ट्रांसलेशनल स्वास्थ्य विज्ञान
एवं प्रौद्योगिकी संस्थान

TRANSLATIONAL HEALTH SCIENCE
AND TECHNOLOGY INSTITUTE

ANNUAL REPORT

2013 - 2014

Our Mission

By integrating the fields of medicine, science, engineering and technology into translational knowledge and making the resulting biomedical innovations accessible to public health, to improve the health of the most disadvantaged people in India and throughout the world.

Contents

THE ORGANIZATION
- Society
- Governing Body
- Leadership
- From the Executive Director's Desk

RESEARCH PROGRAMS
- Flagship Programs
  - Discovery Programs
  - Early Translational programs
  - Late Translational Programs
- Investigator Driven Research Projects
- Profiles of Research Investigators & Programme Officers

ACADEMIA

PARTNERSHIP & EXTRAMURAL CENTERS

ORGANIZATIONAL SUPPORT SYSTEM

ACHIEVEMENTS
- Extramural Grants
- Publications
- Patents and Technology Transfer
- Awards and Recognitions
- Students' Achievements

THSTI AT SCIENTIFIC EVENTS

SEMINARS

EVENTS

DELEGATIONS

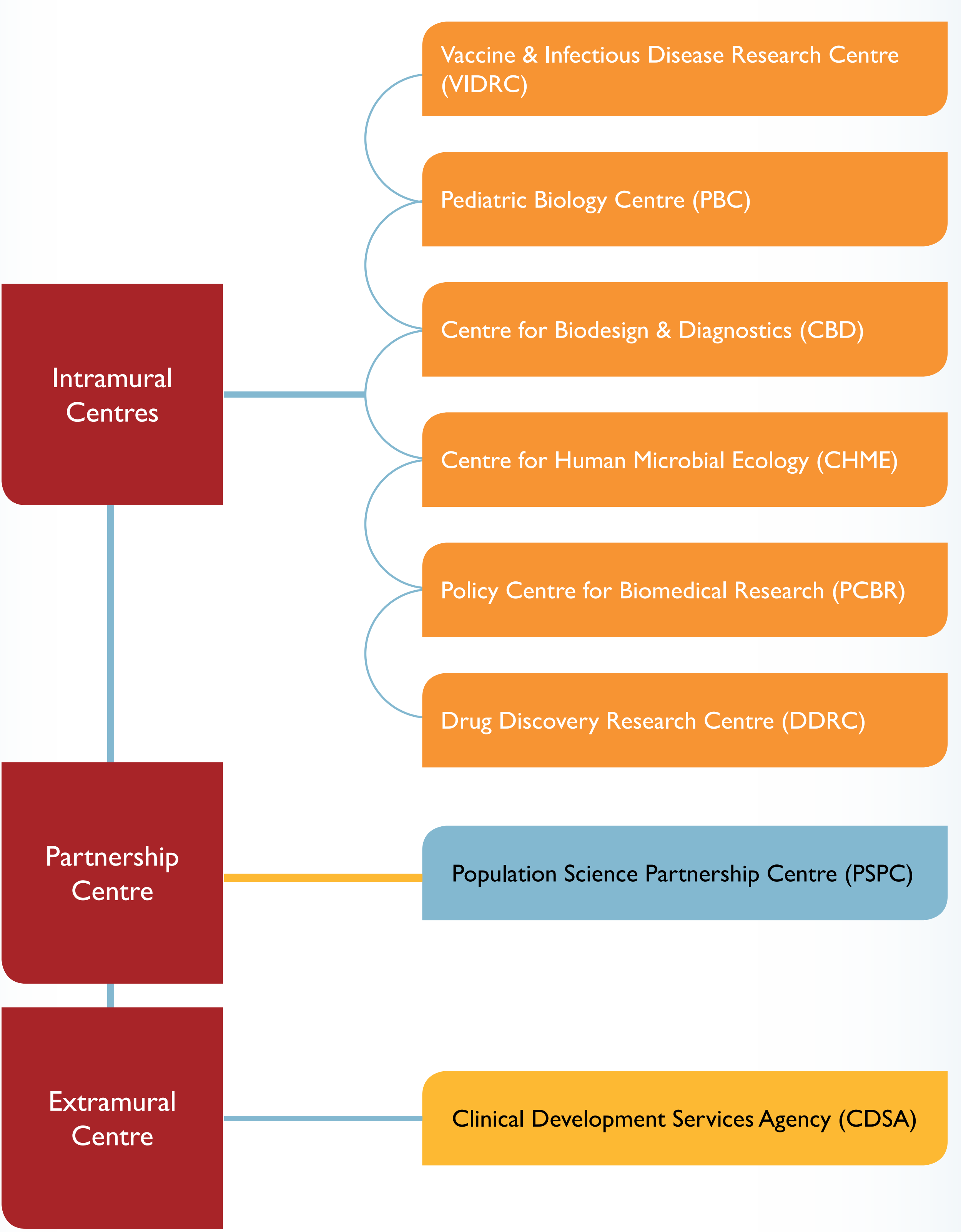
HUMAN RESOURCE

THSTI ADMINISTRATION

THSTI SOCIALS

The Organization

ORGANOGRAM



Our new campus at Faridabad

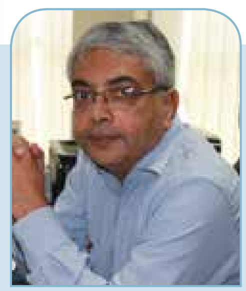
THSTI Society

Dr. G. Padmanaban	**Distinguished Professor, IISc Bangalore**	**President**
Dr. K. VijayRaghavan	Secretary, Department of Biotechnology Govt. of India, New Delhi	Member Ex-officio
Dr. V.M. Katoch	Secretary, DHR and DG ICMR, New Delhi	Member Ex-officio
Mrs. Anuradha Mitra	Joint Secretary and Financial Advisor, Department of Biotechnology, New Delhi	Member Ex-officio
Dr. T.S. Rao	Nodal Officer, THSTI, Sr. Advisor, Department of Biotechnology, New Delhi	Member Ex-officio
Dr. Chandrima Shaha	Director, National Institute of Immunology, New Delhi	Member Ex-officio
Dr. M. Radhakrishna Pillai	Director, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram	Member
Dr. Ashok Jhunjhunwala	Professor, Indian Institute of Technology, Chennai	Member
Dr. J. Gowrishankar	Director, Centre for DNA Fingerprinting & Diagnostics, Hyderabad	Member
Dr. B. Ravindran	Director, Institute of Life Sciences, Bhubaneshwar	Member
Dr. G.C. Mishra	Eminent Scientist, National Centre for Cell Sciences Pune	Member
Dr. G.B. Nair	Executive Director, Translational Health Science and Technology Institute, Gurgaon	Member-Secretary

THSTI Governing Body

Dr. K. VijayRaghavan	Secretary, Department of Biotechnology, Government of India, New Delhi	Chairperson
Dr. V.M. Katoch	Secretary, Department of Health Research & Director General ICMR, New Delhi	Member
Dr. Dinakar M. Salunke	Executive Director, Regional Centre of Biotechnology, Gurgaon	Member
Dr. Subrata Sinha	Director, National Brain Research Centre, Manesar, Gurgaon	Member
Dr. G. Padmanaban	Distinguished Professor, Indian Institute of Science, Bangalore	Member
Dr. P. N. Tandon	President, National Brain Research Centre, Manesar, Gurgaon	Member
Dr. T. S. Balganesh	Distinguished Scientist and Head of OSDD, CSIR, New Delhi	Member
Dr. Balram Bhargava	Professor, All India Institute of Member Medical Sciences, New Delhi	Member
Dr. K. Srinath Reddy	President, Public Health Foundation of India, New Delhi	Member
Dr. M.S. Ananth	Ex-Director, Indian Institute of Technology, Chennai	Member
Dr. Ashutosh Sharma	Institute Chair, Professor, Indian Institute of Technology, Kanpur	Member
Dr. T.S. Rao	Nodal Officer, THSTI, Sr. Advisor, Department of Biotechnology, Government of India, New Delhi	Member
Mrs. Anuradha Mitra	Joint Secretary and Financial Advisor, Department of Biotechnology, Government of India, New Delhi	Member
Dr. Shinjini Bhatnagar	Dean, Clinical Research, Translational Health Science & Technology Institute, Gurgaon	Member
Dr. Sudhanshu Vrati	Dean, Academics, Translational Health Science and Technology Institute, Gurgaon	Member
Dr. G.B. Nair	Executive Director, Translational Health Science and Technology Institute, Grugaon	Member-Secretary

THSTI Leadership

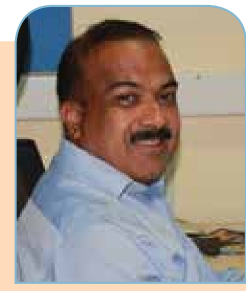


G. Balakrish Nair is the Executive Director of THSTI. His prior assignment, spanning over two decades, was at the National Institute of Cholera and Enteric Diseases (NICED), Kolkata, culminating as the Institute's Director. The tenure at NICED was bridged with a seven year stint as Director, Laboratory Sciences Division, International Centre for Diarrhoeal Diseases Research, Dhaka, Bangladesh. His contributions to the discovery of *Vibrio cholerae* O139 Bengal, earned him the prestigious Shanti Swarup Bhatnagar award for Medical Sciences in 1998. In his role as the head of the organization, he has brought a unique culture of gentle reshaping of scientific minds towards translational research at THSTI. He also leads the Centre for Human Microbial Ecology at THSTI.

Dr. Sudhanshu Vrati is the Dean of Academics at THSTI. Previous to working at THSTI, he was a Senior Scientist at the National Institute of Immunology. In his capacity as the Dean, Academics at THSTI, he is instrumental in initiating collaboration with the Jawaharlal Nehru University for affiliation of THSTI's Ph.D. program and designing the academic curricula in the institute. He also leads the Vaccine and Infectious Disease Research Centre at THSTI.

Professor Shinjini Bhatnagar is the Dean of Clinical Research at THSTI. She served as Senior Research Scientist and Pediatric Gastroenterologist at the Department of Pediatrics, AIIMS. She is the Head of Pediatric Biology Centre and also the co-ordinator of Centre for Biodesign and Diagnostics and the National Biodesign Alliance. In her role as the Clinical research Dean, she has brought in an innovative approach of amalgamating clinical research into biological sciences to enhance translational capacity of THSTI.

Dr. Kanury Rao is the Head of Drug Discovery research Centre at THSTI. He is a faculty in the International Centre for Genetic Engineering and Biotechnology (ICGEB). A Fellow of several academies, Dr. Rao was awarded The Shanti Swarup Bhatnagar Award for Biological Sciences, in 1997. As an Adjunct Faculty in THSTI and the head of a focused product and pipeline development team of scientists, he leads the major drug discovery research program at THSTI.



Dr. Sudhakar Bangera joined CDSA with experience of 21 years in diverse areas of healthcare (Hospitals and Medical Schools), global Contract Research Organisations (CRO), Academic Research Organisation (ARO), Site Management Organisation (SMO), Medical Imaging, Clinical Bioavailability and Bioequivalence (BA-BE), and a global pharmaceutical company. He is a multifaceted, dynamic healthcare and clinical research professional leading the CDSA team at THSTI.

Mr. M.V. Santo, is a HR and IR professional with a substantial blend of public and private enterprise experience. A specialist in organization building, his contributions to THSTI are in the multiple facets of administrative functions. He has built a team which contributes significantly to ensure seamless support to all aspects of scientific and academic activities at the Institute.

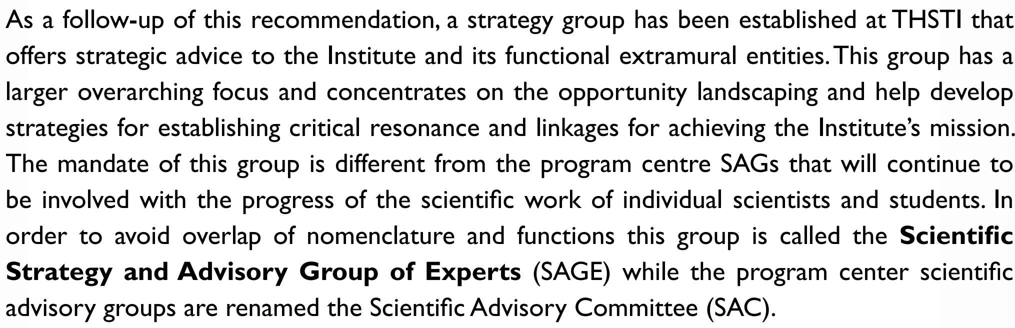
Scientific Strategy and Advisory Group of Experts (SAGE)

Background

In the THSTI Society Memorandum of Association and its Rules and Regulations a "Scientific Advisory Committee"was envisaged "to guide the development of scientific and technical programmes of the Institute, review them periodically and take further course of action as would be deemed fit for furthering the scientific and technological research and other functions of the Institute". This was to be in addition to the centre-based, narrow-focussed Technical Advisory Groups (TAGs) that are currently known as centre-based Scientific Advisory Groups (SAGs).

The THSTI Governing Body in its meeting held on July 31, 2012 recommended that a THSTI Scientific Strategy and Advisory Council should be formed to evolve and periodically review the national and the international scientific program of THSTI with particular focus on innovation, multidisciplinary and translational aspects. The council will look at the bigger picture for the future of THSTI including its extramural centres (e.g. CDSA, partnership centres and medical links). The need for a strategic body, as originally envisaged, is becoming obvious as programs and linkages have expanded at THSTI during the last couple of years and many barriers are coming up to achieving our mission.

Prof. M.K. Bhan

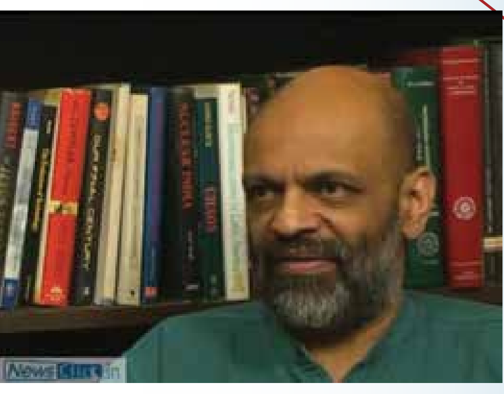


As a follow-up of this recommendation, a strategy group has been established at THSTI that offers strategic advice to the Institute and its functional extramural entities. This group has a larger overarching focus and concentrates on the opportunity landscaping and help develop strategies for establishing critical resonance and linkages for achieving the Institute's mission. The mandate of this group is different from the program centre SAGs that will continue to be involved with the progress of the scientific work of individual scientists and students. In order to avoid overlap of nomenclature and functions this group is called the **Scientific Strategy and Advisory Group of Experts** (SAGE) while the program center scientific advisory groups are renamed the Scientific Advisory Committee (SAC).

The specific functions of SAGE

- Advice on new multidisciplinary programs that will connect scientific disciplines with medicine, health and engineering.
- Advice on establishment of platforms for the creation of transformative biotech tools.
- Help develop instruments for the Institute's leadership for idea generation, idea filtration, resource for new translational programs, novel education, measurement of matrices for process relevant to translation, research and translational resources, mission program design and delivery.
- Advise on addressing barriers and provide tactical strategy on how to overcome these.
- Develop the strategy to help connect the Institute as a whole with other entities nationally and internationally and maximize output of such linkages at the Institute level.
- Advice on networking strategies with hospitals, public health, and industry.
- Critically review and guide the mission of CDSA from a strategy perspective and help develop measurement of progress matrix.
- Develop a strategy for mobilizing non-DBT resources.
- Advise on cluster development, and inter-cluster institutional and centre linkages with regards to THSTI mission.

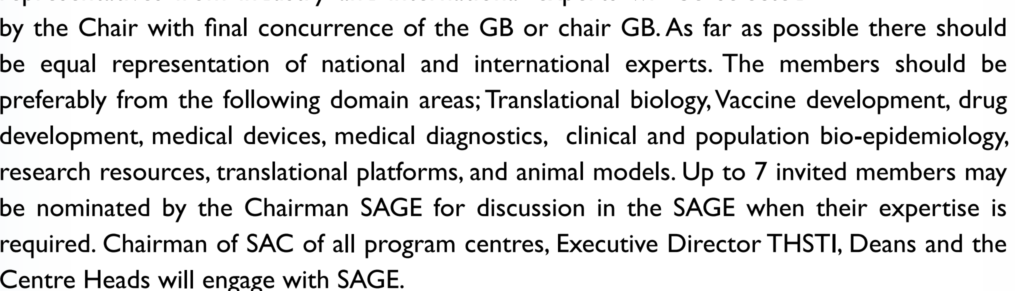
- Advice on educational programs that will be specific to THSTI such as the Master's in Clinical and Translational Science.
- Any other issues around strategy, relevant to the THSTI mission.



Dr. Satyajit Rath

Constitution

SAGE should be chaired by a renowned and distinguished scientist in area of development, optimization and evaluation of technologies for public health and interdisciplinary research for translation of technologies for public health. He/she will be nominated by the THSTI Governing Body (GB). Up to six distinguished Scientists/ Medical Biotechnologists including representatives from industry and international experts will be selected by the Chair with final concurrence of the GB or chair GB. As far as possible there should be equal representation of national and international experts. The members should be preferably from the following domain areas; Translational biology, Vaccine development, drug development, medical devices, medical diagnostics, clinical and population bio-epidemiology, research resources, translational platforms, and animal models. Up to 7 invited members may be nominated by the Chairman SAGE for discussion in the SAGE when their expertise is required. Chairman of SAC of all program centres, Executive Director THSTI, Deans and the Centre Heads will engage with SAGE.



Presently, Prof. M.K. Bhan is the SAGE Chairman at THSTI and Dr. Satyajit Rath is also a member reviewing research programmes and contributing to SAGE recommendations.

The SAGE is a purely advisory body; In general it will not make any administrative recommendations but will focus on strategies to increase likelihood of achieving the mission of THSTI. The SAGE recommendations will be made to the THSTI leadership and the GB.

Feedback to THSTI GB

SAGE gives a technical report to the GB after each SAGE meeting and interacts with the GB members at least once in a year.

OUR AUGMENTED STRENGTH

Chair & Honorary Faculty

Biotechnology Chair

Prof. John David Clemens
Executive Director
International Centre for Diarrhoeal Disease Research
Dhaka, Bangladesh

Visiting Professor of Eminence

Prof. N. K. Ganguly

Honorary International Visiting Faculty

Dr. Madhukar Pai, MD, PhD
Associate Professor, McGill University
Associate Director, McGill International TB Centre.

Adjunct Faculty / Honorary Visiting Professor

Dr. Satyajit Rath
Sr. Scientist, National Institute of Immunology

Dr. Vineeta Bal
Sr. Scientist, National Institute of Immunology

Prof. Anil K. Tyagi
Vice Chancellor, Indraprasth University

Dr. Navin Khanna
Group Leader, ICGEB

Dr. Kanury Venkata Subba Rao
Head-DDRC

Dr. Nita Bhandari
Jt. Director, CHRD-SAS

Dr. Amit Sharma
Group Leader, ICGEB

Dr. Jaya Sivaswami Tyagi
Professor, Department of Biotechnology
All India Institute of Medical Sciences

Major International Collaborations

Indo-Finnish Collaboration

The goal of the Indo-Finnish Diagnostic Research Centre (IFDRC) is to complement and enhance the research capabilities of its Indian and Finnish scientific networks from academia and industry in the area of diagnostics. Through the IFDRC, the intention is to stimulate the exchange of both junior and advanced students and researchers between the countries around common collaborative endeavors and research topics. To create a sizable pool of researchers who specialize in development of diagnostics in India, the Department of Biotechnology has instituted five postdoctoral fellowships in the field of diagnostics for training in various Finnish Institutes for a period of two years.

Indo-Japanese Collaboration

Translational Health Science and Technology Institute and Osaka University mutual Ph.D. program in Biomedical Science at the Graduate School of Medicine, Osaka University, Japan

Translational health science and technology institute (THSTI) and Osaka University, Japan are jointly conducting interview to select bright Indian students for Ph.D. program at Osaka University, Japan under interdisciplinary program for biomedical sciences (IPBS). The program was initiated in the academic year 2013. In last two years four students were selected for the Ph.D. program. Details of the program, selection procedure, and schedule are published in THSTI official website as well as national newspapers in each year. Since its inception in 2013, the program is being coordinated by Dr. Bhabatosh Das, Assistant Professor, THSTI.

Indo-Norwagian Collaboration

There is a long standing partnership between scientists from Centre for International Health (CHN-CIH) University of Bergen and the investigators at PBC, THSTI. They are now a part of a consortium called 'Centre for Intervention Science in Maternal and Child Health' (CISMAC), which is being funded by the Research Council of Norway. It represents a unique opportunity for interaction between the Centre for International Health (CIH) at the University of Bergen (UiB), the Norwegian Institute of Public Health (NIPH), and the Christian Michelsen Institute (CMI), and the Society for Applied Studies (SAS) in India, and 6 other LMIC institutions, and the World Health Organization's Department of Maternal, Newborn, Child and Adolescent Health (MCA). This convergence of competencies will foster integrated approaches to measure the impact of biomedical, nutritional, educational, behavioral and health systems interventions addressing the continuum of MNCH care from preconception, pregnancy, during labor and childbirth, in the postnatal period, during infancy and into early childhood. We have also recently been awarded a grant from the Research Council of Norway for doing a large multisite muticountry randomised controlled study to see the efficacy of zinc given as an adjunct for the treatment of very severe disease in infants younger than 2 months. This study will be done in collaboration with the Tribhuvan University Nepal, Centre for International Health (CIH) at the University of Bergen (UiB), and Stanford University School of Medicine.

From the Executive Director's Desk

Milestones and Mind-sets

THSTI has reached an important milestone this year. Our first of the six Centres, the Vaccine and Infectious Diseases Research Centre (VIDRC), was externally reviewed after completion of five years starting 2009. It must be emphasized that THSTI became functional only in late 2010 after the interim infrastructure in Gurgaon was set in place. Milestones are good intervals to measure our progress and performance. Instead of cataloguing our achievements, I will review the year's bygone in an introspective way and recount how we are gently reshaping the Institute. An important guiding principle at THSTI has been to create an ambiance that will foster the creative space of our colleagues. So instead of haranguing them with accomplishing translational science we have allowed the concept to permeate and I am pleased to see that a silent but certain change in mind-sets is pervading.

How are we novel is a question often asked? We are novel by our mandate in being translational, in taking a holistic approach to viable health solutions and in seeking multi-disciplinary collaborative research efforts. As an Organization we are different in assembly and our research programs span targeted discovery and focused translation. Our Academic programs are being crafted to prepare young minds to absorb the complexities of translational science in the health arena. We nurture our new faculty by giving freedom to develop independent programs and yet provide a platform to plug-in to large multi-disciplinary programs. Our faculty and scientists are multidisciplinary and we have augmented our academic and research strengths by a blend of distinguished visiting and adjunct Scientists and national and international Chairs. Uniquely, the Institute is being mentored by SAGE, an acronym for the Scientific Advisory Group of Experts, chaired by Dr. M.K. Bhan that gives direction and overall guidance to the Institute and acts as an external oversight to the developments at the Institute.

Large multidisciplinary research programs embedded in health problems of India are the direction we have taken. The Multidisciplinary Program on Preterm birth nested in the Pediatric Biology Centre (PBC) that you will find described in this annual report is our first foray. The scale is mind-boggling. Pediatricians, Gynecologists, Epidemiologists, Biostatisticians, Molecular Biologists, Geneticists, Microbiologists, Protein Chemists, Biochemists and Computational analysts from within and from different institutions have got together to craft this program. At the site, 75 research staff will help to enroll 8000 women, screen 20,000 mothers, perform 25,000 ultrasounds and analyze 150,000 clinical samples. Another model of collaboration well in place is the "plug-in" model. One such program is ongoing at the Population Science Partnership Centre where colleagues from the Centre for Human Microbial Ecology are commissioning their microbiome skills in an attempt to answer questions that have arisen during an interventional trial on severe acute malnutrition in children. A third model, which I believe is happening, is where discovery driven projects are coalescing their individual expertise into a research program on Tuberculosis. Therefore given the ambience and an inclination, team based research programs are happening catalyzed by the environment. There are several challenges and there are that many numbers of limitations when embarking into programmes of this scale and dimension but that is something we are bracing ourselves to resolve.

Focused early translational programs with teams of diverse domain experts working towards the same goal are ongoing. For example in the Drug Discovery Research Centre, a group of Scientists are working together towards identifying drugs with a focus on metabolic diseases. Likewise, using the same philosophy, Scientists at the HIV Vaccine Translational Research laboratory (in collaboration with the International AIDS Vaccine Initiative) are working towards identifying candidate immunogens against HIV-1 using high-throughput vaccine design, screening and selection processes. An example of a successful late translation study is where VIDRC has partnered with the Society for Applied Studies (SAS), New Delhi for the clinical development of rotavirus 116E vaccine. While SAS was responsible for managing all clinical and field studies, VIDRC provided validated lab assays to establish the vaccine safety, efficacy and rotavirus shedding in the stools of children receiving the vaccine. THSTI in this way is a multi-modeled organization and the future will show what works and what does not.

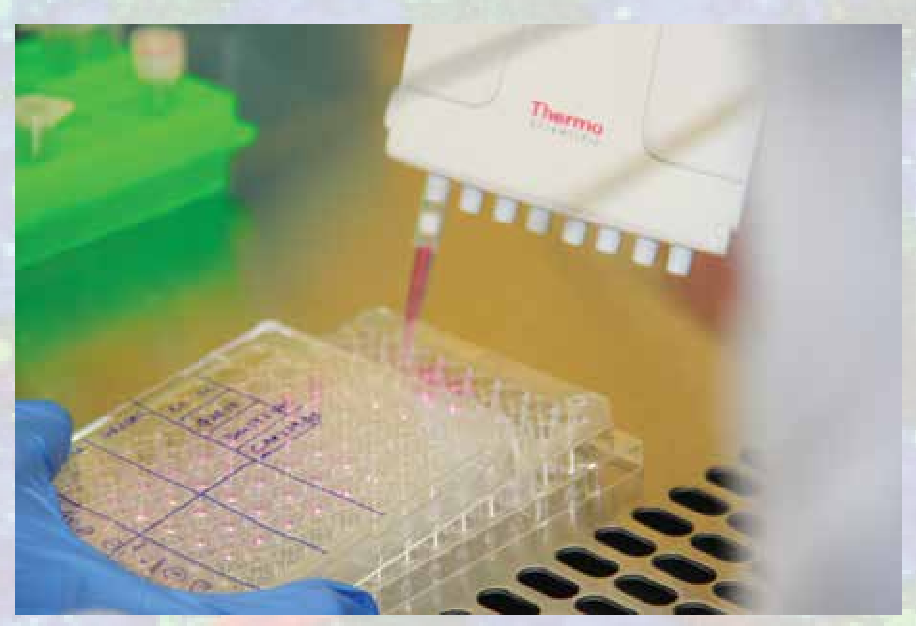
The Centre for Biodesign received a shot in the arm this year by the recruitment of a Mechanical Engineer. The CBD is involved in user inspired identification of problems, prototype and product development, clinical development and commercialization. The Policy Centre for Biomedical Research plays an important role for imparting information on identification of problems amongst its other multifarious portfolios. An alternate approach towards healthcare innovation at THSTI is Clinical and Social Immersion. CBD and PBC have initiated a program in the domain of Maternal and Child Health. The CDSA is now entrenched in monitoring of public health trails for GCP and regulatory compliance and is facilitating training of Scientists and physicians in ethics.

We are novel by our mandate in being translational, in taking a holistic approach to viable health solutions and in seeking multi-disciplinary research collaborations.

Large multidisciplinary research programs embedded in health problems of India are the direction we have taken.

There is still multitude of things to be done to complete the incomplete. There are not many Institutes, which have so early in life taken these challenging steps. We have developed unique access to the General Hospital Gurgaon, set up ethics committees, done collaborative clinical research and in return augmented their clinical services. The support systems of translational science like the Animal facility, platform technologies, data management for large cohort studies, imaging systems and technology business incubators are in various stages of completion. Much of the work to establish these support systems is well underway.

We recognize ourselves as being only a component of the 'whole', the whole being the National Capital Region Bioscience cluster. Our ultimate success will be on how we operate as a cluster in harmony. 2014 in many ways will be etched in our history since the shift to the new campus at Faridabad is anticipated later this year. THSTI, in all ways, is a huge experiment and we are continuously reinventing ourselves. Much has been possible because of the advice, support and constant encouragement from our Governing Board Chaired by Professor Vijay Raghavan, Secretary Department of Biotechnology and also to Dr. T.S. Rao, Senior Advisor at DBT and Nodal officer THSTI. And finally a word of appreciation to the Scientists and Staff of THSTI for being a supportive partner to all that is happening; it's for us to leave a legacy for them.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Research Programmes

Flagship Programmes

Discovery Programmes

Inter-Institutional Program for Maternal Neonatal and Infant Sciences: A Translational Approach to studying Pre-term Birth (PTB)

Background

Neonatal mortality now accounts for over 40% of all under-5 child deaths worldwide, and globally PTB is the single largest cause of neonatal deaths. In India's 27 million born annually, 3.6 million are born preterm, and over 300,000 of them die each year. India, contributes the highest number of PT birth and deaths worldwide, specifically 25% of the overall global preterm related deaths. Despite considerable introduction of several therapies for prevention, the problem persists and contributes notably not only to neonatal and infant deaths but also to significant morbidity. It is also important to note that babies born early have significant long-term consequences in their late childhood and adult life.

Despite this global burden, much is still unknown about the causes of preterm birth and how best to prevent its occurrence and associated morbidity and mortality. PBC given its mandate, realised that it is critical time to advance a comprehensive and cohesive research solution pathway to address the multiple strategic priorities in preterm discovery, and development, needed in our country and other low-middle income countries.

Despite considerable research efforts, our understanding of the fundamental processes underlying PTB is still very limited. Most of the available evidence for mechanistic pathways in PTB has come from animal studies or from clinical and biological assessments at a single time of the pregnancy as snap-shot evaluations. Progress in understanding the pathological mechanisms underlying PTB has been greatly hampered by the complex and polygenic nature of the disease. Therefore, a study design involving serial data collection and a multifaceted approach may hold promise for identifying causal factors and gaining a mechanistic insight into disease progression. It is our belief that the nature and extent of risk to PTB imparted by various causal factors are not static but evolve dynamically with the progression of pregnancy. It is also our belief that the major limitation of past studies has been that data and biospecimens were collected and analyzed at a single time point, usually immediately after a woman gave birth to a child.

The purpose of this study is to overcome limitations of the study designs undertaken in the past, by forming a large cohort of women early in pregnancy and following them through their pregnancy until childbirth that will help capture important environmental, clinical and biological risk factors that are often dynamic in nature. We believe incorporation of biological correlates will provide more reliable epidemiological estimates and a functional biological model will help develop therapies to prevent PTB by blocking appropriate biological pathways.

A hospital-based cohort of pregnant women is being established at a district hospital at Gurgaon, Haryana, starting from the first trimester, each of whom will be followed up until delivery to identify:

Modifiable clinical, & epidemiological determinants for better sub-classification of PTB; this will also facilitate a better understanding of mechanisms within these well defined sub-categories for which preventive & therapeutic interventions are feasible to develop.

Maternal genotype & epigenomic factors that can predict PTB and aid in disease stratification.

Proteomic alterations at different stages of pregnancy to predict, monitor & prevent preterm birth.

Composition and diversity of the vaginal & gut microbiome during different stages of pregnancy and its association with PTB and its outcomes.

The objective would then be to carry out an integrative analysis of genomic, epigenomic, proteomic and microbiomic alterations in order (i) to study mechanistic pathways for better targets for prediction & therapeutic interventions and (ii) identify potential biomarkers that can be used for risk stratification & early diagnosis of PTB and/or intervention modalities.

The long-term goal envisages clinically relevant research outputs that would aim to (i) achieve appropriate risk stratification of women early in pregnancy (ii) identify simple and better prediction tools that will recognize the optimal time of prediction & clinical intervention, (iii) develop additional strategies to identify presence of unusual/novel microbes that could serve as biomarkers, (iv) identify focused remedies targeting one or more mechanistic pathways (e.g. infection, inflammation, hormonal), (v) apply currently available interventions based on better understanding of biological mechanisms.

The cohort and the biospecimens collected from enrolled women will serve as a resource for future studies and additional research questions from new investigators. Apart from addressing the basic biomedical research questions it would also help in training manpower, enhancing research capacity and formulation of viable policies.

Conduct of study: This program actively involves bridging expertise from disparate fields, such as, pediatrics, gynecology, infectious disease biology, epidemiology, microbiology, immunology, platform technologies, cellular & molecular biology, genetics, statistics and computational & systems biology. The study is being conducted at General Hospital Gurgaon . A team comprised of the clinical coordinator, research physicians, nurses, attendants, field workers and field supervisors are stationed at General Hospital Gurgaon , will collect the data. The project management team comprises of specialized groups looking after quality management, site management team and the data management.

Management and Monitoring:

The Program will be monitored by a Steering Committee responsible for strategic guidance, review of study scientific data and advice on new directions for future research. The Steering Committee is represented by eminent national and international experts in important domain areas. The Program Management Committee would address matters related to scientific, technical and financial aspects on regular basis and report to the Steering Committee. Further details are provided below:

The Team:

1. **Translational Health Science and Technology Institute (THSTI), Gurgaon**: An autonomous Institute of DBT and houses two more components involved in the PTB program, viz.:

   (a) Pediatric Biology Centre (PBC): PBC will be the main coordinator of the program. It will be responsible for establishing and managing the cohort, for implementing the SOPs, and for conducting the epidemiological studies.

   (b) Centre for Human Microbial Ecology (CHME): CHME will be responsible for **the microbiome analyses**. Phylotyping, abundance, functional prediction and significance

of vaginal microbiome will be done jointly by **CHME and TCS** Innovation Labs.

2. **General Hospital Gurgaon** : This is the main study site where the cohort will be established.
3. **Regional Centre for Biotechnology (RCB), Gurgaon**: It is a category-II institution under the auspices of UNESCO, established by the Department. It will be responsible for proteomic analysis.
4. **National Institute of Biomedical Genomics (NIBMG), Kalyani, West Bengal**: An autonomous institute of DBT which would be responsible for genomic and epigenomic assays.
5. **Safdarjung Hospital:** This is the referral study site.

NIBMG and RCB will exchange information on an ongoing basis, as a part of designing new experiments or for validating inferences drawn by each other. **THSTI and NIBMG** will also exchange information on micronutrient intakes and epigenomics. **THSTI and**

Preterm Birth and Maternal-Newborn R&D: Current Investment

Discovery

Risk Factors
Mechanisms and Pathways
Therapeutic & biomarker target identification/validation

Key emphasis areas

Multidisciplinary research effort to predict & prevent preterm birth (PTB) by increasing understanding of the pathophysiological mechanisms involved, which would facilitate use of existing or novel therapeutic agents & timing of clinical intervention

A hospital-based cohort of pregnant women is being established at a district hospital at Gurgaon, Haryana, starting from the first trimester, each of whom will be followed up until delivery to identify:

- Modifiable clinical, & epi determinants for better sub-classification of PTB; this will also facilitate a better understanding of mechanisms within these well defined sub-categories for which preventive & therapeutic interventions are feasible to develop.
- Maternal genotype & epigenomic factors that will aid in disease stratification to study mechanistic pathways for better targets for prediction & therapeutic intervention.
- Proteomic alterations at different stages of pregnancy to predict, monitor & prevent preterm birth
- Quantitative dynamics of the vaginal & gut microbiome during pregnancy and its association with PTB and its outcomes.

Development

Biomarkers / Diagnostics
Therapeutics / Interventions

Key emphasis areas

Genetic and/or proteomic biomarkers for PTB particularly in identified subgroups where there is potential for intervention

- Novel vaginal microbiome based tools that have potential for intervention
- Focused studies on diagnostic tools for short cervix and on locally available treatment
- Development of a clinical & community immersion based innovation program to create affordable products addressing the needs in national priorities such as maternal and child health in India (with emphasis on PTB)

Delivery

Science / Operations research
Health services
Quality improvement

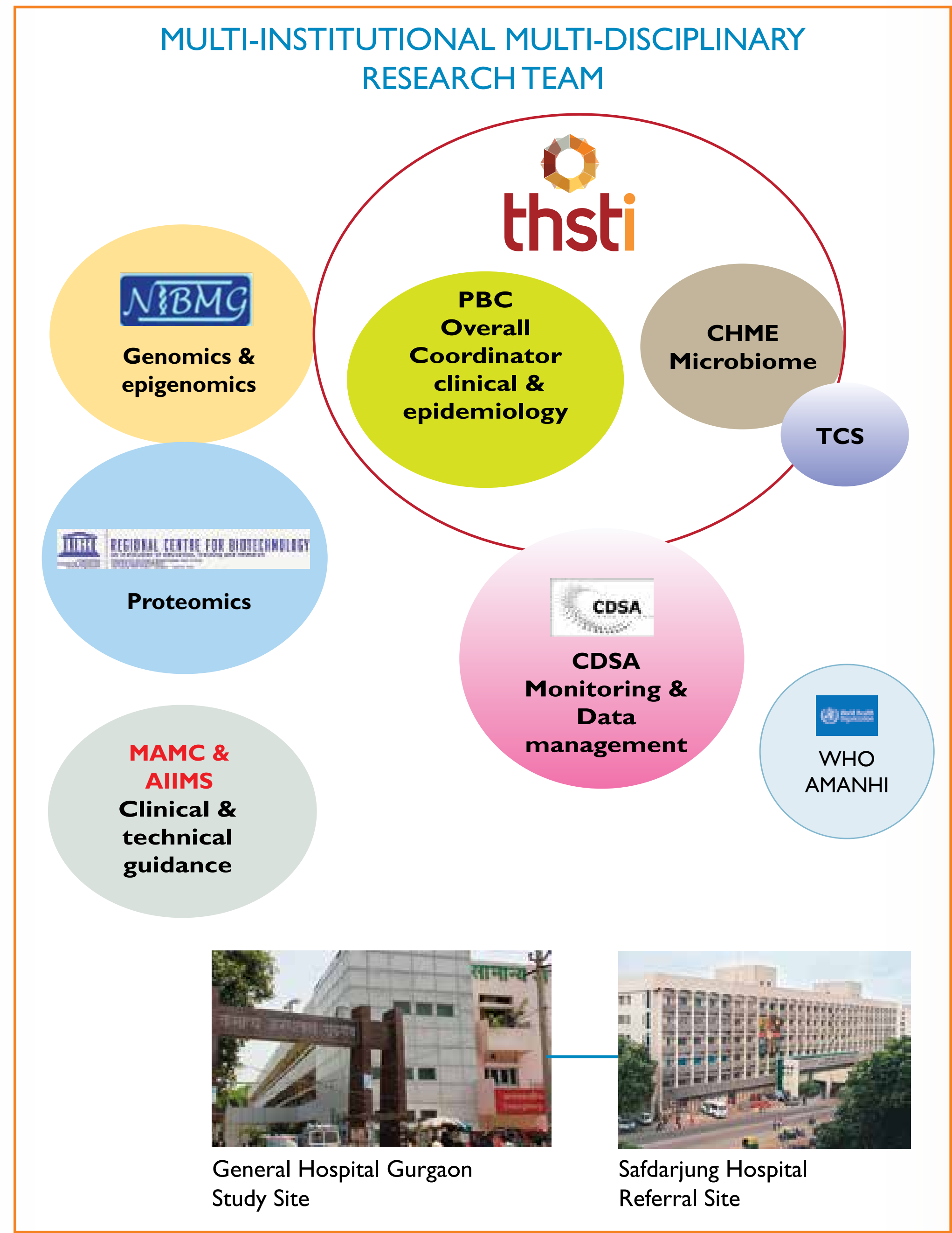
Key emphasis areas

This area is being developed using the DBT-ICMR &/or the THSTI-SAS collaborations.

RCB will be constantly engaged with each other because the microbiome ecology and levels of various proteins change in a dynamic manner and their changes are expected to be correlated. **NIBMG**, with a major arm that specializes in biostatistics and statistical genomics, will provide help to the other institutions in respect of epidemiological and other statistical analyses, as required.

5. **CDSA**: This is an extramural unit of THSTI and would be involved in quality and data management of the study.

In addition to the aforesaid institutes, other institutes/organizations involved are Maulana Azad Medical College, All India Institute of Medical Sciences, New Delhi, Tata Consultancy Services, Department of Health Research & Indian Council of Medical Research and the National Rural Health Mission.



General Hospital Gurgaon Study Site

Safdarjung Hospital Referral Site

Multidisciplinary Program on Preterm birth

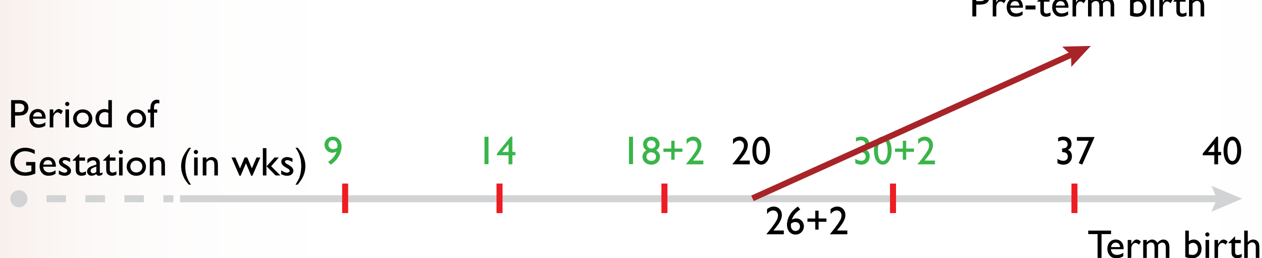
Multivariate & time series approach to identify clinical & epi risk factors

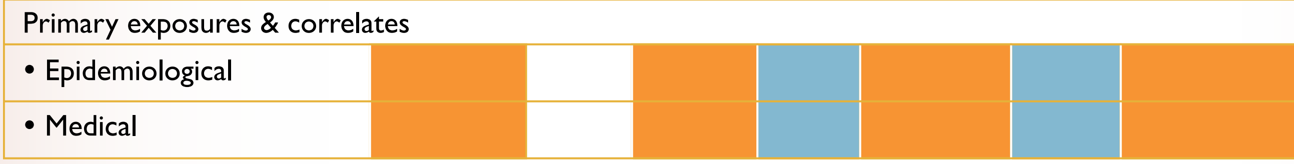
Study biological correlates & functional bio-models to develop preventive & therapeutic strategies

- 8000 mothers followed from first trimester till child birth
- Bio-specimens at different time points during pregnancy for genomic, epigenomic, proteomic & microbiome studies
- Serial ultrasound imaging to study fetus & the placenta

Progress update: Preparation of site, CRF, SOP; standardization of collection of clinical & lab data, quality assurance, data management; harmonizing of protocols

Assessment of exposures and predictors during different time points in pregnancy





Serial sonography in all enrolled women

Visit 1:9 - 14 wks - POG, no of fetuses; fetal, uterine & ovarian abnormalities

Visit 3:18 ± wks - Anomaly Scan, Cervical length, Fetal growth & maturity

Visit 5:30 ± wks - Cervical lenght, Fetal growht & maturity

Study governance

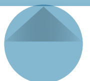
Steering Committee (established by funding agency)

International & national experts; DBT representative

Overall strategy & periodic review

Directions for additional goals

Meet twice a year; Regular feedback to the funding agency

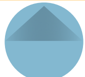


Project Management Committee

Principal Investigators, Invited subject experts

Overall governance & timely progress

Meet monthly on skype/ telephone & every 3 months in person

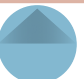


Study Co-ordination Unit

Representative from each collaborating partner

Overall coordination of study sites

Meetings: weekly



Clinical Team

Project Management Team

Role of Gut Microbiome and Gut Inflammation Markers in Severe Acute Malnourished Indian Children

(Done in partnership with the Population Science Partnership Centre and Centre for Health Research and Development Society for Applied Studies)

Overall Background: Malnutrition is a global health problem affecting more than 300 million pre-school children worldwide. It is one of the major health concerns in India since around 50% of children below the age of two suffer from various forms of malnutrition. The gut microbiome plays an important role in nutrient pre-processing, assimilation and energy harvest from food. In its journey down the human alimentary canal, food is intercepted by trillions of microbes (10^{13}–10^{14}) residing in the human gut. The human gut microbiome, collective genomes of all the microbes residing in the gastrointestinal tracts, provides several metabolic functions that are not encoded in our own genome. Examples of these functions include fermentation of dietary polysaccharides, anaerobic metabolism of proteins and peptides, biosynthesis of vitamins, absorption of ions and regulation of a number of host metabolic pathways. These functions facilitate the pre-processing of dietary nutrients and efficient harvest of dietary energy for the host. Consequently, dysbiosis of the gut microbiota has been implicated in malnutrition. Malnourished children may have underlying inflammation of the gut as a part of an enteropathy. This leads to malabsorption of processed dietary compounds. In addition, inflammatory molecules could affect gut homeostasis and there can be critical nutrient diversion.

The Society for Applied Studies is coordinating a multicentre study to evaluate the impact of novel therapeutic foods embedded in various potentially usable feeding regimens for management of uncomplicated severe acute malnourished children (SAM) in children aged 6-59 months. SAM contributes to 25% of under 5 deaths.

Preliminary results show that nearly half the children do not respond to treatment with ready to use therapeutic foods. We hypothesize that exposure to microbes and dietary deficiencies cause chronic gut inflammation and immune activation that contribute to poor response. A substudy was designed to ascertain presence of gut inflammation through measurement of specified biomarkers and examine the relationship between the gut microbiome, inflammatory markers and the response to treatment.

The specific objectives are:

To assess gut inflammation, by presence of elevated specified biomarkers and gut microbiota at enrolment and its ability to predict treatment response. To assess the persistence of gut inflammation during early treatment phase (at recovery or 8 weeks post enrolment, whichever is earlier). To measure the association between gut inflammation biomarkers and gut microbiota pattern at enrolment and recovery and gain in weight and length/height To examine gut microbiota of the children who recover and those that do not recover at recovery or 8 weeks

To assess association between inflammation makers and gut microbiota.

Approach Of The Program: 170 children aged 6 to 59 months with weight for height less than 3 SD of WHO standard or oedema of both feet or both, were selected for this study. Enrolled children are randomized to one of the three regimes; commercially produced Ready to use therapeutic food (RUTF), locally produced RUTF and Augmented Home prepared foods. Faecal samples from 170 children under study will be collected aseptically in sterile stool containers at enrolment and at 8 weeks or recovery whichever is earlier and transported to the laboratory in ice within 6-8 hours of collection. Total bacterial DNA will be extracted from 200mg of each faecal sample. Isolated DNA sample will be used for targeted metagenomic analysis using 454 GS FLX Plus pyrosequencer. The composition and abundances of different taxonomic groups (at the level of OTU, genus, family, order, class and phylum) in each sample will be evaluated using pyrosequencing data and information available in public database. Gut inflammatory markers, Calprotectin, Neopterin and Myeloperoxidase will be analysed by competitive or sandwiched ELISA using commercially available kits.

