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ट्रांसलेशनल स्वास्थ्य विज्ञान
एवं प्रौद्योगिकी संस्थान

TRANSLATIONAL HEALTH SCIENCE
AND TECHNOLOGY INSTITUTE

ANNUAL REPORT

2017 - 2018

Our Mission

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

Our Vision

THSTI is a collective of physicians and scientists who work to improve health in India by creation of new knowledge for innovation, development of innovative solutions based on existing knowledge, and new strategies for implementation of existing solutions. THSTI complements the discovery, design and development of interventions by building rigorous research capacity through high quality training.

Contents


THSTI
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THSTI Society

The Society of THSTI was registered under the Societies Registration Act, 1860 on 15th July 2009 with eminent scientists as nominated and ex-officio members. The President of the Society and most members are nominated by the Honorable Minister of Science and Technology, Government of India. The Society is the apex authority of THSTI and manages, administers, directs and controls the affairs of THSTI through the Governing Body as per the relevant rules, bye-laws and various orders issued by the Government of India. In 2017-2018, the Society continues to have its founding nominated and ex-officio members.


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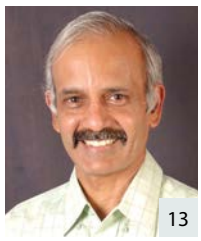
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1. **Prof. G. Padmanaban**
Distinguished Professor,
Indian Institute of Science,
Bangalore
Nominated President

2. **Prof. K. VijayRaghavan**
Secretary,
Department of Biotechnology,
New Delhi
Ex-officio member

3. **Dr. Soumya Swaminathan**
Director General,
Indian Council of Medical Research,
New Delhi
Ex-officio member

4. **Mr. B. Anand**
Additional Secretary and Financial Advisor,
Department of Biotechnology,
New Delhi
Ex-officio member

5. **Dr. Alka Sharma**
Advisor/Scientist-G,
Department of Biotechnology,
New Delhi
Scientific Coordinator, THSTI
Ex-officio member

6. **Dr. Amulya K. Panda**
Director,
National Institute of Immunology,
New Delhi
Ex-officio member

7. **Dr. M. Radhakrishna Pillai**
Director,
Rajiv Gandhi Centre for Biotechnology,
Thiruvananthapuram
Nominated member

8. **Prof. Gagandeep Kang**
Executive Director,
THSTI, Faridabad
Member Secretary, Ex-officio

9. **Dr. B. Ravindran**
Emeritus Professor,
Institute of Life Sciences,
Bhubaneswar
Nominated member

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NASI-Senior Scientist,
National Centre for Cell Science,
Pune
Nominated member

11. **Dr. Ashok Jhunjhunwala**
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Indian Institute of Technology,
Chennai
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12. **Dr. G.B. Nair**
Regional Advisor,
Research Policy and Cooperation Unit,
World Health Organization
Nominated member

13. **Dr. J. Gowrishankar**
Project Coordinator,
DBT Centre of Excellence (CoE) for
Microbial Biology,
Centre for DNA Fingerprinting and Diagnostics,
Hyderabad
Nominated member

THSTI Governing Body

The first Governing Body of THSTI was founded on 15th July 2009. It is chaired by the Secretary, Department of Biotechnology and comprises of ex-officio members and eminent scientists nominated by the Minister of Science and Technology, Government of India. It carries out and pursues the objectives of the Society, as set forth in the Memorandum of its Association. The management of all the affairs and funds of the Society, for this purpose, vest in the Governing body.


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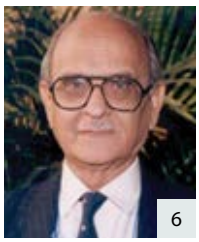
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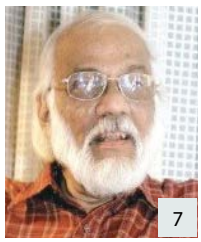
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6. **Dr. P.N. Tandon**
   President,
   National Brain Research Centre,
   Manesar
   Nominated member

7. **Prof. G. Padmanaban**
   Distinguished Professor,
   Indian Institute of Science,
   Bangalore
   Nominated member

8. **Dr. Ashutosh Sharma**
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   Department of Science and Technology,
   New Delhi
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    National Brain Research Centre,
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    Regional Centre for Biotechnology,
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    National Institute of Plant Genome Research,
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    Ex-officio member

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    Dean,
    Clinical Research
    THSTI, Faridabad
    Ex-officio member

15. **Dr. Vaskar Saha**
    Senior Consultant,
    Department of Paediatric-Haematology and Director,
    Translational Cancer Research Center
    Tata Medical Center,
    Kolkata
    Nominated member

16. **Mr. Utkarsh Palnitkar**
    Independent Consultant
    Nominated member

17. **Dr. Mahima Datla**
    Managing Director,
    Biological E. Limited
    18/1&3, Hyderabad
    Nominated member

18. **Dr. Sangeeta Bhatia**
    Director,
    Laboratory for Multiscale Regenerative Technologies,
    Koch Institute for Integrative Cancer Research at MIT,
    Cambridge
    Nominated member

19. **Dr. Gagandeep Kang**
    Executive Director,
    THSTI, Faridabad
    Member Secretary, Ex-officio

Summary of activities 2017-2018

The Translational Health Science and Technology Institute (THSTI), at the NCR-Biotech Science Cluster, Faridabad, is an autonomous institution of the Department of Biotechnology, Ministry of Science and Technology, Government of India. The institution was established in 2009 to facilitate the development, optimization and evaluation of technologies for public health.

