACCOUNTING POLICIES AND NOTES ON ACCOUNTS	24		
CONTINGENT LIABILITIES	-		

Schedules 1 to 24 form an integral parts of Accounts

-

As per our separate Repo
of even date attached
For Mehra & Sistani
Chartered Accountants

M.V. SANTO	**DR. HARMEET SIDHU**	**DR. G.B. NAIR**	**SANJIV RAI MEHRA**
(AO-P&A)	**(PROGRAM DIRECTOR)**	**(EXECUTIVE DIRECTOR)**	**(PARTNER)**

Place: Gurgaon

Date: 24/09/2012

CLINICAL DEVELOPMENT SERVICES AGENCY

INCOME AND EXPENDITURE ACCOUNT
FOR THE YEAR ENDED 31st MARCH, 2012

Amount (in Rs.)

INCOME	**Schedule**	**Current Year**	**Previous Year**
Income from Sales/ Services	12	-	-
Grants/Subsides	13	3,443,000	-
Fees/Subscriptions	14	-	-
Income from Investments	15	-	-
Income from Royality,Publication etc.	16	-	-
Interest Earned	17	37,876	-
Other Income	18	9,000	-
Increase/(Decrease) in stock of Finished goods and works in progress	19	-	-
Deferred Income-Fixed Assets		393,032	
TOTAL (A)		**3,882,908**	**-**
EXPENDITURE			
Establishment Expenses	20	3,957,740	-
Other Administrative Expenses etc.	21	8,088,967	-
Expenditure on Grants , Subsidies etc.	22	-	-
Interest	23	-	-
Depreciation (Net Total at the year-end-corresponding to Schedule 8)		393,032	-
Prior period Adjustment A/c (ANN-A)		-	
TOTAL(B)		**12,439,739**	**-**
Balance being excess of Expenditure Over Income(A-B)		**(8,556,831)**	**-**
Transfer to special Reserve(Specify each)		-	-
Transfer to /from General Reserve		**(8,556,831)**	-
CORPUS/CAPITAL FUND		**-**	**-**
SIGNIFICANT ACCOUNTING POLICIES AND NOTES ON ACCOUNTS	24		
CONTINGENT LIABILITIES	-		

Schedules 1 to 24 form an integral parts of Accounts

As per our separate Report of even date attached
For Mehra & Sistani
Chartered Accountants

M.V. SANTO	**DR. HARMEET SIDHU**	**DR. G.B. NAIR**	**SANJIV RAI MEHRA**
(AO-P&A)	**(PROGRAM DIRECTOR)**	**(EXECUTIVE DIRECTOR)**	**(PARTNER)**

Place: Gurgaon

Date: 24/09/2012

INTERIM THSTI LABS

INTERIM THSTI LABS

THSTI's upcoming campus in Faridabad

Translational Health Science and Technology Institute

Plot No. 496, Udyog Vihar, Phase-III, Gurgaon - 122016, Haryana, INDIA

Phone: 0124-2876300 Email: info@thsti.res.in

Designed & Produced by Communicators India