Early Translation:

Drug Discovery

The past two decades have seen a marked transformation in both the quality and quantity of pharmaceutical research. The formerly rigidly isolated efforts in academic institutions and biopharmaceutical industry have now become increasingly transparent to one another. An important trend in recent years is that industry has begun to scale down its internal efforts, while enhancing its outreach to basic research in academic institutions. Concomitant with this, there is now increasing pressure on academic institutions to enhance their focus on translational goals. This latter goal is now being facilitated by the increasing porosity between academia and industry (Bauer & Cohen, J. Investig. Dermatol. 132, 1033-1036 [2012]). Another important resultant trend is the greater collaborations between clinicians and the basic scientists. As a cumulative result of these changes, the opportunities for translational research are greater now than ever before. The changing scenario is nowhere more evident than in the field of drug discovery research, at least in the West. Thus, several multinational giants have forged significant agreements with several academic institutions in USA and Europe for drug discovery research. Indeed, it is anticipated that major academic institutions might even become the focus of a collaboration 'bubble', with corporations intensifying efforts to exclusively tie up large swathes of research expertise (King, Nature Biotech, 29, 555-556 [2012]). Thus, for example, over 25 new agreements have been established in the US between academia and the pharmaceutical industry in the last year alone. As a result of these initiatives, small molecule drug discovery in the academia has documented a large jump over the last six years in the US, with the number of dedicated centers more than doubling over this period (Kotz, SciBX, 1-4 [2011]). In contrast to the rapidly evolving situation in the rest of the world, the situation in India has however, unfortunately remained moribund. There has been no aggressive initiative to enhance small molecule drug discovery research and the academic institutions have remained largely impervious to trends elsewhere. The numbers of academic institutions that engage in this sphere of activity have not changed significantly over the decades. Further, barring one or two exceptions, the few initiatives that exist have also not made any noticeable impact in this field. An added restrictive feature here is that the evolving methodologies and approaches for drug discovery have not been adopted with any great zeal by researchers in India. The net outcome of this has been that this area has especially lagged behind in our country, and the fear is that we may lose whatever IP space that may remain. This is particularly important given that India is a prominent home to many infectious disease (e.g. tuberculosis, malaria, dengue etc.), as well as to several systemic diseases (e.g. diabetes, CVD, cancer etc.). Therefore, vigorous stimulation of small molecule drug discovery research is of imminent importance in India. The DDRC hopes to represent at least one such initiative that seeks to fill this gap. An encouraging trend that has occurred as a result of government investments over the last few years has been the rising quality of biological research in India. Today the number of laboratories with the state-of-the art infrastructure has increased significantly, allowing investigators to probe the systems of interest with high molecular resolution. As a result, the probability of arriving at a finding that may have translational potential has increased substantially. Thus, at one level, in the course of their research, investigators may identify a key protein or sets of proteins that may govern a disease phenotype. On a similar vein, work on infectious diseases often results in identifying proteins essential for pathogens to either remain viable, or infect host tissue. Another encouraging trend here is the burgeoning network programs where academicians and clinicians are beginning to collaborate to explore

genotype-phenotype relationships for specific diseases in human populations. All of the above ventures offer excellent opportunities for adding on a complementary dimension directed towards drug discovery. This, however, has unfortunately not happened so far because of lack of know-how on the part of the investigators involved. Small molecule drug discovery research requires a separate skill set where an understanding of cellular and biochemical mechanisms needs to be integrated with a knowledge of chemistry/medicinal chemistry and pharmacology. Importantly here, with increasing recognition of the network architecture of cellular pathways, a deep understanding of systems behavior is also becoming essential. Analysis of the network structure, and capturing the regulatory dynamics that controls function represents one of the dominant challenges of the day. It is now accepted that biological responses (including disease states) represent outputs from complex, non-linear dynamic systems. Addressing this issue then, requires an integrative approach that in itself synthesizes a wide variety of disciplines such as physics, mathematics, engineering, and computer sciences among many others. Indeed a major thrust area today is to develop better tools for managing/integrating high-throughput experimental data, and then to extract meaningful insights related to various aspects of a given disease state. This, in turn, is essential for identifying those molecular targets that can be exploited for drug discovery efforts It is the gap between primary research findings and the development of a candidate drug that the DDRC intends to fill. Its goal is to provide an integrated pipeline by which initial, laboratory-level findings can be converted into a candidate drug. While the composition and other relevant details of this pipeline are discussed later, it is emphasized that each project will be taken to the point where it is ready for transfer to a pharmaceutical company.

Mission of DDRC

The DDRC is a multi-disciplinary research center that integrates basic with translational research in the field of drug discovery. The overall mission of the center is to combine multiple disciplines in order to generate a robust and versatile pipeline for drug discovery research. This includes capabilities for analyzing large-scale data in order to identify the most promising targets for further drug development. The emphasis is to apply systems-level approaches and perspectives for both understanding disease-specific perturbations, and for the development of therapeutic strategies.

The DDRC Working Structure

A hub-and-spoke model that:

- Is embedded with an integrated perspective spanning the biological, chemical, pharmacological, computational and mathematical sciences
- Is strongly networked with clinicians and basic researchers is actively engaged in co-developing research themes with industry
- Assimilate '-omics' with systems approaches to extract disease specific networks
- Modeling networks to delineate novel drug targets
- Development and preclinical validation of new drug candidates
- Cutting edge infrastructure and technologies for phenotypic drug discovery
- High throughput fractionation and screening platforms for exploring the universe of natural products
- Prospecting ethno-botanicals for wellness based strategies

Scientific Domains

In order to meet its objectives, the scientific expertise in DDRC spans the following areas:.

Assay development and high-content screening: Development and standardization of robust, sensitive, and reproducible platforms for high content, medium-throughput screening. The platforms developed vary depending upon either the target or activity being examined, and will include both whole cell and in vitro assays. All relevant infrastructure for this purpose is available. synthetic and medicinal chemistry: Strong capabilities for organic synthesis and SAR optimization. Medicinal chemistry expertise also available with the necessary supporting infrastructure. Key infrastructure includes 500Mhz and 700Mhz NMR machines, mass spectrometer, and a SepBox system for high-throughput fractionation of complex mixtures/ natural products.

Cell and Molecular Biology: Expertise in developing new tools and approaches for analyzing the basis of disease-specific phenotypic perturbations in cellular systems. Research emphasis is on integrating highthroughput experimental approaches with the tools of systems biology to delineate disease specific networks. Strength in mass spectrometry for interrogating the cellular proteome, lipidome and metabolome. Infrastructure includes multiple mass spectrometers, confocal microscope, flow cytometer etc.

Pharmacology and Analytical Biochemistry: Provides the downstream analysis for a candidate drug once it has been identified. This includes evaluation of pharmacological properties such as PK/ADME in vivo and in vitro, and tissue distribution of compounds using rodent models.

Computational and Mathematical Biology: Incorporate and develop expertise in all aspects of highthroughput data analysis, network biology and mathematical modeling of network dynamics.

Capabilities for data handling extends across all molecular components and processes of a cell and includes analysis of the genome, transcriptome, epigenome, proteome, lipidome and the metabolome.

This capability is complemented by strong expertise in the modeling of complex systems behavior, which is synergistically approached from both network-based and purely mathematical strategies. Additional areas of expertise include chemoinformatics, bioinformatics, and in silico drug design. All of the required software and hardware is available.

Integration of the 'omics' sciences with the tools of Computational & Mathematical Biology

Chemistry
Assay development and Validation

Early Translation:

HIV Vaccine Translational Research Program

Aim

- To identify candidate immunogen that elicits broadly neutralizing antibody responses against HIV-1 by establishing an innovative discovery program employing high throughput technology.
- HIV Vaccine Design Program for novel immunogen and testing through development of high throughput assays
- Developing unique set up for accelerating the effort for vaccine development for IAVI and other R&D partners
- Integration of this unique facility in other labs of IAVI and Appropriate R&D Partners globally.

Overall Scientific Rationale

The Env protein is responsible for cell entry and it is also the target of neutralizing antibodies. In its active form, it is composed of gp120 and transmembrane gp41 polypeptides, derived from the cleavage of gp160 precursor protein. The cleaved envelope proteins, which form a trimer by non-covalent association on the viral membrane, bind to the primary receptor CD4, followed by co-receptor, to mediate entry into host cells. A key strategy of HIV vaccine design is to identify immunogens that elicit antibodies that recognize the native Env and thus block viral entry into target cells. The recent isolation of several broadly neutralizing MAbs demonstrates that the human B cell repertoire can generate broadly neutralizing antibodies targeting Env. However, the target of these inhibitory antibodies, the HIV Env, displays a high degree of genetic and structural variability, requiring the elicitation of broadly reactive antibody responses to functionally conserved elements. Recent progress in isolating potent, broadly neutralizing monoclonal antibodies (MAbs) from HIV-infected individuals and characterization of their cognate epitopes has increased the number of potential Env antibody targets. Several of these new targets recognize trimeric Env, suggesting that in some cases it is the functional trimer that drives the elicitation of broad neutralization during natural infection.

The lab is currently organized to pursue 3 overall projects

- Screening for cleaved functional Envs HIV-1
- Env immunogens that will only present the neutralizing epitopes
- Development of rapid and high-throughput screening of Env immunogens
- Screening for B-cell activation as one of the algorithms for animal study
- Isolation and characterization of Broadly Neutralizing Antibodies from Indian Patients
- Molecular specificities
- Genetics

Identification of signatures for efficient cleavage of JRFL Env

Rationale: Clade-B Env, JR-FL is the only Env, which is found to be fully cleaved when it is expressed on cell surface by transfection. So, when we compared the sequences of several

Env (from Clade-C Indian isolates?) with JR-FL Env, we detected the difference in two N linked glycosylation sites. In order to examine the effects of differential glycosylation pattern of Env on its cleavage efficiency, we compared JRFL with several inefficiently cleaved Env isolates and identified two PNLG (Protein N Linked glycosylation) sites (aa 187 and aa 197) where JRFL shows a distinct pattern than all other Env examined.

Progress: Developed the necessary mutations to either remove (N187D) or introduce (D197N) a glycan site in JRFL Env and tested their effects on its cleavage efficiency. Though majority of the mutants remained ,unaffected only the D197N mutation conferred neutralization resistance to b12 antibody.

Investigating the effects of exogenous furin protease induced cleavage of Env on HIV-1 viral infectivity and antigenic properties

Rationale: It has been previously shown that replacing the native furin cleavage recognition site (REKR) on HIV-1 Env with six arginine (RRRRRR) and co-express it in presence of furin enhances cleavage efficiency. However, this observation is limited in the context of Env protein with no knowledge of this modification of the virus.

Progress: Introduced such changes (REKR → RRRRRR) in an inefficiently cleaved Env, HxBc2 and generated pseudovirus in presence or absence of exogenous furin. The results show that while co-expression of exogenous furin has no effect on the viral titer of JRFL, which is efficiently cleaved; such modifications significantly reduced viral titer for HxBc2, which is cleaved relatively inefficiently. Furthermore, neutralization sensitivity of HxBc2 (generated in presence of furin) against an EMPR targeting antibody, 2F5, is also affected while JRFL remains unchanged. Our data shows that artificial induction of cleavage in an otherwise inefficiently cleaved Env may adversely affect its structure. These hypotheses will be tested in pseudoviruses for their ability to activate B cells in vitro and to find out whether such modifications also affect their immunogenic property.

Screening for efficiently cleaved Indian Clade-C HIV-1 Env

Generating a soluble, trimeric, cleaved envelope (Env) immunogen is a significant challenge towards developing an effective vaccine against HIV-1. Efficient intracellular proteolytic processing of HIV-1 gp160 Env glycoprotein results in a positive correlation between antibodies binding to Env on cell surface. This has been well documented for only one Clade-B Env, JR-FL, which is fully cleaved when it is expressed on cell surface. However, very little information exists about Clade-C Env proteins, especially those that are obtained from Indian patients, which are cleaved and can be used as the basis for candidate immunogens. The aim of this project is to identify Clade-C Env proteins obtained from Indian patients that are cleaved and demonstrate characteristics of a good candidate immunogen.

Progress: Have screened (preliminarily by Western blot) 38 HIV-1 Env isolated from acutely infected Indian individuals and selected 9 Env showing better cleavage when expressed in 293T cells. Have confirmed their cleavage efficiency by 293T cell surface binding assay to neutralizing and non-neutralizing antibodies. Presently in the process of further characterizing these Env.

Development of trimeric Env immunogens that behave like cleaved functional spike that is present on virus

Rationale: The envelope protein, gp160 is found on the surface of HIV and is a target for vaccine development. In the viral context, this protein undergoes a furin (a protease) dependent cleavage to form gp120 and gp41. This cleavage is essential for its normal function, i.e. fusion with the host cell.

When the Env is expressed in mammalian cells, a majority of the expressed gp160 do not undergo cleavage. Clade-B Env, JR-FL was found to be fully cleaved when expressed on cell surface. The first part of this objective addresses variability in cleavage as described below.

Aim: To identify the sequence/structure features in the gp160 sequence that result in some envelopes to cleave better than others. To study this, envelopes from the strains, JR-FL and JR-CSF that were isolated from the same patient were selected. Of these, JR-FL is cleaved very well, whereas JR-CSF is uncleaved. With the aim of ascertaining the part of the protein responsible, i.e. containing a cleavage signature, started to swap domains between these proteins and look for cleavage response by western blot and flow-cytometry.

Progress: Preliminary results suggest that such a cleavage signal might be present in the gp120 part of the protein. When gp120 from JR-FL is swapped into JR-CSF, we see an increase in conformationally cleaved protein.

Future Direction: This study will follow a fine mapping, where individual portions of gp120 from JRFL will be swapped into JR-CSF. In addition, we also plan to extend these studies to clade C envelopes.

Rationale: Another approach is to introduce flexible linkers between gp120 and g41 to achieve 'cleaved-like' conformation. Since cleaving results in flexible movement between gp120 and gp41 domains, it was thought that adding a long enough linker between the two domains might result in flexibility similar to what is seen in a cleaved envelope.

Progress: Till now 3, 6, 9, 15, 18 and 21 amino acids between the gp120 and gp41 domains have been introduced. With 3, 6 and 9 amino acid linkers the envelopes did not present the expected conformation. Process of evaluating envelope clones with the longer linkers is going on.

Incorporation of full-length gp160 in nanometer-sized lipid bilayers. A number of studies have been done both at the lab and at the clinical trial levels to induce the production of bNAbs using a variety of immunogens. Till date, these attempts have yielded very little success. The protein component in these vaccines ranged from just the gp120 domain to slightly larger proteins that included parts of gp41 as well. Here the question is asked that if using an intact full-length gp160 trimer, where the transmembrane portion of the protein is also included, can be a better immunogen. To achieve this goal, plans to incorporate full-length gp160 trimers into nanometer sized lipid bilayers called nanodiscs have been finalized. An earlier study has shown that incorporating H1N1 hemagglutinin into nanodiscs elicits an immune response comparable to commercially available vaccines. The process of making a variety of envelope clones that will be evaluated for trimer status and incorporated into nanodiscs is going on.

Progress: Project just initiated.

Identifying cleaved functional trimeric Clade C Env of Indian origin

Rationale: Generating a soluble, trimeric, cleaved envelope (Env) immunogen is a significant

challenge towards developing an effective vaccine against HIV-1. Efficient intracellular proteolytic processing of HIV-1 gp160 Env glycoprotein results in a positive correlation between antibodies binding to Env on cell surface. This has been well documented for only one Clade-B Env, JR-FL, which is fully cleaved when it is expressed on cell surface. However, very little information exists about Clade-C Env proteins, especially those that are obtained from Indian patients, which are cleaved and can be used as the basis for candidate immunogens. The aim of this project is to identify Clade-C Env proteins obtained from Indian patients that are cleaved and demonstrate characteristics of a good candidate immunogen.

Progress: Out of env clones, some are clade-C and some are either clade-B or B/C recombinant. The process of screening these Clade-C Envs for expression of a fully cleaved envelope on cell surface is going on. It is important to note that till now JR-FL Env (clade-B) is the one and only Env reported to be fully cleaved when expressed on cell surface. Western-blot (WB) of the whole cell extract after transfecting with the plasmid expressing the Env of interest was chosen as a first step for screening for cleavage. We screened 38 Envs cloned into pSVIII vector by transfecting 293T cells followed by WB by using HIV-1 IgG pooled sera as probe. Cleavage-competent and cleavage-defective JR-FL Envs were kept as controls. Out of 38 Envs, 9 Envs showed varied degree of cleavage as determined by the appearance of gp120 bands in western blots. Four of these Envs have been tested for their ability to bind a panel of neutralizing and non-neutralizing antibodies by cell surface staining (FACs analysis). As the cleaved Env should not bind to the CD4-bs directed on-neutralizing antibody we included F105 for our initial screening. These selected cleavage competent Envs did not bind to non-neutralizing antibodies but they bound efficiently to neutralizing antibodies. Of these four, the focus is on Env, HVTR-E-019 as it was found to bind to neutralizing antibodies better than others and it did not bind to non-neutralizing antibodies at all to the highest concentration tested. Furthermore, the mutation in cleavage site (SEKS to REKR) rendered the Env, HVTR-E-019 cleavage defective as reported in case of JR-FL ENV by Pancera et al in 2005. The cleavage defective mutant was found to bind not only to neutralizing antibodies but also to all non-neutralizing antibodies tested here. This finding corroborated well with earlier reports that cleavage-defective JRFL binds to non-neutralizing antibodies as well as neutralizing antibodies whereas the cleavage competent JR-FL Env only binds to the neutralizing antibodies. Like cleavage mutant JR-FL Env (REKR to SEKS), the mutated Env, HVTR-E-019 (REKR to SEKS) also binds to the non-neutralizing antibody, F105 as efficiently as neutralizing antibody, VRC01 and 10E8. These data suggested that the newly isolated clade-C Indian Env is fully cleaved like JR-FL. Cleavage of these Env proteins was confirmed by gp120 shedding analysis using immuno-precipitation (IP) followed by western blot (WB) analysis. This was further confirmed by Env specific ELISA. Env-HVTR-E-019 showed the evidence of natural gp120 shedding and it increased as we added soluble CD4 (sCD4) with the same Env expressed on 293T cell surface.

Comparing binding ability with a broader panel of Env specific neutralizing antibodies to recently identified Indian cleaved Clade-C Env, HVTR-E-019 and the cleavage competent Clade-B Env, JR-FL it can be concluded that the newly identified Indian Clade-C Env, HVTR-E-019 could be an appropriate platform for immunogen design.

Future direction: Confirmation of the effect of sCD4 on gp120 shedding by Env-HVTR-E-019 is going on. Furthermore, the Envs selected from these studies will be further characterized to determine (i) their binding affinity for different bnAbs by SPR, (ii) the ability of different bnAbs to neutralize pseudo-typed viruses made with these Envs, and (iii) their ability to activate B cells. Future work will involve studying the immunogenic properties of these Envs, their biochemical and biophysical characterization to identify Envs that are trimeric as present on viral surface. It is to be noted that it has been shown that trimeric Env is better than monomeric Env as an immunogen.

Identification and characterization of HIV envelop surface exposed areas to be used as immunogen for successful vaccine development

Rationale: Targeting regions around CD4 binding site will give us alternative approach to probably masking, inhibiting or blocking CD4 binding to gp120, which has been so far not successful by targeting CD4 binding site.

Specific Aims:

- Identification of exposed surface area on HIV Envelop protein as immunogenic candidate, (specifically targeting surface area near to CD4 binding site but not directly involved in CD4 binding).
- Designing and characterization of scaffolds to express identified immunogen targets.
- Antibody generation through Scaffolds harboring immunogen targets and check for the neutralization potential.

Progress: Three distinct exposed regions have been identified so far around CD4 binding sites and targeted for designing scaffold. We collaborated with Dr. M. S. Madhusudhan (Associate Professor, IISER, Pune) for this project.

Using several in-house analysis programs, he was able to identify 44 structurally similar hits for region I (Scaffold searching for other regions are under progress). Based on different biochemical parameters, 6 out of 44 identified hits were selected for *in-silico* grafting experiments (modeling of scaffold proteins with replaced Env sequences and to check for any structural perturbation). On the basis of results from grafting experiments 3 scaffolds have been selected so far for further studies.

Future Directions: Future goal includes grafting of envelop sequences on to the scaffold protein through cloning (replacement of structurally similar motif sequences of the scaffold protein by Envelop sequences), expression and purification of scaffold proteins. Purified scaffold protein will be used for antibody generation in animals. Polyclonal sera from immunized animals will be tested for neutralization. The sera will also be tested for competitive inhibitor for CD4 binding.

Designing of native trimeric HIV Env as candidate vaccine (with approach of fusion protein)

Rationale: Soluble, trimeric Env are potential target for vaccine development. An approach of biological trimeric protein or trimeric domain as a fusion protein has been utilized to design and express native trimeric HIV Env as a candidate for successful vaccine development.

Specific Aims:

- Identification of biological trimeric proteins or domain suitable for the expression of HIV Env as soluble native trimeric form

- Characterization and validation of trimeric immunogen as vaccine candidate

  In order to express HIV Env protein in its native trimeric form as successful vaccine candidate an approach of trimeric fusion tag has been targeted. Several biological trimeric proteins with known structure (www.rcsb.org) have been analyzed for this purpose. Currently trimeric protein PCNA (Proliferating cell nuclear antigen) has been selected for this purpose and several different constructs with varying length of linkers have been prepared.

Progress: Project initiated.

Future directions: Includes introduction of mutations to stabilized gp120-gp41 interaction and purification of stabilized Env-fusion protein. Validation of fusion protein tag HIV Env as successful vaccine candidate will be done by checking its antibody response (binding experiments using neutilizing and non-neutralizing antibodies)

Screening of HIV-1+ sera/plasma from chronically infected Indian patients to identify broad and potent cross neutralizing sera/plasma (Protocol-G)

Rationale: Patients who are chronically infected with HIV-1 and are anti-retroviral therapy naïve (ART naïve) are likely to develop broadly cross reactive neutralizing antibodies over the course of infection. Isolation of novel broadly cross reactive human monoclonal antibody/ antibodies from such individuals will help in designing strategies for HIV-1 immunogen design through reverse vaccinology. The present study is designed to carry out high throughput screening using engineered reporter cell line of sera/plasma obtained from ART naïve and asymptomatic Indian patients chronically infected with HIV-1 with no disease progression with specific aim to identify broadest neutralizing serum antibody / antibodies.

Specific aims proposed at the initiation of the project:

Specific goal is to screen 200 HIV-1 positive patient sera/plasma against a panel of HIV-1 virus pseudotyped with Envs from tier 2/3 viruses (multi-clade panel predominantly with Clade-C) for detecting the presence of broadly neutralizing antibodies. The aim is to achieve reasonable amount of data by end of Year 2013, given that patients' samples are received in a timely manner.

If broad sera/plasma antibodies by end of year 2013 can be identified, examining the specificities of most broad and potent sera/plasma samples against specific and defined HIV-1 envelope mutants and other reagents such as HIV-2/HIV-1 chimeric viruses will be initiated.

Subsequently by the end of year 2013 the processing for sorting memory B cells towards isolating human monoclonal antibodies from donor PBMC's which were narrowed down based on their broad and potent neutralizing antibodies were started.

Highlights of Progress:

Starting July 2013, obtained to date a total of 200 HIV-1 Positive serum and plasma samples from YRG Care, Chennai in two batches. The second batch was obtained on August, 2013.

All the 200 serum samples were screened against a comprehensive panel comprised of viruses pseudotyped with different HIV-1 Env. At this moment, 11 plasma/serum samples were shortlisted that showed neutralization breadth across different clades. We confirmed that the virus neutralization by serum/plasma samples was IgG mediated.

Initiated mapping of selected broadly neutralizing plasma/serum samples and preliminary data indicated that the neutralization susceptibility was not due to CD4 binding site and V3 directed antibodies. Additional experiments are going on with peptides mimicking MPER, V3 loop, HIV-2/HIV-1 MPER chimera and specific point mutants to delineate specificities of the broad neutralizing serum IgGs. The plan is to subsequently make use of chimeric viruses to delineate fine specificities of these broadly neutralizing sera which will help us to rationalize target specific B cell cloning towards obtaining human monoclonal antibodies.

Dissecting the epitope fine specificities of broadly neutralizing sera derived from HIV-1 (type C) infected individuals

Antibody mapping to either CD4bs specific, MPER specific, PG9/16 and PGT specific, other glycan specific or unknown epitope by single or multiple point mutation.

To identify residues within autologous envelope that conferred resistance to autologous BCN serum/plasma. This will help to identify the fine specificity.

Progress:

Four clade C envelopes that showed moderate sensitivities to most of the broad cross neutralizing plasma antibodies were identified and used as template to introduce point substitution replacing key residues required for recognition of kniwn briad and ootent neutralizing monoclonal antibodies. These constructs will be then used to map antibody specificities of the BCN serum/plasma samples.

These knock out envelope constructs will be used to map antibody specificities using both BCN serum/plasma samples and total IgG derived from the same.

Identification of neutralzing antibody epitopes on Indian and South African HIV-1 subtype C viruses for HIV vaccine design:

International collaboration between India and South Africa

Funded by: Department of Science and Technology, Govt of India

Late Translation:

Clinical Development of Rotavirus Vaccine Candidate 116E

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 diarrhea and nearly 125,000 rotavirus attributable deaths occur among children under-five 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 104 ffu and 105 ffu dosages of the vaccine were safe and the 105 ffu dosage of 116E demonstrated a robust immune response after three administrations. The vaccine has undergone Phase III efficacy trial this year. This is a randomized, double-blind, placebocontrolled trial with the primary objective of evaluating the efficacy of three doses of ORV 116E, 105.0 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 are being 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 is 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 is 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 in operation with trained manpower. Vaccine efficacy and immunogenicity results for the 2-year study was conducted till end of 2013.

Late Translation:

Zinc in treatment of Clinical Sepsis

Indian and Nepalese policy-makers, academic organizations (like the academy of pediatrics and the national neonatology fora) and program managers, not only in the states where the trial hospitals are located but also at a national level, will at an early stage be informed about the trial. The results will be communicated to the public not only through publications in peer reviewed scientific journals, but will be combined with a written approved press release for main stream media to avoid misinterpretation of results. Most of the investigators are actively involved with the academic bodies such as the National Neonatology Forum and the Academy of Pediatrics. They have been convenors/members of the committees that have made recommendations for management of various diseases on behalf of these Academies and other Foras. Some have been actively involved with teaching the WHO and the national Integrated Management of Neonatal and Childhood Illnesses strategy to physicians, medical students and also community workers. These platforms will be used to disseminate the knowledge gained from the results of this study. The results will be publicized at National and International academic meetings and will be circulated to relevant scientific bodies and institutions. Various non- government organization will be involved to disseminate the information further. Some of the investigators have advised the Government on recommendations for various diseases. Their constant involvement with the Government will be useful in propagating evidence based recommendations in clinical practice such as the results of this study. Our engagement with Department of Maternal, Newborn, Child and Adolescent Health (MCA), of the World Health Organization (Geneva) as part of the trial Technical Steering Committee will be important because if our results are confirmed the MCA Department will have a crucial role in translating these results into recommendations and guidelines following the process established by the Guideline Review Committee of the WHO.

Zinc as an adjunct for the treatment of very severe disease in infants younger than 2 months

Scientific basis: The prognosis of sepsis in early infancy is poor. While appropriate antibiotics are available in many hospitals in India and Nepal, second-line antibiotics may be unavailable in peripheral health facilities or are prohibitively expensive. It is important to develop inexpensive, effective and accessible interventions that can be added to standard therapy for severe infections to improve clinical outcomes and to reduce case fatality. In a recent randomised controlled trial in India, we found that daily oral zinc treatment had an efficacy of 40% against treatment failure in 7-120 days old infants with probable serious bacterial infection. The trial was not powered to evaluate the effect of the intervention on the risk of case fatality, and we accordingly propose this new multi-centre trial.

Study design: Individually randomized double-blind placebo-controlled hospital-based trial.

Study participants and site: Young infants aged 1 day up to 2 months hospitalized in district hospitals of India and Nepal with very severe disease as defined by IMNCI.

Intervention: Daily oral administration of 10 mg of elemental zinc along with standard antibiotic therapy.

Comparator: Placebo along with standard antibiotic therapy.

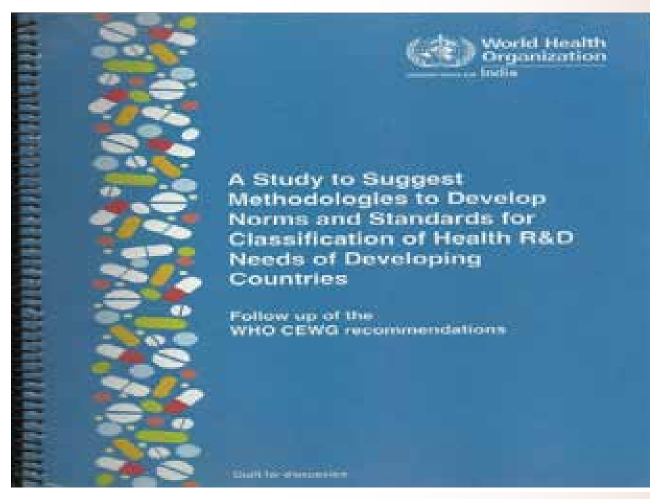
Outcomes: Primary: (i) case fatality. Secondary: (i) primary treatment failure (ii) time from enrolment to cessation of symptoms and signs of very severe disease (iii) time to failure of primary treatment (iv) time to hospital discharge (v) survival and function of peripheral blood mononuclear cells and innate immunity (vi) an evaluation of the incremental cost effectiveness of zinc supplementation will be conducted to inform policy.

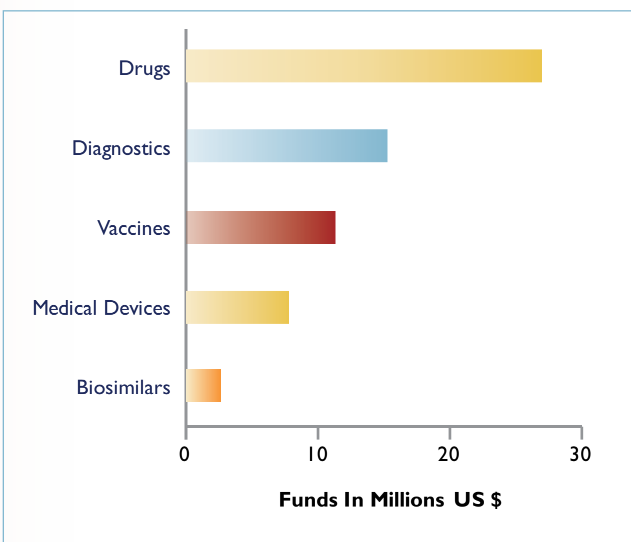
Relevance for programs and public health: If zinc treatment of young infants with very severe disease reduces the risk of death it should be incorporated into global and national guidelines.

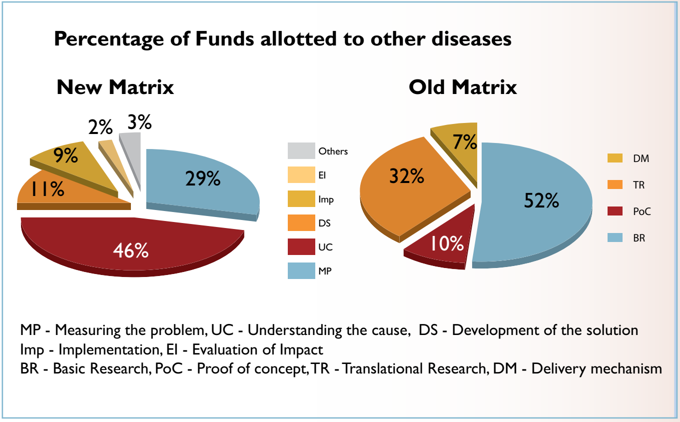
Policy Research on Health Science Research Funding and Resources

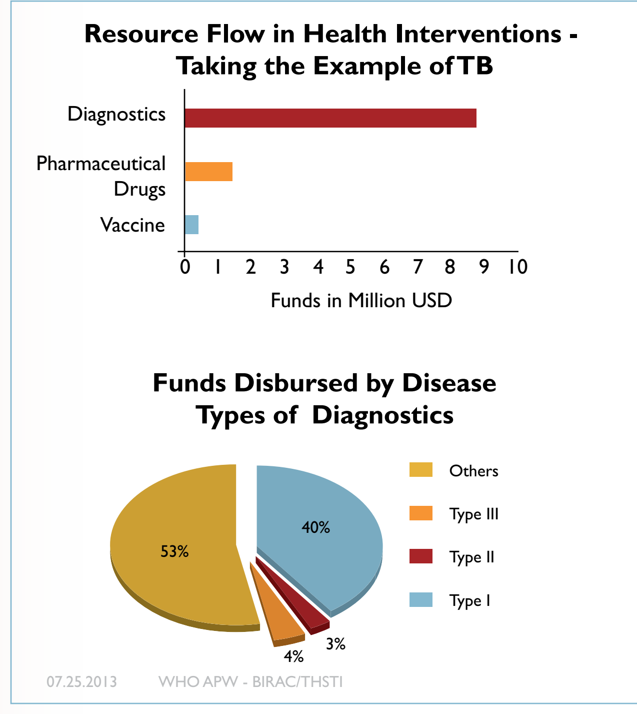
The study is in the area of a mapping exercise of health interventions R&D, human resource and infrastructure, in collaboration with World Health Organization (WHO) with two consecutive Agreement for Performance of Work (APW) spanning the work on:

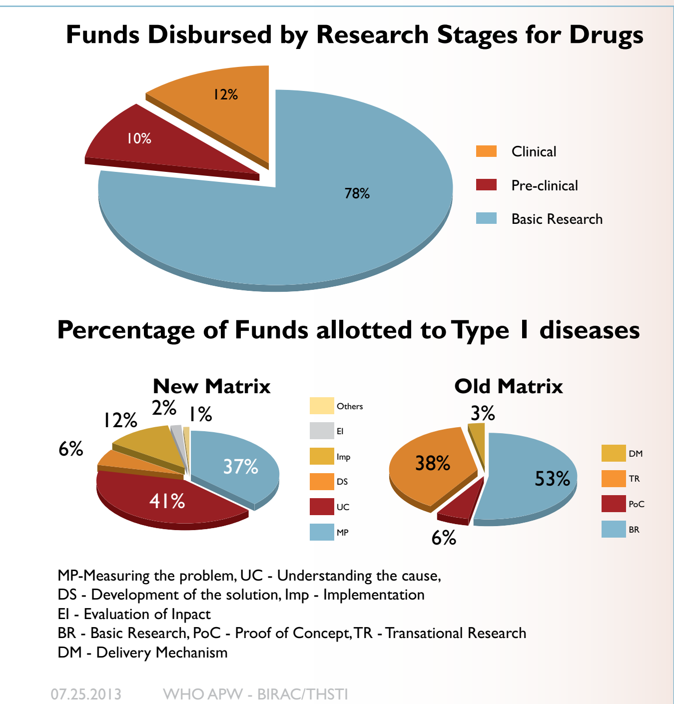
A study to suggest methodologies to develop norms and standards for classification of Health R & D needs of Developing Countries as a follow up of the CEWG Recommendations











Investigator Driven Research Projects

DR. RAMANDEEP SINGH

Team members

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Focus research area

Tuberculosis kills 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. This situation has further aggravated due to HIV-TB nexus and emergence of various drug resistant strains of M. tuberculosis. Eradication of this dreaded disease requires understanding of the pathways that enables the bacteria to persist in the host and design of strategies aimed at targeting these non-replicating/latent bacteria residing in host tissues. It has been hypothesized that latent bacilli are metabolically inactive due to orchestrated shutdown of microbial metabolism in response to hypoxic and nutritional stress and are drug tolerant. Another explanation for this drug tolerance is heterogeneity in microbial metabolism even within a single lesion such that bacterial populations contain a fraction of drug tolerant persisters although the cellular mechanisms that drive this heterogeneity are unknown. The correlation of metabolic activity with sensitivity to drugs has been shown to be dependent on cell density. The current focus of the activities of my research group is to identify metabolic pathways that enable M. tuberculosis to adapt to various conditions and to persist in the host. Another focus of the lab is to identify synthetic molecules that are active against non-replicative/persistent bacteria and to understand their mechanism of action.

Intramural projects

Identification of scaffolds with activity against M. tuberculosis and to understand their mechanism of action

Background: The situation of tuberculosis has aggravated due to emergence of various drug-resistant strains of M. tuberculosis. The advent of new computational methods, combinatorial synthetic chemistry approach, whole cell and target based HTS assays have led to identification of several anti-tubercular scaffolds that are currently at various stages of clinical trial development but still there is an urgent need for identification of new scaffolds that can (i) shorten treatment duration; (ii) target MDR/XDR-TB strains

Progress: In the laboratory we have developed a cell based screening system (which takes into account cell wall penetration and pro-drug activation) to identify scaffolds with good anti-tubercular activity. In a collaborative study with Prof. Rawat we have screened various diamine (SQ-109 derivatives, compound currently in clinical trial) and INH-triazole derivatives for anti-tubercular activity. In this collaborative project, we have identified few analogues that inhibit

mycobacterial growth by 99% at concentration of ~3 µM. In another collaborative study with Dr. Avinash Bajaj, we propose a new concept where we show that antimycobacterial activity of bile acid amphiphiles is driven by virtue of their interactions with mycobacterial lipids. We demonstrate that these hard-charged amphiphiles interact with trehalose dimycolates and penetrate through rigid mycobacterial membranes via barrell-stave mechanism.

In another project we have screened nearly 5,000 compounds in our whole cell based assays. Based on these screening efforts, we have identified scaffolds that are more potent against slow growing mycobacteria in comparison to fast growing mycobacteria and E. coli. These observations suggest that these scaffolds target a metabolic pathway that is specific for slow growing mycobacteria. The exact MIC_{99}values for some of these compounds is< 1 µM, with the most active compound has a MIC_{99} value of 300 nM. Most of the compounds (~30) were observed to be non-cytotoxic in THP-1 cells even at 100 µM concentration (highest concentration tested in the study). Based on these readings, therapeutic index (MIC_{99}/TC_{50}) was calculated for all these 40 compounds and compounds with Ti value >25 were evaluated for their ability to inhibit intracellular mycobacterial growth using BCG infected macrophages. In our macrophage experiments, these shortlisted compounds demonstrated dose dependent killing of bacteria in THP-1 macrophages. These compounds were able to inhibit bacterial growth by 50-fold at 4 days post-treatment. Similar levels of killing were observed in the case of isoniazid, positive control used in the study. We are currently collaborating with various medicinal chemists to make derivatives of these scaffolds in an attempt to improve upon their activity. In addition to these whole cell based screens, we have also standardized target-based screens for enzymes involved in either polyphosphate metabolism or serine metabolism. We have biochemically characterized both PPK-1 (main enzyme involved in synthesis of polyphosphate) and SerB2 (enzyme involved in synthesis of L- serine). We have also developed a high through put assay system for identifying molecules that inhibit their enzymatic activity. Using these HTS based assays we have identified scaffolds that specifically inhibit either PPK-1 enzyme of SerB2 enzyme in vitro.

Extramural projects

Investigating the role of MazF toxins in Pathogenesis and Persistence of M. tuberculosis
Funding agency: *Department of Biotechnology*

Background: Bacterial drug-tolerance is reported to result from lower metabolic requirements for processes that characterize actively growing cells such as transcription, translation, replication and cell wall synthesis. An attractive hypothesis for the origin of these persisters is that they arise from stochastic over expression of endogenous regulators of macromolecular synthesis in a subset of cells. The best studied of these systems are the "toxin-antitoxin" (TA) modules found within many prokaryotic genomes. These modules are generally expressed from a bicistronic operon wherein the upstream gene encodes an unstable antitoxin and the downstream gene encodes a stable toxin. The antitoxins neutralize their cognate toxins by forming tight protein-protein complexes that abrogate toxicity of toxins if both modules are present in equimolar concentration. Bioinformatic analysis revealed that genome of M.tuberculosis $H_{37}Rv$ encodes >80 TA modules out of each 9 TA modules belong to MazEF family of TA proteins. Several of these TA modules have been bio-chemically characterized. In contrast, the related obligate intracellular parasite M. leprae appears to have lost all functional toxin genes due to the unchanging nature of the niche M. leprae occupies in the human host.

Progress: In our lab we have biochemically characterized MazEF family of TA systems and shown that overexpression of 3 MazF homologs induces bacteriostatic effect in M. tuberculosis. We also report that these MazF toxins are differentially regulated under various disease relevant stress conditions and upon exposure to anti-tubercular drugs. In order to understand the role of these

MazF toxins in survival of M. tuberculosis under various disease relevant stress conditions and drug induced persistence, we have constructed single, double and triple mutant strains of M. tuberculosis devoid of activity associated with MazF toxins. We observed that triple mutant strain was impaired in its ability to survive in oxidative and nutritional stress. We also observed that growth kinetics of parental strain and MazF triple mutant strain was comparable in macrophages at different time points. For animal experiments, guinea pigs were infected with various strains of M. tuberculosis via aerosol route and intracellular bacteria were enumerated at 4 weeks and 8 weeks post-infection in lungs and spleens. Aerosol infection was carried out such that it resulted in implantation of 100 – 200 bacilli at Day 1 post-infection. We observed that deletion of these MazF toxins significantly impaired the growth of M. tuberculosis by 10-fold in both lungs and spleens of guinea pigs at 4 weeks post-infection. This growth defect in the survival of MazF triple mutant increased to 50-fold at 10 weeks post-infection in both tissues.

Understanding the role of polyphosphate kinases and polyphosphatases in physiology of M. tuberculosis

Funding agency: Department of Biotechnology

Background: Stringent response is one of the regulatory mechanism by which bacteria adapts to poor nutrient conditions through the production of various alarmones such as guanosine pentaphosphate ((p)ppGpp) which regulates various metabolic processes and bacterial virulence. Another important player in adaptation of bacteria to various stress conditions is polyphosphate (polyP). In bacteria, enzymes involved in polyP metabolism are polyphosphate kinase - 1 (PPK-1) which catalyzes the reversible transfer of the terminal (☐) phosphate of ATP to form polyP and polyphosphatase (PPX) that processively hydrolyzes the terminal residues of polyP to liberate Pi. Polyphosphate kinase -2 (PPK-2) is another enzyme involved in polyP metabolism that drives synthesis of GTP and ATP using polyP as phosphate donor.

Progress: In the study we show that M. tuberculosis responds to various stress conditions by accumulating higher levels of polyP. M. tuberculosis possesses a single homolog of ppk-1 and we have generated Δppk1 mutant strain of M. tuberculosis. The mutant strain exhibited negligible levels of intracellular polyP, decreased expression of sigF and reduced growth in stationary phase. The mutant strain showed survival defect in nitrosative stress and in THP-1 macrophages as compared to the wild type strain. In addition, polyP accumulation was also observed upon exposure of mycobacteria to various drugs. Deletion of ppk-1 in M. tuberculosis genome significantly reduced the number of persisters in the presence of isoniazid or levofloxacin. The mutant strain survived as well as the wild type strain in oxidative stress and acidic conditions. Our results suggest that polyP accumulation is required for persistence of M. tuberculosis invitro and it plays an important role in physiology of bacteria residing within human macrophages. We have also biochemically characterized polyphosphate kinase – 2 and polyphosphatase proteins of M. tuberculosis. To understand the role of these enzymes in physiology of M. tuberculosis, we have generated a ppk-2 mutant and polyphosphatase deficient mutant strain of M. tuberculosis and our initial results suggests that the double mutant is highly attenuated in guinea pigs at both 4 and 8 weeks post-infection.

DR. NISHEETH AGARWAL

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Dr. Madhu Pareek (Technical Officer)

Focus research area

Tuberculosis (TB) remains a global health challenge and is ranked as the second leading cause of death from an infectious disease worldwide after HIV. Despite the tremendous efforts by World Health Organization to curb this disease, the global burden of TB cases remains daunting. According to recent estimate ~9 million new cases and 1.4 million TB deaths were reported in 2011. Emergence of drug-resistant cases and TB-HIV co-infection further complicate the TB treatment. Hence, there is an urgent demand to identify new targets in M. tuberculosis, the causative agent of TB in humans, which can be explored in designing novel inhibitors and vaccines.

The long-term goals of this lab are: a) to characterize essential genes of M. tuberculosis and establish them as new drug targets, and b) to design novel TB vaccine by manipulating the cumulative expression of cell envelope antigens. With these objectives, the lab is currently working on the following projects:

- To explore P-loop GTPases as novel drug targets by systematic characterization of their function in M. tuberculosis.
- To characterize the function of a novel preprotein translocase, YidC in M. tuberculosis.
- To understand differential host response to infection by pathogenic (M. tuberculosis) and attenuated (M. bovis BCG) strains of mycobacteria.
- Analysis of cAMP-regulated gene expression profile of M. tuberculosis.

Intramural projects

To characterize the role of putative preprotein translocase in M. tuberculosis

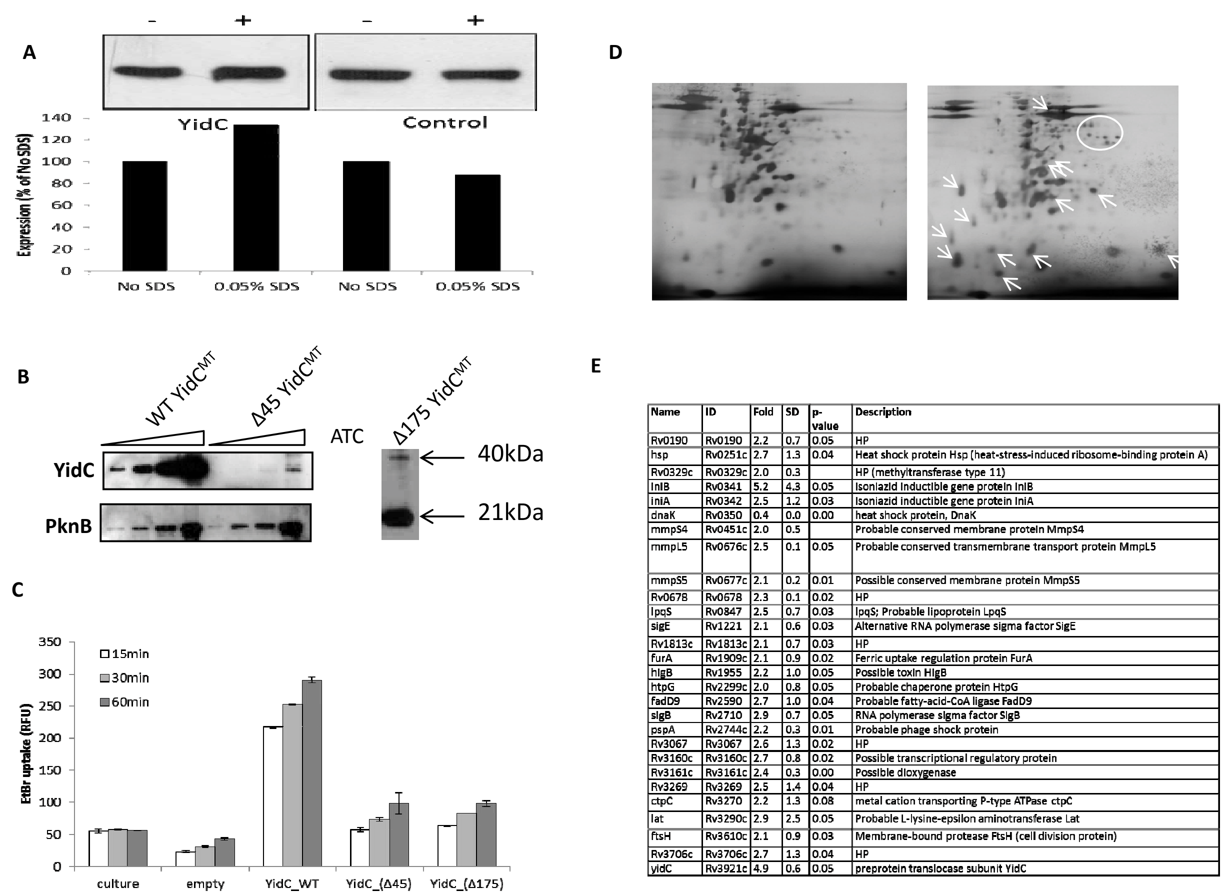
Background: Membrane organization of a pathogen plays significant role in determining its virulence. The host-pathogen interaction is driven by the unique arrangement of several membrane proteins on the envelope of both the partners. The fate of these membrane proteins is in-turn governed by specialized transporters known as protein translocases. In M. tuberculosis three essential pathways are reported which regulate majority of protein export viz. the general secretion (Sec) pathway, the twin-arginine transport (TAT) pathway and the early secretory antigenic target 6 export (ESX) pathway. Recent studies suggest that in mitochondria, bacteria and chloroplasts a new membrane protein insertion pathway is present known as Oxa1p. The homologue of Oxa1p in bacteria, annotated as YidC, participates in Sec pathway where it interacts with SecYEG via SecDF complex. Despite conserved occurrence across different mycobacterial species, role of YidC in mycobacteria is hitherto known, which warrants a comprehensive study characterizing its function in mycobacteria.