In line with the institute's mandate, various research programs were designed and initiated, and these are organized as themes in the annual report. Ongoing efforts are focused on addressing multiple aspects of many diseases with a larger aim revolving around finding applications relevant to societal health.

In the past year, research on infectious diseases has dealt with identifying potential targets for drugs and gaining deeper insights into the pathogenesis and host-pathogen interactions in tuberculosis and viral infections. For tuberculosis and hepatitis E viruses, we have focused on screening and identification of novel drugs and inhibitors. In dengue, we have identified signatures of severe disease. The dedicated program on HIV vaccine design in partnership with the International AIDS Vaccine Initiative has successfully built capacity for the isolation of broadly-neutralizing antibodies from patients who are infected with the Indian subtype C, which is an important step in the development of potential HIV vaccines. We are also trying to understand the spread of antibiotic resistance. Our research shows that gut bacteria have antibiotic resistance genes that are physically linked with mobile genetic elements, which could help these resistance genes to spread. The research group is devising strategies to re-sensitize the resistant pathogens against routinely used antibiotics.

Tuberculosis is the most advanced diagnostic platform at THSTI, where, in partnership with AIIMS, we have developed aptamer-based diagnostic tests for pulmonary tuberculosis and tuberculous meningitis. Both tests work well and we are exploring adapting the tests for use as a point-of-care test. Efforts are also underway to develop point-of-care diagnostic tests for tropical fevers, blood-borne infections, and pneumonia.

In exploring the development and progression of autoimmune diseases, primarily inflammatory bowel disease with physicians at AIIMS, we have shown that urinary potassium is a potential biomarker of ulcerative colitis, a type of inflammatory bowel disease. We are also exploring disease prediction in other areas. Through analysis of metabolites in blood of patients before they develop disease and application of machine learning methods, we have developed a tool that can predict whether a person who is healthy today will develop diabetes with a sensitivity of >90%. To make this into a widely deployable test, we need to validate it and reduce the number of metabolites to the least possible, but this has immense promise for India.

A unique collaborative interdisciplinary program was started in 2015 to study preterm birth - a major global public health problem with significant immediate and long-term implications in low- and middle-income countries. This ongoing large cohort of pregnant women from early pregnancy is the only such cohort in India that uses an interdisciplinary approach to discover ways to predict preterm birth. The study has enrolled 4146 women, out of which information on 2768 delivery outcomes has been gathered. The 14% preterm birth is very high compared to global rates, both emphasizing the magnitude of the problem and indicating that there will be sufficient cases of pre-term and term delivery for robust testing.

The research on interventions for sepsis in young children continues with the evaluation of the role of zinc as an addition to standard antibiotic therapy. A multi-country (India and Nepal), multi-center (6 hospitals) clinical trial was initiated in 2017 and a total of 758 infants across the 6 sites have been enrolled in the last year. The research team proposes to complete the enrolments by August 2020.

In the past year, 78 peer-reviewed papers were published in national and international journals and 8 patents were filed. The scientific fraternity had shown enthusiastic participation in many national and international conferences and symposia held across the globe where their research has won recognition and fetched awards. The collaborations with industry, academia, and hospitals have been increasing.

A training and clinical development agency forms an integral part of the clinical research ecosystem at the institute. The Clinical Services Development Agency, an extramural unit of THSTI, is working to build capacity

and capability for clinical studies. The highlight of the year was marked by deepened collaboration with ICMR in multiple areas of focus, including the development and testing of common ethics forms, discussion meetings on controlled human infection models and support of the Clinical Trials Registry of India.

Research infrastructure at the institute has grown over the last year. Progress on this front includes the establishment of a bioassay laboratory with the objective of becoming a nodal laboratory, initially for testing clinical specimens from vaccine studies. A biobank that houses processed bio-specimens from humans was established in 2016. Over the last year, the biorepository has been expanded to cover an area of 2766 sq. feet with an increase in its capacity to store ~14 lakh bio-specimens. The biorepository is a resource to facilitate national and international collaborations on maternal and child health. An Advanced Equipment Facility is now available to provide access to sophisticated scientific instruments for scientists from research institutes, at discounted costs. Presently, 16 high-end instruments form the facility. The process for upgrading the animal house facility in the campus to meet international standards has been initiated.

Academic research training at THSTI offers doctoral, post-doctoral and short-term training programs. In the reporting period, 17 and 8 researchers joined the doctoral and post-doctoral programs, respectively. 10 undergraduate students were trained under the short-term program which caters to external students seeking to complete their Bachelor's or Master's thesis at a research laboratory in THSTI.