Objectives: The major objectives are-

- Study the role of putative YidC encoded by Rv3921c/MSMEG_6942 in protein translocation,
- Identify YidC-dependent substrates in M. tuberculosis/M. smegmatis,
- Evaluate YidC's essentiality in mycobacteria, and
- Characterize the role of YidC in virulence of M. tuberculosis and elicitation of host immune response.

Progress: We have identified that-

- YidC-encoding gene, Rv3921c is transcribed as operon with three other genes preceding yidC.
- YidC is a constitutive cell wall-localized protein whose expression is moderately increased upon exposure to membrane stress agent such as SDS and under low iron.



Name	ID	Fold	SD	p-value	Description
Rv0190	Rv0190	2.2	0.7	0.05	HP
hsp	Rv0251c	2.7	1.3	0.04	Heat shock protein Hsp (heat-stress-induced ribosome-binding protein A)
Rv0329c	Rv0329c	2.0	0.3		HP (methyltransferase type 11)
InIB	Rv0341	5.2	4.3	0.05	Isoniazid inductible gene protein InIB
iniA	Rv0342	2.5	1.2	0.03	Isoniazid inductible gene protein IniA
dnaK	Rv0350	0.4	0.0	0.00	heat shock protein, DnaK
mmpS4	Rv0451c	2.0	0.5		Probable conserved membrane protein MmpS4
mmpL5	Rv0676c	2.5	0.1	0.05	Probable conserved transmembrane transport protein MmpL5
mmpS5	Rv0677c	2.1	0.2	0.01	Possible conserved membrane protein MmpS5
Rv0678	Rv0678	2.3	0.1	0.02	HP
lpqS	Rv0847	2.5	0.7	0.03	lpqS; Probable lipoprotein LpqS
sigE	Rv1221	2.1	0.6	0.03	Alternative RNA polymerase sigma factor SigE
Rv1813c	Rv1813c	2.1	0.7	0.03	HP
furA	Rv1909c	2.1	0.9	0.02	Ferric uptake regulation protein FurA
higB	Rv1955	2.2	1.0	0.05	Possible toxin HigB
htpG	Rv2299c	2.0	0.8	0.05	Probable chaperone protein HtpG
fadD9	Rv2590	2.7	1.0	0.04	Probable fatty-acid-CoA ligase FadD9
sigB	Rv2710	2.9	0.7	0.05	RNA polymerase sigma factor SigB
pspA	Rv2744c	2.2	0.3	0.01	Probable phage shock protein
Rv3067	Rv3067	2.6	1.3	0.02	HP
Rv3160c	Rv3160c	2.7	0.8	0.02	Possible transcriptional regulatory protein
Rv3161c	Rv3161c	2.4	0.3	0.00	Possible dioxygenase
Rv3269	Rv3269	2.5	1.4	0.04	HP
ctpC	Rv3270	2.2	1.3	0.08	metal cation transporting P-type ATPase ctpC
lat	Rv3290c	2.9	2.5	0.05	Probable L-lysine-epsilon aminotransferase Lat
ftsH	Rv3610c	2.1	0.9	0.03	Membrane-bound protease FtsH (cell division protein)
Rv3706c	Rv3706c	2.7	1.3	0.04	HP
yidC	Rv3921c	4.9	0.6	0.05	preprotein translocase subunit YidC

Fig.: Effect of YidC expression on M. tuberculosis. A) Immunoblot analysis exhibiting the expression of YidC in M. tuberculosis after 2hr exposure to 0.05% SDS. An unrelated protein was used as loading control. B) Effect of truncation of 45 amino acid residues (Δ45YidCMT) and 175 amino acid residues (Δ175YidCMT) from the N-terminus on protein expression. Expressions of wild-type, Δ45YidCMT and Δ175YidCMT were analysed after induction with different doses of anhydrotetracycline (ATC). C) Effect of YidC overexpression on integrity of mycobacterial cell envelope. Cell envelope integrity was assessed by fluorescence estimation after uptake of ethidium bromide by M. tuberculosis containing empty plasmid, or plasmid expressing wild-type, Δ45YidCMT and Δ175YidCMT, respectively. D) Effect of wild-type YidC overexpression on mycobacterial proteome. The white arrows and a circle indicate differentially expressed proteins in M. tuberculosis overexpressing wild-type YidC. E) Effect of YidC overexpression on whole gene expression profile, as identified by microarray analysis.

- The first 45 amino acids are important for optimal expression and stability of YidC in mycobacteria.
- Overexpression of YidC in M. tuberculosis or E. coli is lethal for in vitro growth and integrity of mycobacterial cell wall.
- YidC overexpression in Mtb results in enhanced expression of several proteins, as identified by 2D-PAGE.
- YidC overexpression in M. tuberculosis modulates gene expression of the membrane-stress regulon.

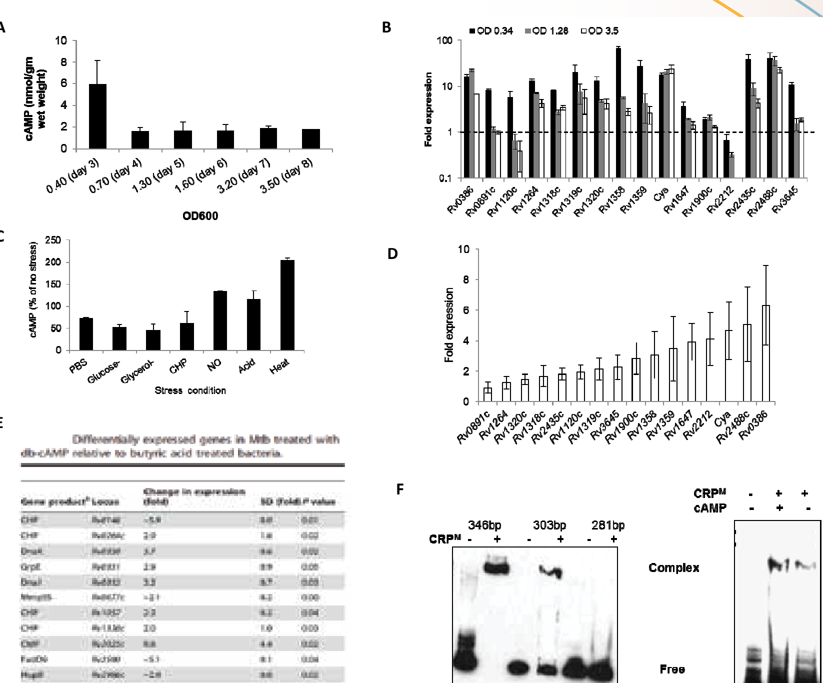
Analysis of cAMP-regulated gene expression profile of M. tuberculosis

Background: M. tuberculosis has evolved a clever strategy of intoxicating host macrophages by secreting a signaling molecule, 3',5'-cyclic adenosine monophosphate (cAMP). Cyclic AMP is continuously produced by M. tuberculosis during in vitro growth as well as into host cells during infection which perturbs signaling pathways and affects bacterial persistence and killing by host macrophages. Though M. tuberculosis produces significant concentration of cAMP which is also secreted into extracellular environment direct role of cAMP in the physiology of M. tuberculosis

is lacking. Here we studied the conditions that affect intracellular cAMP levels in mycobacteria. Further, we identified by microarray cAMP-regulated genes that exhibit differential expression in cells treated with exogenous cAMP.

Objectives: The major objectives are-

- Analysis of intracellular cAMP levels in M. tuberculosis during in vitro growth and under various stresses,
- Expression analysis of Mtb ACs by real-time quantitative reverse-transcription PCR (qRT-PCR),
- Identification of cAMP-regulon by microarray, and
- EMSA to validate direct binding of CRP^{M} to 5'-UTR of cAMP-regulated gene.



Differentially expressed genes in Mtb treated with db-cAMP relative to butyric acid treated bacteria.

Gene product[a]	Locus	Change in expression (fold)	SD (Fold)	P value
CHP	[illegible]	-5.9	[illegible]	0.01
CHP	[illegible]	2.9	[illegible]	0.02
DnaK	[illegible]	3.7	[illegible]	0.02
GrpE	[illegible]	2.9	[illegible]	0.05
DnaJ	[illegible]	3.3	[illegible]	0.03
MmpS5	[illegible]	-2.1	[illegible]	[illegible]
CHP	[illegible]	2.3	[illegible]	0.04
CHP	[illegible]	2.0	[illegible]	0.03
CMP	[illegible]	8.8	[illegible]	0.02
FadD6	[illegible]	-5.1	[illegible]	0.04
HupB	[illegible]	-2.8	[illegible]	0.02
TRP	[illegible]	-6.5	[illegible]	0.03

[illegible]

Fig.: Analysis of cAMP-regulated gene expression profile of M. tuberculosis. A-B) Intracellular cAMP levels (A) and expression of 16 ACs by RT-PCR (B) in M. tuberculosis at different growth stages. C-D) cAMP levels (C) and RT-PCR expression analysis of 16 ACs (D) in M. tuberculosis following 2hrs of exposure to different stresses. Comparisons were made between stressed and unstressed cultures. E) Effect of exogenous cAMP on whole gene expression profile, as identified by microarray analysis. F) EMSA between cAMP-receptor binding protein (CRPM) and promoter region of various lengths of dnaK operon, identifying minimal region for binding (left panel). Subsequent effect of cAMP on binding between dnaK346-CRPM was observed by EMSA (Right panel).

Progress: We have identified that-

- M. tuberculosis exhibits maximum intracellular cAMP at day3 post-inoculation when the OD600 is 0.4, and this level sharply declines and remained constant for next four days of growth when cultures reach to stationary phase.
- Majority of ACs exhibit similar pattern of expression as is the intracellular cAMP levels, i.e., maximum expression on day 3-post inoculation when culture OD600 is ~0.3 followed be gradual decline over a period of growth.
- Cyclic AMP levels are significantly elevated in M. tuberculosis following heat stress, whereas other stress conditions such as oxidative, nitrosative or low pH do not affect intracellular cAMP pool in vitro.
- Expression of five adenylate cyclases namely Rv1647, Rv2212, Rv1625c, Rv2488c and Rv0386 was significantly increased by > 2-foldafter heat stress.
- Cyclic AMP regulates expression of a subset of heat stress-induced genes comprising of dnaK, grpE, dnaJ, and Rv2025c.
- CRP^{M} specifically recognizes a sequence $_{-301}$AGCGACCGTCAGCACG$_{-286}$ in 5'-untranslated region of dnaK, in a cAMP-dependent manner.

These results were recently published in PLoS ONE (Choudhary et al. (2014) PLoS ONE DOI: 10.1371/journal.pone.0089759)

Extramural projects

Toward the characterization of multiple P-loop GTPases in mycobacteria

Funding agency: Department of Biotechnology

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.

Objectives: The major objectives are-

- Assessment of GTPase activity in putative P-loop GTPases of mycobacteria.
- Characterization of the role of multiple P-loop GTPases in mycobacteria.
- Identification of interacting partners of P-loop GTPases in mycobacteria.

Progress: We have identified that-

- ObgE, Era and EngA exhibit significant GTPase activities, whereas the YchF protein which is annotated as GTPase, is actually an ATPase and lacks the GTPase activity. The GTPase activities in these proteins were also confirmed by mutating the G-domain residues which abolished their activity. Interestingly, expression of HflX could not be obtained despite repeated efforts because of lethality in E. coli and M. smegmatis due to overexpression of HflX.
- EngA interacts with 50S ribosomal subunit and the C-terminal domain of EngA is required for this interaction under the regulation of N-terminal G-domain (Agarwal et al., PLoS ONE 7(4) e34571).
- EngA, ObgE and YchF are localized to both cell envelope and cytoplasm, whereas the Era GTPase is restricted to only envelope of M. smegmatis and M. tuberculosis.
- EngA and YchF are required for optimal growth of M. smegmatis in 7H9 culture medium.
- Conditional depletion of EngA results in ~40% reduction in cell length compared to EngA-sufficient wild-type M. smegmatis. Moreover, average length of ~80% of the EngA-deficient cells was reduced to <4µm whereas only ~20% cells exhibited wild-type length.
- EngA significantly up-regulates expression of genes in M. tuberculosis that are involved in amino acid metabolism, cell wall biosynthesis, immune modulation and protein synthesis. Interestingly 40% of EngA-regulated genes encode envelope proteins, and >40% genes are essential for the survival of M. tuberculosis. Similarly, 40% of ObgE regulon also encode essential proteins, whereas >80% of HflX-regulated genes are essential, suggesting that these GTPase perform essential functions in mycobacteria.
- EngA and Era GTPases interact with few mycobacterial proteins, whereas other three GTPases, ObgE, YchF and HflX do not show any interaction in Co-IP experiments.

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Ms. Deepika Kannan (Lab manager)

Focus Research Area

Despite multiple interventions, Tuberculosis (TB) prevails. BCG, the widely used TB vaccine fails to protect adolescents and adults. Since Mtb-specific therapeutic interventions fail to eliminate TB and stop its transmission, designing superior vaccine alternatives seems a rationale decision. However, designing right vaccine remains a challenge as appropriate TB-tolerant/resistant human immuno-correlant profiles are yet undeciphered. Thus far, improvised BCG and designer subunits vaccines have failed in clinical trials. Consequently this raised questions on the rationale behind selection of "RIGHT" Mtb antigens. So, do all immunogenic-Mtb proteins become the "right" antigens?

By deploying a battery of virulence arsenal, Mtb suppresses and manipulates host immune and other cellular responses. Despite sustained efforts, very few Mtb virulent protein effectors have thus far been identified. Their functions being limited, they fail to explain Mtb pathogenesis to its entirety. The absence of a precise inventory and lack of Mtb's stockpile functions not only severely impairs our understanding of Mtb exploits, but also limits our ability to identify the "right" immunogens for TB vaccine. At this juncture, we hypothesize that Mtb deploys both "decoys" and "virulent effectors", wherein, in the backdrop of decoys which deliberately drive onto themselves host immunity focus, the "virulent effectors" manipulate the host cellular processes at will.

Using novel genetic, proteomic and biochemical strategies, Dr. Atmakuri's lab is currently exploring to (i) Decipher Mtb arsenal and their interacting host counterparts; (ii) Differentiate "decoys" from "effectors" for identifying "right" antigens; and (iii) Design possible alternate subunit vaccine vehicles that hoard "effectors" but not "decoys".

Intramural projects:

- Mycobacterial membrane-derived vesicles: Role in pathogenesis and exploration as novel subunit vaccine vehicles against Tuberculosis
- Deciphering Mycobacterium tuberculosis artillery

Collaborator: Dr. Jonathan Pillai

Extramural projects:

Mycobacterium tuberculosis pathogenesis and vaccine(s) design

Mycobacterial membrane-derived vesicles: Role in pathogenesis and exploration as novel subunit vaccine vehicles against Tuberculosis

Funding agency: DBT (through Ramalingaswami Fellowship plus grant)

Background: Despite worldwide use of BCG, TB continues to prevail. Though effective in children, it fails to protect adolescents and adults. Neither boosting BCG nor using BCG as booster works. Subunit vaccines that can supplement BCG as boosters are currently being explored. Most boosters involving 1-4 purified antigenic-Mtb candidates put together with an adjuvant have failed or are in clinical trials. Experts predict that an ideal subunit vaccine should contain multiple antigens targeting different stages of Mtb pathogenesis. As an alternate to liposomal-derived boosters, here we explore if membrane vesicles of Mtb could serve similar purpose.

Most bacteria generate membrane/outer-membrane vesicles (MVs/OMVs). Pathogenic bacteria exploit them towards pathogenesis. MVs are nanoscale (approx. 10-300 nm) proteoliposomes produced naturally and thus constitute a unique system in which the antigens and the delivery vehicle per se are naturally derived from the pathogen. Additionally, MVs circumvent safety limitations of attenuated/killed organisms administered as vaccines. Finally, MVs can be engineered to include several naturally un-incorporated antigens. The prediction is, since the

pathogen per se delivers the vaccine antigens of interest into recombinant OMVs, they retain native conformations to immune-stimulate better.

Objectives:

- Purify Mtb-derived OMVs, determine their contents and delineate their role in Mtb-mediated pathogenesis.
- Explore Mtb-derived OMVs as a subunit vaccine vehicle.

Progress: We intend to generate recombinant MVs (rMVs) from Mycobacterium smegmatis (Msmeg), a nonpathogenic mycobacterium species. Towards this, we have standardized conditions to enrich MVs from large volumes of culture filtrates of Msmeg grown invitro in minimal media. Using Mass Spectrometry, we identified ~110 Msmeg proteins in MVs. Currently we are deciphering ways to (i) understand the mechanism by which proteins get loaded into MVs and (ii) generate Msmeg rMVs with Mtb proteins.

Collaborators: Internal – Dr. Jonathan Pillai; External – Dr Aswin Sai Narain Seshasayee, NCBS

Deciphering Mycobacterium tuberculosis artillery

Funding agency: Department of Biotechnology

Background: Mtb's stockpile consists of a combination of lipids, proteins, sugars and small molecules. Surprisingly however, thus far, very few Mtb effectors have been identified and characterized. Lack of precise inventory of the Mtb's stockpile impairs our understanding of how Mtb wields its artillery. This limitation dilutes our strategies to initiate a co-ordinated assault on Mtb's virulent machinery and its "persistent" armour. Thus, for a better understanding of its virulence mechanisms and for designing superior vaccines and therapeutics against Mtb, it is critical to (i) identify its entire virulence artillery, (ii) delineate their host-specific functions, (iii) define their host molecular targets.

Objectives:

- Identify Mtb's entire protein stockpile that gain access into macrophages
- Determine the corresponding host cellular targets to the identified protein arsenal

Progress: To identify Mtb's protein effectors that access macrophage environment, we designed a genetic approach that exploits Cre-recombinase as a reporter. Using Gateway technology we first tag each ORF with NLS-Cre. Then we move them into virulent Mtb that infects recombinant macrophages carrying loxP-nptII-loxP-gfp genetic element under a ubiquitous promoter. When such a Cre-fused Mtb protein accesses host environment, the NLS promotes it to enter the nucleus. The hitch-hiking Cre then promotes recombination of loxP sites bringing the promoterless gfp in close proximity to the promoter for continued expression. Macrophages that receive an Mtb-fused protein thus turn green.

We procured the Mtb ORFeome entry clone library from BEI Resources, USA. We designed and constructed two complex destination vectors that help fuse Mtb ORFs in frame at their C- and N-termini with NLS-Cre. We have thus far moved 576 Mtb genes into the N-NLS-Cre vector and PCR amplified at least 100 missing (from ORFeome library) genes. We have recently procured the license to ship the recombinant mice required for infections. Once we receive the parents, we will breed them, generate bone marrow-derived macrophages and use them for our screen to decipher out the players.

DR. AMIT PANDEY

Team members

Dr. Gunjan Arora (Vaccine Research Innovation Awardee/ Postdoctoral Fellow)
Ms. Sakshi Talwar (Ph.D. Student)
Mr. Manitosh Pandey (Junior Research Fellow)
Ms. Arpita Mishra (Assistant Vaccine Technologist)

Focus research area

Carbon metabolism in Mtb and its implications on mycobacterial persistence

Very little is known about the nutritional requirements of Mycobacterium tuberculosis (Mtb) while replicating inside the host cell. After infecting host macrophages, Mtb replicates logarithmically for the first three weeks. On induction of host mediated adaptive immune response, the rate of Mtb growth declines, but maintains a constant level throughout the course of the infection. Although, Mtb is thought to survive on lipids inside the host macrophages, the exact intra-cellular diet of Mtb is not very clear. Various research findings suggests sugars along with lipids, derived from the host could be a major source of carbon for Mtb during the intracellular logarithmic growth phase. After the onset of the host mediated adaptive immunity, Mtb infection moves into the persistent stage. This team is working on the hypothesis that cholesterol is required for the maintenance of the persistent stage of Mtb infection. It is believed that this carbon switch is very critical for Mtb to slow down its replication and metabolic rate thereby activating a more latent form of infection. To clearly understand the implications of varied intracellular diet of Mtb, it is necessary to clearly understand what Mtb ingests inside the host cell. A better understanding of the type of intracellular carbon source available and the carbon source specific genetic signature would widen knowledge of the disease process. This would extend the range of potential genes that can be targeted for better therapeutics.

Intramural projects

Characterization of Mtb acetylome and its implications on carbon source utilization in Mtb

Regulation of metabolic pathways at the transcriptional level is well documented but recent reports highlight the importance of post-translational modification of enzymes modulating critical biochemical pathways. One such modification is Lysine-acetylation of proteins. Information on reversible lysine acetylation of metabolic enzymes in various pathogens also exists. It is therefore hypothesized that the lysine acetylation of proteins in Mtb might contribute significantly towards regulating metabolic pathways specific to various growth and stress conditions. In this project, lysine acetylation profiles of proteins from Mtb grown in cholesterol and glycerol media will be catalogued. The differential acetylation pattern will be further analyzed for its effects on cholesterol metabolism in Mtb. Initial lysine acetylation profiling of total Mtb proteins isolated from different growth conditions are intriguing. Standardization of the protocols for further analysis is underway. Initial observation suggests that a majority of Mtb proteins get acetylated and a detailed analysis of the lysine acetylome of Mtb under various growth and stress conditions would certainly reveal its implications on mycobacterial pathogenesis.

Cholesterol catabolism as therapeutics target

Current tuberculosis treatment regimen involves multiple drugs for a prolong period. The duration could be from three months to two years depending on the type of infection. Prolong treatment leads to non-compliance and emergence of newer drug resistance strains. Shortening the therapy would go a long way in alleviating this problem. It is widely perceived that the major culprits are the so-called non-replicating and metabolically inactive "persister" population. The importance of cholesterol metabolism during the persistence stage of Mtb infection and its potential role in generation of persisters is very intriguing. In light of the above facts and hypothesis the focus of the current proposal is to screen for chemical inhibitors that specifically target these pathways. The long-range goal would be identify novel anti-tubercular drugs that specifically targets "persisters". These novel compounds in combination with the standard frontline anti-tubercular drugs would significantly enhance the success rate in tuberculosis therapy.

Extramural projects

Dr. Pandey's postdoctoral work at UMASS has demonstrated that although Mtb ingests cholesterol throughout the infection process, cholesterol becomes essential only during the later stage of chronic infection. The proposal involves generation and characterization of Mtb strains lacking genes critical for cholesterol utilization. Genetic and molecular understanding of cholesterol utilization, its mechanism and relevance would contribute significantly in designing novel intervention strategies in the treatment of tuberculosis. The knowledge acquired on the genes involved in uptake and metabolism of cholesterol in Mtb is very likely to generate new and more efficient drug targets. The role of cholesterol metabolism in mycobacterial persistence would also be better understood. Information from the project on regulatory genes and the motifs of the related regulatory proteins would be very helpful in unraveling the complex regulatory network. The ultimate goal will be to generate an interactome map of the regulatory pathways of cholesterol utilization in Mtb.

Genetic essentiality study of Mycobacterium tuberculosis under various growth and stress conditions

Funding Agency: Department of Bio-Technology

Advancement in new cost-effective high throughput sequencing techniques has led to the identification of complete genome of various pathogens. The volume of the data generated, failed in its objective of further understanding of microbial pathogenicity. Genetic essentiality study of a pathogen is one such technique where in a gene is functionally characterized and associated with a phenotype. In this laboratory the process of standardizing protocol to study genetic essentiality of Mtb under various growth and stress condition is in progress. To achieve the goal, the use of mariner based mycobacteriophage system for generating high-density transposon mutant library is planned. The library will passage through different growth and stress conditions and the genetic essentiality would be determined by comparing input and output libraries.

Since it is demonstrated that cholesterol is required only during the late stages of Mtb infection, the hypothesis, that a genetic essentiality screen for the gene required for bacterial growth in cholesterol would be more relevant physiologically, if done under hypoxic conditions, is proposed. A better understanding on cholesterol metabolism at the molecular level under physiologically relevant conditions would definitely help in designing of effective therapeutic solutions for TB.

DR. GURUPRASAD MEDIGESHI

Team members

Tanvi Agrawal (Post-doctoral fellow – Vaccine research innovation awardee)
Rinki Kumar and Meenakshi Kar (PhD students)
Vijay Kumar S.R. (Senior Research Fellow)
Sharvani and Manisha Bhardwaj (Junior Research Fellows)
Mojahidul Islam (Research Assistant – Glue Grant scheme)

Focus research area

34 % of the global dengue infections occur in India and currently there are no vaccines or antivirals against dengue. The primary objective of our group is to understand the interplay between dengue virus and host responses both in cell culture models of infection and also in infected patients. We have employed targeted screening approaches to identify host factors and new chemical entities that are active against DENV and are characterizing the mechanism of action. We are also focusing on the human immune response to dengue virus to establish correlations between the viral load, genetics and disease outcome in pediatric patients.

Intramural projects

Characterizing the role of DENV capsid interacting proteins in dengue virus replication and assembly

Background and objective: Flavivirus assembly process is very rapid, as budding intermediates and cytoplasmic nucleocapsids have not been frequently observed but fully formed viruses can be found in the lumen of the ER. The highly basic C protein interacts with the viral RNA in the cytoplasm to form a nucleocapsid precursor that acquires an envelope by budding into the ER lumen. As nucleocapsid assembly is one of the most crucial steps in producing infectious virus, we intend to understand this key process by identifying host factors that participate in the formation of nucleocapsid and lead to maturation of viral particles to infectious virus.

Progress: DENV-2 capsid protein was expressed with a 6X-histidine tag in bacteria and the purified by nickel affinity chromatography as per standard protocols (Figure A). The capsid protein obtained after purification was dialyzed against the interaction buffer (Figure B) and was used in experiments to identify interacting proteins from Huh-7 cell lysates. We have performed interaction assays and have identified some interacting proteins by mass spectrometry (MS). We are currently validating the MS results by biochemical studies and will further elucidate the role of positive hits in DENV infection.

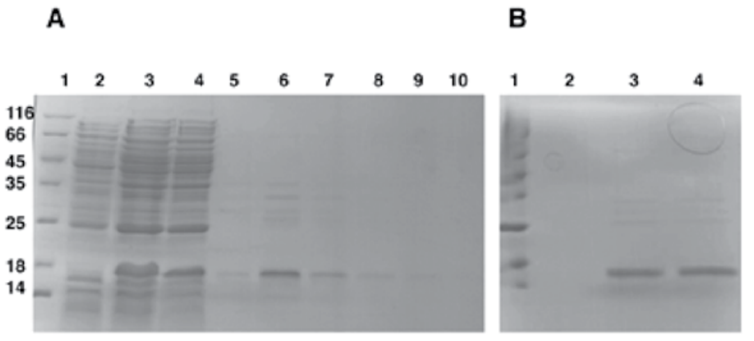


Figure : Purification of DENV-2 capsid. A. DENV-2 capsid was purified in BL21-DE3 cells using nIckel affinity chromatography. Ladder (1), vector lysate (2), capsid lysate (3), unbound fraction (4), eluates (5-10). B. Dialysis of purified capsid protein. Ladder (1), vectrol control (2), pooled capsid eluate (3), dialysed capsid eluate (4). Size of molecular weight marker bands are indicated.

b. Identification of DENV inhibitors from a chemical compound library

Background and objective: There are currently no vaccines or antivirals against DENV and recent vaccine clinical trials have not yielded promising results. Although a number of inhibitors targeting

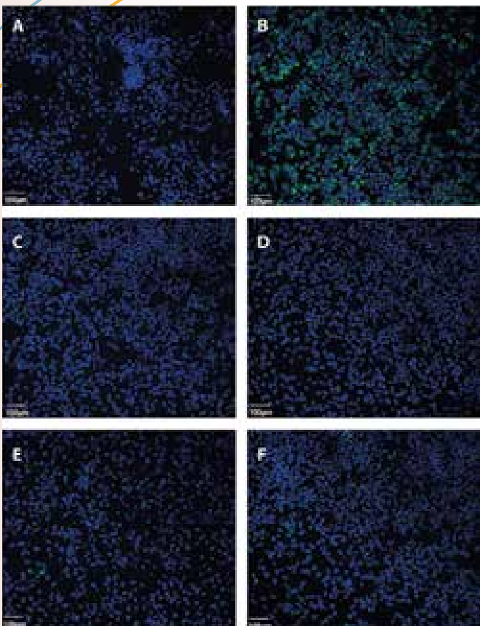


Figure: Screening of a chemical library for DENV inhibitors. Huh-7 cells were infected with DENV-2 and cells were incubated with inhibitors for 24 h, fixed and stained for DENV E protein (green). Nuclei are stained with DAPI (blue). A. Uninfected, B. DMSO, C-D: Four positive hits that inhibit DENV infection. Scale - 100 mM.

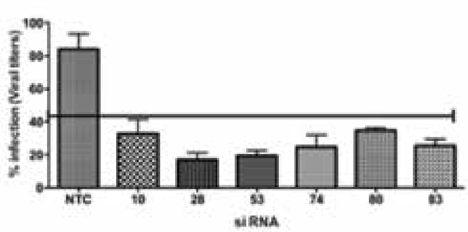


Figure: Identification of TKs involved in DENV infection. Huh-7 cells were transfected with the indicated siRNAs and infected with DENV 48 h post-transfection. Viral titers from the supernatants were measured by plaque assay at 24 h post-infection. Horizontal line indicates the 50% mark compared to non-targeting control (NTC) siRNA. Error bars indicate mean with SD of two experiments performed with triplicate samples.

77 children enrolled

37 M **40 F**

68 confirmed as DENV-2 by stereotyping

2 dual infections, 2 DENV-1 infections, 1 DENV-3 infection, 4 negative. 40 positive by C6/36 infection

Virus isolated from 3 patients after 3 passages

Cloned structural region from two isolates for sequencing and genotyping

Figure: Identification of correlates of disease severity in dengue patients. Workflow of dengue patient enrollment and virological studies during the previous two dengue seasons.

the viral protease and polymerase have been discovered the safety and efficacy of these compounds are yet to be proven. Our approach is to repurpose drugs that are approved for other conditions to treat dengue infections.

High-throughput screening: We have screened a library of pharmacologically active compounds by using a immunofluorescence-based high-throughput screening approach for DENV-2 infection in Huh-7 cells. After two iterations and elimination of false-positive hits and cytotoxic compounds we have identified 6 inhibitors that completely inhibit production of DENV-2 virus in cell culture. The following figure is a representative staining of four of the identified inhibitors. We are in the process of identifying the targets of these inhibitors and to characterize the stage of viral life-cycle that is affected due to the action of these compounds.

Extramural projects

Role of tyrosine kinases in dengue virus replication

Funding Agency: Department of Biotechnology

Objective: To identify human tyrosine kinases (TK) involved in DENV infection in cell culture

Progress: We have successfully completed siRNA library screening for 88 human TKs and after two rounds of screening and elimination of false positive hits, we have identified 6 TKs that are inhibiting DENV titers by over 50 % consistently without cytotoxicity . We also have identified 2 TKs that enhance dengue viral titers. We are in the process of characterizing the exact role of these TKs in dengue entry, replication and assembly/egress.

Identification of correlates of disease severity in pediatric dengue patients

Objective: To evaluate the qualitative and quantitative differences in the innate and adaptive immune responses in dengue infection with varying degrees of severity and to identify the soluble factors that could potentially be involved in causing vascular leakage.

Progress: A flow-chart of the progress of work in the virology component of the project is shown in the following figure.

A total of 77 dengue-positive children with different grades of severity were enrolled into the study and T- cell and B-cell responses were analyzed. Majority of the cases were DENV-2 positive as confirmed by serotyping. Dengue positivity was also confirmed in most of the cases by virus growth in mosquito cells. We are currently isolating DENV-2 isolates from these patients for genotyping and phenotypic characterization and to identify correlates between virulence and disease severity if any.

DR. MILAN SURJIT

Team members:

Mr. S.Chandru (Ph.D. student)
Ms. Nidhi Kaushik (Ph.D. student)
Ms. Saumya Anang (DST Inspire fellow)
Akriti Srivastava (Project Junior Research Fellow)
Ms. Karishma Bakshi (Project Junior Research Fellow)
Ms.Vidya Padmanabhan Nair (Project Junior Research Fellow)

Focus research Area

Hepatitis E Virus (HEV) causes acute hepatitis characterized by jaundice, anorexia, nausea, abdominal pain, malaise, fever and hepatomegaly. A peculiar property of HEV is its ability to induce high mortality (~20%) in pregnant women; otherwise, the disease is self-limiting, with ~0.2-1% mortality. Chronic HEV infection is observed in ~60% liver transplantation patients. HEV is a positive strand RNA virus belonging to the genus Hepevirus. It has been classified into 4 genotypes. HEV genotype -1 and 2 are known to infect only human whereas genotype 3 and 4 viruses have been found in human as well as swine, cattle, rabbit, deer and mongoose. Globally, 3.4 million cases of acute Hepatitis E are attributed to infection with HEV genotypes -1 and 2. HEV accounts for ~50% cases of acute hepatitis in India. Genotype -1 HEV is more prevalent in India. Therefore, in the Indian context, it is practically important to study the life cycle of genotype -1 and 2 HEV and develop intervention strategies against it.

Although HEV was discovered more than 20 years ago, little is known about the viral life cycle, owing to lack of an efficient model system. Limited information exists about viral encoded proteins, only some of them have been studied and characterized in vitro to some extent. From developing an efficient model system, to identifying new targets for therapeutic intervention, since its inception, my laboratory has been focused at understanding the various aspects of genotype 1-HEV biology, with the ultimate aim to eliminate or control genotype 1-HEV induced health problems in human.

Intramural project

Construction of the protein interaction map of Hepatitis E virus to understand the mechanism of HEV life cycle and identify crucial targets for therapeutic intervention

Background and progress: Protein-protein interactions (PPI) are essential for relaying information and maintaining physical integrity of an organism. Since viruses depend on host cells for survival, interaction between virus & host proteins are crucial for survival of the virus. No report exists regarding the network of PPI among Hepatitis E virus (HEV) and host proteins except for one on ORF3 protein. We propose to establish a map of PPI network among HEV and host factors, which will advance our understanding of the molecular mechanism of HEV life cycle & unravel new targets for anti-HEV intervention strategy.

We intend to identify direct and indirect interactions among HEV and host proteins by following two different approaches: Yeast two hybrid library screening and Affinity Purification-Mass spectrometry, using HEV proteins as bait. These data will be assembled to construct the map of protein-protein interaction network between HEV and host factors. Relevance of these interactions during the life cycle of HEV will be initially evaluated using the HEV replicon model

developed in my laboratory. Depending on the outcome, further studies will be planned to identify crucial targets for therapeutic intervention.

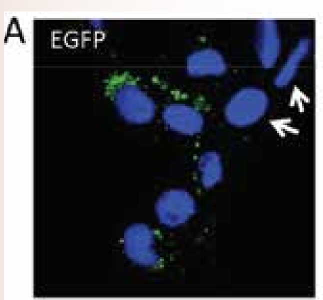
Towards developing an efficient model system for studying HEV life cycle: exploring the mechanisms dictating poor replication efficiency of genotype-I HEV

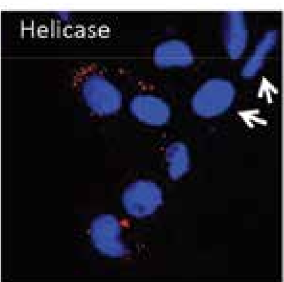
Background and progress: Despite sharing similarity in genome organization and encoding similar proteins, genotype-3 HEV replicates more efficiently in cell culture system than genotype-I HEV. We have been exploring the possible mechanisms underlying this discrepancy using a variety of biochemical and molecular biology techniques. Our study has revealed a new virus encoded factor, which appears to play a significant role in genotype-I HEV replication. Ongoing work aims at further characterizing the function of this protein and utilize the information thus obtained in establishing a better laboratory model of genotype-I HEV.

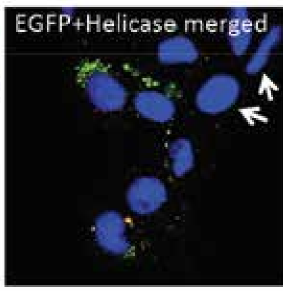
Extramural project

Establishment of a mammalian cell culture based Hepatitis E Virus (HEV) expression system to study the viral life cycle and application of the secreted virion as a candidate vaccine

Funding agency: Department of Science and Technology







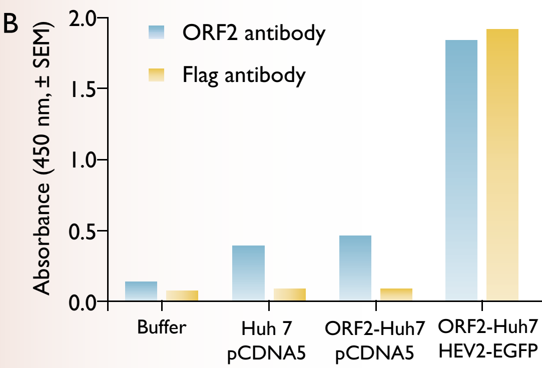


Figure (A) Immunofluorescence image of ORF2-Huh7 HEV-EGFP cells showing the expression of EGFP (left), Helicase (anti-Helicase primary and Alexa fluor 568 secondary antibody staining, middle) and superimposed image of EGFP over Helicase (right). Blue color denotes DAPI stained nuclei and arrow denotes cells without EGFP and Helicase signal, which demonstrates specificity of the signals. (B) ELISA of indicated cell culture medium using ORF2 and Flag antibody.

Background and progress: One of the major hurdles in studying genotype-I HEV life cycle (which is more prevalent in India) in the laboratory is attributed to lack of an efficient cell culture based or small animal model system. Two different host systems are being explored for establishing a cDNA based model of genotype I Hepatitis E infection, which include (A) mammalian cells (such as human hepatoma cells), (B) Yeast (Saccharomyces Cerevisiae).

Up to now, we have been successful in establishing a EGFP based replicon model of HEV in human hepatoma cells. These cells (named ORF2-Huh7 HEV-EGFP) stably express EGFP fused HEV genome (central part of ORF2 coding sequence is replaced with that of EGFP) and flag-tagged ORF2 from two different expression cassettes. Upon replication of the viral genome, EGFP is expressed, as indicated by green fluorescence (Figure A). Trans-expressed ORF2 allows encapsidation and release of the EGFP encoding genome to the culture medium, which can be quantified by ELISA using antibodies against ORF2 and Flag (Figure B). These secreted virions are able to infect normal Huh7 cells, although at a lower efficiency. As it allows performing two independent assays to monitor viral replication and release, this replicon model would be instrumental in studying the mechanism of HEV life cycle as well as for screening anti-virals against HEV. Ongoing work aims at further characterizing the model.

To identify novel therapeutic compounds that inhibit the interaction between Hepatitis E Virus ORF3 protein and TSG 101 and to explore the molecular mechanisms controlling the release of Hepatitis E virions from infected cells.

Funding agency: Department of Biotechnology

Background and progress: No drug is available against HEV induced hepatitis in human. A recent report has demonstrated the essential role of the interaction between HEV ORF3 protein and cellular TSG 101 (Tumor Susceptibility Gene 101) protein in mediating genotype 3 HEV virion release. Since my earlier study has demonstrated the interaction between genotype 1-HEV ORF3 protein and TSG 101, similar mechanism may be operational in the case of genotype-1 virus too. We are interested in identifying cell permeable, small cyclic peptide based inhibitors of this interaction, which could be an effective way of blocking viral spread. A similar approach may be adopted to identify inhibitors of additional crucial targets, to enable the development of a more robust combinatorial formulation against HEV. We are also focusing on identifying additional factors responsible for genotype-1 HEV release, which might be targeted using cyclic peptides.

DR. RANJITH-KUMAR

Team members

Dr. Rajpal (Research Associate)
Ms. Smita Hingane (PhD. Student)
Mr. Nishant Joshi (Junior Research Fellow)
Ms. Abhilasha Madhvi (Junior Research Fellow)

Focus research area

We are interested in studying the replication mechanisms of hepatotropic RNA viruses such as hepatitis C virus and hepatitis E virus with the aim of developing better direct-acting antivirals. The study extends to understanding the strategies used by viruses to evade host innate immunity responses with the goal of developing attenuated vaccines.

Intramural projects

Screening of small molecule compounds to identify inhibitor(s) of hepatitis C virus (genotype 3a) RNA-dependent RNA polymerase

Background: According to World Health Organization, hepatitis C virus (HCV) affects more than 180 million individuals worldwide. In India, nearly 12.5 million individuals are suffering from HCV infection, with more than 100 thousand people getting infected every year. Chronic infection of HCV is one of the leading causes of liver cirrhosis and hepatocellular carcinoma. The high rate of chronicity along with the lack of successful vaccine makes HCV a serious health issue. Effective antiviral drug for the treatment of HCV remains a serious need for the entire world in general and for India in particular. Currently, HCV infection is treated for 48 weeks with a combination of modified interferon and ribavirin. A significant portion of patients cannot tolerate the side effects of these treatments or will not respond to treatment, likely due to genetic predisposition. There is an urgent need to develop better direct acting antiviral drugs that could be used in conjunction with interferon or to develop an ideal interferon free regimen. Since HCV genotype 3a is the most prevalent form of HCV in India, focus is on its RNA dependent RNA polymerase (RdRp) for developing antivirals.

Progress: A cell-based assay to characterize HCV genotype 3a RdRp in mammalian cells has been established. This assay is used to screen small molecule compound library with the goal of identifying HCV 3a RdRp specific inhibitor. Upon screening around 3500 compounds, about 10 compounds were found to inhibit the RdRp at a concentration lower than 10 μM. To study the efficacy of these compounds on HCV replication, a replicon-based assay was established. The potential inhibitors of RdRp were tested on the replicon and observed that about 5 compounds showed concentration dependent inhibition of HCV replication. The process of further characterization of these potential inhibitors is in progress. These compounds will also be tested against RdRps of all the major genotypes of HCV to identify a potential pan genotype inhibitor.

Interference of innate immunity response by hepatitis E virus

Background: How RNA viruses can establish successful infection in the face of the host innate response is important for pathogenesis and will offer potential solutions to some of the most deadly diseases. Viral RNAs contain molecular signals known as pathogen associated molecular patterns (PAMPs) that are detected by innate immunity receptors to activate a suite of cellular defense responses. Viruses are known to have evolved strategies to interfere with the host responses either by blocking recognition of molecular patterns or by cleaving adaptor proteins.

Hepatitis E virus (HEV) is one of the most important pathogenic viruses infecting humans and is a major cause of enterically transmitted epidemic as well as sporadic hepatitis worldwide. The prevalence and persistence of hepatitis E virus in the underdeveloped and some industrialized countries have spurred the need for generation of antiviral drugs and vaccines. This laboratory is interested in characterizing biological role of the HEV proteins during viral infection with special focus on their involvement in interfering with innate immunity response.

Progress: The role of HEV proteins in interfering with innate immune response has been investigated and it was observed that a couple of the HEV encoded proteins block signaling by innate immune receptors. Further characterizations of these proteins are in progress.

Extramural Project

Characterization of hepatitis E virus RNA-dependent RNA polymerase and its associated proteins in the replicase complex

Funding agency: Department of Biotechnology

Background: HEV is a difficult virus to cultivate in cells. Absence of efficient cell culture system has long hindered HEV research and replicon mediated approaches has been the primary method used to study HEV replication. However, these approaches have its limitations especially to study mechanism of action and regulation of RdRp. Unlike RdRps from hepatitis C virus and poliovirus, there is very little information available on the mechanism of action of HEV RdRp.

The RdRp is an essential enzyme found in all RNA viruses and hence is a potential target for drug design and development. The viral replicase complex, which is responsible for the replication of the viral RNA, is formed by the association of RdRp with other viral non-structural proteins and some of the host proteins. In spite of the critical role of RdRp in the viral life cycle, the replication of HEV is poorly understood. Understanding viral replication will be crucial for the development of more effective antivirals.

The main objectives are to establish a non-radioactive assay for HEV RdRp and to characterize the requirements for RNA synthesis by HEV RdRp.

Progress and future plans: All the clones required for expression of HEV RdRp in bacterial and mammalian cells have been generated. The conditions for purification of recombinant RdRp are being standardized. Purified RdRp protein will be used to develop a fluorescence based sensitive assay to characterize viral RNA replication. Furthermore, role of HEV encoded structural and non-structural proteins along with host proteins involved in regulation of RNA synthesis will also be analyzed. Characterization of viral RdRp will provide important information on the replication of HEV and help in development of better direct acting antivirals.

Collaborator: Dr. Milan Surjit

DR. MANJULA KALIA

Team members

Manish Sharma (PhD student)
Minu Nain (PhD student)
Renu Khasa (Senior Research Fellow)

Focus research area

Flaviviruses are important arthropod-borne viruses that cause human disease globally. Japanese Encephalitis (JE) is the leading form of viral encephalitis in South-East Asia and India. Around 30,000-50,000 cases of JE and up to 15,000 deaths are reported annually. The major focus of research in our group is on the broad objectives of virus receptors, virus entry pathways and the role of autophagy in virus pathogenesis. We plan to extend our studies from tissue culture to animal models and patient samples in order to enhance our understanding of the molecular basis of disease. We hope to apply this knowledge to benefit patients through identification of possible therapies and vaccine candidates and by the development of anti-viral drugs.

The obligatory dependence of an infecting virus on host-encoded factors, provides an opportunity to develop therapeutic regimes, which would target host pathways. The development of viral encephalitis in only a fraction of humans inoculated with JEV by a mosquito bite, suggests a critical threshold of inoculum or viral replication which can be successfully undertaken by the host immune system. Therefore a therapeutic regime which, although not very dramatic in effect, is able to attenuate the viral replication to a level beneath that threshold, can be potentially developed to eliminate or at the minimum limit the virus-induced damage. We focus on the host responses to virus infection, which include innate anti-viral response and endoplasmic reticulum stress pathways. The death or extensive neuronal damage in survivors, caused by JEV infection, emanates from a combination of these two host pathways. Neuronal damage is caused by the blend of a burst of cytokine release and apoptotic cell death from uncontrolled ER-stress. A characterization of these pathways is being performed and is providing interesting leads with respect to potential therapeutic target. Using known drugs that target ER-stress pathway, we have shown that inhibiting specific enzymatic reaction can significantly attenuate viral replication. A detailed characterization of this observation in addition to exploration of new targets in the same pathway is being followed.

Intramural projects

Identification of the Japanese Encephalitis Virus Attachment and Receptor system

Background: Binding of a virus to its specific receptor is a key event that initiates infection.

To identify the JEV receptor we are using the JEV-Envelope Protein Domain III (ED3) as an exploratory system. The envelope (E) protein of JEV folds into three structural domains, and it is the third domain (ED3) that mediates viral attachment to the host cells, and carries epitopes that elicit a neutralization response. JEV-ED3 was expressed and purified using a bacterial expression system. The recombinant JEV-ED3 binds to the surface of host cells and can compete for infection by JEV, thus establishing it as a valid tool to initiate receptor studies. Biochemical Studies to find interacting partners of JEV-ED3 were done and membrane proteins that specifically interact with JEV-ED3 were resolved on 2D gels and specific proteins/spots were analysed by Mass Spectroscopy.

Mass spectroscopy analysis showed GRP78 as a JEV-ED3 binding protein. GRP78 (glucose-regulated protein of 78 kDa) is traditionally regarded as a major ER chaperone facilitating protein folding and assembly, protein quality control and regulating ER stress. GRP78 is also expressed on the surface of cells where it regulates cell signalling and cell viability. GRP78 also serves as a co-receptor for Dengue virus serotype 2 and Coxsackie virus.

Progress: GRP78 interacts with JEV-envelope protein.

Our studies indicate that GRP78 is expressed on the surface of several cell lines. Antibodies directed against GRP78 block JEV infection highlighting the possible role of GRP78 as a virus receptor. The interaction between JEV-Envelope and GRP78 has been further validated by Mammalian 2- hybrid studies. Docking studies between GRP78 and JEV-E have been done (in collaboration with Dr. Sowdhamini's group at NCBS, Bangalore). By these studies we have been able to identify putative interacting residues between these proteins. Currently we are validating these results by biochemical experiments.

Elucidating the cellular entry mechanisms of JEV using high-resolution imaging based studies

Background: A complex network of endocytic pathways is operational at the eukaryotic plasma membrane, which can be exploited by pathogens to gain entry into a permissive cell and establish infection. The route of virus entry can differ between cell types. In addition to utilizing the already-operational endocytic pathways, in several cases viruses can induce pathways conducive to entry by receptor binding and signaling events. 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, endocytic pathways display extensive cross-talk with respect to molecular players and cargo sorting and recent studies have demonstrated that a high degree of plasticity exists in eukaryotic cells. We are interested in defining the endocytic pathways utilized by JEV for entry into cells in terms of key molecular players using fluorescently labelled virus particles and high-resolution imaging.

Recent studies in our lab have shown that JEV entry in neuronal cells occurs via a clathrin independent endocytic mechanism. By using fluorescently labeled virus particles, a combination of pharmacological inhibitors, RNA interference (RNAi), and dominant-negative (DN) mutants of regulatory proteins involved in endocytosis we established that JEV infects fibroblasts in a clathrin-dependent manner, but it deploys a clathrin-independent mechanism to infect neuronal cells. The clathrin-independent pathway was shown to require the scission molecule-dynamin and plasma membrane cholesterol. Virus binding to neuronal cells leads to rapid actin rearrangements and an intact and dynamic actin cytoskeleton, and the small GTPase RhoA plays an important role in viral entry (Kalia et al., 2013).

We are further extending these studies to identify host membrane trafficking genes involved in Japanese Encephalitis Virus life cycle- entry, replication and infectious virus particle production,

by RNA interference screen in human neuronal cells and fibroblasts.

Progress: We are currently in the process of standardizing the RNAi screen in human fibroblasts and neuronal cells.

Role of the host autophagy pathway in the JEV infection process

Background: Autophagy is an important cellular process that maintains cellular homeostasis. Autophagic cargo such as long-lived cytoplasmic proteins and dysfunctional organelles are sequestered by double-membrane vesicles (autophagosome) and are degraded after autophagosome-lysosome fusion. The autophagic mechanism is constitutive and generally operates at a basal level in all cells, but is up-regulated in response to extracellular or intracellular stress, and pathogen infection. It is also an important component of the innate and adaptive immune response against a variety of viral and bacterial pathogens. Viruses can abrogate and/or exploit the autophagic process to enhance their replication or transmission.

We have examined the role of autophagy in the life-cycle of JEV. We observe that JEV infection leads to induction of autophagy in several cell types. Quantitative real-time PCR shows that JEV infection leads to transcriptional upregulation of key autophagy genes and accumulation of autophagic vesicles in the cell.

Progress: To elucidate the role of autophagy in the JEV life-cycle we employed cells where autophagy was disrupted by depletion of key autophagy genes. We observed that JEV replication was significantly enhanced in neuronal cells where autophagy was rendered dysfunctional by ATG7 depletion, and in Atg5 deficient Mouse Embryonic Fibroblasts (MEFs), resulting in higher viral titers. Autophagy was functional during early stages of infection however it becomes dysfunctional as infection progressed resulting in accumulation of misfolded proteins. Autophagy deficient cells were highly susceptible to virus induced cell death. We also observed that JEV replication complexes that are marked by Non-structural protein 1 (NS1) and dsRNA colocalized with endogenous LC3 but not with GFP-LC3. Colocalization of NS1 and LC3 was also observed in Atg5 deficient MEFs, which contain only the nonlipidated form of LC3. Viral replication complexes furthermore show association with marker of the ER Associated Degradation (ERAD) pathway- ER Degradation Enhancing □-Mannosidase-like 1 (EDEM1). Our data suggests that virus replication occurs on ERAD derived EDEM1 and LC3-I positive structures referred to as EDEMosomes. While silencing of ERAD regulators EDEM1 and SEL1L supressed JEV replication, LC3 depletion exerted a profound inhibition with significantly reduced RNA levels and virus titers. While autophagy is primarily anti-viral for JEV and might have implications for disease progression and pathogenesis of JEV, nonlipidated LC3 plays an important autophagy independent function in the virus life-cycle.

DR. MOHAN APPAIAGARI

Team members:

Ms. Vishavjeet Khairwal (Senior Research Fellow)

Focus Research Area:

Adenoviruses had been the subject of intense research for several reasons; one among them is their role as delivery vectors. Initially, human adenoviruses type 2 (HAdV2) and type 5 (HAdV5) have been extensively studied and vectors derived from these viruses were used

to deliver therapeutic genes/genes coding for vaccine antigens. Soon it was realized that pre-existing immunity to these viruses reduces the bioavailability of vector viruses after intravenous administration and, in the recent STEP trial, has also been shown to increase the risk of HIV infection. To overcome this limitation, several non-human adenovirus-based vectors are being developed. However, most of these vectors are IPR protected and, hence, are not freely accessible for use in India. Thus, we collected nasal and fecal samples from domestic animals and birds to identify novel adenoviruses, and we are currently investigating their suitability for novel vector development.

We are also interested in investigating the usability of existing vaccine delivery platforms for the development of effective vaccines against viral diseases that are important in Indian context. Currently, we have considered ovine adenovirus and Mycobacterium bovis BCG to investigate their ability to express flaviviral antigens and induce protective immune responses in animal models. Ovine adenovirus vector has been tested in several studies to express therapeutic antigens and, in some, to express vaccine antigens in animal models. On the other hand, M. bovis BCG is used to immunize infants to protect from tuberculosis and some of the studies have also shown its ability as vaccine delivery vector.

Intramural projects:

Use of Mycobacterium bovis BCG as a vaccine vector

Mycobacterium bovis BCG is used to immunize infants to protect from tuberculosis. It has also been explored as a vector to deliver heterologous antigens. A recombinant BCG expressing JEV envelope (JEV-E) protein might be an attractive vaccine candidate. In this direction, we made constructs carrying cDNAs encoding the anchored or the secretory form of JEV-E either alone or in combination with those encoding other structural proteins. As M. bovis BCG is an intracellular parasite that generally persists in antigen presenting cells (APCs), expression of vaccine antigens in BCG would allow efficient presentation to the host immune system. The secretory signal component of Ag85B was used to facilitate secretion of the recombinant proteins into the infected host cell environment, which may in turn result in secretion into the extracellular environment. Based on the direct western blot analyses as well as immune-precipitation followed by western blot analyses, we found that three constructs – prM-Es without secretory signal, secretory form of JEV-E with and without the signal – showed easily detectable expression in M. smegmatis as well as in M. bovis BCG. Currently, we are producing the immunization stocks of these BCG recombinants for mouse immunization experiments.

Use of Ovine Adenovirus as a vaccine delivery vector

Ovine adenovirus based vector has been shown to be a potential gene delivery vector and some of the studies have explored its usefulness as an efficient vaccine delivery vector even in the presence of HAdV5-neutralizing immunity. To further strengthen this claim and also to explore its ability to deliver flaviviral antigens to induce protective immune responses, we have generated a recombinant ovine adenovirus expressing JEV-E protein (ROAdVEs). Recently, we have shown that this recombinant virus is as good as RAdEs, a HAdV5-based recombinant expressing JEV-E protein, in inducing JEV-specific neutralizing immunity in naïve mice. Our next aim is to compare its ability to induce anti-JEV protective immunity in the presence of HAdV5 neutralizing immunity with that induced by RAdEs. Currently, we are producing the recombinant adenoviruses in large scale for purification, which will then be used to carry out the immunogenicity studies in HAdV5 exposed/unexposed mouse models.

Extramural projects:

Development of non-human adenovirus-based vaccine delivery vectors

Funding Agency: Dept. of Biotechnology,

Adenoviruses had been used to study various eukaryotic cell processes as well as to understand the complex structural assembly of viral capsids. Besides this, their ability to deliver therapeutic genes/vaccine antigens is being constantly explored. Initially, HAdV5 and HAdV2 had been the vectors of choice due to the wide range of advantages they offer. Studies in clinical settings have raised concerns over the interfering effect of Ad-specific immunity in human subjects, which led to the development of novel non-human adenovirus-based vectors. However, these vectors are IPR protected and cannot be used freely in India for the development of novel vaccines and/or therapeutics. We therefore collected samples from domestic birds and animals with an aim to isolate novel adenoviruses that can be used to develop novel vectors for use in India.

Until now, we have isolated adenoviruses from Fowl, Equine, Bovine and Porcine samples and adapted these isolates to cell cultures. One isolate each from Fowl and Equine species were grown in large scale, purified and their genomic DNAs were sent for NGS analyses. We have completed the de novo assembly for the fowl adenovirus and the same for the equine adenovirus is currently going on. De novo assembly followed by bioinformatic analyses for FAdV isolate suggested that this isolate is a member of species C of Aviadenovirus and that the virus may be a result of recombination events between FAdV4 and FAdV10, both members of species C. Further, we investigated its ability to replicate in cells other than fowl origin, including those from human, which indicated that the virus failed to show any detectable genome replication in cells other than the fowl cell line. However, these studies do not rule-out its ability to infect and deliver its genome in to non-fowl cell types. With respect to vector development, we are in the process of constructing the infectious clone, which will ultimately be used to develop the delivery vector. As a part of this, we have sequenced the RNA preparations from cells harvested at different time points post-infection. Currently, we are analyzing the RNA-seq data to establish the transcriptome map, which would let us identify sites for foreign gene insertion.

DR. DEEPAK SHARMA

Team members:

Pragya Priyadarshini (Junior Research Fellow)

Focus research area

The complete sequence of Japanese Encephalitis Virus (JEV) strain P20778, isolated from human brain in 1958, was determined about 15 years ago. Since then, it was passaged >100 times through porcine kidney or mouse brain cells. Sequencing of this laboratory passaged strain (P20778-lab) revealed that its divergence from the parental strain was comparable to that between two distinct JEV isolates indicating that P20778-lab is almost a new strain. In support, phylogenetic analysis showed that P20778-lab strain was closer to a recently isolated JEV H225 strain than its own parental strain. Comparison between P20778 and P20778-lab strains revealed 58 nucleotide alterations and 16 amino acid changes. Strikingly, 14 (out of 16) amino acid changes were also present in H225 strain. Similar evolutionary changes in P20778-lab and H225 strains despite being in different environments (laboratory vs. field; diverse geographical location) suggest that these alterations are beneficial for JEV growth and/or infection. Additionally, relative to the parental strain, there was no change in the protein sequence of NS1 (even after such extensive timespan/

passaging in the absence of selection pressure) as also observed for the three key proteins - Capsid, NS2b and NS3 (latter two form serine protease). This implies that NS1 is as crucial and invariable as other key proteins. Molecular dynamics simulations indicate reduced thermodynamic stability of the E dimer from P20778-lab compared to that from P20778.

DR. SANKAR BHATTACHARYYA

Team members

Utsav Sen (Junior Research Fellow).

Focus research area

The obligatory dependence of an infecting virus on host-encoded factors, provides an opportunity to develop therapeutic regimes, which would target host pathways. The development of viral encephalitis in only a fraction of humans inoculated with JEV by a mosquito bite, suggests a critical threshold of inoculum or viral replication which can be successfully undertaken by the host immune system. Therefore a therapeutic regime which, although not very dramatic in effect, is able to attenuate the viral replication to a level beneath that threshold, can be potentially developed to eliminate or at the minimum limit the virus-induced damage. We focus on the host responses to virus infection, which include innate anti-viral response and endoplasmic reticulum stress pathways. The death or extensive neuronal damage in survivors, caused by JEV infection, emanates from a combination of these two host pathways. Neuronal damage is caused by the blend of a burst of cytokine release and apoptotic cell death from uncontrolled ER-stress. A characterization of these pathways is being performed and is providing interesting leads with respect to potential therapeutic target. Using known drugs that target ER-stress pathway, we have shown that inhibiting specific enzymatic reaction can significantly attenuate viral replication. A detailed characterization of this observation in addition to exploration of new targets in the same pathway is being followed.

DR. ARUP BANERJEE

Team members:

Ms Bharti Kumari; PhD Student
Ms Pratistha Jain, (Junior Research Fellow, Project)

Focus research area

- To understand the role of miroRNAs in Japanese Encephalitis virus infection and pathogenesis
- Understanding early transcriptional signature of Dengue virus and clinical features associated with disease progression

Intramural projects:

Identification of host microRNAs that potentially target JEV genome and inhibit JEV replication

MicroRNAs (miRNAs) are 21–23nt long regulatory, non-coding, small RNAs that repress target gene translation through base pairing to complementary sequences in the 3'-untranslated region (3'-UTR) of targeted transcripts. The potential involvement of host miRNAs in JEV infection is interesting, particularly given the documented participation of host miRNAs in the replicative cycles of other mammalian viruses. For instance, host miR-32 restricts primate foamy virus 1 replication and host liver-specific miR-122 facilitates the replication of the hepatitis C viral RNAs. Recent reports suggested that JEV infection can alter host gene microRNAs to alter cellular immune response against the virus. Using microRNA array analyses of *in vitro* JEV-infected human microglial cells, we find that several host microRNAs are significantly up- or down regulated around the time JEV infection peaks *in vitro*. Using Bioinformatics analysis, we have found several down regulated miRNAs that have perfect seed match homology with the 3'UTR of the JEV genome. Binding energy and the accessibility of binding site are also calculated with bioinformatics software. Based on stability and accessibility of multiple binding sites we have identified several microRNAs that can target multiple region of 3'UTR of the JEV genome. Few of them are also highly enriched in Brain. We are now validating the expression of those microRNAs in microglial, neuronal cells as well as mouse brain infected tissue and RNA. We are now making a reporter based construct to validating the targets. We believe, to the end of the study, we will able to identify host microRNAs that could efficiently block JEV replication. Further, the change of transcriptome profile due to overexpression of these miRNAs on brain will be monitored in vivo using Next Generation Sequencing.

Extramural projects

Role of microRNAs in establishment of Japanese Encephalitis Virus (JEV) infection and disease progression

Funding agency: Department of Biotechnology

Background: Japanese encephalitis (JE) is an acute central nervous system inflammatory disease caused by infection with Japanese encephalitis virus (JEV), a small, enveloped, plus-strand RNA virus belonging to the family Flaviviridae. It is the leading cause of viral encephalitis in South-East Asia, India and China, where 3 billion people are at risk of contracting the disease, yet its pathogenesis remains poorly understood. In the past decades there has been an expansion of the geographic distribution of the virus in Asia and the Asia-Pacific region (van den Hurket al., 2009) and there is an urgent requirement for improved human JE vaccines. An understanding of the immunological responses that lead to recovery from infection with JEV and account for vaccine-mediated protection is important in the design of rational approaches to new treatments and vaccines against the disease. MicroRNAs (miRNAs) are small RNA (~22 nt) molecules expressed endogenously in cells. They are involved in the regulation of gene expression. Considering that cellular miRNAs play important roles in many mammalian viral life cycles, it is presumed that they may also participate in the molecular pathogenesis of viral infection.

Our focus in this project is to understand how miRNAs cross talk with innate immune response during JEV infection and explore miRNAs based system to attenuate JEV replication. We hypothesize that viral and host interactions are likely to provide powerful selection forces that can modulate host immune responses by altering host cell miRNA expression.

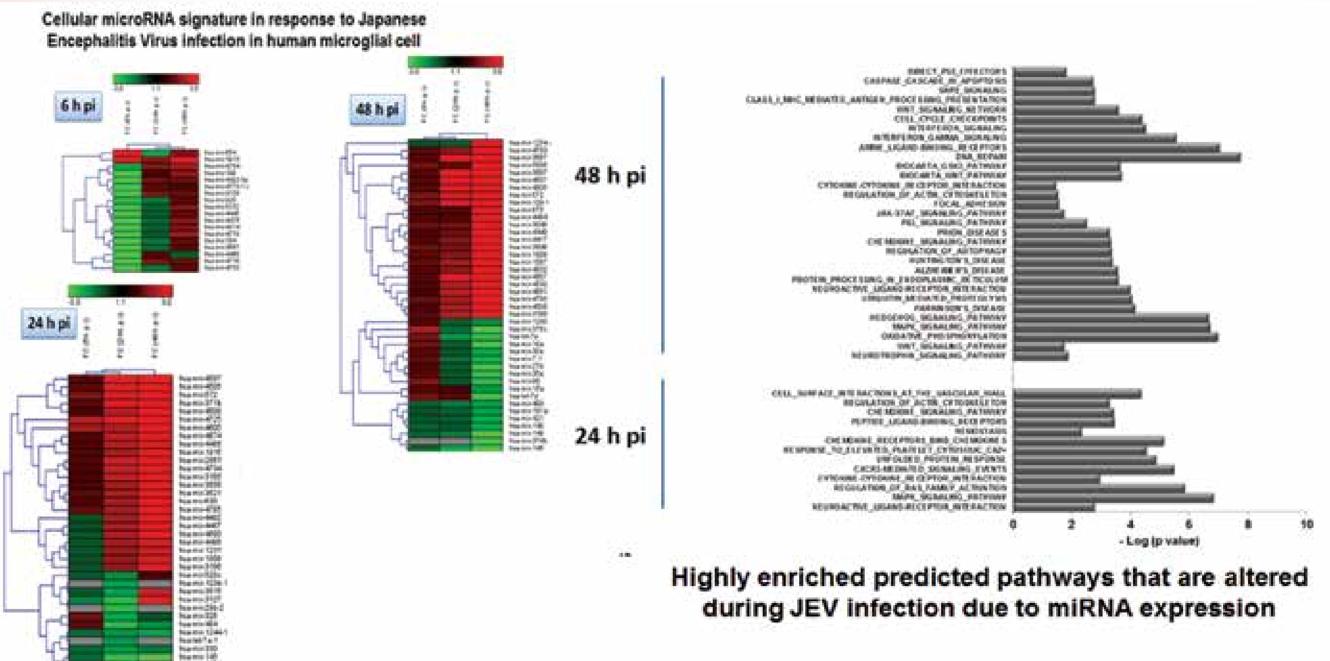
The current research work includes complementary but independent aims to address

Objective 1: Identify microRNAs (miRNAs) that are involved in innate immune modulation during JEV infection in microglia cells

Objective 2: Validate the predicted target and their functional consequences in context to host immune response in JEV infected microglia cells

Objective 3: Verify in vivo the role of miRNAs to attenuate JEV replication

In previous studies where small RNA-Seq has been applied to any virus infected cells, the focus has typically been on virally encoded microRNAs or on single time points, providing static snapshots of infection. In this project, we use Affymetrix GeneChip® miRNA 3.0 Array, cover all the microRNAs reported in miRbase version 17, to observe dynamic changes in cellular miRNAs from JEV-infected human microglia cells. To this end, we sampled multiple time points, including those preceding detectable JEV replication, to identify signatures of different stages of infection in vitro. To characterize microRNAs, we will then integrate our microRNA data set with mRNA data derived from the same experimental samples and thereby identified



microRNAs that may contribute to phenotypic changes (microglia polarization between M1 and M2 phase) in infected cells over time.

So far, we have completed microRNA and mRNA profiling from JEV infected human microglial (CHME3) cells.

- MicroRNA expression was significantly altered in JEV infected human microglial cells. A time dependent change in microRNA profile was noted. Bioinformatics analysis identified anti correlation between differentially expressed miRNAs and the gene expression at different time point which ultimately affected several signalling pathways in microglia cells. The following highly enriched pathways were identified.
  - MAPK_signaling_pathway;
  - Wnt_signaling_pathway
  - Notch_signaling_pathway
  - Cell_adhesion_molecules_(cams)
  - Tight_junction
  - Complement_and_coagulation_cascades
  - Antigen presentation & Processing pathways
  - TLR & NF-kB mediated inflammatory cytokine pathways
  - Apoptosis

MicroRNA validation and their role in immune modulation will be investigated.

Expected outcome and Significance: We anticipate that our study will provide valuable information regarding the role of miRNAs in JEV infection. Our integrative molecular and bioinformatics approach will help us to define signature miRNAs that might play important role in JEV induced microglia activation and allow us to use as a biomarker for prediction of clinical outcome. Knowledge on the molecular determinants involved in JEV mediated disease progression will open avenues for novel therapeutic approach and will help to take long term policy to combat the spread of JEV infection.

Transcriptome analysis for identification of novel biomarker for disease progression in Dengue patients

Funding agency: Department of Biotechnology

Background: Dengue virus infection is now recognized as one of the most important mosquito-borne human infections of the 21st century. The virus is known to promote vascular permeability, cerebral edema leading to Dengue hemorrhagic fever [DHF] or Dengue shock syndrome (DSS). The global epidemiology of dengue fever/DHF is changing fast. Dengue infection has known to be endemic in India for over two centuries as a benign and self limited disease. In recent years, the disease has changed its course, manifesting in the severe form as DHF and with increasing frequency of outbreaks. Delhi has experienced 11 outbreaks of dengue virus infection since 1997 with the last reported in 2010. There are no vaccines available against Dengue and no biomarkers available which can help us to predict disease outcome. The ability to predict which patient may develop DHF and DSS may improve the triage and treatment. With the recent discovery of microRNAs (miRNAs) regulating the inflammatory responses, their role in Dengue virus pathogenesis remains to be elucidated. Considering that cellular miRNAs play important roles in many mammalian viral life cycles, it is presumed that they may also participate in the molecular pathogenesis of viral infection.

Our focus in this grant application is to study the early transcriptional signature in the peripheral blood mononuclear cells (PBMCs) in a large number of clinically and virologically well characterized patients with mild and severs dengue infection and establishes their correlation with disease progression.

Objective 1: Identification of disregulated gene/s and host miRNAs in the PBMCs of Dengue patients that may be associated with the progression of Dengue fever to Dengue hemorrhagic fever

Objective 2: In silico analysis and validation of NGS data to identify miRNAs and host genes for clinical utility in predicting the progression of Dengue fever to Dengue hemorrhagic fever

Objective 3: Identification of circulating miRNAs in the sera of Dengue patients in order to discover potential biomarker for predicting the outcome of DENV infection

Our experimental approach will focus on understanding the role of microRNA with disease progression during DENV infection. Cross sectional studies will be used to identify miRNA expression patterns using an unbiased next generation sequencing approach and the derived data validated for translation into novel biomarkers with clinical utility in aiding patients monitoring for early diagnosis of disease progression. The information derived from this proposal will be integrated with the transcriptome profile of same clinical sample, which will be analyzed as part of the project. Together, the integrated data on both the transcriptome and miRNAs has a potential to serve as a platform for development of novel diagnostics as well as provide a rational basis to improve Dengue treatment modalities. We believe that this proposal is highly significant contributing to a better understanding of the molecular basis of DENV mediated disease progression.

DR. SUPRATIK DAS

Focus research area

HIV/AIDS affects millions of people world-wide leading to high morbidity and mortality. Yet, an effective vaccine has not been invented. The target for any vaccine candidate is the cell surface envelope glycoprotein (Env) on the virus. The overall goal is to design an Env based immunogen that is cleaved, trimeric, monodisperse and stable to be used in clinical trials for development of vaccine against HIV/AIDS.

DR. SAIKAT BOLIAR

Focus research area

His current research interest lies in (a) the understanding of the B cell immune response and antibody repertoire diversity in HIV-1 infection, and (b) isolation and characterization of broadly neutralizing antibodies against HIV-1 Env to aid in the development of a successful vaccine.

DR. SWEETY SAMAL

Focus research area

Her current research focuses on dissecting the epitope fine specificities of broadly neutralizing serums from patients infected with HIV-1 clade-C viruses and identifying the cleavage signature for vaccine design. My long-standing interest is in understanding the mechanism of limited antibody distinctive of broad and potent serum Nabs in selected HIV infected patients.

DR. TRIPTI SHRIVASTAVA

Focus research area

Her major research areas are (a) identification and characterization of HIV envelop surface exposed areas to be used as immunogen for successful vaccine development (b) designing of native trimeric HIV Env as candidate vaccine.

DR. UMA CHANDRA MOULI NATCHU

Focus research area:

Our 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. In one approach, led by Dr Anna George and colleagues at the National Institute of Immunology, Delhi, we attempt to understand the role of Vitamin D in generating primary systemic and mucosal immune responses as well as memory responses to cutaneously administered antigens.

Our focus is to look at relationships between nutritional status and immune function in pregnant women, the fetus and infants. This includes associations between components of the 'immune cytome' (cellular profiles of the immune system determined by flowcytometry) and serum Vitamin D concentrations in the umbilical cord and a clinical trial to assess if daily Vitamin D supplementation to newborns for 6 months affects immune responses to vaccines administered at birth and early in infancy. As an additional research activity, we 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. The group attempts to link clinical research exercises with fundamental biological experiments to efficiently nest efforts to understand human biology within well executed clinical trials and cohort studies. We often incorporate questions of biological mechanisms with collaborators early in the process of designing and structuring clinical research projects.

We collaborate extensively for a number of these approaches internally across the Pediatric Biology Centre and THSTI; with Dr Nitya Wadhwa, Prof Shinjini Bhatnagar for clinical research and Drs Shailaja Sopory, Savit B Prabhu, Vineeta Bal, Satyajit Rathand Guruprasad Medigeshi for research involving biological mechanisms. The bulk of our clinical research is conducted at the General Hospital, Gurgaon in collaboration with the departments of Pediatrics and Gynecology. In addition, we work with Dr Jeremy Goldhaber-Fiebert at Stanford University for modeling based research and with Professors Halvor Sommerfelt and Tor A Strand at the Centre for International Health, Bergen for clinical and community health research. With Dr Jonathan Pillai at the Centre for Biodesign, THSTI we offer an 18 month fellowship program for creative individuals to design solutions that target bottom of the pyramid maternal and child health gaps.

Intramural Projects

Evaluation of novel adjuvants for mucosal priming following cutaneous delivery of vaccines

Poor responses to vaccines have hampered efforts towards control and eradication of infectious diseases like poliomyelitis, rotavirus diarrhea, typhoid and tuberculosis in India and have been a major setback for public health programs. Apart from morbidity and mortality from the disease, the loss of credibility arising from poor effectiveness further affects vaccine coverage rates. As more and more vaccines are being added, discovery and evaluation of novel adjuvants that can improve vaccine responses will be critical to their success. In this project, the ability of a safe but novel adjuvant like Vitamin D to enhance the quality and duration of systemic immune responses to antigens and its ability to generate priming at mucosal sites to cutaneously delivered vaccines is being evaluated in collaboration with Dr Anna George at NII.

We began working on Vitamin D receptor KO mice with Dr George. In initial experiments, we have assessed the frequency of neutrophils and lymphocytes in blood smears from wild-type (WT) and VDR-/- (KO) mice and found differences in neutrophil counts between the strains. B cell frequencies in the spleen were similar in the two strains. However, when we assessed serum Ig levels and frequencies of IgM- and switched- memory B cells in WT and KO mice, differences were observed. IgG1 levels were lower in the KO mice, while IgG2c and IgG3 levels were higher. Interestingly, when the frequency of memory B cells were estimated by flow cytometry, IgM memory, as well as IgG1 and IgG2a memory cell frequencies were lower in the KO mice. IgM

memory has been characterized based on the surface expression of the markers CD73, CD80 and CD273, with elevation of these markers being associated with maturation of IgM memory. We gated on IgM memory cells as shown in Figure 27 and estimated the frequencies of CD73+. CD80+ and CD273+ cells in WT and KO mice. We had previously observed that administration of vitamin D3 promoted IgA responses following subcutaneous immunization and we also showed that this related to migration of APCs from lymph nodes draining the skin to the spleen and to mesenteric lymph nodes (MLN) where mucosal priming can occur. We have confirmed these results in mixed bone marrow chimeras containing WT and VDR-/- cells. Eight weeks after reconstitution, the chimeras were immunized subcutaneously with OVA with or without vitamin D3 administration, and WT and KO cells were sorted from the spleens 48h later. These were used as APCs to stimulate purified CD4+ cells from the OVA-specific TCR transgenic mouse DO11.10. As expected, we found no APC activity in splenocytes from either donor in the absence of vitamin D3 treatment. However, WT splenocytes were able to stimulate T cells in vitamin D3 treated mice while KO splenocytes were unable to do so. This is a direct demonstration of the role of vitamin D3 in the migration of APCs from the site of immunization to distal sites.

Extramural Projects

Vitamin D supplementation to improve immune responses to vaccines administered in early infancy - The NutriVac-D Trial

Funding Agency: Department of Biotechnology

This project aims to assess the impact of vitamin D supplementation on immune responses to vaccines in Indian infants. Vitamin D deficiency has broad consequences on the immune system and is hypothesized to affect a number of normal processes in antigen presentation and the innate immune system that could have a bearing on immune responses to antigens. Also, the deficiency is highly prevalent (˜80%) at birth and early in life when most vaccines are delivered. A number of events like the ability of murine dendritic cells (DCs) to migrate from skin sites of vaccination to mucosal lymphoid organs and migration of human CD8+ T cells to inflamed skin sites have been shown to be calcitriol (vitamin D) dependent. In this trial on newborns the effect of daily vitamin D supplementation (vs. placebo) for 6 months of life on immune responses to OPV, Hepatitis B and BCG is being evaluated.

The trial has just begun enrollment and nearly 1000 pregnant women have been screened for enrolment. About 200 women have provided consent and 6 infants have been enrolled. In addition to assessing immune responses,th e evolution of the immune system over the first 6 months of life is also being analyzed using flowcytometry. A representative plot of the gating strategy being used to analyze iNKT cell frequencies and numbers is shown.

In addition, we have analyzed Vitamin D levels in a large number of cord blood samples and are analyzing correlations between the immune cytome in cord blood and vitamin D levels. Preliminary analysis suggests a very high prevalence of biochemical vitamin D deficiency and insufficiency in cord blood.

DR. NITYA WADHWA

Team members

Research Staff-One Clinical Coordinator: Dr. Mona Chaturvedi
One Senior Research Officer: Dr Kanika Sachdeva
Two Research Officers: Dr Sumit Mishra & Dr Rana Pratap Singh
Eighteen Research Nurses
Eleven Field Supervisors and Technicians

Focus research area

In my present role as a Clinical investigator, I am working in the area of Neonatal and infant immunobiology and Nutritional immunobiology. I have just completed a multicenter cross sectional study as a Principal Investigator, to characterize the leukocyte subpopulations in term neonates and compare the leukocyte immunophenotypes of AGA and SGA newborns. We have also done a study on the immunophenotypic comparison of leukocyte subpopulations from term newborns and healthy adults. At present I am preparing to initiate a large cohort study of pregnant women coming to a district hospital to look for biological and non biological predictors of preterm birth. We will soon be initiating a large muticentre, multicountry randomized controlled trial to see the effect of zinc supplementation (as an adjunct to standard treatment) in infants with very severe disease in reducing case fatality.

Extramural project:

Underweight full-term Indian neonates show differences in umbilical cord blood leukocyte phenotype: a cross-sectional study

While infections are a major cause of neonatal mortality in India even in full-term neonates, this is an especial problem in the large proportion (~20%) of neonates born underweight (or small-for-gestational-age; SGA). In order to examine the possibility that differences in immune status may underlie the susceptibility of SGA neonates to infections, we enumerated the frequencies and concentrations of 22 leukocyte subset populations as well as IgM and IgA levels in umbilical cord blood from full-term SGA neonates and compared them with values from normal-weight (or appropriate-for-gestational-age; AGA) full-term neonates. An analysis of 502 such samples, including 50 from SGA neonates, showed that SGA neonates have significantly fewer plasmacytoid dendritic cells (pDCs), a higher myeloid DC (mDC) to pDC ratio, more natural killer (NK) cells, and higher IgM levels in cord blood in comparison with AGA neonates. Other differences were also observed such as tendencies to lower CD4:CD8 ratios and greater prominence of inflammatory monocytes and neutrophils, but while some of them had robust effect sizes, they did not quite reach the standard level of statistical significance. These differences in diverse cellular lineages of the immune system are more likely to reflect altered maturation of the immune system due to the intrauterine conditions causing growth retardation rather than simply retarded immune system maturation. Our findings open new avenues for examining both the molecular-cellular genesis and the functional-clinical consequences of immune dysfunction in underweight neonates.

DR. SHAILAJA SOPORY

Team members

Dr. Amita Sharma (Research Associate)
Ms. Bhavya Khullar (Ph.D. student)

Focus research area

Currently there are two main areas in which my research is focused.

- Understanding the molecular mechanisms of childhood diseases, with the current focus on pediatric renal diseases, specifically minimal change nephrotic syndrome (MCNS),

which is associated extensive proteinuria. A small project has also been initiated to look at loss of barrier integrity in the intestine during infection.

- Characterizing the transcriptional and functional differences in some immune cell subsets in neonates born at extremes of birth weight and also Vitamin D levels.

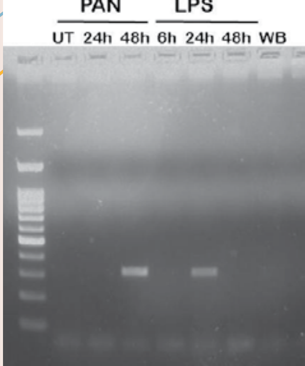


Figure . Caco-2 cells were treated with 50µg/ml of LPS or PAN for indicated time, following which cells were lysed and RNA was prepared, cDNA synthesized and PCR carried out using CD80 specific primers

Intramural projects

Epithelial barrier disruption during inflammatory responses

Based on our work being carried out in kidney podocyte cells, where we are interested in looking at the role of CD80 expression (a T cell co-stimulatory molecule, present on classical antigen presenting cells) in the podocytes during inflammation, we decided to look at the function of CD80 as a universal barrier disrupter based on literature where CD80 has been shown to be upregulated in keratinocytes, bronchiolar, alveolar, gastric and colonic epithelial cells on infectious or allergic stress.

Our preliminary work with Caco-2 cell line has shown induction of CD80 in these cells on incubation with lipopolysaccharide (LPS) and Puromycin amino nucleoside (PAN) (Figure 1).

We are currently trying to overexpress CD80 in Caco-2 cells in order to look for possible interactions with tight junction proteins.

Extramural projects

Molecular Mechanisms of Minimal Change Disease nephrotic Syndrome: Role of CD80

Funding agency: Department of Biotechnology, Bio-Care

Background: The most common type of nephrotic syndrome in children is minimal change disease (MCD) and is associated with massive proteinuria. It has been reported that a T- cell co receptor, CD80 (B7-1) is induced in the kidney podocyte, resulting in alteration of the glomerular permeability and proteinuria characteristic of MCD. Moreover the full-length membrane associated form of CD80 is elevated in urine of patients with MCD.

Podocytes are highly differentiated, specialized epithelial cells of the renal corpuscle. These cells give rise to large primary processes called major processes (MP), which send out foot processes (FP) that wrap around the capillaries and interdigitate with each other leaving filtration slits between them that are bridged by a structure called the slit diaphragms (SD). The highly dynamic foot processes contain an actin based contractile apparatus. Mutations affecting several podocyte proteins lead to rearrangement of the actin cytoskeleton, disruption of the filtration barrier and subsequent renal disease.

The purpose of this initiative is to understand the mechanism of CD80 mediated proteinuria at the level of cellular and molecular changes in the podocyte. The study is looking at the effect of artificially increasing CD80 levels in podocyte cell lines on expression and localization of various podocyte specific proteins and signaling at the slit diaphragm.

Our detailed characterization of podocyte cell lines overexpressing CD80 did not show any major changes in the expression of SD proteins as assessed by Western blot and RT-PCR analysis. We are taking a candidate approach by overexpressing important SD proteins along with CD80 in a heterologous system to look at interactions.

DR. PALLAVI KSHETRAPAL

Team member:

Ms. Shilpi Sehgal (Ph.D. student)
Ms. Anica Dadwal (Junior Research Fellow)

Focus research area:

The broad focus of our lab is to study pediatric development and health. We are interested in understanding of the molecular mechanisms that could lead to Pediatric cancers, especially investigating the role of Notch synergies in Acute Lymphoblastic Leukemias (ALLs). We are also engaged in identification and characterization of biomarkers to predict adverse pregnancy outcomes, which could lead to interventional approaches to improve neonatal health.

Extramural projects:

The role of Notch synergies in pediatric T-ALLs

Funding agency: Department of Biotechnology

Our study focuses on the role of Notch and its synergies in pediatric T and B-ALL. Childhood acute lymphoblastic leukemia (ALL) is an aggressive type of hematologic malignancy that results from malignant transformation of normal developing T or B cells.. T-ALL accounts for about 15% and 25% of ALL in pediatric and adult cases respectively. Deregulated signaling of Notch is considered a major contributing factor to leukomogeneis of T –ALL that are usually associated with chromosomal rearrangements, which result in dramatic changes in gene activity. The most commonly found translocation in pediatric T-ALLs is a rearrangement between chromosomes 7 and 9 that results in the fusion of the coding region of the intracellular region of the NOTCH1 gene to the T-Cell Receptor (TCR) enhancer, driving constitutively an active form of NOTCH1 in T cells (1). Recent reports about the involvement of Notch 3 and Hes5 in B–ALLs (2) further substantiate our objective to investigate for the Notch synergies in these disease conditions. The Notch signaling pathway plays important roles in the regulation of cell differentiation, prolife ration and apoptos is in many developmental systems. Aberrant Notch activity has been associated with congenital diseases and its significance in various forms of cancers has been increasingly recognized. Notch receptor activation per se can be oncogenic, as has been shown to be the case in more than 50% of T-cell lymphoblastic leukaemia (T-ALL). Though it is now becoming clearth at Notch signals are synergistically involved in many on cogenic events, the complete roster of genes capable of cooperating with Notch receptor activation to influence proliferation events is not yet known. I carried out a modifier screen utilizing *Drosophila* genetics and a unique collection of mutations housed at the HMS to search the genome systematically for genes capable of synergizing with a constitutively active Notch receptor to influence proliferation in vivo. I have identified 265 modifier genes. Initial analysis of the modifiers obtained from the screen has been encouraging and demonstrates that many of the human homologues of these fly modifiers have be reported and documented to be involved in cancers, like Hepatocellular carcinoma, prostrate cancer, Breast carcinoma, colorectal cancers and many more.

Using Jurkat cell line, a T-ALL specific cell line we have standardized q PCR conditions for the gene expression profiling of receptors (Notch), ligands of Notch, candidate synergistic factors e.g. Transcription factors Mef2A and LMO2 and few more from our list. We see synergy

in the levels of the Notch receptor 1 and the transcription factor Mef2C. Using these assay conditions we will now examine the expression of these genes in pediatric ALL blood samples to ascertain whether the synergy holds true in its true translation term.

Association studies to decipher the role of MHC-I molecule in pregnancy outcomes

Funding Agency: Department of Biotechnology

The burden of small for gestational age (SGA) neonates when compared to appropriate for gestational age (AGA) neonates in developing country like India is ~ 20 %. The development and growth of the developing fetus in the maternal environment depends both on intrinsic and environmental factors. The intrinsic factors could be genetic, placental and maternal factors that under normal circumstances yield a healthy newborn. It is the reprograming of the local maternal immune responses that end up in a successful semiallogenic pregnancy. The atypical MHC-class I molecule is involved in the dampening of the cytolytic activity of the NK, T and dendritic cells and transforms the maternal fetal side of the placenta into a tolerogenic zone for the normal development of the fetus.

Figure.8 % agarose gel electrophoresis demonstrating the PCR products for the amplified region of HLA-G promoter.

Lane1 - the 1kb ladder, lane 2 – PCR product from human sample 1, lane 3 – Negative control, lane 4 - PCR product from human sample 1 (HLA-G promoter ~2Kb), lane 5 - Positive control, lane 6 - Negative control and lane 7 - 100 bp ladder

We would like to study HLA-G polymorphisms in the 5' URR of the human HLA-G gene in Indian population with the idea to investigate any association that may exist between these polymorphisms and the outcome of pregnancy particularly those leading to SGA and AGA conditions.

We have standardized the PCR amplification of a 2 Kb region of the promoter region and have listed the SNPs that would be accessed for the Indian pregnant population.

We anticipate that outcome of our research could significantly improve understanding of the genetic basis of development of SGA and AGA babies. This study will not only shed light on the potential association of the different HLA-G allelic haplotypes to the birth weight of neonates, but will also describe the different allelic frequencies prevalent in the Indian population. This demographic study could provide pivotal insights into the genetic and mechanistic understanding of the role HLA-G that leads to different complications of the pregnancy outcomes.

DR. BHABATOSH DAS

Team members

Dr. Sourav Sen Gupta (Innovation Awardee)
Dr. Reena Kumari (Innovation Awardee)
Dr. Satyabrata Bag (Technical Officer-II)
Ms. Shruti Saxena (Senior Research Fellow)
Ms. Ojasvi (Research Fellow)
Ms. Mayanka Dayal (Junior Research Fellow)
Ms. Archana Pant (Junior Research Fellow)
Ms. Preety Rana (Lab Technician)
Mr. D. Anbumani (Technical Assistance (Lab))

Focus research area

Structure, function and diversity of the human microbiome

Studies of the human microbiome have revealed that the microbiomes are heterogeneous across population. Diverse microbiota reside in or on the different body sites play crucial role for normal health. Several factors like diet, environment, host genetics could influence microbial diversity and stability and could alter host physiology. It is really important to know the structural and functional configuration of normal microbial communities of healthy population for translational application of the human microbiome. No study has been conducted to reveal the structure and functions of native microbiome in Indian population. Given the environment and unique socio-economic-cultural set up within India, the microbiome of the Indian population is expected to be different from those reported for other geographies. Currently, we are exploring the microbiome of Indian population with the aim of developing intervention like probiotics that could favorably modulate intestinal and vaginal microbiota.

Microbial homeostasis: From ecology to molecular genetics

The disruption of homeostatic interactions between members of a define ecology often direct toward disease development. Therapies are mostly relies on complete elimination of a single species to replacing the entire microbial community. We are currently interested on identification and regulation of microbial secondary metabolite synthetase for modulation of growth of selected microbiota in a complex ecosystem without directly affecting host physiology.

Bacterial pathogenesis and antimicrobial resistance

Rise of antibiotic resistance in pathogenic bacteria poses major health concern world-wide, but the problem is particularly worrying in India, where hospital standards are inconsistent and antibiotics are readily available over the counter. Both Gram negative and Gram positive bacteria are resistant to some or all antibiotic classes commonly used to treat Gram-negative bacteria: penicillins, cephalosporins, carbapenems, monobactms, quinolones, aminoglycosides, tetracyclins and polymixins. Several mechanisms can confer antibiotic resistance in bacteria, but the most common mechanism of resistance in pathogenic bacteria to antibiotics of common classes involve the enzymatic inactivation of the antibiotic by hydrolysis, or by formation of inactive derivatives. Pathogenic bacteria from a pool of resistance genes generally acquire such resistance determinants.The resistance gene sequences are either integrated into autonomously replicating mobile genetic elements or into host chromosomes by site-specific recombination using tyrosine or serine recombinases. An understanding of resistant determinants circulating in bacterial pathogens will provide information not only about resistance frequencies but also about identify new mechanisms that may help to eradicate resistance determinants from the existing pathogens. Our present works focus on the acquisition and dissemination mechanisms of integrating mobile genetic elements carrying virulence or antibiotic resistance traits.

Intramural projects

Structure, function and diversity of the human gut microbiome

The microbial community composition of the gut may vary substantially among individuals and may be associated with the susceptibility of individuals to malnutrition, enteric infections, metabolic disorders, cancer development and cardiac arrest. Furthermore, while a healthy subject typically harbors a stable and distinct gut microbiome, the composition may be dramatically altered depending upon the exposure to different environmental factors. Compare to developed countries, limited information is available about the structure and functions of microbiome of Indian population. Given the environment and unique socio-economic-cultural set up within India, the microbiome of the Indian population is expected to

be different from those reported for other geographies. The possible unique gut microbiome of Indian population may have impact on development resistance against enteric infection. Determination of the difference in gut microbiomes in diverse Indian individuals and define possible "normal" microbiome composition with ceratin degree of variations within apparently healthy people in different population will definitely have great impact on health management. Currently, we are exploring the structure, function and diversity of the human gut microbiome in Indian population.