The institute organized several meetings and workshops throughout the year, independently or in collaboration with other organizations. Key meetings, symposia, and workshops included the:

- First Annual Asia-Pacific Meeting on Rotavirus and Rotavirus Vaccines (with the World Health Organization South-East Asia Regional Office)
- International Chikungunya Vaccine meeting (with the Coalition for Epidemic Preparedness Innovations)
- Indo-US Vaccine Action Program on dengue (for Department of Biotechnology)
- 5th Global Forum on TB vaccines (with AERAS)
- India-EMBO Symposium on RNA viruses (supported by the Wellcome Trust-DBT India Alliance)
- Indo-US Workshop on Genomics and Bioinformatics to explore human microbial ecology in health and diseases (with National Institute of Allergy and Infectious Diseases, NIH)
- Cardiovascular Research Convergence (with All India Institute of Medical Sciences)
- Liquid Biopsy in Precision Medicine meeting (supported by the Wellcome Trust-DBT India Alliance)
- Lecture and Workshop series on big data science and its management, and education outreach efforts using research as a tool (with the National Institute of Immunology)

THSTI has the capability and capacity to go beyond discovery research to translation, as we have demonstrated in the past year, and we will continue to strive to serve society through science.

From the Executive Director's Desk

The Translational Health Science and Technology Institute is located within the National Capital Region Biotech Science Cluster (NCR-BSC), and in the past year in addition to the many activities of THSTI itself, we have begun to think about how best to leverage the strengths of the institutions that make up the Cluster and other institutions in the NCR Region. In order to do this, it has been critical to examine progress so far in order to build pathways for the future.

In the past year, through processes of consultation, review and discussion at THSTI, in the NCR-BSC and with DBT, we have attempted to define the areas of promise for research at THSTI. The focus on vaccines, infectious diseases and immunology will continue. A bioassay laboratory for providing the clinical testing that is needed to support vaccine trials has been established. In tuberculosis, we are exploring larger collaborative programs with other groups in the NCR and beyond. In immunology, we have restructured the training, and intend to focus on developing depth in human immunology. With the strengths developed by the HIV Vaccine Translational Research programme, we are well positioned to develop more detailed B- and T-cell immunology. These studies will all require more clinical links and collaboration and will be a focus for the coming year.

The maternal and child health studies are going well, and it is increasingly recognized that these ambitious programmes, which are now at the stage of having begun to measure outcomes, will serve as a resource for investigation of disease biology for multi-disciplinary researchers now and in the future. The pregnancy and pre-term cohort study encounters challenges every day, with the need for constant monitoring and trouble-shooting to ensure that the clinical sites continue to function optimally, and the team led by Shinjini Bhatnagar has been committed and diligent in its efforts. A key resource that has been established through this study is the data, sample and image repository, which has real-time monitoring of sample and data quality. Early data that has begun to emerge from the cohort demonstrate the value of DBT's investment in large, long-term programme. The pediatric biology and maternal and child health programmes have demonstrated that world class clinical and laboratory infrastructure can be established in India to address questions that are important and relevant for our women and children. For small institutions such as THSTI, the limited number of faculty and scientists mean that inter-institutional programs and collaborations are a necessity, and this approach has been fully supported by DBT, which encourages and supports the partnerships that have led to the building and strengthening of science at

THSTI, with institutions in the NCR-BSC and other parts of India.

The study of the microbiome in health and disease over the past five years would also not have happened without partnerships. In addition to existing links, over the past year, we established a new collaboration in microbiome research which will build strengths in this area. With support from the Indo-US Vaccine Action Program, we will be further studying the vaginal microbiome from the pre-term birth study, as well as investigating the mechanisms of antimicrobial resistance. This is an area with opportunities for translation, but a long-term approach to building a translational program around the human microbiome requires resource on scale, so we will need to consider how best this can be achieved.

In diagnostics, the technology platforms have been built over the past five years and we will move from the proof-of-concept stage to testing of clinical samples. These efforts require sample access and building of collaborations for third-party testing, which have been initiated. The focus on blood borne viruses, acute febrile illnesses, typhoid and tuberculosis continue, but we have now also initiated a program on snake bite, which is a major, but under-recognised problem in India.

In the drug discovery and metabolism research group, this has been a year of change which ended with Madhu Dikshit joining as National Chair. A consolidation of research areas was necessary, and a new strategy has been evolved with a more limited but deeper research agenda, focusing on non-alcoholic fatty liver disease, better industry relationships and a service and collaboration model where the resources available at THSTI are made broadly available within and outside the institution. The utility of such an approach is evidenced by the emphasis on intra-mural research collaborations, which has resulted in multiple projects that would not otherwise have been feasible.

The broad recognition of the unique contributions of the Clinical Development Service Agency to the clinical research ecosystem in India, has been a welcome development, and both training programmes and contributions to research studies in many areas have expanded. Extramural funding allowed us to bring in senior outstanding scientists who are strengthening clinical research capacity as well as training. The last year saw collaboration with the Indian Council for Medical Research deepen, with multiple areas of focus, including the development and testing of common ethics forms, discussion meetings on controlled human infection models and support of the Clinical Trials Registry of India. In the past year, we significantly expanded our national and international meeting and training agenda, with support from multiple agencies, which permits more engagement and collaboration with extramural scientists.

THSTI tries to differentiate itself by being aimed beyond discovery research, but also has the potential to be a catalyst for other institutions that have a translational mission. It has enthusiastic, well-trained interdisciplinary young faculty who have a spectrum of scientific strengths that bridges clinical, basic and applied sciences. The Annual Report, organized by themes, demonstrates the capacity and achievements of our scientists in discovery science, early and late translation. In partnership with DBT and other agencies of government, academia and industry, we will continue to leverage our understanding of human and population biology for discovery and development for new and improved diagnostics, preventive strategies and therapies for human health.