Extramural projects

Integration and Excision Mechanisms Of Integrative Mobile Genetic Elements Essential For Vibrio cholerae Pathogenicity

Funding agency: Department of Science and Technology

Vibrio cholerae, the etiological agent of diarrhoeal disease cholera, harbors large numbers of Integrative Mobile Genetic Elements (IMGEs), which notably contributes in bacterial pathogenesis and provide fitness factors to the pathogen that help the bacterium to compete with other bacteria in natural environment. Vibrio pathogenecity islands-1 (VPI-1), a 41-kb DNA segment physically linked to a tmRNA gene (ssrA), flanked by two nearly identical repeat sequences, is a well known IMGE and present in all epidemic V. cholerae isolates. VPI-1 is essential for V. cholerae pathogenesis and disease development. Most IMGEs encode a single transposase or integrase to mediate their site-specific integration in the host chromosome. In this regard, VPI-1 is particularly interesting since it carries two putative recombinases (Intvpi and VpiT) and both can mediate excision reaction independently. Sequence analyses of the two putative recombinases indicate that they are quite different from each other. The Intvpi contains the conserved R-H-R-Y signature motif of the tyrosine recombinases, while the similar motif is not distinct in VpiT. This raised a considerable interest for the understanding of the different molecular mechanisms driving the integration and excision of VPI-1.

MicrobDiab - Studies of interactions between the gut Microbiome and the human host biology to elucidate novel aspects of the pathophysiology and pathogenesis of type 2 Diabetes

Funding agency: Department of Biotechnology, Govt. of India; Govt. of Denmark

The incidence of Type 2 Diabetes (T2D) increases at a pandemic scale and is accompanied by severe organ damages, which results in enormous costs on the health care systems and lowers the quality of life and life expectancy of millions of people in India and Denmark. Recent research indicates that altered gut microbiota composition and function may be involved in the pathogenesis of T2D and its co-morbidities. Therefore, there is a strong rationale to explore whether interactions between the gut microbiota as evaluated at the collective microbial genome level (the microbiome) and the host biology can provide novel insights into the pathophysiology and pathogenesis of pre-diabetes and T2D. The overall objective of the proposed project is to identify gut microbiome signatures in Indian and Danish study participants which associate with pre-diabetes and T2D thereby enabling development of novel biomarkers for early diagnosis of people at high risk of progression to overt T2D.

Tata Consultancy Services Innovation Labs (TCS IL) works on Computational Life Sciences. TCS IL is partnering with CHME for studying microbial metagenomics, performing computational analysis of metagenomics sequence data. CHME collaborates exclusively with Dr. Sharmila Mande, Principal Scientist and Head, Bio-Science R & D, TCS Innovation Labs, Tata Consultancy service Ltd.

Madras Diabetes Research Foundation (MDRF) specializes on well-structured epidemiological studies that help the ongoing biochemical, genetic, molecular and cell based

studies on diabetes. MDRF is working with CHME to explore the gut microbiome of diabetic patients and identifying microbial signatures for early prediction and possible intervention.

DR. AMIT AWASTHI

Team members:

Srikanth Elesela (Post Doctoral Fellow)
Sakshi Malik, (Ph.D. Student)
Suyasha Roy, (Ph.D. Student)
Ritika Rampal, (Ph.D. Student)
Ramendra Pati Pandey, (Junior Research Fellow)
Srikanth Sadhu, (Junior Research Fellow)
Manas Ranjan Triphaty (Technician)
Rajkumar (Lab attendent)

Research projects:

Interplay between effector and regulatory T cells in the pathogenesis of intestinal inflammation

This project is supported by extramural funding from DBT-Wellcome Trust Alliance through which Dr. Awasthi proposes to understand and identify the factors induces the development of pathogenic Th17 cells over non-pathogenic Th17 cells. It will also investigate whether these pathogenic Th17 cells are involved in the tissue inflammation in intestinal inflammation in inflammatory bowel disease (IBD). Dr. Awasthi is also interested to understand if and how regulatory T cells can regulate intestinal inflammation in IBD. Newly discovered Th17 cells, which produces IL-17A and IL-17F are crucial for inducing tissue inflammation in various autoimmune diseases such as multiple sclerosis, psoriasis, rheumatoid arthritis and IBD. In addition, Th17 cells are also essential for eliminating both intra- and extracellular pathogens. Inflammatory Bowel Diseases (IBD), comprising Crohn's Disease (CD) and ulcerative colitis (UC), are severe disorders of the gastrointestinal tract. IL-12- induced Th1 cells were thought to be major effector cells to develop colitis as neutralization of IL-12 prevents tissue inflammation in colitis. Interestingly, IFN-g deficient T cells were still inducing disease suggested the role of other helper T cell subset other than Th1 cells in disease induction. Recently discovered Th17-IL-23R axis plays a critical role in the development of IBD, as IL-23-/- and IL-23R-/- mice are resistant to development of colitis. Naïve T cells can differentiate into Th17 cells by TGF-b and IL-6, which further amplify by IL-21. However, the addition of IL-23 on Th17 cells makes them pathogenic in most of the autoimmune diseases. The mechanism by which IL-23 induces pathogenic functions of Th17 cells and restrains the functions of regulatory T cells (Foxp3+ Tregs and IL-10+ Tr1 cells) is not clear. We will be identifying the mechanisms of interplay of effector (Th17 cells) and regulatory T cells (Foxp3+ Tregs and IL-10+ Tr1 cells) in context of IL-23 functions in the intestinal inflammation in IBD.

There are bodies of evidence that both pathogenic and non-pathogenic Th17 cells exist. However, how Th17 cells acquire the pathogenic phenotype during tissue inflammation is not very clear. Here in this study we are delineating the factors that drive the development of pathogenic Th17 cells. We have revealed using whole genome expression profile TGF-b3 plays a vital role the in the development of pathogenic Th17 cells . In fact expression profile of these pathogenic Th17 cells looks very distinct than the non-pathogenicTh17 cells.

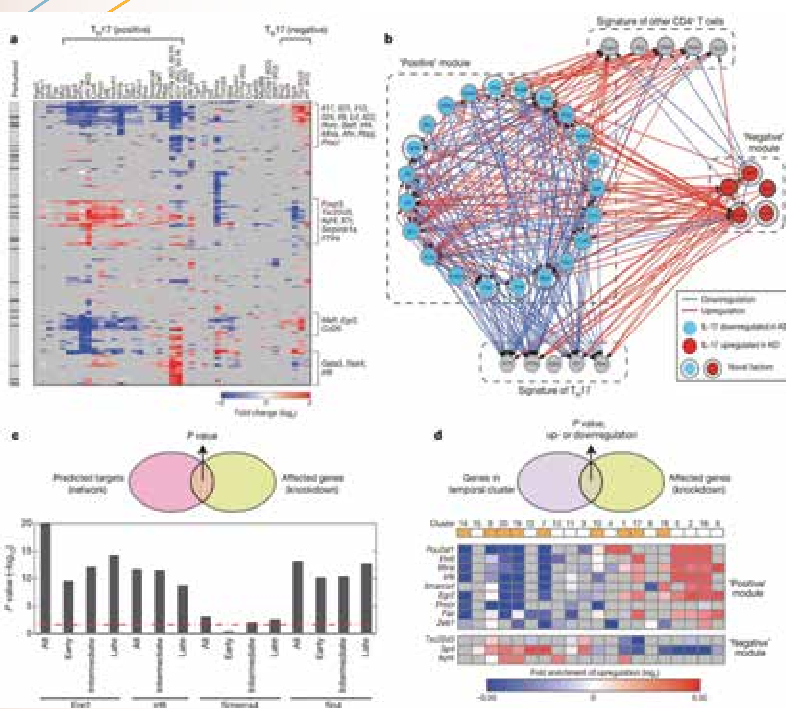


Figure: *Coupled and mutually antagonistic modules in the TH17network.Nature. 2013 Apr 25;496(7446):461-8.*

IL-27 dependent regulation of Th17 and regulatory T cells

In this project, we propose to understand the molecular mechanism by which IL-27 inhibits the development of Th17 cells. IL-27, a heterodimeric cytokine of IL-12 family, shown to antagonize the development of Th17 cells. In addition, we have shown that IL-27 on the other hand induces the development of type-1 regulatory T cells (Tr1), which massively produce IL-10.Based on our work, we proposed a model in which IL-27 not only inhibits the functions of effector cells (Th1 and Th17 cells) but also increses the development of Tr1 cells. These IL-10-producing Tr1 cells are beneficial to control tissue inflammation in various autoimmune inflammation, however consistent increase in the number of Tr1 cells might enhance the various infection and can be pro-pathogen. Understanding the mechanism of IL-27 induce regulation of Th17 cells and Tr1 cells could lead to design new therapeutic intervention in autoimmunity and infection.

DR. GAURAV BATRA

Team members

Mr. D. Ramu (Ph.D. Student)
Mr. Deepak Rohila (Sr. Research Fellow)
Mr. Sreeraj Surendran (Jr. Research Fellow)
Ms. Neha Kaushik (Jr. Research Fellow)

Focus research area

Knowing the cause responsible for a patient's illness remains fundamental to evidence based treatment and care. Despite the fact that the reliable diagnostic tools affect health care decisions to a degree well out of proportion to their cost, in the developing world healthcare workers are forced to use empirical approaches of treatment which often result in inappropriate clinical outcomes because of lack of reliable, affordable and practical in vitro diagnostic solutions.

Goal of my lab is to provide diagnostic solutions which are reliable in local conditions, affordable and practical. Major focus of our work is on the development of high quality diagnostic assays for acute febrile illnesses e.g. dengue, typhoid etc. To generate high quality diagnostic intermediates, we are involved in protein and antibody engineering, cost effective recombinant antigen and antibody production in *E. coli* and yeast *Pichia pastoris*, expression host engineering and high throughput clone screening. We are using genome fragment phage display libraries and antibody libraries for immune epitope mapping and biomarker discovery.

Intramural projects

Development of a diagnostic panel for Acute Febrile Illnesses

The team was involved in the development of an indigenous test for the detection of anti-dengue virus (DENV) antibodies with very high specificity using DENV specific chimeric antigen. Now this team at CBD is focusing on improving the sensitivity of DENV specific assay by identifying new DENV specific immunodominant epitope/ antigenic fragment using phage display library based approaches. Several new dengue immunodominant epitopes have been identified for dengue serotypes 1 and work is in progress to identify epitopes of other DENV serotypes. The idea is to incorporate these sequences in the new generation assay to increase the assay sensitivity without compromising on specificity front.

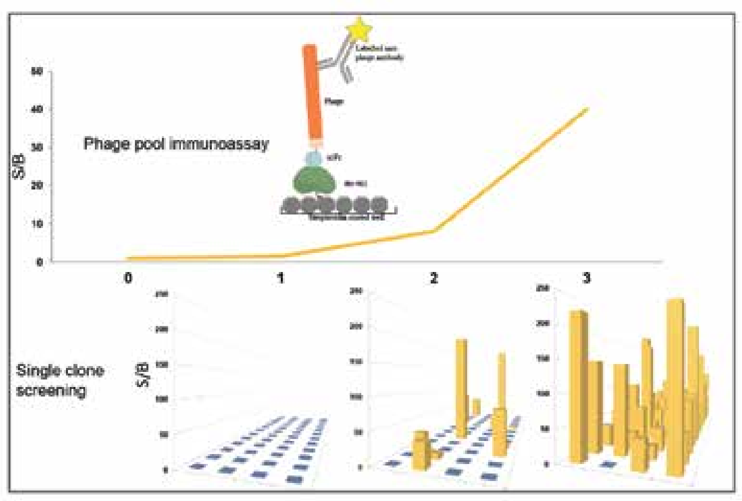


Figure. Enrichment of anti-NS1 binders between panning rounds

The team was also involved in the generation of indigenous DENV NS1 antigen detection assay. The current efforts are being put on the generation of new pairs of monoclonal antibodies to increase the NS1 antigen detection window. Several anti-NS1 antibodies have been isolated using human framework synthetic antibody libraries and these MAbs are being characterized and will be affinity matured in near future. The group is also generating serotype specific anti-NS1 antibodies which can be used for surveillance/epidemiological studies.

In a phased manner, the project will be extended to epitope/antigen (biomarkers) discovery, generation of pathogen specific chimeric antigens, recombinant antibody generation, and assay development work to other important febrile illness e.g. typhoid/paratyphoid, leptospirosis, malaria, chikungunya and influenza. Some progress has already been made towards typhoid diagnostic development. The larger goal is to develop a single multiplexed test for differential diagnosis of major febrile illnesses prevalent in India.

Extramural projects

Technology Platform for Simple and Efficient Production of Recombinant Antibodies

Funding Agency: Department of Biotechnology

This project seeks to remove bottlenecks related to the production of recombinant antibodies of diagnostic use in commercially viable manner. There is an increasing demand of recombinant antibodies for the development of ultra-sensitive in-vitro diagnostic immunoassays. The use of recombinant antibody fragments like Fab in immunoassay gives several advantages e.g. elimination of interference caused by heterophilic antibodies, site specific labeling, high performing capture surface through oriented immobilization and better performance in miniaturized rapid diagnostic assays. Recombinant antibody fragment can be generated from existing hybridoma clone or can be directly isolated from antibody libraries. Despite the advantages of recombinant antibodies fragments, their use in commercial diagnostic assays is not widespread largely because of availability, cost and production related issues (expression yields and aggregation). In this project, an expression toolbox based on yeast Pichia pastoris is being developed, which can be applied for simple, cost effective, high yield production of recombinant antibodies of diagnostic use.

Acute Febrile Illness Diagnostic Panel

An innovative proposal on Multiplexed Point-of-Care Test for acute febrile illness (mPOCT-AFI) was submitted to WHO for CEWG Health R&D Demonstration project scheme. Proposal was first shortlisted by WHO regional office (SEARO) and then evaluated by a panel of 24 international experts at Global Technical Consultation (3-5 Dec 2013 at WHO-HQ, Geneva) which placed this proposal at 2nd position globally based on science, concept and need. WHO-HQ, in March 2014, re-evaluated 8 shortlisted proposals on innovative financial and coordination mechanism where this proposal was placed at no. 5. Proposal is being further improved for consecutive rounds of appraisal. This is a big achievement as the other participants were big international organizations like MSF, US-FDA, MMV, DNDi, Fiocruz, and networks like ReAct (Action on Antibiotic Resistance) and ANDi.

DR. JONATHAN PILLAI

Team:

A team of four multi-disciplinary Fellows under the SPARSH Social Innovation Fellowship Program will initially seed the "implants and devices" focus of the lab. Over the next year the lab will recruit both post-docs and PhD students from a multi-disciplinary background (both engineering and medicine) to establish the research program in drug delivery systems.

Focus research area

Our lab has two major strategic foci for research and innovation. The research focus in Biomedical Engineering is centered on drug-delivery systems, primarily in the area of respiratory disease and particulate vaccines. We will leverage recent advances in aerodynamically engineered micro- and nano-scale particulates and biomaterials to create novel implantable, aerosol and intravenous delivery systems. These include diagnostic carriers and therapeutic payloads for the treatment of diseases like tuberculosis and asthma.

The innovation focus is driven by clinical problems in the area of Maternal and Child Health (MCH). Working closely with faculty from the Pediatric Biology Center, we use the Biodesign process of clinical and social immersion to identify high-impact unmet clinical needs in MCH. After rigorous landscape mapping and needs filtering, we carefully choose problems with the highest potential for public health, typically those for which no viable technology solution is available to patients and physicians. Adopting a technology agnostic approach, we then invent concepts that consider all technologies deemed feasible to providing the most impactful solution to the unmet need.

For example, to address the problem of congenital orthopedic malformations like cleft palate, we are exploring tissue-engineering approaches. Other interests are in the development of non-invasive imaging for establishing clinical decision-making platforms for addressing pre-term birth and pregnancy-related complications.

Intramural projects

As the lab is still being set up, various projects are in different stages of initiation. In collaboration with Dr. Krishnamohan Atmakuri from VIDRC, we are exploring the potential of outer membrane vesicles (OMVs) for vaccine adjuvants and drug delivery systems. Projects

in implants and devices include a preliminary exploration into the use of Tissue Engineering for generation of bone implants for pediatric patients, analysis of soft-tissue biomechanics of tissue-device interaction of surgical tools and methods to control internal hemorrhaging.

Extramural projects

SPARSH Fellowship for Social Innovation in MCH

Funding agency: Biotechnology Industry Research Assistance Council

Background: The overwhelming majority of innovation in the health sector, and particularly in MCH, has focused on cost-blind devices for use in tertiary hospitals (e.g. Ventilation and ICU monitoring). A predominant reason for this is the limited exposure that innovators have to health care in community settings. However, over 90% of all births in India take place at home, small nursing homes and non-referral public hospitals. The majority of health services provided to pregnant women and infants are in their homes and villages (e.g. antenatal checks, immunization, nutrition, IMNCI care).

Objectives: The program would aim to uncover and resolve unmet clinical needs by sustained clinical and social immersion in the field, with a particular focus on factors contributing to infant and maternal morbidity and mortality. We will then train a multi-disciplinary team of social innovators in developing need-inspired product solutions in MCH for the tail end of healthcare delivery (i.e. Primary and secondary care).

Internal and External Collaborators: Our lab will jointly host the SPARSH program along with Dr. Uma Chandra Mouli Natchu from the Pediatric Biology Center (co-PI for this grant). The program will leverage established ongoing collaborations and memoranda of understanding with General Hospital Gurgaon, Haryana, All India Institute of Medical Sciences, Moulana Azad Medical College and Society for Advanced Studies.

DR. ASHUTOSH TIWARI

Developing a rapid test for diagnosis of Celiac Disease (CD):

The objectives of this project is to develop in-house point of care test (POCT) to detect anti human tTG antibodies in human blood or serum/plasma. Towards POCT, we have generated high affinity anti tTG mouse monoclonal antibodies, which specifically bind to native conformation of human tTg and showing stable antigen–antibody interaction. One monoclonal antibody has been purified and given to industry partner for its further validation. This is being done in partnership with ICGEB, AIIMS and THSTI.

Concept of POC test: Celiac Disease test is based on rapid immune-chromatographic test that detects the anti-tTG antibodies from a blood sample. If the sample contains anti-tTG antibodies, these will bind with the gold-labelled anti-human antibodies (mouse IgG) and the tTG. The tTG will then bind the complex to the stationary protein line (test line) forming a visible, red line. The test will also contains an integrated control system consisting of stationary anti-mouse IgG antibody line that binds labeled mouse IgG (anti-human antibody) and a red control line will the proper functioning of the test.

Identification of novel biomarkers and development of highly specific and senstive diagnostic test for typhoid

We have initiated a project to develop an accurate, highly sensitive and specific diagnostic test for typhoid. The approach is to search for novel antigens that are specific for *S. typhi.* A pool of highly purified specific antigens could be screened using serum from typhoid patients and appropriate controls. Testing in a cohort of patients could reveal specific patterns or quantities of antibodies, which would be indicative of typhoid infection. Ultimately, novel antigen(s) could be placed onto membrane to form the basis of a low cost rapid test.

Approach: (1) Immune profiling with Salmonella Typhi secretome to identify new diagnostic biomarkers of human typhoid:

Our aim was to achieve a comprehensive overview of antigenic targeting using sera from patients infected with *S. typhi,* with active typhoid fever. Towards this end we are analyzing the

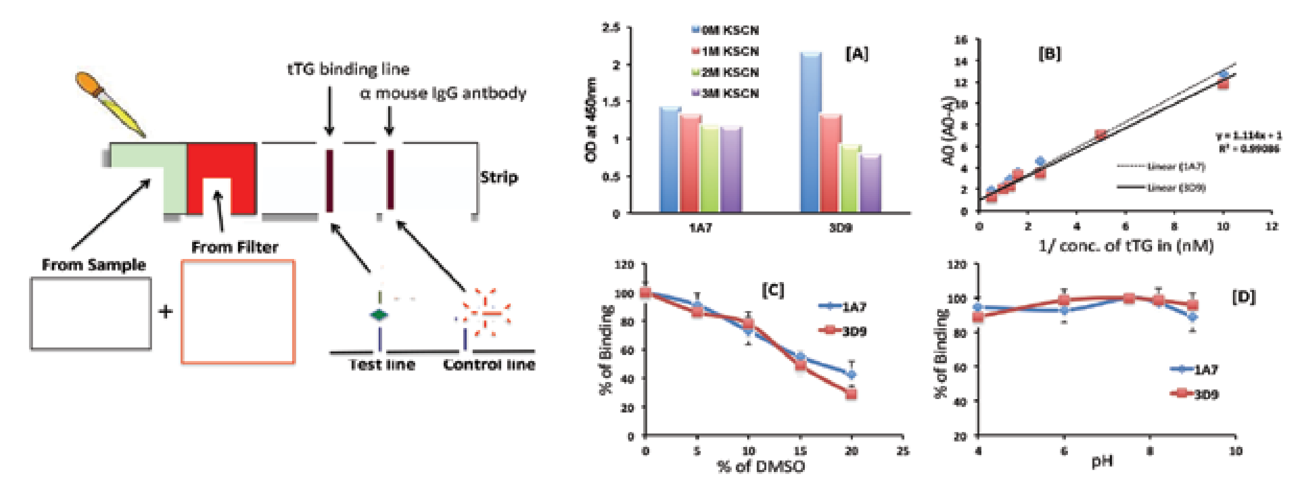


Figure: Diagrammatic representation of POC test concept. [A] Comparative binding affinity of of anti-tTG mouse monoclonal antibodies (1A7 and 3D9) in the presence of various conc. of KSCN. [B] Determination of binding affinity constant (KD) of 1A7 and 3D9 (in nano molar range). [C] Binding stability analysis in the presence varying conc. of DMSO. [D] Binding stability analysis at various pH ranges.

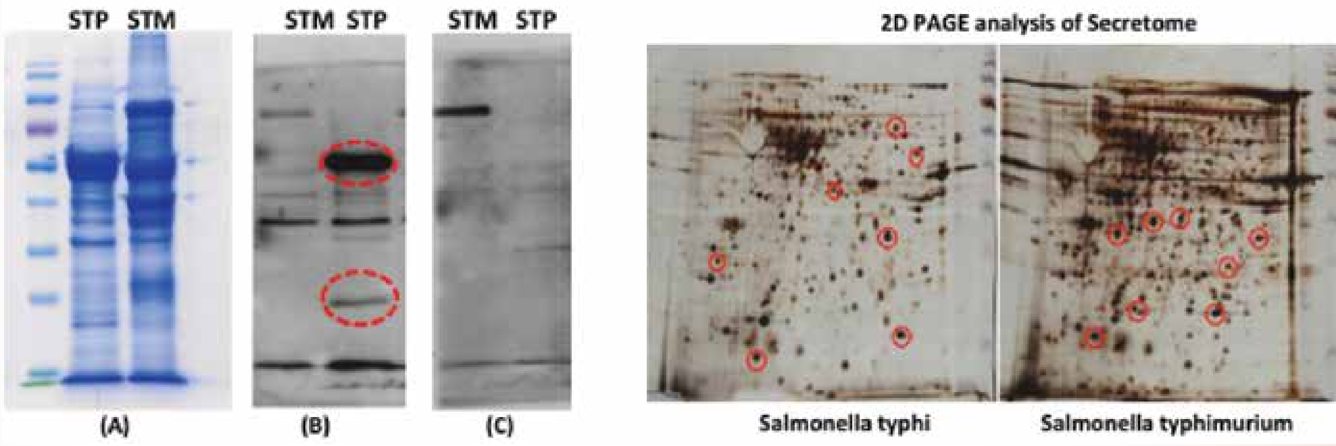


Figure :A: SDS PAGE analysis of Salmonella secretome; S. typhi (lane1) and S. typhimurium (lane 2) B: Immunoblot with S. typhi immune sera from mouse Day 35. C: Immunoblot with pre-immune sera. Unique secretory proteins are marked by red circle in 2D PAGE gel analysis.

secretome of *Salmonella* serovars by proteomics approach. The immune reactive secretory proteins will be identified by LC/MS and will be further assessed as potential diagnostic candidates. Our preliminary data suggest that S. typhi specific immune sera (from mouse) specifically recognize some of the secretory proteins (circled in red), suggesting a possibility of *S. typhi* specific seroreactive antigens. 2D-PAGE analysis of *S. typhi* and *S. typhimurium* secretome also intimate a possibility of over and down regulation of unique proteins (Figure 2). Currently we are trying to get clinically validated human sera samples to further validate and delineating the novel antigens in *Salmonella* secretome.

Approach: (2) Identification of uniques antigens secreted exclusively after infecting human cells

Using *in vitro* infection model, we have identified three *S. typhi* specific proteins that are secreted exclusively after infection to human cells. To validate the possibility of these three proteins as specific biomarker for diagnostic assay, we have cloned, expressed and purified these proteins using *E.coli* expression system. One of the candidate protein was purified from inclusion bodies under denaturing condition, and was dialysed to remove denaturants. This purified protein was then used in IgM serum ELISA performed with patient serum samples along with healthy volunteers serum as control (Figure).

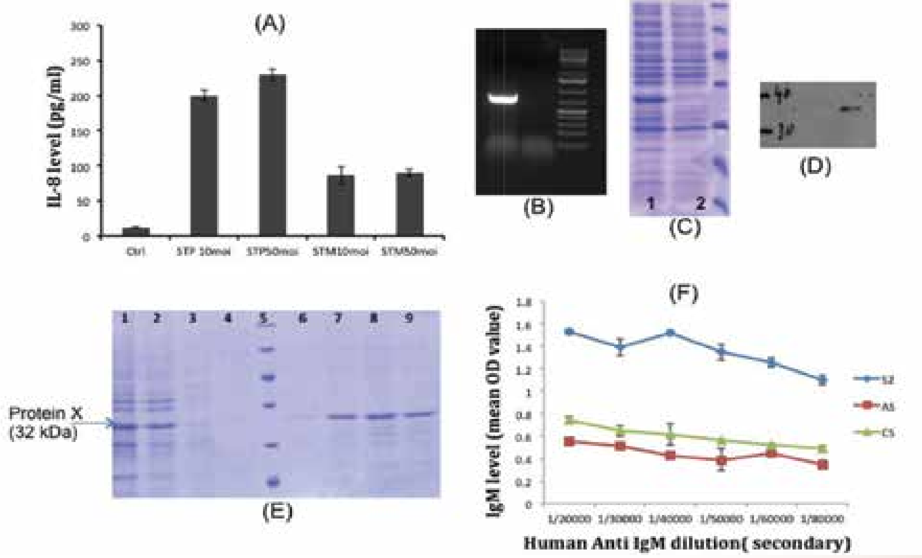


Figure : (A) Measurement of human IL-8 cytokine followed by Salmonella infection in polarized human intestinal epithelial cells. This validates the proper infectivity of salmonella in in-vitro polarized model. (B) PCR amplification of host-infection dependent S typhi specific gene using genomic DNA as template. (C) Expression of S.typhi protein using E.coli expression system; lane 1: induced and lane 2 uninduced (D) Validation of protein expression by Western blot using tag specific antibody. (E) Purification of S.typhi specific protein Lane 1: Input refolded protein, Lane 2: Flow through, Lane 3,4: wash with 20mM Imidazole; Lane 5-10: Eluted fractions 100mM Imidazole.

Approach: (3) Developing an antigen detection based daignostic assay using typhi specifc immunodominant motifs:

Salmonella H antigen represents flagellar protein which is one of the major immunomodulatory, immunogenic and secretory protein. This antigen is the basis of many diagnostic assay available in the market. But the major problem with

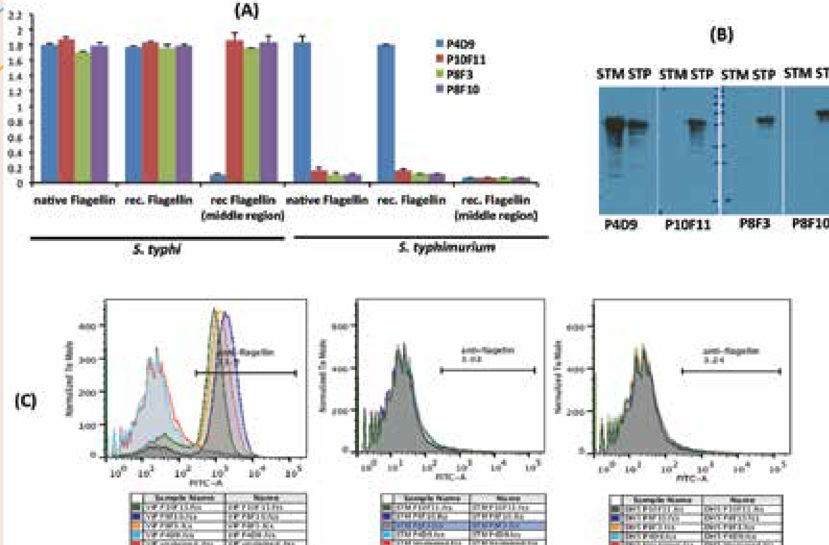


Figure : (A) Binding analysis of four different monoclonal antibodies to native, recombinantly expressed full length and recombina fragment containg typhi specifc unique domain. (B) Western blot analysis showed one antibody is cross reactive to typhimurium flagellin and other three typhi specifc antibodies. (C) Flowcytometric analysis of antibody binding to flagellin present on bacterial surface. These antibodies are specifically binding to typhi flagellin, but not showing any cross reactivity to typhimurium and E.coli strain DH5alpha.

this antigen is its considerable homology with other *Salmonella* serovars and with some other gram negative bacteria, resulting in a high false-positive diagnostics. As one of the rapid approach we are working toward to clone and express various *S. typhi* specific recombinant fragments of flagellin protein to identify typhi specific immune dominant region, so that a smaller and more specific epitope can be used to diminish the IgM and IgG cross reactivity with other bacterial infection.

To use these *S. typhi* specific recombinant fragment as potential diagnostic candiate in a lateral flow based assay we have also generated capture and detection antibodies that are very specific to typhi flagellar protein. The characterization of these antibodies have been done by all lab possible techniques (ELISA, WB, Flowcytometry). (Figure.4). The affinity of these antibodies is also in nano molar range. Out of four antibodies, three antibodies are showing specifc binding to typhi flagellin and one antibody showing cross reactivity with typhimurium serovar. This antibody can be used as capture antibody in lateral flow based assay. Recently we have provided the purified antibodies to interested industry collaborators to validate and for possible design of POCT. The initial data shows promising indication towards specific diagnostic assay for typhoid, but it needs more and intensive validation in larger sample size.

DR. NIRAJ KUMAR & DR. SUSMITA CHAUDHURI

Team member:

Ms. Manpreet Kaur (Ph.D. student)
Ms. Pooja Kumari (Junior Research fellow)

Focus research area:

Genomics and proteomics technologies have witnessed significant development during the last decade. These technologies enable improved high-throughput and quantitative genome-wide analysis of various biological phenotypes and hence offer great potential for novel biomarker discovery for efficient diagnosis of various diseases. Our group is utilizing various genomics and proteomics based concept for identifying potential biomarker for early-diagnosis of acute coronary syndrome and differential diagnosis of bacterial pneumonia, besides developing reagents for developing diagnostic tests for these diseases.

Diagnosis of Acute Coronary Syndrome

India has been reported to have the highest burden of acute coronary syndromes (ACS, which includes heart attack) in the world. ACS refers to a spectrum of clinical symptoms of obstruction of the coronary arteries (ischemia) due to atherosclerotic plaque rupture and

subsequent thrombosis. The reduced blood supply due to the obstruction of the coronary arteries leads to the scarcity of the oxygen and vital nutrients resulting to the necrosis in the cardiac tissue. ACS includes ST-segment elevation myocardial infarction (STEMI), nonSTEMI (NSTEMI) and unstable angina (UA).

Inflammatory stage IL-6, IL-10, TNF-a & **CRP**

Plaque destablization stage **MMP9, MPO**

Plaque rupture stage **fPAPP-A**

Thrombos is stage sCD40L, D-dimer

Necrosis stage **Troponin** I/T, CK-MB, NP-ProBNP

Myocardial dysfunction **BNP/NT-proBNP**

Figure : Schematic representation of disease progression. The potential of biomarkers marked in 'Red' are being evaluated in the mentioned study.

Currently, measurement of C-reactive protein (CRP) and cardiac troponin-I (cTnI) is the most commonly used method of molecular diagnosis ACS. A number of other potential biomarkers for efficient diagnosis of ACS have also been identified, these includes pregnancy associated plasma protein-A and B-type natriuretic peptide (BNP) (Figure). Therefore first aim of the project is to develop high affinity binders against selected biomarkers for efficient diagnosing acute coronary syndrome (ACS) and to develop/evaluate multi-analyte based diagnostic cardiac panel. For this, native antigens were acquired and quality checked before immunization into the mice (Figure). The splenocytes were hybridized with SP2 cell lines and the hybridized clones were selected using HAT selection pressure. The clones producing antibody against specific antigens were screened using ELISA with respective antigen. A number of antibody producing clones have been identified (Figure). Further screening is ongoing to identify most suitable antibody producing clones.

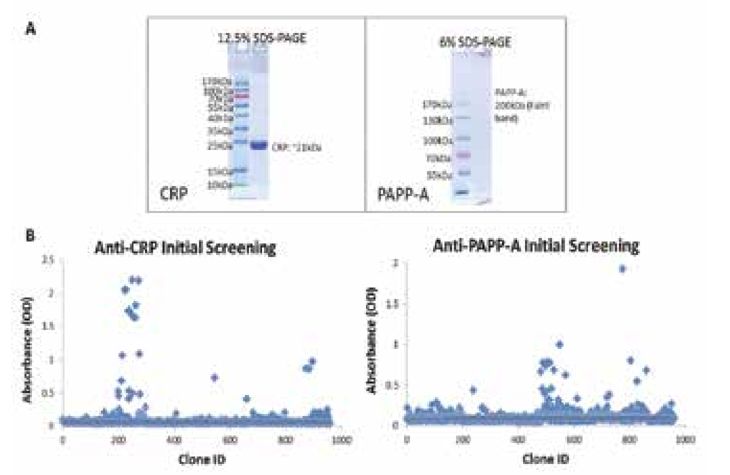


Figure: Development of high affinity monoclonal antibodies against selected biomarkers. A: Initial characterization of native antigens before immunization. B: initial screening for hybridomas secreting monoclonal antibodies against specific antigens.

We have also been working towards production of selected high-quality recombinant antigens as purification of native antigen from patients have been challenging since decades and hence they are very costly. For this, PAPP-A was cloned into the pcDNA backbone along with an artificial secretory signal to facilitate its secretion and His-tag to facilitate its purification (Figure). The plasmid has transfected into the Chinese Hamster Ovary (CHO) cells and screening for identifying producer clone is ongoing.

The second aim of the project is to identify novel biomarkers that may enable early-diagnosis of the disease with high sensitivity and specificity. This is of immense importance since currently used biomarker (CRP and cTnI) have their own limitations. CRP results low sensitivity and specificity in early-diagnosis which may lead unnecessary medication to the non-ACS subjects and cTnI elevates in serum only once cardiac tissue necrosis has occurred which is already late. For this, we are culturing primary human cardiac myocytes under *in-vitro* conditions reflecting nutritional- and hypoxic-stress. The proteins secreted under different level of stress will be identified using gel-free and/or gel-based proteomic approaches and will be evaluated as potential biomarker for ACS early-diagnosis.

Extramural project:

Pneumonia Biomarker Discovery and Diagnostic Development Program

Pneumonia is by far the single largest cause of death (27.5%) among children in post-neonatal

period in India. It is caused primarily by bacterial and viral acute lower respiratory infections, and also to a minor extent by fungal infections, environmental insults and other autoimmune medical conditions. Determination of the etiology of the lower respiratory tract infections in young children will tremendously help in the rational use of antibiotics and efficient patient care.

The major obstacle in determining the etiology is obtaining a representative lower respiratory tract sample, which involves invasive methods and cannot be recommended for routine clinical scenarios; upper respiratory tract samples are likely to yield colonizers.

The most efficient existing diagnostics (PCR-based bacterial nucleic acid-detection) can differentiate bacterial pneumonia from non-bacterial pneumonia to some extent, however, they are empowered to detect only a few bacterial species and also do not provide information about invasion vs. colonization and drug sensitivity of the pathogens and hence the clinical demand remains unmet.

Therefore in this project, we propose to develop probes against potential targets from pneumonia causing pathogens in Indian context that could differentiate between

- Bacterial vs. non-bacterial pneumonia
- Colonizing vs. invading bacterial species
- Drug-sensitive vs. drug-resistant bacterial species

DR. SAGARIKA HALDAR

Focus research area

We are involved in the development of improved diagnostic tests for both pulmonary and extrapulmonary TB. A low-cost rapid and accurate test has become at par with the search for the Holy Grail for TB diagnosis. Most of the current diagnostics at all laboratories begin with the direct smear microscopy test, a test which was developed around 125 years ago. Despite its limitation of low sensitivity, it is the most coveted test in high disease burden settings and the Revised National TB Control Programme also depends on it for case detection. It is believed that even a 10% increment in detection sensitivity will significantly impact case detection and drug resistant disease transmission. The team is targeted to improve the safety and performance of existing direct smear microscopy test for TB diagnosis and at providing a rapid PCR-based method for TB, Multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) diagnosis using DNA extracted from the stained/unstained slides/filters used in smear microscopy. The efficient diagnosis of TB/MDR-TB by the proposed approach has a huge public health impact associated with it and has the twin advantage of detecting and treating subjects with active disease and blocking transmission of TB/

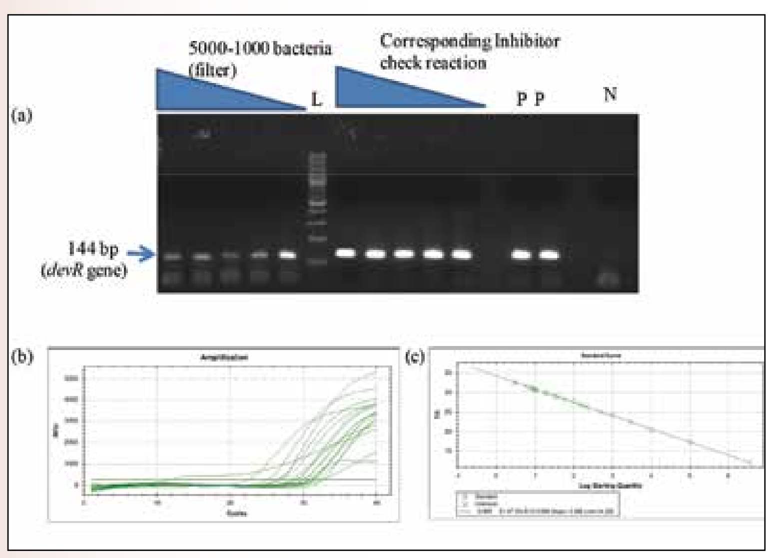


Figure: Sputum samples spiked with bacteria ranging from 5000 to 1000 bacteria were subjected to Bio-safe filtration and inhibitor free DNA isolation. (a) PCR results of inhibitor-free DNA extracted from stained filters in gel-based format. (b) Real time-PCR results of inhibitor free DNA extracted from stained filters. M. tuberculosis genomic DNA over a range of 50-5×105 genome has also been used in the reaction to plot the standard curve. (c) qRT-PCR standard curve was generated using M. tuberculosis DNA over a range of 50-5×105 genome equivalents. Ct (threshold cycle) is plotted vs. logarithm of the number of M. tuberculosis genome equivalents added to each tube at the start of the reaction.

MDR-TB/XDR-TB. The team is also involved in assessing the utility of antigen detection in improving the diagnosis of extrapulmonary TB.

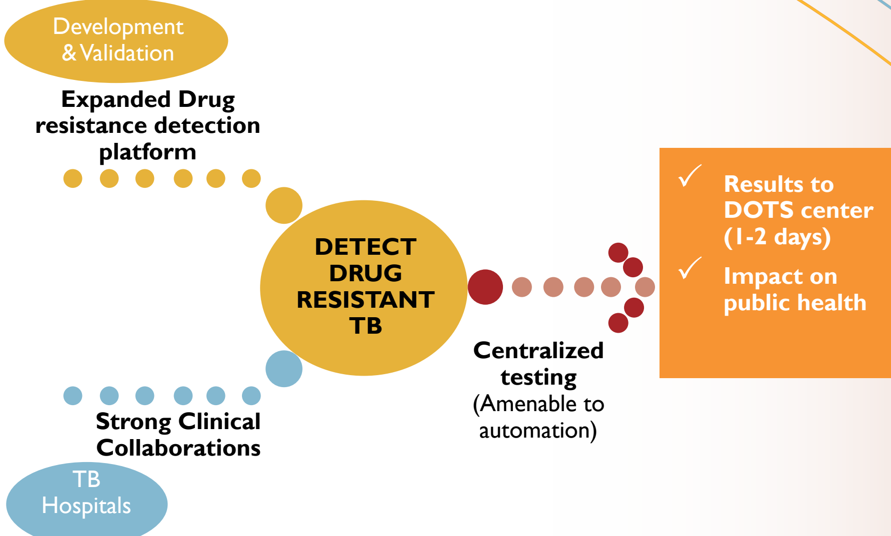


Figure: Strategy for development of the Central molecular platform.

Intramural projects

Utility of antigen detection for the accurate and rapid diagnosis of extrapulmonary TB (EPTB)

Background: We have earlier demonstrated that the detection of Mycobacterium tuberculosis GlcB/ HspX antigens/devR DNA in CSF improves the utility of existing algorithms for TB meningitis diagnosis and also hastens the speed of diagnosis (Haldar et al., 2012). Based on these encouraging results, we plan to assess the utility of antigen detection in other forms of EPTB such as pleural TB and abdominal TB using the existing antibody reagents used for TB Meningitis diagnosis. Also, novel and specific reagents i.e. DNA aptamers for antigen detection-based TB diagnosis are being developed by our collaborators. These aptamer reagents are currently being developed and their utility will be validated on appropriate clinical samples.

Progress: Currently efforts for standardization of the antigen detection assay for other forms of extrapulmonary TB (pleural TB and Ascitic TB) are going on. Aptamer generation for some of the antigens has been completed and is currently in the validation mode.

Extramural projects

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

Funding Agency: SBIRI, Department of Biotechnology

Background: This project is proposed firstly; to improve the safety and performance of existing direct smear microscopy test for TB diagnosis and secondly, at providing a rapid PCR-based method for TB, Multi-drug-resistant tuberculosis (MDR-TB) and Extensively drug-resistant tuberculosis (XDR-TB) diagnosis using DNA extracted from the stained/unstained 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. At the second and higher level, the smear microscopy slides will be transported to National Reference laboratory or equivalent laboratory for DNA extraction and real time PCR for the diagnosis of smear-negative TB as well as for the diagnosis of for MDR-TB and XDR-TB.

Objectives:

- Development of filtration device for concentrating M. tuberculosis from sputum samples.
- Establishment of sensitivity and specificity of Molecular Drug susceptibility testing (Mol-DST) assay.

- Validation of bio-safe filtration based smear microscopy method and its comparison with gold standard.
- Validation of Mol-DST assay on suspected MDR-TB and XDR-TB.

Progress:Currently efforts for standardization of the Molecular Drug susceptibility testing (Mol-DST) assay are ongoing at THSTI. The bio-safe filtration methodology is being developed at AIIMS. A novel DNA isolation protocol has been developed and validated for efficient and inhibitor free DNA isolation from stained filters in a small pilot study (Fig. 1). A plasmid DNA library database of existing mutations for MDR-TB has been created. HRM method development and validation is under development.

External collaborators:Advanced Microdevices P Ltd, Ambala, India; Dr Jaya S. Tyagi, AIIMS, Delhi, India; Dr R. Sarin, Dr V. P. Myneedu, Dr A. Verma and Dr P. P. Sharma from NITRD Hospital, Delhi, India; Dr H. Verma and Dr V. Malhotra from TB Hospital, Ambala, India

Dynamic Molecular Platform for the rapid detection of Drug Resistant TB

Funding Agency: Department of Science and Technology

Background: One of the major factors responsible for this current TB epidemic is the increase in various forms of drug resistant TB. Multidrug resistant TB (MDR-TB) is now widespread globally with an estimated half a million cases reported in 2011 and extensively drug-resistant TB (XDR TB) has been reported in 84 countries. Only 19% of the total estimated numbers of MDR TB cases worldwide were notified to WHO in 2011 and less than 4% of MDR TB cases are currently diagnosed worldwide. The treatment of DR-TB is based on in vitro drug-susceptibility testing (DST) results for each patient's isolate. Conventional culture-based systems are time consuming, while commercial liquid culture decreases turnaround times but is expensive. WHO-endorsed molecular tests such as the Line Probe assays and the Xpert MTB/RIF tests require either extensive time/infrastructure/technical expertise. This is why DST is not available for over 95% of patients with DR-TB and majority of cases are missed or treated empirically. The project proposes the establishment of a Central Molecular platform for Tuberculosis Drug susceptibility testing. This will involve (i) development of an unique and efficient DNA isolation technology which will be compatible with pulmonary, extra pulmonary and paediatric TB samples; ii) Interrogation of all known mutations responsible for MDR and XDR-TB and iii) making the platform adaptable for detecting emerging mutations. The project has an important public health impact as the platform will also be linked to providing the result to patient within 1-2 days to start anti tubercular therapy as soon as possible to avoid further spread of resistance.

Objective: Establishment of a Central Molecular platform for Tuberculosis Drug susceptibility testing.

DR. SAMRAT CHATTERJEE

Team members

Rajat Anand (postdoctoral fellow)

Focus research area

The research area includes development of different mathematical (numerical and analytical) tools to identify potential drug targets and help to accelerate experiments for drug

development. Drug development efforts against disease like cancer are often hampered by the complex properties of signaling networks. Thus a special attention is made to develop models that will understand the complex network structure in a better way and also provide tools to speed up the screening process. Identifications of targets are done through hub proteins and modules significantly affecting the whole disease progression. But identification of these hub proteins and important modules are often very difficult. This is an aspect that needs further tool development. Through mathematical model we define the relation between the position of a molecule in a network and its sensitivity towards any perturbation. This will help us to identify targets based on their structural positions (a handling tool for screening).

We are also working on the gene signature to predict the future outcome in terms of disease development and drug efficacy. At present, we are working on the model for obesity and diabetes, where the aim is to predict body weight and blood glucose from early gene expression values. Also to trace temporal changes at gene level that cause phenotypic change at different time points.

Intramural projects

Use of model trajectories to understand the regulatory mechanisms underlying metabolic diseases

Metabolic disease such as obesity has been recognized as a health concern for decades. The network of molecular interactions associated with this disease is not very clear especially the sub-networks perturbed in this disease.

We will study the temporal gene expression patterns from microarray data obtained from mice fed with high fat high sucrose diet (HFHSD) and mice fed with normal diet (ND) for different amount of times. We will use different tissues to get the microarray data. Now, we can correlate each gene's transcriptional response with some characteristic pattern and find groups of genes with similar patterns. Various methods such as Singular Value Decomposition (SVD) or manual methods can be used to find characteristic patterns used to group data. Now, these groups of genes can be assigned Gene Ontology (GO) functions and checked whether correlated expression patterns is related to a specific function.

We intend to study these functions and see whether they relate to known functions perturbed in obesity. Network analysis of network obtained from the correlations of genes is also possible and can give sub-networks as well as important genes (nodes)/hubs. In our case, the complexity lies to incorporate the temporal dimension in the obtained network to make a dynamical network.

In the next step, mathematical models involving differential equations describing the disease progression will be used to understand the disease progression and possible underlining mechanism through model trajectories derived from the solution of these differential equations.