Gagandeep Kang
Executive Director

RESEARCH ON INFECTIOUS DISEASES

TUBERCULOSIS

FLAVIVIRUS INFECTIONS

- *DENGUE*
- *JAPANESE ENCEPHALITIS*

VIRAL HEPATITIS

ACQUIRED IMMUNODEFICIENCY SYNDROME

ANTIMICROBIAL RESISTANCE IN BACTERIA

DIAGNOSTICS FOR INFECTIOUS DISEASES

Tuberculosis

Tuberculosis (TB), caused by *Mycobacterium tuberculosis (Mtb)*, is an enormous health burden in developing countries. The World Health Organization (WHO) currently estimates that there are approximately 2 million deaths and 9 million new infections with *Mtb* every year and 1.8 billion people are latently infected. Moreover, there has been a constant increase in the number of drug-resistant TB cases over the past few years. The Govt. of India targets to eliminate TB by 2025. This calls for intensified research and interventions to contain the infection and spread of TB. In view of this, the TB research program at THSTI is designed to understand TB pathogenesis, emergence of the persisters, identification of drug targets and development of novel vaccines against TB.

Understanding the molecular mechanisms of *Mtb* virulence and disease pathogenesis

- **Host-pathogen interactions upon infection by *Mtb***
- **Characterization of essential metabolic pathways in *Mtb***

Dr. Nisheeth Agarwal

Dr. Nisheeth Agarwal's research is focussed on **understanding the pathogenesis of TB, emergence of drug resistance in the bacterium, and identification of novel anti-TB therapeutic targets**. Primarily, his team is analyzing the effect of mycobacterial infection on the host proteome profile and its impact on the intracellular survival of the *Mycobacterium*. They have characterized a new role of the host inflammasome pathway in the intracellular survival of *M. bovis* BCG. They have shown that host macrophages lacking the expression of a gene involved in inflammasome complex formation have altered phago-lysosome formation and intracellular killing of mycobacteria (Figure 1). The capacity of *Mtb* to enter a dormant state leading to latent infection is the key to its survival inside the host, thus delaying the efficacy of currently available therapies.

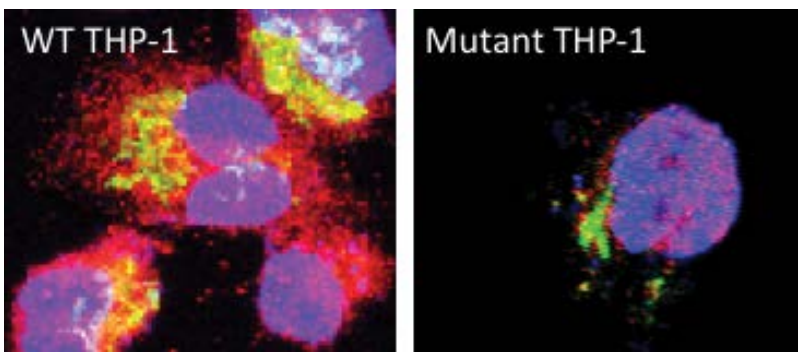


Figure1: Fusion of GFP-expressing *M.bovis* BCG phagosomes (green) with lysosome (red) in wild-type (WT) and mutant THP-1 lacking the expression of inflammasome (mutant). As can be seen, there is more co-localization of bacterial phagosomes with lysosomes in WT cells than in mutant.

Dr. Ramandeep Singh's research group is working towards the **identification of the metabolic pathways that enable *Mtb* to persist in the host**. The research group is focused on characterizing toxin-antitoxin (TA) systems, inorganic polyphosphate metabolic pathways, transcription factors and reductive tricarboxylic acid pathways in *Mtb*.

Mtb genome encodes 88 putative TA systems that are considered to be associated with either bacterial genome stability or its adaptation to the unfavorable environment.

The majority of TA systems belong to the Virulence associated protein B and C (VapBC) family. In order to investigate the potential regulatory interplay between the type II TA systems, they have studied the effect of ectopic expression of "active" toxin on the transcript levels of the chromosome copy of "active" toxins in *Mtb*. They observe that over expression of various VapC toxins results in transactivation of non-cognate toxins such as *vapC15*, *higB1* and *mazF6* (Figure 2a). Their results demonstrate that transcriptional cross-activation exists between TA systems of *Mtb*. Further, qPCR analysis has revealed that a subset of VapC toxins is differentially expressed upon exposure to stress conditions such as nitrosative or nutritional or low oxygen conditions (Figure 2b). These observations are in agreement with the previous findings that exposure to different stress conditions results in the induction of multiple ribonucleases in *Mtb.* They have shown that these TA systems are individually redundant upon exposure of *Mtb* to stress conditions or drugs. However, these toxins are essential for *Mtb* to establish infection *in vivo*. They observe that *ΔvapBC3* and *ΔvapBC4* are attenuated for growth by 100.0 fold and 1000.0 fold, respectively, in lungs and spleens of infected guinea pigs at 8 weeks post-infection. In agreement with lung bacillary loads, the gross pathology in lung sections from *ΔvapBC3*- and *ΔvapBC4*-infected guinea pigs was significantly reduced in comparison to lung sections from wild type-infected guinea pigs (Figure 3a). Taken together, these findings suggest a signaling and biochemical process that results in specific activation of VapBC3 and VapBC4 TA systems. The current hypothesis being tested in the laboratory is that overexpression of toxins results in reduced protein synthesis, which in turn would lead to protease dependent cleavage of antitoxins. This might lead to transcriptional de-repression and induction of non-selective TA systems. Therefore, it is tempting to speculate that functional and regulatory crosstalk between non-cognate TA systems provides *Mtb* the capability to adapt to ever-changing host environment (Figure 3b). In collaboration with Dr. Krishan Gopal at IMTech, they have also

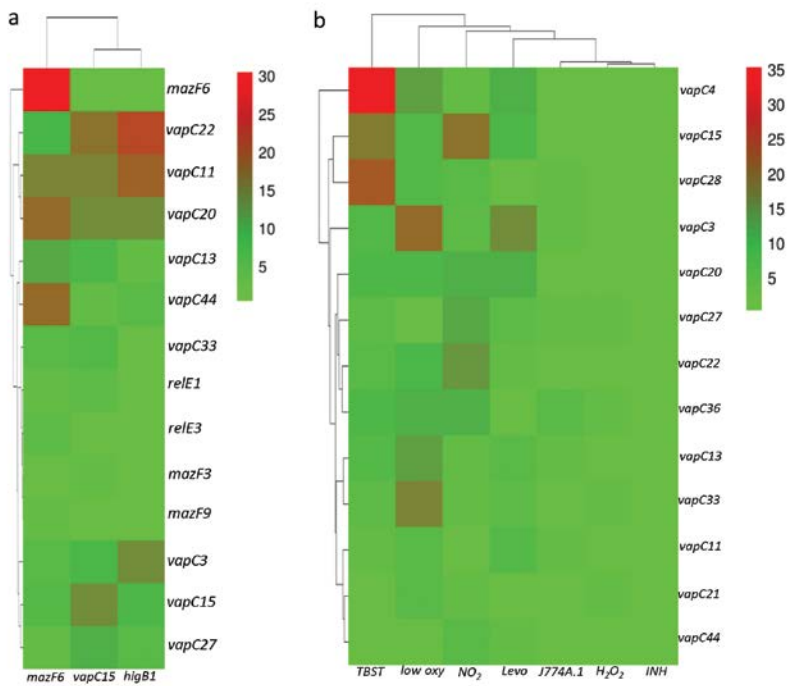


Figure 2: (a) qPCR studies to measure the transcript levels of chromosome encoded *mazF6*, *vapC15* and *higB1* in various overexpression strains. (b) Expression analysis to measure transcript levels of *vapC* toxins *in vitro* upon exposure to different stress conditions such as nutritional (TBST), hypoxia (low oxy), nitrosative (NO_2), oxidative (H_2O_2), drugs (Levo, INH) and macrophages (J774A.1).

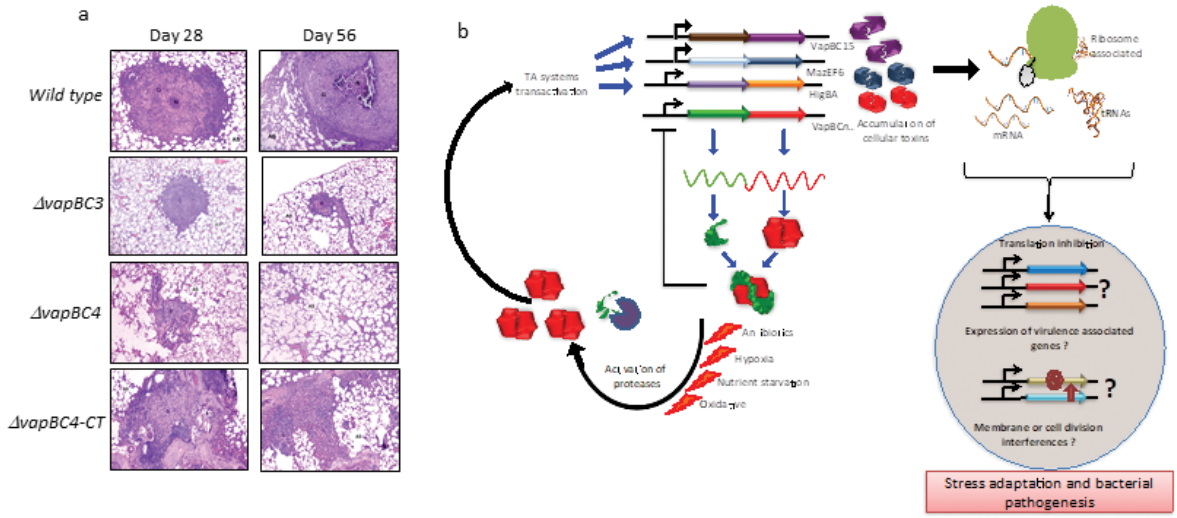


Figure 3: (a) **VapBC3 and VapBC4 are important to establish infection in guinea pigs.** This panel depicts 40X photomicrographs of haematoxylin and eosin stained lung sections from guinea pigs infected with various strains and euthanized at 4 weeks and 8 weeks post-infection.

(b) **The proposed model for regulation of TA systems from *Mtb*.** The genome of *Mtb* harbors multiple TA systems and these are differentially induced in stress conditions. In normal growth conditions, TA complexes act as repressor and negatively regulates the transcription in a feedback manner. In stress conditions, proteolytic cleavage of antitoxins results in accumulation of free toxin. The presence of free toxin results in cross-activation of non-cognate toxins such as VapC15, HigB1 and MazF6 in a direct or indirect manner. This accumulation of free toxins results in reprogramming of the transcription machinery that leads to morphological changes and establishment of the disease in animals.

solved the three dimensional structures for few of these toxins either alone or in complex with their cognate antitoxin. Future experiments would focus on understanding the mechanisms by which these TA systems contribute to virulence *in vivo*.