Unraveling the architecture of biological networks to identify points of sensitivity under random perturbation

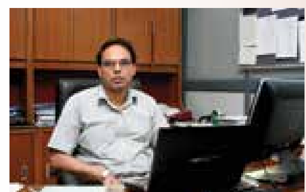
Therapeutic strategies that target key molecules have not fulfilled expected promises for most common malignancies and a major reason for that is the use of single-pathway targeted approaches in the identification of key molecules. To overcome this we need to consider and analyze the system as a complex network of interacting components. Such departure from the traditional paradigm of studying single pathway to more global approach will aid in designing novel therapeutics and also to overcome the shortcomings of the existing therapeutic strategies.

Diseased condition is typically considered as perturbation(s) in components of a cellular network. On the other hand there is noise whose presence causes inappropriate and non-specific responses in signaling network. Here, we dissect the network into smaller structures and then using mathematical models study the importance of motif structure in determining the cellular function in presence of noise and their distribution in a signaling network. For this we use mathematical model build from ordinary differential equations (ODEs) to capture the system dynamics in terms of motif structure and then incorporate noise in the system through stochastic differential equations (SDEs). There are number of ways one can model the system and incorporate noise within it. For example one can replace a constant parameter with a random parameter. Secondly, one can add the randomly fluctuating driving force directly to the deterministic growth equations without altering any particular parameter. Further, "noise" could be a simple white noise or one can also use colour noise and there are available methods to solve these models. We will explore all these possible strategies depending on the need of the system.

The above study will help us to quantitatively measure the sensitivity of a node in the signaling network under noise and thus enable us to develop a formula that could rank the nodes according to their sensitivity profile. This rank could then be used to identify hot-spot in a network with potential candidate for drug target. We can also use the knowledge on the sensitiveness of a node to develop "noise filtration" strategy by re-engineering the node position within the network. This will help to overcome the effects of perturbation in the system due to the disease causing agent.

Profiles of research investigators and programme officers

Dr. G.B. Nair's PhD is from Annamalai University specializing in Marine Microbiology of seafood borne diarrheal pathogens. His research since then encompasses Clinical Microbiology, Molecular Epidemiology and Molecular Pathogenesis of enteric bacteria. His interest has recently widened to the Human Microbiome with particular interest in the human gut microbiota and he was instrumental in the genesis of the Centre for Human Microbial Ecology at THSTI.

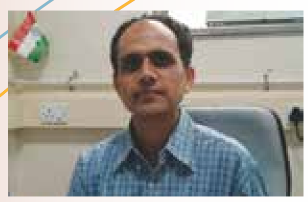


Dr. Sudhanshu Vrati got his M.Sc. from G.B. Pant University, Pantnagar and Ph.D. from the Australian National University, Canberra. His post-doctoral training was at CSIRO, Sydney. Previous to working at THSTI, Dr. Vrati was a senior scientist at the National Institute of Immunology, New Delhi. His research interests include understanding flavivirus replication and development of antivirals and viral vaccines.

Professor Shinjini Bhatnagar is a post graduate in Pediatrics and a PhD from All India Institute of Medical Sciences (AIIMS), New Delhi. She served as Senior Research Scientist and Pediatric Gastroenterologist at the Department of Pediatrics, AIIMS. She heads PBC where her current interests are hypothesis driven and hypothesis generating studies to facilitate development of knowledge based interventions and public health tools for child health. She has recently initiated a program to study biological and non- biological risks of preterm birth and their clinical consequences. She also co-ordinates the Center for Biodesign and Diagnostics (CBD), where she is focused on diagnostics and low cost health products for childhood diseases. In a collaborative program between PBC, CBD, ICGEB, AIIMS and an industry partner, a rapid point of care test for diagnosis of celiac disease (CD) is under development. She is the co-ordinator of the National Biodesign Alliance. She is also the Dean of Clinical Research at THSTI.

Dr. Kanury Rao obtained his PhD in Organic Chemistry from M.S. University, Vadodara, India in 1983. He did a short stint as a post-doctoral fellow in the Division of Environmental Chemistry of the Johns Hopkins University. He switched his interest to Biology, when he moved as a post-doctoral fellow to the Molecular Biology Institute in UCLA in early 1985. He joined the International Centre for Genetic Engineering and Biotechnology (ICGEB) in December 1988 and initiated work on mechanisms regulating T-dependent humoral responses. His current focus of research is to use the tools in Systems and High-throughput biology to decipher the dynamics of host-pathogen interactions in human macrophages infected with Mycobacterium tuberculosis. His team is also engaged in developing novel approaches for chemotherapy, as well as in developing new vaccines against TB. A Fellow of several Academies, Dr. Rao was awarded The Shanti Swarup Bhatnagar Award for Biological Sciences, in 1997.

Dr. Bimal K Chakrabarti did his post-graduation in Biochemistry and Ph.D. in Biochemistry (Molecular Virology) from the University of Calcutta. His post-doctoral work on HIV/SIV and vaccines was from the Learner Research Institute ,Cleveland, Ohio and University of Michigan, Ann Arbor, Michigan, USA. Dr. Chakrabarti continued his HIV vaccine research at VRC, NIH, Bethesda, USA as a Staff Scientist for 10 years. Since 2009, he was a Principal Scientist at IAVI Neutralizing Antibody Center at TSRI, La Jolla, California, USA. Dr. Chakrabarti has over 19 years of experience in HIV vaccine research. His current research interest lies in the designing of novel immunogen based on structure functional relationship of the HIV-1 Env protein for the elicitation of broad and potent neutralizing antibody against HIV-1.



Dr. Guruprasad Medigeshi is a post-graduate from the University of Mysore and is a Ph.D. from Georg-August University, Goettingen, Germany. His post-doctoral training was at Oregon Health & Science University, Portland, Oregon, USA. The main focus of his research group is on understanding the host-pathogen interactions in viral infections with particular focus on dengue virus.

Dr. Ramandeep Singh earned his M.Sc and Ph.D in Biochemistry from the Department of Biochemistry, Delhi University in New Delhi. His Postdoctoral work was at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA. Dr. Singh's work at THSTI involves research in tuberculosis. The focus at his lab is to identify and validate metabolic pathways that enable mycobacteria to adapt to stressful conditions. This would lead to identification of effective new drug targets for M.tuberculosis.

Dr. Nisheeth Agarwal did his M.Sc. in Biotechnology from Banaras Hindu University and Ph.D. in Biochemistry from the University of Delhi. His Postdoctoral work was from the Centre for Tuberculosis Research at the Johns Hopkins University, Baltimore, USA. His current research interests are: regulation of gene expression and pathogenesis of Mycobacterium tuberculosis, drug design, and development of a new TB vaccine.

Dr. Amit Kumar Pandey is a veterinarian by training. After his bachelors in Veterinary Sciences from Orissa Veterinary College, Bhubaneswar, he received Mastersdegree in Animal Biotechnology from National Dairy Research Institute (NDRI) Karnal, Haryana. He is a PhD from Indian Veterinary Research Institute (IVRI), Izatnagar, Bareilly, India. DrPandey's postdoctoral stints were at University of Nebraska-Lincoln, Nebraska, USA and University of Massachusetts Medical School, Worcester, Massachusetts, USA. Dr. Pandey's long-term research interests lie in contributing towards a better understanding of mycobacterial pathogenesis. Currently, his lab is engaged in understanding carbon metabolism in Mycobacterium tuberculosis and its implications on mycobacterial persistence.

Dr Krishnamohan Atmakuri is primarily engaged in deciphering how TB-causing pathogen, manipulates its host for survival and infection exploiting diverse molecular approaches,. After obtaining his PhD from Madurai Kamaraj University in Biotechnology, he pursued his postdoctoral trainings - first at University of Texas HSC, USA and second in the Dept. of Immunology and Infectious Diseases, Harvard University, USA. At UTHSC, he was instrumental in deciphering the molecular mechanistics behind gene delivery into plants by *Agrobacterium tumefaciens*. At Harvard, he helped decipher how *Mycobacterium tuberculosis* exploits its artillery systems for pathogenesis. Currently, he has initiated teasing apart pathogenesis behind bacterial-mediated neonatal sepsis.

Dr. Milan Surjit holds a Master's degree in Zoology from Banaras Hindu University. His Ph.D. in Molecular Biology (Virology) is from the International Centre for Genetic Engineering and Biotechnology, New Delhi. He pursued Postdoctoral Research in Functional Genomics and Cancer at Strasbourg, France. At THSTI, his research is directed at understanding the biology of Hepatitis E virus and development of vaccine and drugs against it.

Dr. Amit Awasthi did his M.Sc. in Biotechnology from Jiwaji University Gwalior and Ph.D in Immunology from National Center for Cell Science, Pune. He did post doctoral work at Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. Dr. Awasthi was appointed as a Junior faculty at Harvard Medical School, Boston, USA before joining THSTI. His present research interest lies in unraveling the interplay between effector andregulatory T cells in IBD and gut infection. A winner of Young scientist platinum jubilee award in biological sciences from National Academy of Sciences of India, Dr. Awasthi is also active in the academia at THSTI.

Dr. Uma Chandra Mouli Natchu is a MBBS and MD in Pediatrics from the All India Institute of Medical Sciences (AIIMS). He practiced pediatrics for three years and devoted a year to clinical research at AIIMS. He then left for the Harvard School of Public Health (HSPH), to qualify for MPH in Quantitative Methods and researched in Nutritional Epidemiology. He has worked on micronutrient supplementation for maternal and child health while at AIIMS and HSPH. At THSTI, his group works on nutrition in pregnancy and childhood, involving fundamental biology, clinical research and public health perspectives. Dr. Natchu is a mentor on the THSTI PhD program and is active on most academic fronts.

Dr. Bhabatosh Das did his M.Tech. in Biotechnology & Biochemical Engineering from IIT-Kharagpur and Ph.D. in Molecular Microbiology from Indian Institute of Chemical Biology, Kolkata. He was a CNRS Postdoctoral Research Fellow at Centre de Genetique Moleculaire, CNRS, Gif Sur Yvette, France. Dr Das specializes in Genetic Engineering with interest in Integrative Mobile Genetic Elements (IMGEs), Small Molecule Signaling Systems and Microbial Metagenomics. Dr. Das joined THSTI this year and is active in academics as a mentor on the THSTIdoctoral program.

Dr. Gaurav Batra did his doctoral work at the International Centre for Genetic Engineering and Biotechnology, New Delhi, India and postdoctoral work at the Division of Biotechnology, University of Turku, Finland, where he was a Marie Curie International Fellow. Major focus of his work is on the development of high quality diagnostic assays for febrile illnesses with special emphasis on tropical infections. To generate high quality diagnostic intermediates, he is involved in protein and antibody engineering, cost effective recombinant protein production in *E. coli* and yeast *Pichia pastoris*, expression host engineering and high throughput clone screening. He is utilizing phage display technique for immune epitope mapping and biomarker discovery.

Dr. Samrat Chatterjee completed his Ph.D from Indian Statistical Institute, Kolkata, in Mathematical Ecology. He did his first post-doc from Department of Mathematics, Torino University, Italy and second post-doc from ICGEB, New Delhi. His area of research use mathematical tools to understand cellular dynamics. He use small conceptual models as well as large scale models to understand relation between a process (variable) and corresponding factor (parameters) that drives the process. His work ranges from the study of simple dynamical behaviour like stability to more complex properties like chaos. His area of research also involves analysis of high-throughput data like micro-array data for gene expression and mass spectrometry data for protein abundance. His current work involves identification of possible candidate for drug targets that can further go for experimental validation.

Dr. Jonathan Pillai comes from a background in Mechanical Engineering (B.E. University of Pune, M.S. Ohio State University), with a Ph.D. in Biomedical Engineering (Ohio State University). He specialized in the use of biodegradable polymers for drug delivery and have worked on systems at various scales from nanoparticles to macroscopic implants. He also have an active interest in medical devices for which he has patents pending. After graduating from the Stanford India Biodesign Fellowship in 2012, he joined THSTI as faculty in the Center for Biodesign in December 2013. He is a Member of the MIT-DBT Subcommittee for promoting Biomedical Engineering in India that launched the new "Biomedical Engineering Visiting Scholar Program".

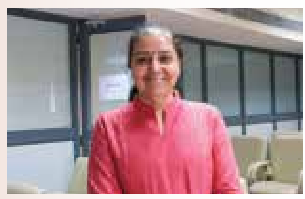
Dr. Jayanta Bhattacharya is a post-graduate in Human Physiology from Vidhyasagar University and a Ph.D in Microbial pathogenesis from Calcutta University. His postdoctoral experiences come from Meharry Medical College and University of Massachusetts Medical School, USA, where Dr. Bhattacharya also served as an instructor. Prior to his current assignment he was Deputy Director (Scientist E), Molecular Virology at National AIDS Research Institute, Indian

Council of Medical Research, Pune, India. Dr. Bhattacharya has successfully supervized five doctoral students at the University of Pune. Dr. Bhattacharya's current research interests are examining vulnerabilities in HIV-1 envelope to aid immunogen design. As Principal Investigator, he also collaborates with scientists at the National Institute of Communicable Diseases (NICD), Johannesburg, to design a common vaccine that would be effective in both India and South Africa.

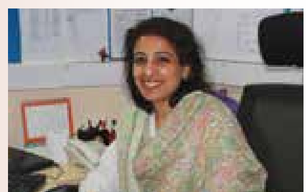
Dr. Rajkumar Haldar did his doctoral studies from the University of Basque country, Spain. He was a Skaggs Postdoctoral Fellow at The Scripps Research Institute, La Jolla, CA, USA and a Scientist at Novartis (GNF), San Diego, CA, USA. At THSTI he will be focusing on 1) Synthesis of small organic molecules and molecular assemblies with novel physiochemical and biological properties and function through development of new chemical methodologies, Diversity Oriented Synthesis, Targeted Oriented Synthesis, Fragment Based Drug Discovery and isolation of natural products from biologically significant marine and plants resources; 2) application of chemical compound library; 3) Study of pharmacology characteristics of compounds of interest; 4) early stage translational research focused on cancer, diabetes and other metabolic disorders; 5) elucidation of the mechanistic pathways affected by compounds of interest by application of chemical and genomics tools.

Dr. Ranjith-Kumar did his doctoral studies from Department of Biochemistry, Indian Institute of Science, Bangalore. Prior to joining THSTI, he was a Research Scientist at the Department of Molecular and Cellular Biochemistry, Indiana University. His postdoctoral stints were at the Department of Biochemistry and Biophysics, Texas A&M University, USA and the Department of Biological Sciences, Purdue University, USA. Dr. Kumar's research focuses on Molecular Virology and Innate Immunity with the aim of developing vaccines and antivirals.

Dr. Pallavi Kshetrapal did her doctoral studies from the Cellular and Molecular Biology (CCMB), Hyderabad followed by Post doctoral work at the Harvard Medical School, USA. She received her Ramalingaswami Fellowship award and joined THSTI with her research focus on studying the underlying mechanisms that could lead to Pediatric cancers, especially the role of Notch synergies in T-cell Lymphoblastic Leukemias (T-ALLs). She is also interested in studying the genetic factors that contribute to fetal tolerance during pregnancy, changes in which could lead to adverse pregnancy outcomes. Using molecular and cell biology techniques she would like to unravel the complex role of the genes that support normal fetal development. She recently bagged the IYBA award for the year 2013 from the Department of Biotechnology.



Dr. Manjula Kalia is a PhD from National Institute of Immunology, New Delhi. Her Post-doctoral training was from University of Calgary, Canada. She has worked as a Visiting Fellow at National Centre for Biological Sciences, Bangalore under the DST-FAST Track Scheme for Young Scientists and, as a DBT Young Scientist at International Centre of Genetic Engineering & Biotechnology, New Delhi under the Innovative Young Biotechnologist Award. At THSTI her research is on Host-Pathogen interactions of Flavivirures with a focus on virus receptors, entry pathways and autophagy.



Dr. Nitya Wadhwa is a clinical scientist with an MD in Pediatrics. After a decade in clinical pediatric practice and neonatology, she ventured into clinical research at AIIMS where she supervised the conduct of five randomized controlled trials. She was involved in studies that evaluated interventions in several commonly occurring infections in children in India. At THSTI, she is a Clinical Investigator, supervising a multi-center crosssectional study. She is also involved in the implementation of a large randomized, controlled trial that aims to determine efficacy of Vitamin D supplementation on vaccine responses in infants. Currently she is involved in the study of cord blood immune markers, The Nutrivac-D Trial, the Hib Meningitis Sentinel

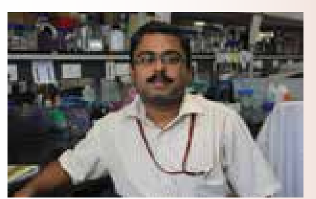
Surveillance among other projects. She is one of the principal investigators of the Inter-Institutional program for maternal, neonatal and infant sciences-A translational approach to studying pre term birth. Dr. Wadhwa's commitment to academics goes beyond her projects to the THSTI Graduate program where she teaches 'Clinical Research Methods'.

Dr. Shailaja Sopory graduated from Indian Institute of Science, Bangalore followed by post doctoral training at Oregon Health and Science University, Portland USA. Her broad area of interest is cellular signaling. Currently she is trying to understand the signaling pathways in the podocyte under specific conditions of injury leading to minimal change nephrotic syndrome in children. She is also interested in the development of the neonatal immune system and susceptibility to infections during initial stages of life.

Dr. Arup Banerjee did his M.Sc. in Biochemistry from Calcutta University and PhD from Jadavpur University Kolkata. His post doctoral training was at the Division of Infectious Diseases & Immunology, Saint Louis University, Missouri, USA, where he studied the molecular basis of hepatitis C virus infection and pathogenesis. Presently, his focus is on (1) to understand the role of miroRNAs in Japanese Encephalitis virus infection and pathogenesis (2) Understanding early transcriptional signature of Dengue virus and clinical features associated with disease progression

Dr. Supratik Das did his doctoral studies from the Albert Einstein college of Medicine, USA. The overall aim of his research is to develop Envimmunogens that are trimeric and cleaved but soluble, monodisperse and stable to be used as candidate subunit vaccine.

Dr. Mohan Appaiagari obtained his masters' degree in Virology from Sri Venkateswara University, Tirupati and then did doctoral research in biotechnology from JamiaHamdard University, New Delhi. At THSTI, his major research interest is in the isolation and characterization of novel Adenoviruses from non-human species for the development of gene/ vaccine delivery vectors. Besides this, development of novel vaccines/molecular therapeutics against medically important flaviviruses is his



Dr. Sankar Bhattacharya did his M. Sc. from University of Calcutta and Ph.D. from the Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore. His research area is the study of host-pathogen interactions with respect to Japanese encephalitis virus. area of special interest.

Dr. Deepak Sharma earned his M.Biotechnology and Ph.D. from All India Institute of Medical Sciences (AIIMS), New Delhi. His research interest lies in the field of Computational Biology. With the copious amount of genomic and experimental data being generated, the imperative to follow a bioinformatics-guided research has never been greater for him. Furthermore, with the use of in silico methods he aims to target any pathogen with a global perspective rather than a locally focused strategy. The emphasis of his research at THSTI is on flaviviral diseases and tuberculosis.

Dr. Ashutosh Tiwari did his MSc in Biochemistry from CSJM University, Kanpur and received his PhD in Biochemistry from All India Institute of Medical Sciences (AIIMS), New Delhi. He also did his postdoctoral research at AIIMS, New Delhi and Wayne State University, Michigan, USA. His present research interest lies in protein engineering technologies for designing new class of scaffolds and synthetic antibodies for therapeutics and diagnostics use. His group works on generating novel antibody binders for various pathogens to improve diagnosis and effective therapy using phage display in conjunction with highthroughputscreening and sequencing.

Dr. Niraj Kumar, holds a PhD (Biotechnology) from the National Institute for Cellular Biotechnology, Dublin, where he also did Post-doctoral work and followed up at Institute of Applied Microbiology, BOKU, Austria. He did his M.Sc (Biotechnology) from Department of Biotechnology, Indian Institute of Technology, Roorkee. Dr. Kumar's focus is on discovery and development of potential biomarkers for earlydiagnosis of acute coronary syndrome and childhood pneumonia using OMICS-based approach. He is intended towards development of efficient, high quality, affordable diagnostic tools for early-diagnosis of these diseases. He aims to accomplish this by multiplexing biomarker in a single test. His interests also extend to cell line development for recombinant protein (antigen and/or antibody) production for use inthe bioprocessing industry.

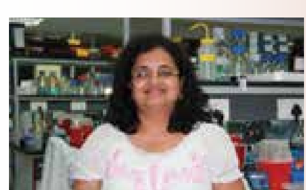
Dr. Susmita Chaudhuri has a PhD. in Microbiology from National Institute of Cholera and Enteric Diseases, Kolkata. She did her M.Sc. in Zoology specializing in Microbiology from Calcutta University. She did her postdoctoral research in Medical Microbiology and Immunology from University of Alberta, Canada. She was a Senior Research Scientist in the R&D of Panacea Biotec Ltd., on therapeutic protein development. Her present research interests are on biomarker discovery and validation, and diagnostic development for cardiovascular and respiratory infectious diseases.

Dr. Amit Kumar Yadav did his doctoral studies in Biotechnology (2012) from from CSIR-Institute of Genomics and Integrative Biology, Delhi, India. At DDRC, his research focus is to understand the patterns of regulatory networks of PTM, their role in modulating protein-protein interactions, cross-talk among different PTMs and their evolution. He is the recipient of the IYBA award for 2013 from DBT.

Dr. Sangeeta Kumari did her doctoral studies in chemistry from the Osmania University followed by post doctoral studies at UC Davis and University of Michigan. At DDRC, she is a DST INSPIRE faculty and her work area is metabolomics involving measurement of concentrations of small molecules in biological samples. Her current responsibilities involve LC-MS method development and mass spectrometry data collection, interpretation, and presentation. Core competencies include both targeted assays for many analyte classes as well as untargeted assays to evaluate the entire metabolome in biofluids and tissues, measurement of flux through various pathways using 13C-isotopomer analyses, and structural identification of isolated unknowns and potential biomarkers.

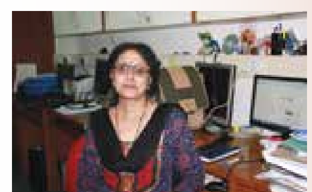
Dr. Sagarika Haldar did her Master's and Doctoral degree in Biotechnology from All India Institute of Medical Sciences (AIIMS), New Delhi. She did her post doctoral research as an Innovation Awardee at the Centre for Bio-design and Diagnostics at THSTI, Gurgaon. Her present research interest as an INSPIRE Faculty includes development of new diagnostic modalities for tuberculosis using nucleic acid-based approaches and antigen-based detection assays in point-of-care formats. One of her major focus is to develop novel molecular tests for drug resistant tuberculosis. She is also involved in assessing the utility of antigen detection in improving the diagnosis of various forms of extrapulmonary TB.

Dr. Saikat Boliar obtained his PhD in Virology from University of Kentucky, Lexington, USA. He did his postdoctoral fellowship in HIV-1 pathogenesis from Emory University, Atlanta before joining the HIV Vaccine Translational Research Laboratory at THSTI as a scientist in 2012.



Dr. Tripti Shrivastava did her M.Sc in Biochemistry from Kanpur University and Ph.D in Structural Biology from Central Drug Research Institute, Lucknow. She did her Postdoc at University of Nebraska Medical center, Omaha, Nebraska, USA before joining the HIV Vaccine Translational Research laboratory at THSTI as a scientist in 2013. Her major goal is to design immunogens which can be used as vaccine candidates.

Dr. Sweety Samal obtained Ph.D in Virology from University of Maryland, College Park, USA in 2012. She worked on understanding the role of Fusion protein of Paramyxoviruses and Paramyxoviruses as a viral vector delivery system for important human and animal pathogens using reverse genetics. She is a Scientist in HIV vaccine Translational Research laboratory at THSTI from 2013.



Dr. Bratati Mukhopadhyay had her Doctoral work in Biotechnology, specializing in the area of "Selective Delivery of anticancer drugs"from the Panjab University, Chandigarh and post-doctoral training on Protein Biochemistry, from the School of Environmental Sciences, JNU, New Delhi. She subsequently shifted her interest and contributed significantly in the rational use of both essential drugs and traditional medicines; also technical management of CPCSEA issues in Delhi Society for Rational Use of Drugs at NII, New Delhi. Then, during her tenure in DBT, New Delhi, she was actively involved in scientific management by scrutinizing project proposals, organizing task-force meetings and coordination with Principle Investigators for successful implementation of the projects.

Dr. Kaushik Bharati is currently Senior Program Officer at the Policy Center for Biomedical Research (PCBR), Translational Health Science and Technology Institute (THSTI), India. Dr. Bharati obtained his Ph.D. from the University of Calcutta in 2001, in Human Physiology, specializing in the area of Vaccines. He then received his post-doctoral training from the Liverpool School of Tropical Medicine, Liverpool, U.K. and the National Institute of Immunology, New Delhi, working in the area of DNA vaccines. He has subsequently specialized in the area of Health Policy. His current area of interest is cholera vaccine advocacy and policy, which has been taken up as a Flagship Program by PCBR.

Dr. Mona Duggal holds MD (Preventive and Social Medicine) from University College of Medical Sciences, Delhi, Master of Health Sciences in Epidemiology from Johns Hopkins University School of Public Health, USA followed by a NIH/NLM fellowship in Medical Informatics from Yale University School of Medicine. Her recent focus of research is at the intersection of behavioural science and mHealth, especially in low to middle income populations.

Dr. Sanjukta Sen Gupta is a B.Sc. (Hons), Human Biology, from AIIMS. Her M.Biotech is from MS University of Baroda. She worked as a CSIR Research Fellow at AIIMS and was awarded her PhD from Faculty of Medical Sciences, Delhi University. During her tenure as a DBT Post Doc fellow at AIIMS, she was a member of the Vi conjugate vaccine development team. Sanjukta is an alumnus of the Advanced Vaccinology Course, FondationMereiux and University of Geneva. She was a consultant for Department of Biotechnology for few new-institution building initiatives, including a Policy Center for Biomedical Research. She was nominated for the Khorana Technology transfer course at University of Wisconsin 2012.

Dr. Gautam Saha has worked on identification and characterization of protein vaccine candidates from pathogenic *S. pneumoniae* in post doctoral studies, in the molecular immunology laboratory of National Institute of Immunology, India. He obtained his PhD from School of Biotechnology, Jawaharlal Nehru University, Delhi, India. In his doctoral studies he has worked on deciphering Mechanisms in regulation of *c-jun* gene expression. During PhD studies he was CSIR fellow(JRF/SRF) by qualifying National Eligibility Test conducted CSIR-UGC. Gautam is also an alumnus of All India Institute of Medical Sciences, New Delhi where he has obtained his post graduation degree in Biotechnology, and his Master thesis work was on analysing cytokine profile in patients with squamous cell carcinoma of the oral cavity.

Ms. Swati Verma has done her Masters degree in Biotechnology from Dept. of Biotechnology,Pune University. She is working as Analyst at PCBR for the past 4 years under the able mentorship of Prof. N.K. Ganguly. She has been associated with public Health documentation and data analysis work. Her expertise includes the Maternal and Child Health. Currently, she is working on Identifying the research prioritization needs for improvement of Women's health, rural health in India and its relation to household air pollution (UC Berkley) and Mapping the Bio-surveillance Framework to prevent and tackle disease outbreaks (CDC). She has been instrumental in collection and Analysis of published Scientific Data, Formulation and Preparation of scientific project reports, documents and policy papers, Reviewing/Evaluation of the projects etc. She has actively participated in the several meetings and conferences organized by the Policy unit.

Ms. Radhika Gigras has an M.Pharm in pharmaceutical Sciences from BITS PILANI. She has nearly 8 years of experience as in medical writing and regulatory dossier preparation with major pharmaceutical companies (Ranbaxy Laboratories, Gurgaon and IPCA Laboratories, Mumbai). As a Senior Research Scientist in Ranbaxy she was dealing with Regulatory filing of clinical studies for various regulatory agencies of US and Europe. Clinical Bioavailability and bioequivalence (BA-BE) studies, development of SOPs, knowledge of GCP and GLP guidelines are her key expertise. She was a part of a team which successfully handled USFDA, ANVISA, WHO, MHRA-U.K audits. She had received Global appreciate award for Excel validation in Ranbaxy.

Ms. Nisha Arora was awarded a Gold Medal in M.Sc (Statistics) from Guru Nanak Dev University, Amritsar. She started her career as an Assistant Professor in Statistics at Khalsa College, Amritsar, Punjab. She has 2.5 years of experience as Statistician cum Assistant Professor in Biostatistics at Punjab Institute of Medical Sciences, Jalandhar. During her tenure as a Statistician, she had been extensively involved in preparing health related vital statistics as per Medical Council of India norms. She joined THSTI in Aug, 2013 as Junior Analyst (Statistician)

Academia

Ph.D Programs

Translational Health Science and Technology Institute (THSTI) is a recognized R&D institute of the Jawaharlal Nehru University (JNU), New Delhi to offer doctoral programs in biomedical and clinical research tracks for candidates with medical, life sciences (including biomedical, health, pharmaceutical, nutritional science, public health, and nursing), veterinary science, engineering, or mathematics background.

The broad domains of ongoing research at THSTI are:

- Biology of infectious diseases such as dengue, Japanese encephalitis, hepatitis E and tuberculosis, vaccine and anti-viral development
- Physiology of nutrition and the developing immune system, immune responses in pregnancy and childhood
- Clinical research and epidemiology focused on maternal and child health
- Auto-immune diseases, infection and inflammation
- Understanding disease through the human microbiome
- Diagnostics and therapeutics
- Medical devices and implants
- Mathematical modelling to understand biological problems

Students selected for the program are required to undergo a pre-PhD course work followed by the submission of a research thesis. The PhD program at THSTI is governed by the JNU rules.

The students admitted to THSTI-JNU PhD program will be required to undertake courses to earn 14 credits to be eligible to undertake thesis research work. THS-1, THS-2, and THS-3 are core courses of 8 credits and compulsory for all students. All other courses are optional and the student has the choice to earn 6 credits by choosing any combination. The courses offered over the two semesters are:

Semester-I

- Biomedical Research : Concepts and Methods
- Clinical Research Methodology
- Research Internship

Semester-II

- Health Policy and Decision Analysis in Health
- Infectious Disease Biology
- Infectious Disease Epidemiology
- Immunology and Immunotechnology
- Special Topics in Epidemiology
- Essentials of Clinical Trials
- Essentials of Regulatory Trials
- Introduction to Biodesign

Biomedical research : concepts and methods

This course has been designed to introduce the students to the practical world of life science research. The curriculum covers fundamental concepts of basic and translational research as well as educates them in identifying and executing innovative research ideas. The course also allows students to gain theoretical and practical understanding of techniques relevant to modern day life science research.

Clinical research methods

Students across life science disciplines require a sound knowledge of the fundamentals of research methods to understand, design, analyze and communicate their research. Students will be exposed to the basics of the components of a good research proposal and the essential epidemiological and statistical concepts that form the framework of sound research. Students will learn to use simple designs and statistical methods to formulate questions and analyze data. In addition to lectures and seminars the course will involve multi-faculty workshops, exercises in biostatistics with STATA statistical software and group tasks. Students across diverse fields are expected to understand the basics of clinical research methods and the language of clinical research by the end of the course.

Research internship

Students are required to work in the lab/clinic of the assigned supervisor in the afternoon and undergo training in various research methodologies and participate in laboratory/clinical discussions. At the end of the semester, students are required to write a report (8-10 pages) on various tasks assigned and make a presentation on their accomplishments to the assessment committee. The supervisor will provide his/her assessment of the student's performance during the internship, participation in laboratory/clinical activities and discussions, and the quality of report. Students are also expected to fine tune their analytical and scientific communication skills by presenting a seminar on a relevant topic (in consultation with their supervisor), detailing the existing knowledge and their opinion about future perspectives on that topic.

Health policy and decision analysis in health

Application of solutions for public health in the real world requires robust decision-making and analysis of risks. Economic analyses of policy decisions become even more critical in contexts of constrained resources. Public health professionals will be trained in techniques of decision and risk analyses. Many of these techniques can be used at the bedside as well for population & community health decisions. These methods can also be adapted to decision making for research priorities, outcomes and funding. Bayesian probability, evaluation of diagnostic tests, decision trees, QALYs, disease burden quantification, utilities and cost effectives analysis are some of the topics that will be covered. The course will involve lecture sessions with active class participation, in-class and take home exercises.

Infectious disease biology

This course aims at educating students about important human infectious diseases prevalent in India and worldwide. Introductory lectures by clinical experts on few important infectious diseases will provide a practical overview of those diseases from a doctor's point of view. Further emphasis will be given to understanding the molecular basis of various bacterial and viral infections. This course will also cover classical as well as modern approaches to developing prophylactic and therapeutic strategies against those pathogens.

Immunology and immunotechnology

This course covers both theory and techniques relevant for immunological research. The first part of the course aims at explaining the fundamental concepts of immune system and its components and illustrate the importance of these under various conditions such as infections, cancer or transplantation therapy. The course also covers the importance of human microbiome in mediating immune functions. The second part of the course will cover theoretical and practical aspects of techniques important for immunological research in the laboratory as well as discuss the concepts of important diagnostic techniques.

Special topics in epidemiology

This course covers advanced topics in epidemiology providing detailed understanding of the design and implementation of cohorts and case control studies as well as other epidemiologic studies. The course will consist of lectures, seminars, and reading material. In addition, a number of in-class and take home exercises will form a strong component of the course. Students will also spend substantial time in group-activity across disciplines to learn to work collaboratively to formulate translational research questions and to design studies to answer them. Students are expected to participate in discussions in classes.

Essentials of clinical trials

This course addresses critical methodological aspects of clinical trials. At the end of this course the student will be able to demonstrate understanding of the principles of clinical trials, assess and select relevant research designs for clinical trials, conduct random allocation, blinding and sample size estimations, critically interpret published results from clinical trials.

Regulatory trials

This course is designed to create awareness about the regulations & guidelines related to clinical research in India as well as globally. The students will understand how to manage a clinical study effectively by good documentation and clinical data management practices. The course prepares the participants to face audit and regulatory inspections from regulatory agencies.

Post-doctoral Program

THSTI provides post-doctoral training under the mentorship of its senior faculty. Young scientists who have recently completed their doctoral training are encouraged to correspond with faculty members whose research area may be of interest to them. THSTI will provide sponsorship for DBT post-doctoral fellowship to deserving candidates based on the recommendation of a faculty member. THSTI offers post-doctoral training to young researchers through specific options for post-doctoral program at various niche centers of THSTI. These schemes usually span for a period of five years and are widely advertised in national newspapers and on THSTI website.

The various post-doctoral options are:

- 'Vaccine Research Innovation (VRI) Award Scheme' in the Vaccine and Infectious Disease Research Center.
- 'Innovation Award' scheme in Biodesign in the Centre for Biodesign and Diagnostics, focusing on diagnostics, implants and medical devices.
- 'Microbiome Innovation Award' scheme in the Centre for Human Microbial Ecology.

Also there is a sandwiched post-doctoral program, 'Indo-Finnish Post-doctoral fellowship in Diagnostics' funded by DBT and administered by THSTI. This program is for young researchers who have inclination for research in areas in diagnostic product development and platform technology development. The fellows get training at THSTI, India and University of Turku, Finland.

Partnership Centre

Population Science Partnership Centre

Population Science Partnership Centre (PSPC) is a 'cost saving, scientific productivity and health impact enhancing' collaborative venture between Translational Health Science and Technology Institute (THSTI), Haryana and Centre for Health Research and Development, Society for Applied Studies (CHRD-SAS), New Delhi. The overall approach and aim is to incorporate hypothesis-driven scientific questions in population cohorts and clinical trials related to diseases of major public health importance. The knowledge gained will provide insights for prevention, diagnosis and treatment of fetal, neonatal and childhood disorders that contribute most to the disease burden in the country. PSPC as a national resource centre of the DBT would gradually add to the on-going transformation of THSTI as a leader of translational science and technology and give it the health connectivity that it essentially requires. PSPC would also be a unique resource for all the DBT institutions in their quest to enhance the practical value of their science.

Aims And Objectives

The aims and objectives are to pursue collaborative research and innovation in population based science, focused on development, evaluation and diffusion of affordable technologies and solutions for improved health and nutrition; emphasize on solutions and technologies of public health importance to India and to the poorest; and promote utilization of under-used existing technologies through appropriate modification and evaluation.

Research Domains

Fetal Growth Restriction

In South East Asia, 10 million low birth weight babies are born. They are at risk of stunting and high risk of chronic diseases including cardiovascular diseases, diabetes and cerebrovascular stroke. In India, despite enormous progress, 20% babies are born low birth weight (birth weight <2500 gm). Infant mortality in low birth weight babies is twice that of normal weight babies. This sub-programme plans to elucidate the scientific basis of fetal growth and fetal growth restriction and its relationship with postnatal growth and development. We will evaluate specific preventive, diagnostic or therapeutic interventions. The scientific approach will be interdisciplinary and will employ biology, biomedical research, nutrition science, health research, and drugs and diagnostic technology.

Neonatal Infections and Immunity

Neonatal mortality contributes to two-thirds of infant deaths in India, which is amongst the highest in the world. Infections also contribute to under nutrition and as a result impaired intellectual development. The environment of a newborn infant and the immune system of a neonate are unique and require focused studies. New ways of prevention and treatment of neonatal infections have to be developed that can be applied not only in hospital born babies but also to those born in rural communities. This has been declared as a national priority. This sub-programme aims to elucidate causes and causal pathways underlying neonatal infections, resistance to disease including immune function and to develop diagnostic and therapeutic modalities. The key disorders are neonatal sepsis, lower respiratory tract infections and diarrheal diseases.

Accelerating Linear Growth in Indian Infants and Children

Forty five percent of infants in India are stunted. This is higher than even what is seen in poor countries in Africa. The factors that affect linear growth include nutrition, alteration in the microbiome, placental transport, breast milk nutrient quality, epigenetic alterations as a result of environmental influence. The rate of linear growth in the first two years of life is an important determinant of all lifestyle diseases. Stunting shows strong correlation with intellectual capital in adult life. This sub-programme aims to understand causal pathways underlying impaired linear growth in Indian infants and children and based on the scientific knowledge generated, develop ways to accelerate linear growth in postnatal life and early childhood

Vaccine Preventable Diseases

Our knowledge of disease burden in India is rudimentary for several infections leading to controversy in vaccine policy and difficulties in planning vaccine trials. Novel strains identified through disease surveillance need to be stored under scientifically valid conditions. This sub-programme plans to determine the disease burden for diseases such as typhoid, cholera, respiratory syncytial virus, influenza, dengue and rotavirus and through application of infection science determine molecular subtypes of relevant infectious pathogens and develop a repository at THSTI.

Evaluation of Novel Public Health Technologies

Population science is critical to understand the product profile most suited in the health care system. The need for such a sub-program is highlighted by the success of evaluation of a rotavirus vaccine through the collaboration between THSTI and SAS. This sub-programme will evaluate safety and efficacy of new technologies through population based studies and in the context of primary and secondary health care. These technologies will be those that have been development by Indian institutions across the country including THSTI.

Microbiome

Research on microbiome is amongst the top five priorities in human biology today. This sub-programme will study the contribution of the gut microbiome to altered growth and development and the effect of diet on the microbiome

Strengthening Research Infrastructure for Population Based Studies

This programme will strengthen field infrastructure for sustained research under the centre. This will include establishing a birth cohort in peri-urban/rural populations, establishing field units and systems for handling biological specimens prior to transfer to THSTI, electronic data capture and transfer of data from field to the Advanced Data Management Centre of CHRD-SAS, regulatory support system and Good Laboratory Practice guidelines.

Programs Running Under at the Centre

The Memorandum of Understanding was signed on November 28, 2013 and at present one project is operational under the centre and another will commence shortly.

Project I: The Effects of Human Intestinal Microbiota on Immune Responses

PSPC Research Team: Translational Health Science and Technology Institute - G. Balakrish Nair; Centre for Health Research and Development, Society for Applied Studies - Nita Bhandari, Osaka University, Japan-K. Takeda and T. Kurakawa.

Background for the Research Study

Recent accumulating evidences have indicated that different environments and diets influence microbial ecology of the human gut (1). We assume that the composition of gut microbiota

varies between people living in Japanese and Indian communities, and hypothesize that resistance to intestinal infection in Indian populations is regulated by their unique intestinal microbiota.

In this study, fecal samples of Indian and Japanese subjects were collected, and the intestinal microbiota analyzed by molecular techniques. Then, fecal samples of Indian and Japanese subjects were orally administered to germ-free mice, and development of intestinal immune cell populations and sensitivity to intestinal pathogenic bacteria was compared between mice harbouring the Indian intestinal microbiota and those with the Japanese one.

Description of the population

The study will be undertaken in 50 Indian healthy adults (10 each from 5 different areas) and 10 Japanese healthy adults.

The study population from India comprised of healthy adults residing in low socioeconomic dwellings in five different urban and rural areas in Delhi and Haryana states. These areas are typical urban resettlement neighborhoods and rural areas in South Delhi-I, South Delhi-II, North-West Delhi and Urban Faridabad and Rural Haryana, in India.

On the other hand, the study population from Japan comprised of healthy adults residing in high or average socioeconomic dwelling in Osaka prefecture. This area is typical urban area with good hygienic environment.

Hypothesis

Resistance to intestinal infection in Indian populations is regulated by their unique intestinal microbiota.

Objectives

- To study the diversity of intestinal microbiota of Indian and Japanese people
- To study the effect of differential intestinal microbial composition on immune responses in germ free mice

Outcomes

- The results of this study will improve our knowledge about;
- The diversity of intestinal microbiota of Indian and Japanese people
- The effect of differential intestinal microbial composition on immune responses

Methods for human subjects

- 50 Indian (10 subjects×5 areas) and 10 Japanese (10 subjects×1 area) healthy adults were enrolled for fecal specimen collection to be used in this research study. Adult volunteers from the specified areas were identified and called to the study clinic for consenting and screening. Eligible subjects were explained the process for stool specimen collection and the fecal specimen collection kit was given to them. The participation of the subjects in the study ended after the collection of an adequate stool specimen.
- A fecal collection kit, which contains a spatula, a paper plate, icepacks and a sterile tube, were given to each subject. Immediately after fresh fecal samples were put into the container, they were delivered to the laboratory. The specimen were transported to THSTI laboratory within 4-6 hours of passing stool.
- Each sample was separated to three portions, for microbiota analysis, administration to mice and organic acid measurement. The samples were homogenized with RNA *later*, anaerobic medium and 10% perchloric acid, respectively. Plastic tubes with each portion were transported from Delhi to Osaka University by World Courier in a cool condition.

Animal study method

Germ-free mice were orally administered Indian or Japanese fecal samples (mixture of 5 subjects with similar microbial composition).

Laboratory Methods

- Analysis of intestinal microbiota
- Nucleic acids were extracted from fecal samples of the human subjects and mice. The intestinal microbiota were analyzed by Reverse transcription-quantitative PCR (2) in Yakult Central Institute for Microbiological Research (Tokyo) and by pyrosequencing in Osaka University.
- Measurement of organic acid
- Concentration of organic acid in fecal samples of the human subjects were analyzed.
- Analysis of immune cell populations

At 4 weeks after the oral administration of fecal samples to the mice, their lamina proprial cells were isolated and analyzed for IgA expression as well as expression of IL-17, IFN-γ, and IL-10 in CD4+ cells by flow cytometry. Immune cell populations (IgA+ B cells, CD4+ T cells expression IL-17, IFN-γ, IL-10 and IL-4) in lymphoid tissues (spleen, mesenteric lymph nodes and Peyer's patches) were also analyzed.

Analysis for sensitivity to intestinal infection

The sensitivity to *Citrobacter rodentium* infection were compared between mice administered and harbouring Indian microbiota and those with the Japanese microbiota.

Results

- The Firmicutes/Bacteroidetes ratio in the intestinal microbiota of Indian was different from Japanese one.
- The OTUs of *Bacteroides* and *Prevotella* detected from Indian were different from those from Japanese.
- The Indian subjects could be categorized to 2 clusters.
- The concentration of propionic acid and total SCFAs in the intestines of Indian was significantly higher than that of Japanese.

The concentration of propionic acid and total SCFAs was different between 2 clusters.

Project II: A Phase III Randomized, Double Blind Placebo Controlled Trial to Evaluate the Non-interference in the Immune Response of Three Doses of ORV 116E to Antigens Contained in Childhood Vaccines and to Assess the Clinical Lot Consistency of Three Production Lots

PSPC Research Team: Translational Health Science and Technology Institute - Sudhanshu Vrati; Centre for Health Research and Development, Society for Applied Studies - Temsunaro Rongsen Chandola, Nidhi Goyal, Sudeep Singh Rathore, Nita Bhandari, Sunita Taneja

The study will be conducted in the urban neighborhoods of Govindpuri- Sangam Vihar-Tigri Dakshinpuri and Tuglakabad in South Delhi, India. The phase I, phase II and phase III efficacy trials of the same vaccine candidate have been conducted in this population. One or more study clinics will be set up within the study areas. In this setting, maternal literacy rates are high; ~80% of mothers have attended school. The median family income is `6,000 per month which is low middle class income in the Indian context. Majority of dwellings are self owned and electricity and water are provided free of cost by the government. Being located in the heart of the city the residents have easy access to public transportation (buses and three wheelers) and tertiary hospitals. In addition, clinics run by the government (that treat free of cost) and private practitioners (who charge nominal sums of money) are located within the colonies at walkable distances. About 70% of the families own a telephone and the remainder have access to telephone booths that charge a nominal sum for a call. Access to telephones in this setting therefore is almost universal as all neighborhoods have several public telephone kiosks established by the government and therefore any potential benefits from participation in the study will be available to all.

Trial objectives and purpose

Hypothesis

The ORV 116E, NLT 105.0 ffu does not interfere with the immune response to childhood vaccines, namely pentavalent vaccine and oral polio vaccine, when co-administered at 6-7, 10-<14 and 14-<18 weeks of age.

The geometric mean titers (GMTs) of IgA antibody with three different production lots of the ORV 116E will be similar as measured on 28 (±5) days after the third dose of the Test Article. Similarity (or "equivalence") is defined as obtaining two-sided 95% confidence intervals (CIs) for ratios of GMTs with limits ³ 0.5 and £ 2, for all pairwise comparisons of the three vaccine lots.

The ORV 116E, NLT 105.0 ffu is safe in the four week period following each of the three doses when given to infants at 6-7, 10-<14 and 14-<18 weeks of age, when co-administered with childhood vaccines.

Objectives

Primary

To determine whether ORV 116E, NLT 105.0 ffu can be successfully co-administered with childhood vaccines (Oral Polio Vaccine, Diphtheria, Pertussis, Tetanus, Hepatitis B and *Haemophilus influenzae* Type B) at 6-7, 10-<14 and 14-<18 weeks of age, without interfering with the immune responses to each of these vaccines.

To determine clinical lot consistency in the immune responses between three different production lots of the ORV 116E, NLT 105.0 ffu.