Dr. Amit Pandey

Dr. Amit Pandey's laboratory has been working on the hypothesis that **inhibiting dormancy or altering the metabolic state of dormant *Mtb* could increase the effectiveness of antibiotics and shorten the treatment duration**. They speculate that the differentially regulated critical metabolic pathways, triggered by the intracellular nutrient availability and requirements, contribute significantly towards the generation of *Mtb* persisters. They have earlier demonstrated that cholesterol metabolism is very critical for *Mtb* persistence and *Mtb* could metabolize and survive on media containing cholesterol as the sole carbon source. This would require *Mtb* to actively modulate the host biosynthetic machinery for the generation of nutrients required for its survival. By utilizing genetic and high dimensional informatics approaches, they have successfully identified nutrient specific pathways critical for generation of persister mycobacteria (Figure 4). These efforts could lead to 1) better understanding of host-pathogen symbiosis and 2) designing of novel intervention strategies targeting persisters. In future, they aim to identify *Mtb* proteins that could potentially be targeted to prevent the generation of persister population during TB infection and validate those in an animal model-Guinea pig model of *Mtb* persistence.

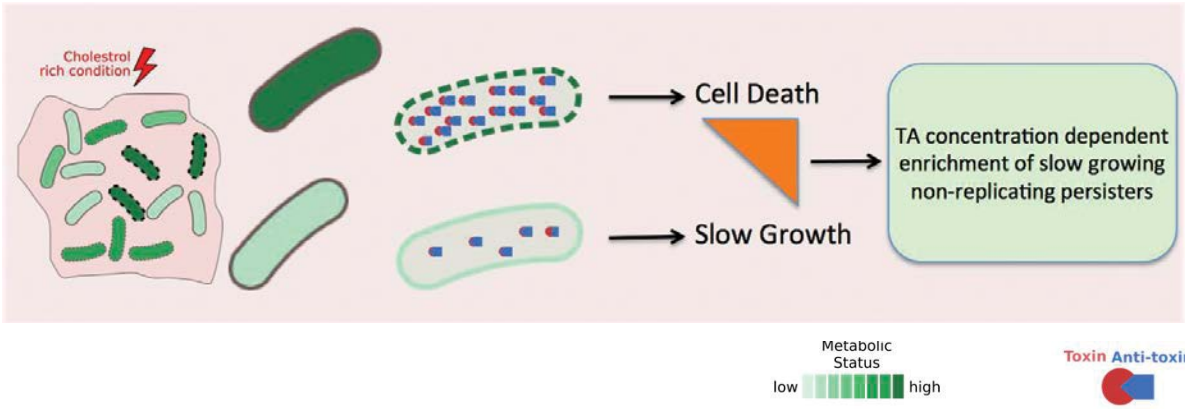


Figure 4: Model representation depicting Toxin-Antitoxin mediated regulation of cholesterol-mediated persistence in mycobacteria.

Identification and screening of drugs and small molecule inhibitors

Dr. Ramandeep Singh

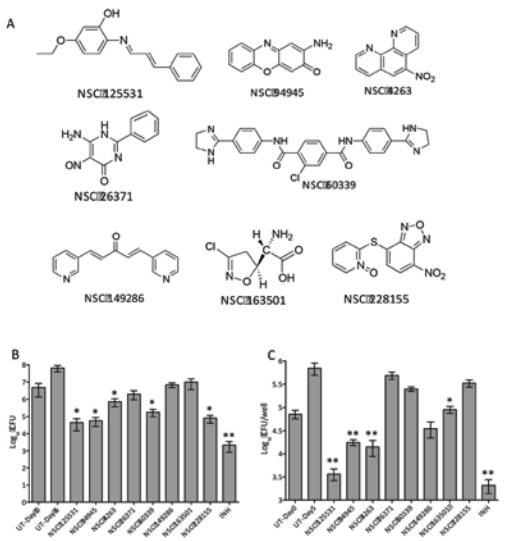


Figure 5: (a) Chemical structures of few of the primary hits identified from phenotypic screening. (b-c) Antimycobacterial activity of identified hits in liquid cultures (b) and THP-1 macrophages (c).

New chemotherapeutics agents with novel mechanisms of action are urgently required to combat the challenge imposed by the emergence of drug-resistant mycobacteria. **Dr. Ramandeep Singh**'s group **utilizes *M. bovis* BCG as host to identify small molecule inhibitors against *Mtb***. They have screened a small molecule library of 2300 compounds and identified few scaffolds that are non-cytotoxic and possess *in vitro* killing activity (Figure 5a). In their *in vitro* growth inhibition experiments, they observe that exposure of *M. bovis* BCG to these scaffolds results in 10.0–100.0 fold reduction in bacterial counts in comparison to the untreated cultures (Figure 5b). Among these, exposure to either NSC 125531 or NSC 94945 or NSC 4263 inhibits the growth of intracellular *Mtb* (Figure 5c). These scaffolds are also able to inhibit the growth of drug-resistant strains of *Mtb*. Using reverse genetics approach, they observe that NSC-4263 (5-Nitro, 1,10-phenanthroline, 5NP) is activated in a F_{420} dependent manner, a mechanism similar to PA-824, the bicyclic nitroimidazole that is currently in clinical trial. In collaboration with Dr. ILL-Young Lee, they have also synthesized various analogs of the hit compound, 5NP. The synthesized lead compound, 5NP displays a MIC_{99} value of 0.78 µM in the phenotypic whole cell-based assays. Using structure-activity relationship studies, they show that nitro group is essential for the activity of lead compound. The 5NP derivative with ethyl substitution at R2 position possesses a MIC of 0.195 µM against both *M. bovis* BCG and *Mtb* (Figure 6a). This derivative is also able to clear the growth of intracellular *Mtb* in a murine model of infection. In addition to the inhibition of lipid biosynthesis in bacteria, this series of compounds

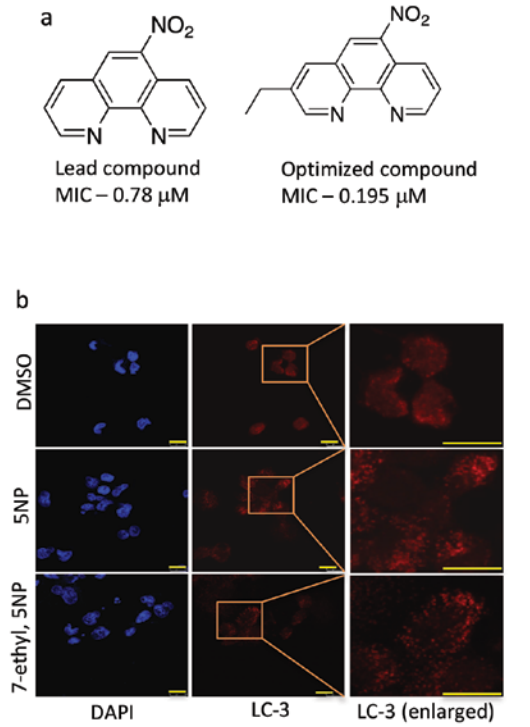


Figure 6: (a) Chemical structures of the the optimized compound (5 NP) and most active compounds 3-ethyl-6-nitro-1,10-phenanthroline (optimized compounds) (b) 5NP or its structural analog pre-treatment increases LC3 puncta formation in THP-1 macrophages. THP-1 macrophages were differentiated and treated with 25 mM of either 5NP or 7 ethyl, 5NP for 24 hours. LC3 puncta formation was visualized by staining with anti-LC3 using confocal microscopy. Scale bar 10 µm.

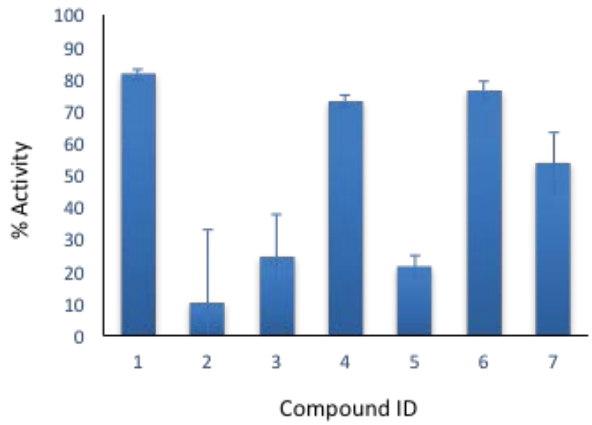


Figure 7: Effect of select small molecule inhibitors on AT Pase activity of ClpC1.

induces autophagy resulting in killing of intracellular bacteria (Figure 6b). In addition to 5NP, they have identified other compounds such as Calcimycin capable of inducing autophagy and inhibiting the growth of intracellular drug-sensitive *Mtb* in THP-1 macrophages. Experiments are in progress to evaluate the activity of the identified small molecules in combination with the known TB drugs such as isoniazid and rifampin.

Dr. Nisheeth Agarwal's team is characterizing the ***in vivo* functioning of DNA gyrase in *Mtb***. Previously, it has been shown that downregulation of DNA gyrase results in accumulation of lipid bodies: a hallmark of persister. His group has identified that genetic suppression of DNA gyrase in *Mtb* affects phenotypic tolerance and subsequent genetic resistance to clinical drugs such as rifampin and isoniazid which is partly attributed to DNA damage response mediated by the poor gyrase activity. Currently, his group is working to identify new molecules to overcome this effect and analyze the rate of emergence of drug-resistant mycobacteria.

The research group is focused to understand the mechanism of proteostasis with an emphasis on the role of bacterial Clp proteases. They have shown that these proteases are activated by selective degradation. They are identifying the **potential substrates of Clp machinery and standardizing conditions to achieve the *in vitro* degradation of substrate proteins so that an *in vitro* assay for screening of small molecule inhibitors can be set up**. In collaboration with Dr. Ramandeep Singh, they have performed a preliminary screen to assess the inhibition of ClpC1 ATPase activity *in vitro*. Interestingly, out of ~200 molecules screened, 3 molecules (#2, 3 and 5) consistently inhibit ClpC1 by >50% (Figure 7). Attempts are on to determine their Minimum Inhibitory Concentration (MIC) *in vitro* as well as in animals.