Secondary

To assess the safety of a 3-dose regimen of ORV 116E, NLT 105.0 ffu given concomitantly with childhood vaccines, for immediate adverse events and serious adverse events occurring till four weeks after the third dose in all subjects

To assess the safety of a 3-dose regimen of ORV 116E, NLT 105.0 ffu given concomitantly with childhood vaccines, for adverse events in the 2-week period following administration of each of the 3 doses of the Test Article/Placebo in all subjects.

To assess the safety of a 3-dose regimen of ORV 116E, NLT 105.0 ffu given concomitantly with childhood vaccines, for intussusception events as confirmed by Brighton Diagnostic Certainty Level I Criteria and deaths occurring in all subjects till one year of age

To examine the immunogenicity of a 3-dose regimen of ORV 116E, NLT 105.0 ffu as assessed through a four fold rise in rotavirus-specific serum IgA antibody titers 28 (+) 5 days after the third dose in comparison to baseline levels

Profiles

Nita Bhandari, MBBS, PhD, MNAMS, Director

Nita Bhandari is an internationally recognized public health researcher with expertise in community based research related to child health and nutrition with special focus on nutritional intervention trials to reduce childhood morbidity and mortality, nutrition-infection interaction, and vaccine trials to prevent childhood infectious diseases.

She is involved in the design, analyses, coordination or implementation of several large, complex trials conducted under difficult field conditions. She was an investigator for various large community based research projects that were undertaken at All India Institute of Medical Sciences (till December 2004) and subsequently at CHRD, SAS.

She played a pivotal role in the coordination of the multisite randomized, double-blind, placebo-controlled Phase III clinical trial and headed the team of investigators from Delhi, Maharashtra and Tamil Nadu. The clinical study demonstrates for the first time that the India-developed 116E rotavirus vaccine is efficacious in preventing severe rotavirus diarrhoea in low-resource settings in India. All the phase I and II trials preceding the phase III trial were also led by her.

She has been a key person in formulation of programs for improving infant and child feeding practices. She is a member of various national and international professional societies and scientific advisory committees constituted by the Government of India; she has served as a consultant for the World Health Organization to develop feeding recommendations for several countries.

She is also an Adjunct Professor at the University of Bergen (Norway) and Christian Medical College (Vellore).

She has numerous research publications in international and national peer reviewed journals.

Sunita Taneja MBBS, PhD, Deputy Director

Sunita is a community health researcher with vast experience in field and clinical trials. Her research interests are diarrheal diseases, child nutrition, micronutrient deficiencies and vaccine trials. She has extensive experience in design and analyses of clinical and field research studies, mostly intervention trials and vaccine trials. She is involved in coordination of implementation of these trials including preparation of case report forms, standard operating procedures, manual of operations and maintenance of essential documents.

She is the Lead, Data Management and Biostatistics for the Phase III Randomized Double Blind Placebo Controlled Trial to Evaluate the Protective Efficacy of Three Doses of Oral Rotavirus Vaccine (ORV) 116E, Against Severe Rotavirus Gastroenteritis in Infants.

Sarmila Mazumder, MBBS, PhD, Deputy Director

Sarmila is a community health researcher. Her main focus is in child nutrition particularly on changing care practices and finding optimal ways to sustainably improve child feeding practices including micronutrient intake. She has extensive experience in evaluation of mortality, hospitalizations and morbidity in intervention trials. She is involved with design, implementation and analyses of several community based research studies, mostly intervention trials or evaluations. She has gained experience in quantitative and qualitative research methods and has fair skills in the use of modern software for analyses.

She was one of the principal investigator for the many trials including "An effectiveness trial examining the addition of zinc to the current case management package of diarrhea in a Primary Health Care Setting", "Evaluation of the Impact of the Integrated Management of Neonatal and Childhood Illness Strategy on Neonatal and Infant Mortality in Haryana, India". She is currently a principal investigator in the "Efficacy of neonatal vitamin A supplementation in improving child survival in Haryana, India: generation of evidence necessary for informing global policy" and the multicentre trial "To Evaluate the Impact of Three Feeding Regimens on the Recovery of Children from Uncomplicated Severe Acute Malnutrition in India and to Use the Evidence to Inform National Policy".

She recently completed her diploma in Epidemiology from the London School of Hygiene and Tropical Medicine (UK).

She has several research publications in international and national peer reviewed journals.

TemsunaroRongsen, MBBS, MSc (Epidemiology), Research Coordinator

Naro, a physician by training with a Masters degree in Epidemiology (London School of Hygiene and Tropical Medicine), is a Research Scientist and has extensive experience in conducting community based clinical trials. She is the Principal Investigator of the Delhi site for the multicentre trial "A Phase III Randomized Double Blind Placebo Controlled Trial to Evaluate the Protective Efficacy of Three Doses of Oral Rotavirus Vaccine (ORV) 116E, Against Severe Rotavirus Gastroenteritis in Infants".

She has extensive experience in development and implementation of study protocols, regulatory documentation, management of field procedures and effective coordination of the field and laboratory activities.

She also served as an investigator in other trials which include disease burden of rotavirus diarrhea, zinc supplementation in low birth weight infants, impact of zinc on diarrhea, the WHO multicentre growth reference study, etc.

Sanjana Brahmwar Mohan, MBBS, MD, PG Diploma (Epidemiology), Research Scientist

Sanjana Mohan is a co-principal investigator in the multicentre trial "To Evaluate the Impact of Three Feeding Regimens on the Recovery of Children from Uncomplicated Severe Acute Malnutrition in India and to Use the Evidence to Inform National Policy".

She possesses in-depth understanding of planning and conducting community based research studies in child health and nutrition; technical and programmatic issues in child health and nutrition in the context of developing countries; health service delivery at various levels of health care; and developing, adapting training material and curriculum and conducting trainings on reproductive and child health.

Sanjana is also involved in analyses of the verbal autopsies of stillbirths, neonatal and post-neonatal deaths which have been performed in rural Faridabad as a part of the IMNCI trial "Evaluation of Integrated Management of Neonatal and Childhood Illnesses on neonatal and infant mortality". She was a coordinator for the trial "Supplementation of Folate and Vitamin B12 for Prevention of Childhood Infections in Young Indian Children".

Nidhi Goyal, MBBS, DTM, PGDHMM, DPH, Research Scientist

Nidhi has varied experience in the fields of transfusion medicine, infectious disease epidemiology and product development. She served as a study coordinator for the disease burden study for rotavirus diarrhea and study on predictors of poor immune response to rotavirus vaccine in infants. She is an investigator in the "Phase III Randomized Double Blind Placebo Controlled Trial to Evaluate the Protective Efficacy of Three Doses of Oral Rotavirus Vaccine (ORV) 116E, Against Severe Rotavirus Gastroenteritis in Infants" and is responsible for providing oversight of trial subjects, identifying and addressing all trial related issues, training of team in protocol related activities.

She has experience in developing and implementing protocols, maintaining regulatory documentation, overseeing clinical operations related to conduct of the trial at the field site, developing internal system for quality assurance and coordinating all field and laboratory activities.

Tivendra Kumar, MBBS, Research Scientist

Tivender is a physician with a Masters in Public Health from SreeChitraTirunal Institute for Medical Sciences and Technology, Trivandrum. He possesses experience in conducting field trials and is actively involved with training of field staff and quality control activities.

Ranadip Chowdhury, MBBS, MD,Young Scientist

Ranadip, MD in Community Medicine was involved as the Surveillance Medical Officer at National Polio Surveillance Project (NPSP), World Health Organization. He has experience of conducting community based research and various aspects of epidemiological and statistical analyses (SPSS, STATA, Epi-Info). He has 14 national and international publications in various field of public health.

Kiran Bhatia, MA, ADCA, Senior Data Manager

As a Senior Data Manager, Kiran is responsible for setting up data management systems for different studies. She also coordinates the functions of the data management unit involving data entry, validation, application of logical checks, conducting data analysis and preparation of monthly data reports. Her technical strengths are Microsoft Visual Basic, Microsoft SQL Server 2000, Visual FoxPro 6.0, ORACLE 8/9i, SPSS and STATA.

Girish Chand Pant, BSc, GNIIT, Senior Programmer

As a Senior Programmer, Girish is responsible to design and develop data management

system for different studies. He is responsible for developing and writing computer programs (window based or web based applications) to store, locate, and retrieve specific data. His technical strengths are Microsoft Dot Net Technology (ASP.Net, ADO.Net, C#.Net, VB.Net), Crystal Report, Microsoft SQL Server 2000/2005/2008 and ORACLE 8i/9i/11g.

BrindaDube, MSc (Food and Nutrition), Coordinator

With background in nutrition, Brinda has extensive experience in community based research. She is actively involved in coordinating field trials, training field staff and quality control activities. She also has skills in conducting qualitative research.

Jasmine Kaur, B.Sc, DDPHN, Coordinator

Jasmine, a Nutritionist with post graduate diploma in Dietetics and Public Health Nutrition is currently pursuing her dissertation for Masters Degree in Nutrition. She has experience in coordinating community based field trials. She is actively involved in training of field staff in conducting verbal autopsies, quality control activities and qualitative data collection.

Sudeep Singh Rathore, MBBS,Study Coordinator

Sudeep is a physician by training and is responsible for handling all activities related to patient safety as an investigator in Phase III Randomized Double Blind Placebo Controlled Trial to Evaluate the Protective Efficacy of Three Doses of Oral Rotavirus Vaccine (ORV) 116E, Against Severe Rotavirus Gastroenteritis in Infants". He has experience in conducting field trials and is actively involved with training of field staff and quality control activities.

Alok Arya, M. Pharm., Study Coordinator

Alok Arya is involved in the oral rotavirus vaccine 116E trial. He is responsible for overall management of field activities and regulatory submissions. He leads the quality control team and he is responsible for training all site personnel on an ongoing basis. He has more than five

years of experience in the field of clinical research. His expertise is in project coordination and GCP training. He has monitored sites in various projects and has conducted GCP training for site personnel. He has vast experience in training sites to conduct clinical trials that are compliant with GCP.

Tarun Batra, Post Graduate Diploma in Clinical Research, Quality Assurance Manager

As the Quality Assurance Manager, Tarun Batra is entrusted with developing quality systems for the organization. He oversees the implementation and requirement of regulatory, GCP and operational compliance in the organization. All organizational SOPs are controlled by him and any modifications in the study documents are centrally monitored and documented under his supervision. He also conducts training of the staff.

Manju Bagdwal, B.Com (Hons), ICWA (Inter), Post Graduate Diploma in Computers Application, Senior Administrator

Manju is the senior Administrator at CHRD-SAS , assisting the Director in all activities related to the different programs.She has extensive experience in the planning, coordinating and supporting the daily operational and administrative work for the projects implemented at CHRD-SAS. She also oversees day-to-day office operations and administrative functions. She is proficient in Microsoft Windows® Office System.

Asha Verma, B.A (Political Science), Post Graduate Diploma in Management (HR)

Asha is the administrator in-charge of the infectious disease group. She has been working with this group for the last 10 years. She is proficient with basic computer skills (MS Office- Word, PowerPoint, Excel) and experienced in handling all administrative related activities. She is responsible for tracking and preparing reports as per the timelines and format for the different agencies that the group collaborates with. She maintains and files important communications and relevant documents received and sent to regulatory authorities, ethical review boards, government agencies and other partners. She is also responsible for handling all logistics for national and international travels for the group.

Nicola Mendes, Bachelor of Physiotherapy, Project Administrator

Nicola is responsible for the management of all official records and documentation. She also supports the administrative work for the project titles "Observational Study to Document Experience of Rotavirus Vaccine Immunization in the Public Health System".

She also assists the Senor Administrator in various project related administrative work.

Swati Naik, (M.A. Marketing), HR Consultant

As the HR consultant at CHRD SAS, Swati is responsible for developing policies and directing Human Resource activities such as employment, compensation, statutory requirements and benefits. She is also responsible for compliance and maintenance of all personnel records of hire, transfer, provident fund, employee insurance scheme, termination and other details required for government reporting and by the organization.

Extramural Centre

Clinical Development Services Agency (CDSA)

Aims and Objectives

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.

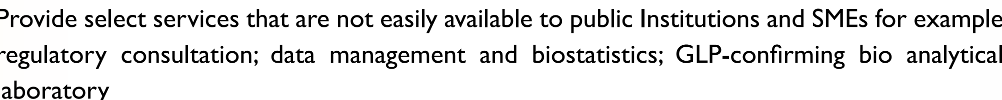
CDSA has a simple governance structure. Led by a high-powered Governing Body, it has 12 members including the Program Director who acts as Member Secretary. Special committees will be appointed to direct and supervise different areas of work. The operational oversight of CDSA is provided by an Executive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

CDSA has currently core staff team of fourteen employees comprising of Program Director, Director Training, Director of Clinical Portfolio Management, Biostatistician, Finance Manager, one Senior Research Officer, one Program Officer, two clinical Research Associates, one Clinical Trial Assistant, IT administrator, two office secretaries and an accountant. In addition CDSA has three consultants in the area of Operations, Administration and Regulatory Affairs.

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 services that are not easily available to public Institutions and SMEs for example regulatory consultation; data management and biostatistics; GLP-confirming bio analytical laboratory

Provide a peer review and consensus forum for formulation of national healthcare policies.

Virtual Learning Platform and Training Portal

CDSA has installed Adobe Connect Virtual Classroom Facility and Learning Management Software (LMS). This Virtual learning platform was supported by Bill & Melinda Gates Foundation through PATH-OWH. This eLearning platform will now be used for various training activities.

CDSA has developed a website portal totally dedicated for training activities was designed and launched (www.cidp.in). This website will have all audio-video recordings, presentations, case studies, resource materials, faculty and participant details, etc. It will enable 'online registration' for all upcoming training programs. This portal is now undergoing up gradation for adding on new features and easier management of online content.

CDSA is building various 'training modules'. Presently the following modules are completed:

- Clinical Trial Designs and Statistical Methods
- Conducting Regulatory Clinical Trials in India
- Presently following modules are under preparation:
- Ethics in Clinical Research

Programs and Activities

- CDSA has a national mandate of capacity and capability building in the area of clinical and translational research in India.
- In 2013-14, CDSA has completed 14 trainings covering approximately 900 participants with 150 resource personnel.

Date	Venue	Workshop/ Courses	Participants	Faculty
Apr 1 to 5, 2013	NIBMG and ISI, Kolkata	Genetics and Epidemiology- Study Design and Statistical Methods	41	10
Apr 6, 2013	Kolkata	National Institute of Biomedical Genomics (NIBMG)	55	1
Apr 20, 2013	Kolkata	Tata Medical Center, Kolkata	36	7
Jun 6-7, 2013	Gurgaon	THSTI	26	1
Jun 17 to 20, 2013	KEM Hospital, Pune	Population based Community Trials	40	17
Jul 30-31, 2013	New Delhi	BIRAC	98	17
Sep 22, 2013	Gurgaon	THSTI	18	3
Oct 7 to 9, 2013	Novotel Techpark, Bengaluru	Serious Adverse Event Reporting in Clinical Trials	39	24
Oct 17 – Dec 21, 2013	Virtual Class room	Bioethics Certificate Course	20	2
Jan 2-5, 2014	Mangalore	Wellcome Trust DBT Alliance	55	10
14-15 Feb 2014	ICGEB, New Delhi	Basics of Good Clinical Practice	101	14
4-5 Mar 2014	GMC, Goa	Basics of Good Clinical Practice	120	16
18-19 Mar 2014	NIMS, Hyderabad	Basics of Good Clinical Practice	159	12
28-29 Mar 2014	NEIGRIHMS, Shillong	Basics of Good Clinical Practice	86	12
			894	**146**

Training Advisory Committee

CDSA has an advisory panel under the leadership of Dr. JP Muliyal, Former Principal, CMC Vellore. This committee evaluates the need assessment; define objectives and approaches of the various training programs. This committee gives necessary advice or assistance on specific scientific, educational or management issues to help in program curriculum design and training implementation plans. CDSA management team is responsible for program management and implementation.

Training Policy & Training Evaluation Manual

CDSA has its training policy that provides foundation, focus and broad direction for all its training activities. In addition to this CDSA is working towards establishment of monitoring and evaluation procedures to assess the effectiveness of the Training Program by developing a 'Training Evaluation Manual' on the basis of Kirkpatrick's level of assessment.

National Database

CDSA is building database of Ethics Committees and their members, Investigators, Institutions, Medical Colleges, Pharmaceutical and Biotech Companies, CRO's, Scientists etc. This will facilitate various surveys and help to reach out to a larger public for any upcoming training programmes.

Quality Assurance & Compliance

CDSA has been proactive by working with SMEs in supporting them for compliance related activities as 'fee for service'. The following were completed or in pipeline.

Synergia Bio Sciences, Bengaluru: Regulatory Toxicology Study – GLP Compliance Support

iLife Discoveries, Manesar: ISO 15189 Accreditation Support

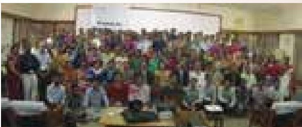
*[*Auditor for ISO 17025, ISO 15189, NABH and GLP Trainer (WHO)]*

Basics of Good Clinical Practice at North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Mawdiangdiang, Shillong

Clinical Trial Services

Clinical Portfolio Management

CDSA actively participates in public health programs to support the development of medical products for diagnosis, prevention or treatment of diseases like severe acute malnutrition, diarrhea, pre-term birth and immunization. It provides a broad range of services like clinical site preparation, monitoring of trials for quality assurance, data management, statistical analysis, establishment and conducting DSMB etc. It also provides technical and advisory services to SMEs related to preclinical and clinical product development and regulatory guidance. Additionally, CDSA has been tasked to commission consultative peer review group; collate evidence from various research projects for review and consensus building to enable formulation of a national policy on specific healthcare areas of interest.



Basics of Good Clinical Practice at Nizam's Institute of Medical Sciences (NIMS), Hyderabad

Currently CDSA is engaged in following clinical trial management and monitoring services:

- Clinical trial design and preparation of study synopsis, protocol, informed consent form and other trial related documents following the ICH guidelines
- Study start-up and initiation
- GCP and project-specific trainings
- Monitoring for protocol and regulatory compliance
- Compiling Trial Master File at clinical sites and CDSA
- Data Safety Monitoring Board (DSMB) – Constitution & Coordination
- Developing SOPs, study logs and forms at clinical sites
- Tracking study progress and representation in project meetings

Basics of Good Clinical Practice at International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi

Ethics in Biomedical Research at Father Muller's Medical college, Mangalore

Data Management and Bio-Statistics

This division aims to provide data management and bio statistical support to various clinical projects. To strengthen this facility CDSA has recently completed the implementation of Statistical Analysis System® (SAS) Version 9.3 as statistical analysis tool, and Promasys® as a solution for clinical data management. Promasys has also been mapped with MedDRA dictionary to enable medical coding. Also, a dedicated IT-infrastructure (data servers, systems, access-controls, etc.) has been deployed to run the activities as per the standards of data security and safety. Currently it is helping ongoing projects for their data management and statistical requirements.

BIRAC CDSA Regulatory Workshop

CDSA is gearing up to provide the following services through its data management & biostatistics group:

- Statistical inputs to study design and clinical trial protocol
- Sample Size Calculation
- Randomization

Ethics Training at THSTI

- Data Management Plan
- Case Record Form (CRF) Development
- Statistical Analysis Plan
- Data Cleaning and Coding
- Statistical Analysis of Data
- Reporting of Statistical Analysis (e.g. Figures and Tables)
- Training and Education
- Preparation of Technical Documents (Reports & Publications)

Key ongoing activities are:

- Statistical help to PI's at THSTI: Scientists are provided help for statistical analysis and interpretation of research data. Assistance is also provided for publication and reporting of the research findings.
- Data management and statistical support to various clinical projects undertaken by CDSA.

Project: Undiluted animal milk with added sugar and micronutrients versus WHO feeding protocol for management of severe acute malnutrition in non-breastfed infants aged 2-6months of age: a randomized controlled trial. Principal Investigator: Dr. Satinder Aneja

Protocol specific Case Report Form (CRF) was designed and finalized for this SAM study. Data management for this study is being done using PROMASYS clinical database. Currently database designing is in progress. Project data entry operators have been trained to work on Promasys. Training for CRF filling and quality control for data management has been imparted to project staff to ensure the quality of data. CDSA has also contributed in statistical aspects of the study including sample size calculation and randomization support.

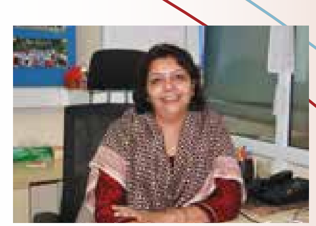
Regulatory Services

CDSA provides regulatory advisory services for development and registration of new drugs, medical devices, diagnostics and biopharmaceuticals/biosimilars including vaccines to SMEs and public funded pre-clinical and clinical stage research projects. The advisory cell provides:

- Advice on regulatory processes encompassing product development & registration
- Consultation on regulatory dossier preparation, egg. IRB; IND; CTD etc.
- Regulatory input to ongoing clinical trials in CDSA
- Regulatory input in planning and compliance certification of GLP- bio analytical lab & Phase I facility.
- Advice on Registration of Ethics Committees as per new notification.
- Advice and review proposals coming from BIRAC (especially clinical trial protocols)
- Technical input (program design, faculty identification & preparation of resource materials).

Profiles

Dr. Sudhakar Bangera joins CDSA with experience of 21 years in diverse areas of healthcare (Hospitals and Medical Schools), global Contract Research Organisations (CRO), Academic Research Organisation (ARO), Site Management Organisation (SMO), Medical Imaging, Clinical Bioavailability and Bioequivalence (BA-BE), and a global Pharmaceutical company. He is a multifaceted, dynamic healthcare and clinical research professional with astute decision-making capabilities and exemplary organizational skills. He is passionate about his work and is able to enthuse, motivate and involve individuals and teams. Dr.Bangera has taken several companies from scratch to profit churning entities through his insight and sheer hard work.



Dr. Monika Bahl is a graduate in medicine with additional specialization in human resource management. Monika brings over 13 years of experience to CDSA. She has substantial experience of managing projects in varied therapeutic indications including immunology, pain management, cardiovascular, respiratory, dermatology, psychiatry and diabetes mellitus. In previous assignments in pharmaceutical/biotech industry (Ranbaxy, Panacea Biotec, Quintiles), she was associated with clinical studies in pediatric, adult and geriatric populations including mega-trials for DCGI/FDA/BfArM submissions. She has significantly contributed to training and mentoring programs for performance improvement and for quality management initiatives on individual, project and organizational levels. Responsibilities in the current position include leading the public health research portfolio in collaboration with WHO, academicians, and scientists/ researchers and funding agencies.

Dr. Sucheta Banerjee Kurundkar joined CDSA as Director of Training after 16 years of experience in the Contract Research Organisation (CRO) industry. She started her career from Pune, India where she was instrumental in setting up a start-up preclinical and clinical research services company to revenue generating level. In her last assignment, she was Chief Scientific Officer (CSO) at a multinational Clinical Research Organization. Sucheta is a WHO-TDR certified Good Laboratory Practices (GLP) Trainer and Auditor for NABL (ISO 15189, ISO 17025) and NABH. She has a PhD in Biochemistry from the University of Pune and her doctoral work on a novel inhibitor received recognition at the World Congress on Insulin Resistance Diabetes and Cardiovascular Research at Los Angeles (2010). She has been a visiting faculty in various clinical research training centers and universities in India.

Mr. Prashant Bhujbal holds a post-graduate degree in Agriculture and a MBA in Finance. He has worked for more than 23 years in the Maharashtra Finance and Account Cadre, under Government of Maharashtra. As a member of finance cadre he served on diverse postings in various Government departments ranging from Account, Audit and Procurement of Goods.

Vinay Kumar, MBA, M.Phil, is a consultant with the CDSA. 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.

Mr. Ramteke retired as Joint Drugs Controller General of India after 31 years in drug regulatory aspects in the office of the Drugs Controller General of India (DCGI). He started his career at Central Research Institute, Kasauli in biological-drug testing. He has extensive experience with new drugs, vaccines and biotech products/ pharmaceuticals, medical devices approvals and development experience. He also reviews and evaluates product dossiers for pre-clinical, toxicological, pharmacological, CMC, and quality control, clinical trial data of new drugs, biological and medical devices (INDs, ANDAs). Quality assurance management, regulatory oversight of clinical trials, development of SOPs and guidelines and drug rules amendments are his expertise. He has contributed to preparation and implementation of Good Clinical Practices (GCP), Good Laboratory Practices (GLP) and Good Manufacturing Practices. He is an Expert on the Pharmacovigilance Program, GCP Training and Inspections of CROs in India.

Organizational Support System at THSTI

Achieving Operational Excellence

External Relations & Institutional Development (ERID)

Context & Conceptual Framework

A consolidated support system for research & innovation related activities, is of critical importance for the success of an organization like THSTI, especially in an era of fast scientific advancement and continuous information exchange. Regardless of organizational model, a support system with defined responsibilities of facilitating research and innovation is an asset to any ambitious organization, more so for THSTI, because of its intrinsic nature of a dynamic, futuristic and translational setting. This support system can establish an effective centralized mechanism to unite all upstream and downstream activities and connect it to the developmental process of the organization.

Goals/ Objectives

- To create a conducive system of innovation management
- To create a transparent machinery of proper implementation of biosafety, environmental safety, animal & human ethics.
- To create a support system for extramural fund generation and build effective investor relations.
- To create an effective communication to enhance the profile of the organization.

Processes at ERID

Innovation Management

ERID will develop and establish IP and technology transfer policy for THSTI. As a support system to the THSTI scientific community it will help in various IP management activities.

Patent activities:

- Carry out IP portfolio analysis for THSTI's flagship programs
- IP landscaping and Freedom-to-Operate (FTO) analysis support
- Support in patent drafting, filing, follow up

Licensing & tech transfer activities:

- Develop confidentiality agreements and maintaining records
- Support in finding industry partner for licensing
- Help in licensing and technology transfer activities
- Help in protecting IP and revenue sharing

Grants and Investor Relations

This function of ERID identifies new grant opportunities and keeps the faculty and scientists updated with various available options. The office aids in preparing grant applications to formats specified by funding agencies. It also supports the THSTI Faculty with registrations mandatory for grant submissions. It will also develop mechanisms to make THSTI's identity more impactful to the investors.

Grants management:

- Providing information on grants opportunities
- Supporting in grant application procedures
- Maintaining updates of grant application status
- Investor relations:
- Networking with investors, both from public and private space

- Arranging meetings and workshops to increase communication between investigators and investors

Statutory Committees

This function will facilitate faculty and scientists at THSTI to meet ethical and regulatory requirements of their research. Guidelines will be developed for biosafety, chemical safety, animal ethics and human ethics in research. All research protocols will be cleared through the secretariat for review by the various statutory committees. The secretariat will organize committee meetings, will keep relevant records as per the regulatory requirements and update faculty on new regulations.

Institutional Biosafety Committee:

- Guiding and supervising biosafety norms in institutional research activities
- Guiding and supervising chemical, electrical and other safety concerns

Animal Ethics Committee:

- Guiding and maintaining ethical practice for animal studies in translational research

Institutional Ethics Committee (Human Research):

- Guiding and maintaining ethical practice in biomedical translational research involving human subjects

Communications

The Communication Unit will help achieve greater visibility and impact by means of various communication solutions. It will also develop mechanisms of effective internal communication among members of the research community at THSTI. Many of the Centre's publications, including the Annual Report, the quarterly newsletter, working papers, scientific reports, monographs, and special publications, will be developed, edited and produced by ERID.

Internal Communications:

- Continuous communication with researchers and students at THSTI to engage them in organizational development
- Develop mechanisms for internal communications regarding events, publications, awards, etc.

External Outreach Programs:

- Arrange outreach programs to raise the profile of THSTI at universities, public forums, etc.

External Scientific Liaison:

- Build external scientific liaison of THSTI for all its major National and International Science and Technology partners

Develop and maintain an effective and dynamic relationship with the ministries, departments, councils, state bodies, NGOs, public and private funding agencies, venture capital farms, private industries and policy makers

Print & Electronic Media & Web Communications:

- Preparation of write-up/ features/ reports on THSTI activities and achievements for website and media coverage
- Design, development and release of special corporate briefings/brochures to help bridge the gap between academia & industry
- Preparation of Annual Report to aptly depict THSTI's unique vision and talent pool
- Improve THSTI website to enhance the brand value of THSTI to national and international scientific community

ERID Profiles

Ms. Vidhya Krishnamoorthy has a Post Graduate degree in Biotechnology followed by over a decade of academic research training in the field of Bacterial Pathogenesis from Madurai Kamaraj University, University of Texas at Houston and Harvard University. She is a non-voting member of the Ethics Secretariat at THSTI and by participating in ethics training conducted in the country she helps the investigators at THSTI to prepare appropriate regulatory documents to conduct research involving humans or human biological materials. She is responsible for organizing the Institutional Ethics Committee (Human Research) and animal ethics committee meetings, maintaining the records and updating the faculty on recent regulations in research involving humans and animals. In addition she is responsible for the grant management activities of ERID.

Dr. Susmita Chaudhuri has a PhD. in Microbiology from National Institute of Cholera and Enteric Diseases, Kolkata. She did her M.Sc. in Zoology specializing in Microbiology from Calcutta University. She did her postdoctoral research in Medical Microbiology and Immunology from University of Alberta, Canada. She had a successful portfolio of bio-similar products as a Senior Research Scientist in the R&D of Panacea Biotec Ltd. She has a diploma in IPR and an MBA in Market Research. She specializes in technology due diligence and management. In the Innovation Management domain of ERID, she developed the Intellectual Property policy and Entrepreneurship policy of THSTI. She has initiated and developed a process of IP protection and utilization in THSTI and takes care of all the IP and technology transfer activities and IP awareness training for students and fellows.

Dr B. Debkumari is the Scientific Liaison Officer for THSTI and is part of the External Relations and Institutional Development team at THSTI. Her role includes raising the profile of the Institute, handling the International Relations and coordinating seminar/workshops/events in the Institute. She did her PhD from Department of Biosciences, Barkatullah University, Bhopal in conjunction with Centre for Microbial and Plant Genetics, Katholieke Universitiet, Leuven, Belgium. Before joining THSTI she worked as Research Associate, CMPG, KU Leuven, Belgium and also founded an NGO Midas Touch Manipur in 2009 working towards Biodiversity Conservation.

Achievements

Project revenue

Details of grants received during the year 2013-14 under extramural projects

(Rs in Lakhs)

S.No	Name of Funding Agency	Receipt during the FY 2013-14
1	Department of Biotechnology (DBT)	2,415.84
2	Department of Science and Technology (DST)	33.52
3	Fellowships (DBT,DST,CSIR,ICMR,UGC etc.)	314.18
4	Other Projects & Programme	224.90
	Total	**2,988.44**

Details of grants received during the year 2013-14 under extramural projects

Title of the Project	Funding Agency	Total Approved Budget	Grant Received in F.Y 2013-14
(A)	**Department of Biotechnology**		
Pediatrics Biology Centre (PBC)	Department of Biotechnology	817.66	-
Vaccine and Infectious Disease Research Centre (VIDRC)	Department of Biotechnology	3,639.96	39.60
Centre for Biodesign and in-vitro Diagnostics (CBD) Ph1 & 2	Department of Biotechnology	2,749.88	361.00
THSTI-IAVI Vaccine Programme	Department of Biotechnology	2,078.90	200.00
Vitamin D supplementation to improve immune responses to vaccines administrated in early infancy- The NutriVac -D Trial	Department of Biotechnology	160.64	67.22
Development of a rapid diagnostic test for diagnosis of celiac disease - Phase I-II	Department of Biotechnology	66.03	22.91
Investigating the role of MazF toxins in pathogenesis and persistence of Mycobacterium tuberculosis	Department of Biotechnology	33.49	5.63
Towards the Characterization of multiple P-loop GTOases in Mycobacteria	Department of Biotechnology	31.63	19.20
Investigating the role of Tyrosine Kinases in the life -cycle of Japanese Encephalitis Virus and Dengue virus (JEVD)	Department of Biotechnology	65.96	13.73
Molecular Mechanisms of Minimal Change Disease Nephritic Syndrome : Role of CD 80	Department of Biotechnology	47.09	11.48

Title of the Project	Funding Agency	Total Approved Budget	Grant Received in F.Y 2013-14
Collaboration for translational and clinical research between Translational Health Science and Technology Institute, National Brain Research Centre, Regional Centre for Biotechnology and Gurgaon Civil Hospital	Department of Biotechnology	211.29	-
*Deciphering Mycobacterium Tuberculosis Artillery	Department of Biotechnology	64.60	-
* Understanding the role of Polyphosphate Kinases and Ployphosphatases in Physiology of Mycobacterium Tuberculosis	Department of Biotechnology	49.48	-
*Role of microRNAs in establishment of Japanese Encephalitis Virus (JEV) infection and Disease Progression	Department of Biotechnology	55.60	-
Identification of Correlates of Disease Severity in Pediatric Dengue Patients in New Delhi	Department of Biotechnology	39.56	11.17
*Policy and forecasting Centre (Bio Spaces)	Department of Biotechnology	712.00	-
*Innovative Young Biotechnologist Award -IL-27 dependent regulation of TH 17 and regulatory cells 2011 (IYBA 2011)	Department of Biotechnology	38.81	-
Human Microbial Ecology (CHME)	Department of Biotechnology	2,355.00	229.00
Establishment of Drug Discovery Research Centre (DDRC)	Department of Biotechnology	5,695.00	750.00
Characterization of Hepatitis E Virus RNA dependent RNA polymerase and its associated proteins in the replicase complex	Department of Biotechnology	77.06	36.72
Genetic requirement of mycobacterium tuberculosis growth in cholesterol under hypoxia using high density mutagenesis RGYI	Department of Biotechnology	46.00	16.90
To identify novel therapeutic compounds that inhibit the interaction between Hepatitis E Visas ORF 3 protein and TSG 101 and to explore the molecular mechanisms controlling the release Hepatitis E Virions from infected cells RGYI	Department of Biotechnology	32.05	10.25

Title of the Project	Funding Agency	Total Approved Budget	Grant Received in F.Y 2013-14
MicroDiab Studies of interaction between the gut Microbiome and the human host biology to elucidate novel aspects of the pathophysiology and pathogenesis of type 2 Diabetes	Department of Biotechnology	374.95	146.54
Technology Platform for Simple and efficient production of recombinant antibodies (Tech Sepra)	Department of Biotechnology	63.76	22.92
Vitamin A is the "Microenvironmental cue" for triggering disease activity in patients with Inflammatory Bowel disease (Ulcerative colitis, Crohn's Disease)	Department of Biotechnology	29.31	10.43
Neonatal immune profiles infections and toxicants	Department of Biotechnology	88.08	53.53
Inter Institutional program for Maternal Neonatal and infant sciences-A translational approach to studying preterm birth (PTB)	Department of Biotechnology	2,922.71	276.77
Acceptability of Combined Mineral Vitamin formulation in children with severe acute malnutrition (SAM)	Department of Biotechnology	2.85	-
Animal Facility for Research on Infectious Disease	Department of Biotechnology	1,828.19	100.00
Evaulation of novel adjuvants for mucosal priming following cutaneous delivery of vaccine	Department of Biotechnology	27.92	9.37
Human Immunology Workshop	Department of Biotechnology	87.88	1.47
Total (A)		24,493.34	2,415.84
(B) Department of Science and Technology (DST)			
Identification of neutralizing antibody epitopes on Indian and South African HIV-1 subtype C Viruses for HIV vaccine design	Department of Science and Technology (DST)	22.52	22.52
India-Singapore Workshop on "Advances in Chemistry, Biology and Technology for Medicine" at Singapore	Department of Science and Technology (DST)	11.40	11.00
Total (B)		33.92	33.52
(C) Fellowships			
Metabolism in mycobacteria: role of PPK-1 and PPK-2 in stationary phase survival and virulence of M. Tuberculosis	Department of Biotechnology	59.60	14.90

Title of the Project	Funding Agency	Total Approved Budget	Grant Received in F.Y 2013-14
Immune function in infancy – special focus on low birth weight and small for date infants and the role of Vitamin D deficiency	Department of Biotechnology	72.85	-
Ramalingaswami Fellowship - Dr. Milan Surjit for the Project Entitled - "Understanding the biology of Hepatitis E Virus and development of vaccine and drugs against it.	Department of Biotechnology	85.60	22.40
Ramalingaswami Fellowship - Dr. Amit Kumar Pandey for the Project Entitled - "Regulation of Cholesterol Metabolism in Mtb	Department of Biotechnology	74.50	14.75
Ramalingaswami Fellowship - Dr. Krishanmohan Atmakuri for the Project Entitled - "Mycobacterial outer membrane-derived vesicles: Role in pathogenesis and exploration as noval submit vaccine vehicles against tuberculosis.	Department of Biotechnology	74.50	22.40
Ramalingaswami Fellowship - Dr. Pallavi Kshetrapal for the Project Entitled - " The role of Notch synergies in pediatric T-Alls	Department of Biotechnology	82.00	19.90
Ramalingaswami Fellowship - Dr. Ranjith Kumar C.T for the Project Entitled - "Modulation of innate immune response and characterization of viral polymerases for the development of potent vaccines.	Department of Biotechnology	85.60	22.40
DBT Fellowship	Department of Biotechnology	19.43	19.43
Indo- Finland Post Doct Fellowship	Department of Biotechnology	223.68	74.56
INSPIRE Fellowship Dr. Sangeeta Kumari	Department of Science and Technology (DST)	35.00	16.92
DST Fellowship	Department of Science and Technology (DST)	2.79	2.79
CSIR -FELLOWSHIP	Council of Scientific and Industrial Research (CSIR)	27.70	27.70
ICMR Fellowship	Indian Council of Medical Research (ICMR)	1.25	1.25
UGC - FELLOWSHIP	University Grants Commission (UGC)	10.58	10.58
Welcome Trust Fellowship	Wellcome Trust	269.13	27.89

Title of the Project	Funding Agency	Total Approved Budget	Grant Received in F.Y 2013-14
Fellowship IISC	Indian Institute of Science, Bangalore	3.72	3.72
IUSSTF Research Fellowship	Indo-US S&T Forum	12.59	12.59
Total (C)		1,140.52	314.18
(D) Other Source of Grant-In-Aid			
THSTI-IAVI Vaccine Programme	International AIDS Vaccine Initiative (IAVI)	1,928.90	121.60
Establishment of a mammalian cell culture based hepatitis E Virus (HEV) expression system to study the viral life cycle and application of the secreted virion as a candidate vaccine	Science and Engineering Research Board(SERB)	25.00	5.00
Integration and excision mechanism of integrative mobile genetic elements essential for Vibrio cholera pathogenicity (IMGE)	Science and Engineering Research Board(SERB)	17.00	6.00
Cellworks DDRC Service Agreement	Cellworks Research India Pvt Limited	19.25	19.25
The HIB Initiative –Hospital based Sentinel Surveillance for Meningitis in Children	The INCLEN Trust	10.39	2.66
IGSTC workshop on " Diagnostics and translational genome sequencing in clinical and public health microbiology	Indo-German Science & Technology Centre	20.40	20.40
The effects of Human Microbiota on Immune Responses	Osaka University,Japan	14.84	14.84
A study to suggest methodologies to develop norms & standards for classification of health R&D needs of developing countries, as a follow up of the CEWG recommendations during WHA65	World Health Organization (WHO)	8.50	8.50
To validate a matrix to collect, analyze and monitor R&D resource flows from public and private sector in order to develop a proposal for National R&D observatory and provide required details on demonstration projects suggested as an outcome of Bangkok Regional Consultation, July 2013 based on CEWG recommendations	World Health Organization (WHO)	26.65	26.65
Total (D)		2,070.93	224.90
Grand Total (A+B+C+D)		**27,738.71**	**2,988.44**

* Grant in Aid received during the financial year 2014-15.

Publications/Patents/tech transfer

Peer reviewed publications

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Yuen-Yi Tseng, BrandenMoriarity, Wuming Gong, Hiroko Kawakami, Ryutaro Akiyama, Ashutosh Tiwari, Peter Ronning, Brian Reuland, M. O'Sullivan, David Largaespada, York Marahrens, Kathryn Schwertfeger, Yasuhiko Kawakami, AnindyaBagchi. (2014) PVT1-Dependence in Cancer with MYC Copy Number Increase. Nature (In press)

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Books

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Patent Filed:

A patent has been filed on "A method and device for detection of anti-transglutaminase antibodies" (Indian patent no. 1133/DEL/2011).

Technology Transferred:

The clone of recombinant human tissue transglutaminase for development of tests for celiac disease have been transferred to J. Mitra Pvt. Ltd. on 25th April 2013.

Develop modern basic biology and platform technologies to rapidly devise, test and adaptinnovative, sustainable solutions for India's child health problems.

Rapid Test for Diagnosis of Celiac Disease (CD)

Celiac disease (CD) is a lifelong intolerance to gluten initiated by the ingestion of gliadin and related prolamines from cereals such as wheat, barley and rye in genetically susceptible individuals resulting in a characteristic small intestine enteropathy. Correct and early diagnosis of CD is essential as it requires life long adherence to gluten free diet and delayed diagnosis is associated with increased prevalence of other autoimmune conditions, mortality, and increased risk of osteoporosis and malignancies. The objectives of the collaborative project was to develop an in-house point of care test (POCT) and ELISA designed to detect antibodies (IgA or IgA+IgM+IgG) in human blood or serum/ plasma, against human recombinant tissue transglutaminase.

Technology transfer of a rapid diagnostic kit of Celiac Disease to industry partner

This project is in partnership with ICGEB, AIIMS and PBC (at THSTI). The clone expressing the human tissue transglutaminase (htTG), used as an antigen in the kit, was developed by Dr. Naveen Khanna and his team at ICGEB. The industrial partner in the project M/s J.Mitra and Co. has been pivotal throughout the development of this kit, with inputs from the laboratory at ICGEB. The ELISA kit (shown here) has been prepared and validated at AIIMS and at PBC, THSTI. Material transfer agreement for the clone to M/s J Mitra and Co. has been formalized.

Awards and Recognitions

Dr. G. Balakrish Nair, Executive Director, received the Membership diploma of the German National Academy of Sciences Leopoldina from President of the Academy, Professor Jorg Hacker.

Dr. Guruprasad Medigeshi, Assistant Professor at the Vaccine and Infectious Disease Research Centre, THSTI, has received the Intermediate Fellowship by Wellcome-DBT India Alliance. His research proposal attempts to understand the dynamics of zinc influx and efflux mediated by zinc transporter proteins during viral infections and to assess if changes in zinc homeostasis has any bearing on the pathogenesis and disease outcome.

Dr. Amit Awasthi, Assistant Professor at THSTI, received the Innovative Young Biotechnologist award from the Department of Biotechnology. This award is given for his research on discovering underlying mechanisms of Inflammatory Bowel Disease (IBD).

Dr. Nisheeth Agarwal, Assistant Professor at THSTI is now a member of a team of 39 eminent TB researchers from USA and India on a prestigious grant, "INDO-U.S. Vaccine Action Program (VAP), on tuberculosis research", C-TRIUMPH, a collaborative consortium, with eight premier institutions in India and USA with objectives to investigate various host and microbial factors associated with progression of TB through different stages. Dr. Agarwal will study signatures of latency and active tuberculosis in the Indian population. He will co-chair the Biomarkers and Diagnostics Scientific Working Group.

Pallavi Kshetrapal, Ph.D. was awarded the Ramalingaswami Re-entry fellowship (2013) to work on the "The role of Notch synergies in pediatric T-ALLs" from the Department of Biotechnology (DBT), Ministry of Science & Technology, Government of India.

Dr. Ashutosh Tiwari was awarded the 'IUSSTF fellow 2013' by Indo-US Science and Technology Forum. This gave him an opportunity to initiate a research project at University of Minnesota, Minneapolis, USA from Oct 2013 to March 2014. The initial finding of the project has given strong leads to build up a collaborative project between THSTI and University of Minneapolis on cancer diagnostics. The finding has huge potential to build-up a diagnostic assay for early cancer detection and led to publication in Nature.

Dr Sagarika Haldar received the Innovation in Science Pursuit for Inspired Research (INSPIRE) fellowship by Department of Science and Technology, GoI, for her project entitled "Dynamic Molecular Platform for the rapid detection of Drug Resistant Tuberculosis" in the field of Bio-Medical Sciences in December 2013. This project proposes a comprehensive open ended molecular platform for drug resistance testing for tuberculosis.

Dr. Tarun Sharma received the Endeavour Research Award of Commonwealth of Australia to design and develop novel diagnostic assay using aptamer and peroxidase-like nanoparticles.

Students' achievements

Mr. Manish Sharma, a Ph.D. student in the Virology division received a travel grant from the Science and Engineering Research Board to present his research findings in the Keystone Symposia in Texas, USA, which finally got published In Autophagy.

Conference/ Seminar/ Workshops/ Symposium outside THSTI

Name of Faculty	Name of Conference/ Seminar/ Workshops/ Symposium Abroad	Date of Visit
Dr. G.B. Nair	Delivered a keynote talk entitled "Gut microbiota related to probiotics for human health" at the National Seminar in Nutrigenomics and the Future of Food Technology followed by general lectures for graduate and undergraduate students at Atma Jaya Catholic University, Jakarta, Indonesia,	24th June to 29th June, 2013
	Received the membership certificate of the German Academy of Sciences, Leopoldina from the President of Leopoldina, Prof. Jorg Hacker at the Leopoldina Nationale Akademie der Wissenschaften, Halle, Germany	22nd May -23rd May, 2013
	Visited the International Centre for Diarrhoeal Disease Research, Bangladesh for initiating institutional collaborations between ICDDR,B and THSTI,	1st -3rd July, 2013
	Attended the meeting of experts for developing a strategic work plan as a follow-up of Consultative Expert Working Group on Research and Development: Financing and Coordination at the World Health Organization, Bangkok, Thailand	25th-26th July, 2013
	Attended the Scientific Advisory Committee meeting at the Institute of Life Sciences, Bhubaneswar	23rd-24th August, 2013
	Delivered an invited talk on Cholera Vaccines at the Advanced Vaccinology Course in India (INDVAC) conducted by the Christian Medical College, Vellore	18th September, 2013
	Delivered a lecture at the plenary session of the Centre for Cellular and Molecular Platforms (C-CAMP) Technology Conclave at the C-Camp, Bangalore	15th November, 2013.
	Attended as an Expert the Global Technical Consultative Meeting on Identification of Health Research and Development Demonstration projects at the World Health Organization, Geneva,	3rd -5th December, 2013
	Attended the IDEA Meeting at the Initiative against Diarrheal and Enteric diseases in Africa, Philippines	13th -17th January, 2014.
	Attended symposium as a guest speaker to present the research activities of infectious diseases especially Cholera in India and to introduce the research activities of Translational Health Science and Technology Institute at Okayama University, Japan	25th January, 2014
Dr. Sudhanshu Vrati	To study Translational medicine & biodesign program at Erasmus University, Medical Center, Rotterdam, Netherland,	10th April to 17th April 2013
	Attended DBT Directors Meeting at Kochin	31st May to 2nd June,2013
	Attended 1st Doctoral committee meeting at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow	27th July to 28th July 2013

Name of Faculty	Name of Conference/ Seminar/ Workshops/ Symposium Abroad	Date of Visit
	Attended Vaccines for Enteric Diseases Meeting at Bangkok	5th November to 9th November 2013
	Attended Guha Research Conference-2013 at Vishakapatnam	6th December to 10th December 2013
Dr. Shinjini Bhatnagar	Attended Erasmus MC and Institute of Biomedical Engineering, UK	10th April to 17th April 2013
	Attended meeting to discuss scientific direction of DBT aided autonomous institutions at Kochi	1st June to 2nd June 2013
	Attended meeting on "Accelerating Research & Development to address the global crisis of Preterm Birth" at Washington-DC	14th July to 22nd July 2013
	To meet Secretary Health cum Mission Director, NRHM, Haryana at Chandigarh	13th August to 14th August,2013
	Discussion on Clinical Training Fellowships with India Alliance at Bangalore	16th August to 19th August 2013
	Attended Selection committee meeting at Wellcome Trust/ DBT India Alliance at Hyderabad	1st October to 6th October 2013
	Attended Indo-Singapore Workshop on " Advances in Chemistry, Biology and Technology for Medicine" at Singapore	13th November to 17th November 2013
	First Opponent at the trial lecture and defence for the degree of PhD of Renat Latipov at the Faculty of Medicine, University of Oslo	6th November to 8th November 2013
Dr. Guruprasad R. Medigeshi	Dengue Meeting, Madurai	24th July to 27th July 2013
	Role of mammalian RNAi in regulating dengue viral infection RNA Silencing, Keystone Sympoisa, Whistler Conference Center, Whistler, Canada.	19th March to 24th March' 2013
	Dengue Sero-epidemiology in Southern India: High prevalence of concurrent infection with multiple serotypes. Third International Conference on Dengue and Dengue Haemorrhagic Fever 2013 (Dengue 2013). Bangkok, Thailand	21st October- 23rd October 2013
	Training programs Two research scholars, Mr. Soham Gupta from the St Johns National Academy of Health Sciences, Bangalore and Mr. Vaseef Rizvi from the Indian Institute of Science, Bangalore were provided training on molecular techniques in dengue virus biology.	2013
	A new seminar series titled "Translational Research – Gaps and Challenges" invited some of the prominent Indian scientists to THSTI who delivered lectures and interacted with our faculty and students.	2012-2013

Name of Faculty	Name of Conference/ Seminar/ Workshops/ Symposium Abroad	Date of Visit
Dr. Ramandeep Singh	TB meeting at IISC, Bangalore	17th July to 21st July 2013
	Presented a talk at conference "Emerging themes in Tuberculosis Research: Creating a Network" held at Indian Institute of Science, Bangalore	July 2013
	Presented a talk at conference "Tuberculosis 2012: moving towards strategies for prevention and intervention" held at Bose Institute, Kolkata	December 2012
Dr. Amit Kumar Pandey	Meeting on Emerging Themes in Tuberculosis Research at Bangalore	17th July to 21st July 2013
	3rd Conclave at National Centre for Cell Sciences (NCCS), Pune	12th September to 15th September 2013
	Invited Speaker in "Emerging themes in TB research at IISc, Bangalore	17th July to 21st July 2013
	Poster presentation at the Keystone Symposium in Vancouver, Canada	2013
Dr. Krishnamohan Atmakuri	Attended C-CAMP and Emerging Themes in TB meeting at Bangalore	11th July to 21st July 2013
	3rd Conclave at National Centre for Cell Sciences (NCCS), Pune	12th September to 15th September 2013
	Attended Workshop on Proteogenomics & Mass Spectrometry	24th October to 1st November 2013
	Attended Collaborative Discussion at Swami Vivekanand Youth Movement at Mysore	7th January to 8th January 2014
	Invited speaker at World TB Day Symposium, AIIMS, India	2014
	Invited speaker in Emerging themes in TB research, IISc, India	2013
	Invited speaker at Exploiting pathogen genetics for new control strategies, ICGEB, India	2013
	Poster presentation at Keystone meeting on Tuberculosis, Canada	2013
Dr. Milan Surjit	3rd Conclave at National Centre for Cell Sciences (NCCS), Pune	12th September to 15th September 2013
	Attended Collaboration for research work at ILS, Bhubaneshwar	13th March to 15th March 2014

Name of Faculty	Name of Conference/ Seminar/ Workshops/ Symposium Abroad	Date of Visit
Dr. Amit Awasthi	Attended AAI Annual Meeting in Immunology at Hawaii	2nd May to 12th May 2013
	Delivered lectures on Immunotechnology to PG students in Department of Zoology & Biotechnology, Garhwal University, Srinagar	23rd May to 24th May,2013
	Delivered a talk in Indian Institute of Science Education and Research, Bhopal	6th September to 8th September 2013
	Attended Annual meeting of Wellcome Trust	30th September 2013 to 2nd October 2014
	Attended Young Investigator meeting at Hyderabad	10th February to 13th February 2014
	To perform Collaborative experiments as proposed in the Wellcome trust Grant	22nd March to 22nd May 2014
Dr. Uma Chandra Mouli Natchu	3rd Conclave at National Centre for Cell Sciences (NCCS), Pune	12th September to 15th September 2013
Dr. Bhabatosh Das	Indo-Danish meeting to discuss different issues related to gut microbiome analysis of T2D patients in Chennai	27th May to 28th May,2013
	Discussion on " MicroDiab-Studies of interactions between the gut Microbiome and the human host biology to elucidate novel aspects of the pathophysiology and pathogenesis of type 2 Diabetes" at University of Copenhagen, Denmark	1st December to 7th December 2013
Dr. Gaurav Batra	Marie Curie Project Work at Turku, Finland	21st April to 30th April 2013
	Attended EU-India STI Cooperation Days in Paris, France	8th October to 12th October 2013
	TECH-SEPRA Project work at Turku, Finland	5th March to 14th March 2014
Dr. Samrat Chatterjee	Lecture on Introductory topics of Systems Biology to M.Sc. Students in Centre for Mathematical Biology and Ecology (CMBE), Jadavpur University, Kolkata	31st January to 9th February 2014
Dr. Jonathan Pillai	Delivered Lectures on Medical Device Innovation Course as visiting faculty at IIT-Chennai	3rd March to 7th March 2014
Dr. Ranjith Kumar C.T.	3rd Conclave at National Centre for Cell Sciences (NCCS), Pune	12th September to 15th September 2013
Dr. Pallavi Kshetrapal	3rd Conclave at National Centre for Cell Sciences (NCCS), Pune	12th September to 15th September 2013
	Attended National worksop on Basis of Good Clinical Practices in Hyderabad	17th March to 20th March 2014

Name of Faculty	Name of Conference/ Seminar/ Workshops/ Symposium Abroad	Date of Visit
Dr. Nitya Wadhwa	To deliver a lecture on Genetics & Epidemology at National institute of Biomedical Genomics, Kalyani, West-Bengal	4th April to 5th April 2013
	To meet Secretary Health cum Mission Director, NRHM, Haryana, Chandigarh	13th August to 14th August 2013
	Workshop on " Observational Studies" at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow	29th September to 2nd October, 2013
Dr. Arup Banerjee	Workshop on "Implementing NGS Genomics and Epigenetics studies" at IISER, Pune	23rd February to 27th February, 2014
Dr. Sankar Bhattacharya	7th RNA Meet, Kolkata	5th March to 9th March 2014
	Role of stress pathway in Japanese encephalitis virus life cycle: Riding on stress; Immunocon	2013
Dr. Deepak Sharma	National symposium on " Innovation in TB Diagnostics, Drug Targets and Biomarkers" at MGIMS, Sevagram, Wardha	26th January to 28th January 2014
Dr. Kaushik Bharati	WHO Meeting, Bangkok, Thailand	24th July to 27th July 2013
	IDEAsia Meeting, Philippines	13th January to 17th January 2014
Dr. Mona Duggal	National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore	28th October to 31st October 2013
	Discussion of Grant project with Maharashtra Government in Mumbai	5th January to 7th January 2014
Ms. Vidhya Krishnamoorthy	Workshop on Ethics on Biomedical Research, Mangalore	1st January to 5th January, 2014
Dr. Vikas Sood	Workshop on " Hands on Training: Implementing NGS in Genomics and Epigenetics Studies" at IISER, Pune	23rd February to 27th February 2014
Dr. Tarun Kumar Sharma	6th Bangalore India Nano Conference at Bangalore	3rd December to 8th December, 2013
Mr. Deepak Rohilla	TECH-SEPRA Project Work, Turku, Finland	5th March to 14th March, 2014
Dr Manjula Kalia	Invited Speaker for 40th Annual Conference of Indian Immunology Society, IMMUNOCON 2013, "Role of Autophagy in Flavivirus Pathogenesis".	15th November to 17th November, 2013
Dr. Sagarika Halder	Participated in the workshop under Clinical Investigator Development Program on 'Discovery Development and Commercialization of Biologicals' from at Indian Institute of Technology, New Delhi.	11th March to 15th March 2013
	Detection of Mycobacterium tuberculosis GlcB or HspX antigens or devR DNA impacts the rapid diagnosis of tuberculous meningitis in children at the National Conference on 'Zoonotic Mycobacterial Infections and their Impact on Public Health organized by Department of Biotechnology, AIIMS, India.	25thFebruary to 27th February 2013

Seminars at THSTI

Title	Speaker	Date
BioMedical Image Analysis	Prof Alison Noble Technikos Professor of BioMedical Engineering Oxford University, UK	10-03-2014
Demo & presentation of MST Model NT.115	Dr. Moran Jerabek, NanoTemper Technologies GmbH, Munich, Germany	04-03-2014
Biomaterial associated infections and its prevention	DrPrashant K Sharma, Associate Professor, Department of Biomedical Engineering, University Medical Center Groningen, The Netherlands	19-01-2014
Innovative Technologies for Gene Expression	Dr. Pankaj Kumar Joshi Application Scientist Sigma Life Sciences, New Delhi	19-09-2013
Cyclic GMP-mediated signalling: getting to the gut of the matter	Prof. Sandhya S. Visweswariah Department of Molecular Reproduction, Development and Genetics Indian Institute of Science, Bangalore	24-09-2013
Introducing Cholera Vaccine Effectively: Lessons from the DOVE Project	Prof. David Sack Johns Hopkins Bloomberg School of Public Health Baltimore, Maryland, USA	05-09-2013
Real PCR Solutions from Life Technologies	Dr. Sangeeta Thatai, Training Lead, South Asia	12-09-2013
Semiconductor sequencing-Paradigm shift in the technology	DrAnupama Gaur, Business Development Lead, NGS	12-09-2013
Mother-to-Child Transmission (MTCT) of HIV-1 – Genotypic and Phenotypic Studies of Transmitted/ Founder Viruses	Dr. Mohan Somasundaran, CFAR Core Leader, Experimental Virology Core, Department of Pediatrics, University of Massachusetts Medical School	12-08-2013
Liver Regeneration during Liver Failure	Prof. Shiv Kumar Sarin, Head, Institute of Liver and Biliary Sciences, New Delhi	13-08-2013
Network, nodes and nexus: systems approach to multi-target therapeutics	Dr. Rajesh S. Gokhale, Director, IGIB, Delhi	30-07-2013
Cost-Effectiveness Analysis and Research Priority Setting	Prof. Margaret Brandeau Coleman F. Fung Professor, School of Engineering, Stanford University, USA	10-04-2013
A Research Development Office for the Bangalore Bio-cluster	Dr. Savita Ayyar, Head, Research Development Office, NCBS, Bangalore	05-04-2013

Events at THSTI

First Public Lecture organized by THSTI, delivered By Dr. Prabhat Jha, University of Toronto Chair in Disease Control

Signing of MoUs

In June 2013, Jawaharlal Nehru University (JNU) accorded recognition to the THSTI academic program leading to the award of the PhD degree. AnMoU to this effect was signed on 30th September 2013 on behalf of the two institutions by Prof. S. K. Sopory, Vice-Chancellor, JNU and Dr. G. B. Nair, Executive Director, THSTI at the JNU campus in New Delhi.

THSTI has entered into a collaboration with Centre for Health Research and Development, Society for Applied Studies (CHRD-SAS - a not for profit Scientific and Industrial Research Organization, dedicated to community health research). A MoU effecting the collaboration was signed at THSTI by Dr. Nita Bhandari (CHRD –SAS) and Dr. G.B. Nair (THSTI).

THSTI has entered into a collaboration with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDRB, B) . A MoU effecting the collaboration was signed at Dhaka, by Dr. John Clemens (icddr,b) and Dr. G.B. Nair (THSTI) on 3rd July 2013.

Scientific Advisory Group meetings at THSTI

Scientific Advisory Group meeting of Vaccine and Infectious Disease Research Center

Scientific Advisory Group meeting of Pediatric Biology Center

Scientific Advisory Group meeting of Center for Biodesign and Diagnostics

Central Advisory Board meeting of Policy Center for Biomedical Research

Lifetime Achievement Honour Award being conferred to Prof.Yoshifumi Takeda, Emeritus Member, National Institute of Infectious Disease, Toyama, Shinjyuku, Japan by Prof N. K. Ganguly, Distinguished Biotechnology Research Professor, Department of Biotechnology.

Welcome address by Dr GB Nair and also giving a brief introduction about THSTI

THSTI in association with Yakult India Microbiota and Probiotic Science Foundation and Apollo Hospitals organized a probiotic symposium ," Probiotics, Microbiome and Gut function – Transforming Health and Well-being on 15th and 16th February 2014 in New Delhi, India. The symposium was especially designed to unravel the factors that shape the microbial communities of the gut and identify the latest developments in probiotic science that will positively affect the microbiota for clinical intervention. Keynote lectures by leading International and national experts allowed a better understanding of the matrix for probiotic delivery , mechanism of action of probiotics, the role of probiotics in preventing infections and an insight into the Alimentary Pharmabiotic Centre that serves as a model of how scientists, clinicians and industry can work together with shared goals. An insight into the epidemiological studies conducted on probiotics and the integration of probiotics in day to day clinical and nutritional practice were also some exciting highlights of the symposium.

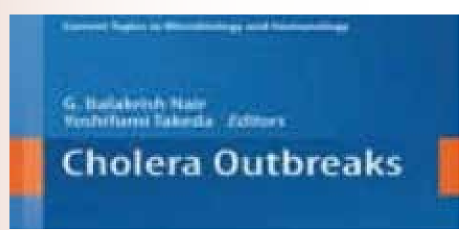
This symposium brought together International and National experts and captured the latest findings on the growing science of the Gut Microbiota and the role of Probiotics for improvement of health and well-being. Welcome address speech were delivered by Prof N. K. Ganguly, Distinguished Biotechnology Research Professor, Department of Biotechnology, Ministry of Science and Technology, Government of India, Prof. G. B. Nair, Executive Director, Translational Health Science Technology and Institute and Prof. AnupamSibal, Group Medical Director and Senior Consultant Pediatric Gastroenterologist and Hepatologist, Apollo Hospitals. During the symposium Prof. Yoshifumi Takeda, Emeritus Member, National Institute of Infectious Disease, Toyama, Shinjyuku, Japan was honored with Lifetime Achievement Honor award. Recognizing the need to promote probiotic research in the country, the Foundation instituted three young Investigator awards to felicitate talent and knowledge.

Science retreat- Deliberations and discussions of ongoing research programs at THSTI

Felicitation of Prof. Mathuram Santhosham – THSTI felicitated Prof Mathuram Santosham for receiving the prestigious Albert B.Sabin Gold Medal. The felicitation was done by THSTI Executive Director Dr. GB Nair in presence of all the faculty, scientists and scholars of THSTI.

Better understanding of Cholera Outbreaks – The book launch

Dr. G. Balakrish Nair, Executive Director, THSTI along with Dr. Yoshifumi Takeda, Kyoto University, Japan, has published Cholera Outbreaks in electronic and print format with Springer's. This book provides a better understanding of cholera outbreaks. The most feared attribute of the human pathogen Vibrio cholerae is its ability to cause outbreaks that spread like wildfire, completely overwhelming public health systems and causing widespread suffering and death. This volume starts with a description of the contrasting patterns of outbreaks caused by the classical and El Tor biotypes of V. cholerae. Subsequent chapters examine cholera outbreaks in detail, including possible sources of infection and molecular epidemiology on three different continents, the emergence of new clones through the bactericidal selection process of lytic cholera phages, the circulation and transmission of clones of the pathogen during outbreaks, and novel approaches to modeling cholera outbreaks. A further contribution deals with the application of the genomic sciences to trace the spread of cholera epidemics and how this information can be used to control cholera outbreaks. The book closes with an analysis of the potential use of killed oral cholera vaccines to stop the spread of cholera outbreaks.



7th Asian Conference on Lactic Acid Bacteria (ACLAB-7)

The 7th Asian Conference on Lactic Acid Bacteria (ACLAB7) was organized by the Translational Health Science and Technology Institute (THSTI) under the aegis of the Asian Federation of Societies of Lactic Acid Bacteria (AFSLAB) at the India Habitat Centre, New Delhi from 6th – 8th September 2013.

The conference with the theme "Lactic Acid Bacteria as Growth Engine for Economy and Integrated Industries" witnessed the participation of a wide audience, with approx. 172 delegates from India and 14 other Asian countries, as well as other foreign countries like USA and South Africa. Parallel sessions with 24 oral presentations and 67 poster presentations were also an important part of the program with prize money for the best oral presentation and the three best poster presentations sponsored by Beijing Science Plus.

The deliberations that ensued over the three days of the conference focused on the utility of Lactic Acid Bacteria to influence various aspects of health and what it would take to exploit the full potential of these microbes. Potential avenues for further research, evaluation of new technologies such as metagenomic studies and regulatory guidelines for the utility of these microbes were the highlight of this conference.

Delegations at THSTI

Prof. HisaoKurazono,Vice-President for Planning, Obihiro University of Agriculture and Veterinary Medicine,Japan, led his delegation to THSTI on 2nd August 2013 to explore potential collaborations.

The THSTI team made a comprehensive presentation to showcase the ongoing scientific programs to visiting representatives from the Bill and Malinda Gates Foundation on 4th June 2013.

Erasmus University Medical Centre Delegates visit THSTI

Maastricht University Medical Centre Delegates visit

Human Resource, Adminstration & Finance

People at THSTI

Faculty and Scientists

Name	Designation
Dr. G.B. Nair	Executive Director
Dr. Sudhanshu Vrati	Dean (Academics) and Head-VIDRC
Dr. Shinjini Bhatnagar	Professor and Dean (Clinical Research)
Dr. Kanury Venkata Subba Rao	Adjunct Faculty & Head-DDRC
Dr. Guruprasad R. Medigeshi	Assistant Professor
Dr. Ramandeep Singh	Assistant Professor
Dr. Nisheeth Agarwal	Assistant Professor
Dr. Amit Kumar Pandey	Assistant Professor
Dr. Krishnamohan Atmakuri	Assistant Professor
Dr. Milan Surjit	Assistant Professor
Dr. Amit Awasthi	Assistant Professor
Dr. Uma Chandra Mouli Natchu	Assistant Professor
Dr. Bhabatosh Das	Assistant Professor
Dr. Gaurav Batra	Assistant Professor
Dr. Samrat Chatterjee	Assistant Professor
Dr. Jonathan Pillai	Assistant Professor
Dr. Rajkumar Halder	Scientist E
Dr. Ranjith Kumar C.T.	Ramalingaswami Fellow
Dr. Pallavi Kshetrapal	Ramalingaswami Fellow
Dr. Manjula Kalia	Research Scientist D
Dr. Nitya Wadhwa	Research Scientist D
Dr. Shailaja Sopory	Research Scientist D
Dr. Arup Banerjee	Research Scientist D
Dr. Supratik Das	Senior Scientist
Dr. Mohan Babu Appaiahgari	Research Scientist C
Dr. Sankar Bhattacharyya	Research Scientist C
Dr. Deepak Sharma	Research Scientist C
Dr. AshutoshTiwari	Research Scientist C
Dr. Niraj Kumar	Research Scientist C
Dr. Susmita Chaudhuri	Research Scientist C
Dr. Amit Kumar Yadav	Scientist C
Dr. Savit B. Prabhu	Scientist C
Dr. Sangeeta Kumari	INSPIRE Faculty
Dr. Sagarika Haldar	INSPIRE Faculty
Dr. NiveditaMitra	Senior Scientist
Dr. Saikat Boliar	Scientist
Dr. Tripti Srivastava	Scientist
Dr. Sweety Samal	Scientist
Dr. Bratati Mukhopadhyay	Sr. Program Officer
Dr. Kaushik Bharati	Sr. Program Officer
Dr. Mona Duggal	Sr. Program Officer
Dr. Sanjukta Sengupta	Sr. Program Officer
Dr. Gautam Kumar Saha	Consultant
Ms. Vidhya Krishnamoorthy	Professional Expert (Grants & Ethics)
Dr. B. Debkumari	Professional Expert (Scientific Liaison)

Research Staff

Name	Designation
Ms. Nisha Arora	Junior Analyst
Ms. Swati Verma	Junior Analyst
Ms. Radhika Gigras	Junior Analyst

Research Fellows

Name	Designation
Mr. Vikas Sood	VRI-Awardee
Dr. Chandresh Sharma	Innovation Awardee
Dr. Sourav Sen Gupta	Microbiome Innovation Award
Dr. Tarun Kumar Sharma	Innovation Awardee
Dr. Reena Kumari	Microbiome Innovation Award
Dr. Tanvi Aggarwal	VRI-Awardee
Dr. Prabhakar Tiwari	Research Associate
Dr. Amita Sharma	Research Associate
Dr. Rajat Anand	Research Associate
Dr. Mukul Kumar Midha	Research Associate
Dr. Varshneya Singh	Research Associate
Mr. Rajpal	Research Associate
Dr. Suprit Deshpande	Research Associate
Nalini J.	Research Associate
Dr. Srikanth Elesela	Post-Doctoral Fellow
Dr. Kamlesh Gidwani	Post-Doctoral Fellow
Dr. Ram Krashan Kasera	Post-Doctoral Fellow
Dr. Sheikh Mohd. Talha	Post-Doctoral Fellow
Ms. Eira Chaudhary	Sr. Research Fellow
Ms. Mamta Singh	Sr. Research Fellow

Name	Designation
Ms. Garima Arora	Sr. Research Fellow
Ms. Deepa Nair	Sr. Research Fellow
Mr. Avinash D. Londhe	Sr. Research Fellow
Ms. Shruti Saxena	Sr. Research Fellow
Mr. Deepak Rohila	Sr. Research Fellow
Ms. Renu Khasa	Sr. Research Fellow
Mr. Sreeraj Surendran	Sr. Research Fellow
Mr. Vijay Kumar S.R	Sr. Research Fellow
Vishavjeet Khairwal	Sr. Research Fellow
Mr. Nishant Joshi	Sr. Research Fellow
Ms. Akriti Srivastava	Jr. Research Fellow
Ms. Mallika	Jr. Research Fellow
Mr. Rahul Sharma	Jr. Research Fellow
Ms. Pratishtha Jain	Jr. Research Fellow
Ms. Vidya P. Nair	Jr. Research Fellow
Mr. Sankalp Srivastava	Jr. Research Fellow
Ms. Sheba Solomon	Jr. Research Fellow
Ms. Nidhi Vishnoi	Jr. Research Fellow
Ms. Neha Kaushik	Jr. Research Fellow
Ms. Mayanka Dayal	Jr. Research Fellow
Ms. Abhilasha Madhvi	Jr. Research Fellow
Mr. Srikanth Sadhu	Jr. Research Fellow
Ms. Archana Pant	Jr. Research Fellow
Ms. Anica Dadwal	Jr. Research Fellow
Mr. Manitosh Pandey	Jr. Research Fellow
Ms. Poulami Dasgupta	Jr. Research Fellow
Ms. Saimah Raza	Jr. Research Fellow
Mr. Prakash Kalwani	Jr. Research Fellow
Mr. Amardeep	Jr. Research Fellow
Ms. PragyaPriyadarshini	Jr. Research Fellow
Ms. Poojakumari	Jr. Research Fellow
Ms. KarishmaBakshi	Jr. Research Fellow
Mr. Utsav Sen	Jr. Research Fellow
Ms. Ojasvi	Research Fellow

Research Students

Name	Designation
Ms. Preeti Thakur	Ph.D. Student
Ms. Minu Nain	Ph.D. Student
Mr. Manish Sharma	Ph.D. Student
Mr. Nishant Sharma	Ph.D. Student
Ms. Bhavya Khullar	Ph.D. Student
Ms. Rinki Kumar	Ph.D. Student
Mr. S. Chandru	Ph.D. Student
Ms. Praapti Jayswal	Ph.D. Student
Ms. Tarang Sharma	Ph.D. Student
Ms. Sakshi Agarwal	Ph.D. Student
Ms. Saumya Anang	Ph.D. Student
Ms. Nidhi Kaushik	Ph.D. Student
Ms. Bharti Kumari	Ph.D. Student
Ms. Anita Chaudhary	Ph.D. Student
Ms. Manpreet Kaur	Ph.D. Student
Ms. Meenakshi Kar	Ph.D. Student
Ms. Sakshi Malik	Ph.D. Student
Ms. Sakshi Talwar	Ph.D. Student
Ms. Shilpi Sehgal	Ph.D. Student
Ms. Smita S. Hingane	Ph.D. Student
Mr. D Ramu	Ph.D. Student

Administration Personnel

Name	Designation
Dr. G.B. Nair	Executive Director
Mr. M.V. Santo	Head-Administration
Mr. C.B. Yadav	Administrative Officer (F&A)
Mr. J. N. Mishra	Administrative Officer (P&A)
Mr. Pitambar Behera	Finance & Accounts Officer
Mr. Mohd. Shahid	Section Officer
Mr. Deepak Bhagirath Baghele	Section Officer (Store & Purchase)
Mr. Shiv Kumar	Management Assistant (P&A)
Mr. Dharmendra Sharma	Programmer
Mr. Mukesh Juyal	Data Entry Operator
Ms. Shilpa Chopra	Data Entry Operator
Mr. Radhesh Notiyal	Executive Management Assistant
Mr. Rajesh Kumar	Management Assistant (F&A)
Mr. Manoj Kumar	Management Assistant (F&A)
Mr. Satish Kumar	Management Assistant
Mr. Pradeep Kumar	Management Assistant
Mr. Hanumantha Rao S	Personal Assistant
Mr. Koushik Chatterjee	I.T Officer
Ms. Taruna Sharma	Programmer
Ms. Greeshma J.	Executive Secretary (P)

Name	Designation
Ms. Sonia Joshi	Data Entry Operator (P)
Mr. Rahul Kumar Chauhan	Data Entry Operator
Mr. Ali Baksh	Data Entry Operator
Mr. Arif Saifi	Management Assistant
Mr. Raj Kumar Tanwar	Data Entry Operator
Ms. Aakriti Upadhyay	Clerical Assistant (P)
Mr. Rahul	Clerical Assistant (P)
Ms. Sweety Jain	Accounts Assistant (P)
Mr. Lalit Kumar	Clerical Assistant (P)
Ms. Priyanka Kapoor	Clerical Assistant (P)
Ms. Upasana Sharma	Clerical Assistant (P)
Ms. Reena Pal	Accounts Assistant (P)
Mr. Rinku Gurahiya	Accounts Assistant (P)
Mr. Amit Kumar	Clerical Assistant
Mr. Pradeep Jakhar	Clerical Assistant

Technical Personnel

Name	Designation
Mr. Gopal Raman Agarwal	Inst. /Elec. Engineer
Dr. Manpreet Kaur	Vaccine Technologist
Mr. Vishal Gupta	Sr. Technical Officer
Mr. Irudayaraj M.	Sr. Technical Officer (IT)
Ms. Arpita Mishra	Asstt. Vaccine Technologist
Mr. Sharanabasava	Asstt. Vaccine Technologist
Ms. Taranjeet Kaur	Asstt. Vaccine Technologist
Dr. Madhu Pareek	Technical Officer I
Ms. Sonali Porey Karmakar	Technical Officer I
Mr. Saqib Kidwai	Technical Officer I
Mr. Uttam Kumar Saini	Technical Assistant
Mr. Gaurav Singh	Technical Assistant
Mr. Imran Khan	Lab. Technician
Mr. Ranjeet Rai	Lab. Technician
Dr. Monika Chaturvedi	Clinical Research Coordinator
Dr. Shipra Mishra	Sr. Resident (P)
Dr. Mahadev Dash	Senior Research Officer
Dr. Kanika Sachdeva	Senior Research Officer
Dr. Sumit Misra	Research Officer

Name	Designation
Dr. Smita Bajpai	Research Officer
Ms. Nisha Piplani	Sr. Resident (P)
Dr. Richa Mehra	Project Manager (P)
Dr. Priya Dalal	Jr. Resident (P)
Dr. Deepak K. Rathore	Research Officer (P)
Mr. Anbumani D.	Technical Assistant
Mr. Satyabrata Bag	Technical Officer II
Mr. Manoj Mahato	Technician - II
Mr. Ajay Kumar	Technical Assistant (P)
Ms. Sushmita Kumari	Staff Nurse (P)
Ms. Neha Thakur	Staff Nurse (P)
Ms. Rinki	Study Nurse
Ms. Kumari Meera	Study Nurse
Ms. Suman Rawat	Study Nurse
Ms. Renu Gehlawat	Study Nurse
Ms. Sangeeta Singh	Study Nurse
Ms. Pooja Shishodia	Study Nurse
Mr. Manas Ranjan Tripathy	Lab. Technician
Ms. Preety Rana	Lab. Technician
Mr. Eklavya Srivastava	Technical Assistant
Mr. Mohd. Usman Khan	Technical Assistant
Mr. Sandeep Goswami	Lab. Technician (P)
Mr. Brihaspati Narayan Shukla	Lab. Technician (P)
Mr. Nakul Kumar Chaudhary	Lab. Technician
Mr. Ashish Tyagi	Lab. Technician (P)
Mr. Shri Chand Pandey	Technician - II
Mr. Manish Bansal	Lab. Technician (P)
Mr. Suresh Kumar	Lab. Technician (P)
Ms. Shilpa Shivanand Patil	Lab. Technician
Ms. Deepika Kannan	Lab. Technician
Mr. Dinesh Kumar	Technician - II Clinial (P)
Mr. Kapil Dev	Technician - II (P)
Ms. Ritu Rani	Technician - II (P)
Ms. Aasma Khan	Technician - II (P)
Mr. Ashok Saini	Technician - II Field (P)
Mr. Brij Mohan	Technician - II Field (P)
Mr. Ashok Kumar	Technician - II
Mr. Vijay Chauhan	Technician - II

The THSTI Administration

Administration

The Administration Division at THSTI performs relentlessly to provide the scientific functions at the Institute with unstinted support or smooth functioning. The personnel at this division comply with the Government of India Rules and related financial norms in their functions.

The THSTI Administration comprises of several functional wings. They are, Personnel, General, Administration, Academics, Finance, Accounts, Stores, Purchase, Engineering and IT.

Some of the major milestones were the following:

- The Recruitment Rules of THSTI were approved by the nodal Ministry and the Bye-Laws of THSTI are in the process of being approved by the Ministry
- Two positions of Dean in the HAG+ scale were filled up on permanent basis- one through absorption and one through direct recruitment
- THSTI expanded its number of Centres with the inclusion of Population Science Partnership Centre (PSPC) by way of a MoU between Centre for Health Research and Development, Society for Applied Studies (CHRD-SAS) and THSTI
- THSTI signed an MoU with Jawaharlal Nehru University (JNU) and Manipal University for registration of our PhD students
- With the support of DBT , THSTI was able to provide all the funds required for the construction of the lab buildings in Faridabad

On the governance front, THSTI conducted two meetings of the Finance Committee and Governing Body and one meeting of the Society.

Communication ensuring transparency and integrity

On the communication front, it has been the endeavour of THSTI to maintain high degree of transparency with regard to all the official processes through the website. This has ensured that the number of applications received under the RTI Act were only 16. Among these applications, only seven were with respect to tenders / selections. The rest were applications transferred from DBT seeking general information. The Parliament questions, references from DBT and other organisations were responded within the stipulated deadlines.

As per the Chief Vigilance Commissioner guidelines, Dr.GuruprasadMedigeshi has been nominated as Vigilance Officer of THSTI from 29th January, 2014 till 28th January, 2017.

THSTI brand promotion

THSTI considers its logo as an important asset. As a consequence, THSTI administration and ERID have formulated a "THSTI logo brand guidelines" which postulates its usage on various items like stationary, website and advertisements in newspapers. This has been circulated to the employees for strict adherence.

THSTI's face on the web

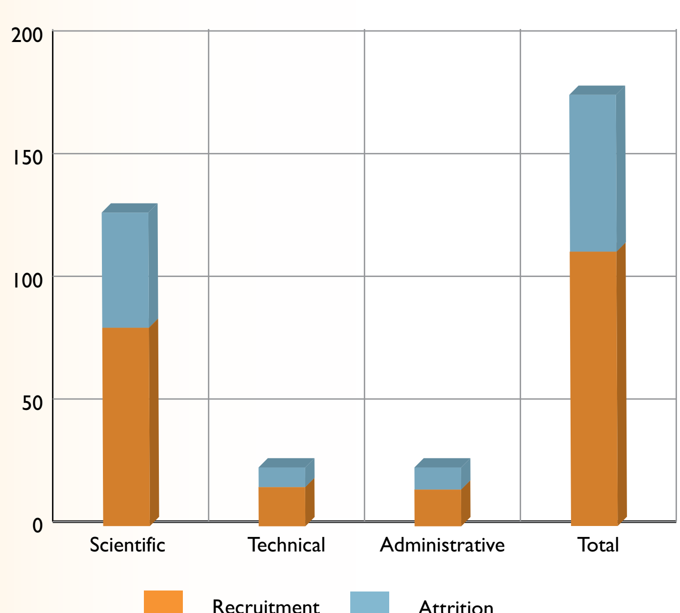
THSTI has received several accolades for having one of the best websites among the other DBT institutions. Keeping this in mind, THSTI has upgraded its website further by improving upon the website content and updating the latest scientific and administrative issues on daily basis. As per the Guidelines for Indian Government Websites (GIGW), THSTI got its website content audited by an external audit firm to obtain a certificate stating that the THSTI website cannot be hacked. THSTI complied with all the requirements and acquired the certificate for the same. This certificate would enable THSTI to upload its website on the NIC

server. THSTI website would be uploaded in the NIC server during the financial year 2014-15. THSTI has also provided VPN access for all its faculty / scientists, so that they will be able to access the THSTI server even outside the institute.

Employee benefits

THSTI has always tried to keep the employees morale very high by giving high priority for employee welfare activities. The Government of India directions for various benefits like LTC, Medical reimbursement, telephone and newspaper reimbursement and Children education allowance were followed by THSTI in its word and spirit. The employees are periodically informed about these benefits so that all of them utilise these benefits to the fullest.

HR analytics



On the HR front, THSTI was successful in issuing 25 Recruitment notices for 160 vacancies. This resulted in 112 recruitments during the financial year 2013-14. For certain popular categories like Clerical assistant, Technical Assistant, Technician and IT officer, where the number of applications received are very high, the selection process included a written test followed by the interview. Since the written test was of objective type and the answers were recorded in the OMR sheets, the results were published within three hours and interview was held on the same day. This ensured that the candidates are put through least hassle for appearing in the selection process. In the case of JRF/SRF/RA and clinical positions, THSTI has introduced a rolling advertisement round the year to cater to the sporadic requirements which would arise frequently.

THSTI had introduced a very stringent probation clearance and contract extension procedures. By following this procedure 40 employees have successfully cleared their probation period and 53 employees were granted extension of contract during the year. THSTI understands the importance of trainings for its employees. It also encourages employees to attend workshops, seminars etc. to widen their scientific knowledge for better output. Accordingly, the Executive Director had approved 85 trips for our employees within and outside this country for various trainings / workshops/ seminars/ meetings during this financial year.

Event organization by the Administration

THSTI has observed all the important days as directed by the Government of India in honour of various occasions such as Anti-terrorism day, Martyr's Day, Independence Day, Republic Day, Hindi Week, Vigilance awareness week, etc. Every year, THSTI celebrates its foundation day with scientific reverence. The celebrations were held at Indian International Centre on 13th July, 2014. Dr. Rita Colwell was invited as the chief guest. She is a distinguished university Professor both at the University of Maryland and The Johns Hopkins Bloomberg School of Public Health; Senior Advisor and Chairman Emeritus, Canon U.S. Life Sciences, Inc.; and President and Chairman of CosmosID, Inc. Prof. VijayRaghavan and Prof. Bhan also spoke on the occasion.

Social involvement

THSTI holds the annual family meet every year for all its employees and their family members. On 8th February, 2014 the same was held atIndira Gandhi Holiday Home nearDamdama Lake, in Bhondsi village.The full day programme had many games / rides which were primarily anchored by the JRF / SRF of the institute.

Finance

The financial statements namely the balance sheet, the income and expenditure statement and the receipts and payments statement for FY 2013-14 are given here:

BALANCE SHEET AS on 31ST MARCH, 2014

Amount (In Rs.)

	Schedule	31.03.2014	31.03.2013
LIABILITIES			
Corpus / Capital Fund	1	1,00,66,67,651	71,64,71,081
Reserves and Surplus	2	7,28,18,285	9,32,69,279
Earmarked/Endowment Funds	3	-	-
Secured Loans and Borrowings	4	-	-
Unsecured Loans and Borrowings	5	-	-
Deferred Credit Liabilities	6	-	-
Current Liabilities and Provisions	7	8,76,05,293	5,05,05,034
TOTAL		**1,16,70,91,229**	**86,02,45,394**
ASSETS			
Fixed Assets	8	1,04,86,99,338	81,78,96,300
Investment From Earmarked/Endowment Funds	9	-	-
Investment - Others	10	-	-
Current Assets. Loans, Advances etc.	11	11,83,91,891	4,23,49,094
Miscellaneous Expenditure (to the extent not written off or adjusted)		-	-
TOTAL		**1,16,70,91,229**	**86,02,45,394**
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

Sd/-
(C. B.YADAV)
Finance & Accounts Officer

Sd/-
(DR.G.B. NAIR)
Executive Director

Sd/-
(SANJIV RAI MEHRA)
Partner
M No.80402

Place: Gurgaon
Date: 2 September 2014

INCOME AND EXPENDITURE ACCOUNT FOR THE YEAR ENDED 31st MARCH, 2014

Amount (in Rs.)

	Schedule	31.03.2014	31.03.2013
INCOME			
Income from Sales/ Services	12	-	-
Grants/Subsides	13	18,04,00,000	12,25,00,000
Fees/Subscriptions	14	-	-
Income from Investments	15	-	-
Income from Royalty, Publication etc.	16	-	-
Interest Earned	17	84,51,613	30,18,665
Other Income	18	21,04,771	23,31,448
Increase/(Decrease) in stock of Finished goods and works in progress	19	-	-
Deferred Income-Fixed Assets		4,73,18,480	3,35,73,882
TOTAL (A)		**23,82,74,864**	**16,14,23,995**
EXPENDITURE			
Establishment Expenses	20	5,91,02,624	2,77,00,460
Other Administrative Expenses etc.	21	11,83,68,626	10,32,79,299
Expenditure on Grants , Subsidies etc.	22	-	-
Interest	23	-	-
Depreciation (Net Total at the year-end-corresponding to Schedule 8)		4,73,18,480	3,35,73,883
Prior period Adjustment A/c (ANN-A)		-	-
TOTAL(B)		**22,47,89,730**	**16,45,53,642**
Balance being excess of Income Over Expenditure (A-B)		**1,34,85,134**	**(31,29,647)**
Transfer to special Reserve(Specify each)		-	-
Transfer to /from General Reserve		1,34,85,134	(31,29,647)
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

Sd/-
(C. B. YADAV)
Finance & Accounts Officer

Sd/-
(DR.G.B. NAIR)
Executive Director

Sd/-
(SANJIV RAI MEHRA)
Partner
M No.80402

Place: Gurgaon
Date: 2 September 2014

CONSOLIDATED RECEIPTS AND PAYMENTS ACCOUNT FOR THSTI, PROJECTS & FELLOWSHIP FOR THE YEAR ENDED 31ST MARCH, 2014

Amount-In-Rupees

RECEIPTS Particulars	31.03.2014		31.03.2013	
OPENING BALANCE:-				
THSTI	4,96,633		1,20,28,395	
Projects	1,54,10,435		9,12,37,236	
Fellowship	1,24,46,387		42,51,420	
Grant-in Aid Received:-				
THSTI	37,00,00,000		32,05,00,000	
Projects	26,74,26,927		7,53,49,712	
Fellowship	3,14,18,667		2,64,55,536	
Other Receipts -THSTI				
Programme Receipts	-		13,18,343	
Miscellaneous Receipts	19,441		20,399	
Overhead THSTI	18,33,936		5,71,270	
RTI Receipt	24		-	
Guest House Receipt	44,950		1,250	
Recruitment Fee	1,31,420		1,20,800	
Tender Fee	75,000		2,93,000	
Security / Hostel Deposit Received	13,67,776		6,29,607	
Earnest Money Deposit	1,14,67,070		15,75,439	
Interest Received	80,51,613		30,18,665	
Accrued Interest Received	-		22,75,684	
Income Tax Refund Received	13,40,418		67,190	
Govt. Dues Payable	11,40,753		6,87,695	
Other Liabilities/Payable	3,73,584		8,47,919	
Decrease in advances	95,17,612		4,39,715	
TOTAL		**73,25,62,646**		**54,16,89,275**

Amount-In-Rupees

PAYMENTS Particulars	31.03.2014		31.03.2013	
THSTI				
Fixed Assets	5,25,57,430		7,48,73,008	
Work -in- Process- Building	14,20,00,000		13,77,70,000	
Manpower	5,90,96,627		2,75,00,449	
Consumables	7,42,67,595		4,81,52,882	
Administrative Expenses	5,24,43,779		4,48,77,813	
Advances , Receivables & Liabilities	1,26,86,148		1,07,24,586	
Projects	19,41,98,905		15,11,76,514	
Fellowship	3,27,49,768		1,82,60,569	
Closing Cash & Bank Balance				
THSTI	**1,28,08,651**		**4,96,633**	
Projects	**8,86,38,457**		**1,54,10,435**	
Fellowship	**1,11,15,286**		**1,24,46,387**	
TOTAL		**73,25,62,646**		**54,16,89,275**

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

Sd/-	Sd/-	Sd/-
(C. B.YADAV)	(DR.G.B. NAIR)	(SANJIV RAI MEHRA)
Finance & Accounts Officer	Executive Director	Partner
		M No.80402

Place: Gurgaon
Date: 2 September 2014

The financial transactions have been audited by M/s Mehra & Sistani and their report is also given below:

Mehra & Sistani
Chartered Accountants
New Delhi

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 2014 and 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 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, 2014 and

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

For Mehra & Sistani
Chartered Accountants

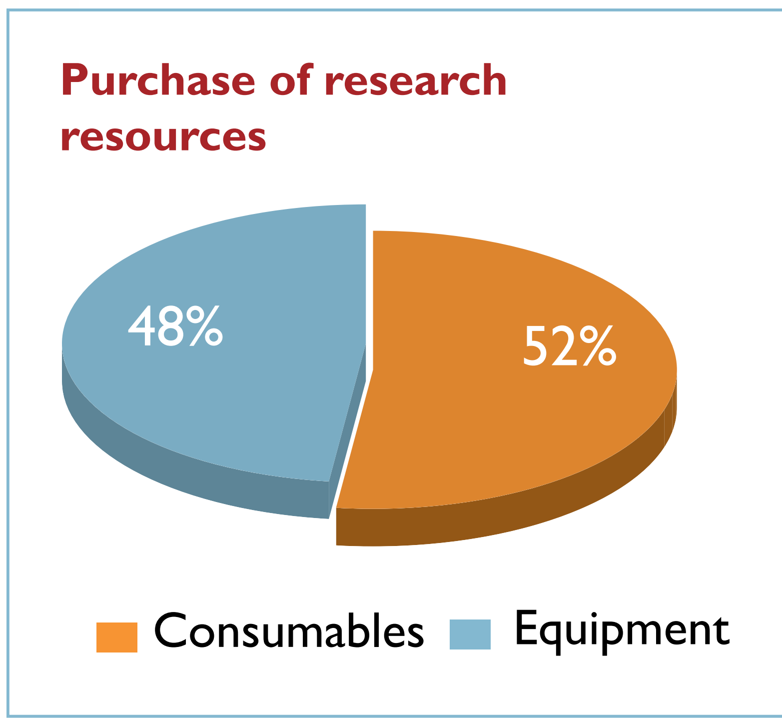
(Sanjiv Rai Mehra)
Partner
Membership No. 80402
Firm Regn. No.000409N

Place: New Delhi
Date: 2nd September 2014

Apptt. 101, I-22, Jangpura Extn. New Delhi-110014 Tel. : 24324085, 24316479, 43580293 Fax : 24326339
E-mail : mehrasistani@hotmail.com , Web-site:mehrasistani.com

Store and purchase

The Store and Purchase section were capable of rising up to the requirement of all the faculty / scientists to meet their requests within a short period.The total consumables and equipment purchases made during the financial year 2013-14 are as shown below:



Provision of adequate and timely supply of material to scientists is of prime importance for carrying out meaningful scientific research as well as for meeting the targets set for completion of various in house& sponsored projects of THSTI, being the primary aim of the THSTI Purchase Committee. On the other hand, any public procurement will not only have to be made in fair and transparent manner but will also have to fall in line with the canon of financial propriety. They are in their way of simplifying things through E-Procurement (Electronic Procurement).

Engineering

The engineering wing has been struggling very hard to ensure that all the equipment are maintained properly. In this connection, they have received 101 work orders for various works during the financial year 2013-14. All the orders have been completed within the stipulated time limits.

THSTI Socials

THSTI Celebrates Hindi Saptah

Taking a pledge on Sadhbhavana Divas, 2013

Independence Day celebrations at THSTI, 2013

In keeping with the national language objectives, THSTI commenced the HINDI SAPTAH celebrations from 16th September 2013. The week long celebrations were rolled out by Rashtrabhashashri and eminent scientist, Prof. Durga Dutt Ozha. The leadership at THSTI urged the members of the Institute to proactively adopt the Hindi language as it is the only medium in which they could interact with the beneficiaries of their Translational Research. As a part of the celebrations, 25 THSTIans participated in an spot essay competition in Hindi. The topic 'TV/ Computer ke prabhav aur dushprabhav' was selected by Prof. Ozha. The winners of the competition are:

- First Prize: Mr. Ekalvya Srivastava
- Second Prize: Mrs. Bhavya Khullar
- Third Prize: Ms. Aakriti Upadhyay

The Institute celebrated its Foundation Day on 12th July 2013. THSTI's Foundation Day Address was delivered by Dr. Rita Colwell, former Director, US National Science Foundation. Dr. M.K. Bhan, Distinguished Professor, Ministry of Science and Technology, GoI, delivered the Keynote address. The Chairman's address was delivered by Prof. K VijayRaghavan, Secretary, Department of Biotechnology, Government of India. Dr. GB Nair, Executive Director, THSTI, highlighted the milestones achieved in fulfilling the Institute's mandate, since inception.

THSTI Foundation Day celebrations

An Autonomous Institute of Department of Biotechnology
Ministry of Science & Technology, Government of India

www.thsti.res.in
Email: info@thsti.res.in