Development of aptamer-based mycobacterial inhibitors

Dr. Tarun Sharma

Dr. Tarun Sharma's group has **developed aptamer-based inhibitors for *Mtb*** aimed at working effectively against drug-susceptible and drug-resistant bacteria alike. Previous studies have shown that *Mtb* HupB protein is an attractive target to develop inhibitors since inhibition of HupB impedes the entry as well as survival of this pathogen within the host. Dr. Sharma's team has generated a panel of novel DNA aptamers that specifically target full length HupB protein of *Mtb*. The aptamers have been characterized using analytical and biophysical approaches along with post-SELEX optimizations. Two aptamers, HupB-4T and HupB-13T spontaneously bind to HupB protein at 2 sites each and inhibit several critical aspects of HupB activity. HupB-4T aptamer significantly inhibits the DNA-binding ability of HupB protein *in vitro*. Both HupB-4T and HupB-13T aptamers bind to native HupB protein

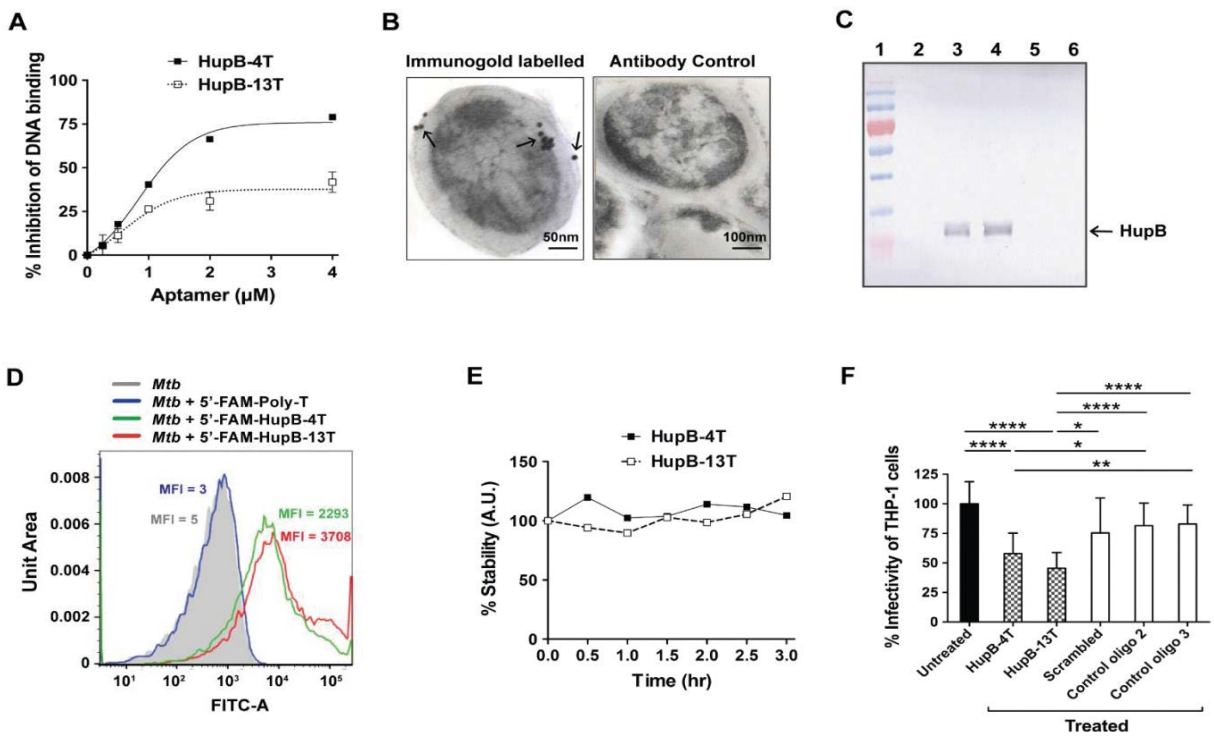


Figure 8: Aptamers HupB-4T and HupB-13T inhibit critical functions of HupB protein. (A) HupB protein binding to 5'-Biotinylated 278bp dsDNA in the absence and presence of varying concentrations of HupB-4T and HupB-13T aptamers assessed by ALISA. (B) Electron micrographs depicting cell-wall localization of the HupB protein in ultra-thin (50nm) sections of Mtb, treated with anti-HupB murine sera followed by anti-mouse gold conjugate. (Magnification X80,000 for antibody control and X150,000 for Immunogold labeled; arrow indicates 15nm gold particles localized along the exterior and cytosolic side of the cell wall). (C) Immunoblot demonstrating presence of HupB protein in 15μg Mtb H37Rv cell wall fraction and whole cell lysate using anti-HupB MAb. Lane 1: Protein molecular weight marker; Lane 2: Culture filtrate proteins; Lane 3: Whole cell lysate; Lane 4: Cell wall fraction; Lane 5: Cell membrane fraction; Lane 6: Cytosol fraction. (D) Unit area normalized histogram overlays depicting significant increase in the Median Fluorescent Intensity (MFI) along the FITC-A channel of gated Mtb H37Rv, following incubation with 5'-FAM labeled HupB-4T (green) or HupB-13T (red) aptamers, compared to 5'-FAM-Poly-T (blue) or unstained (grey) control. (E) Stability of HupB-4T and HupB-13T aptamers in arbitrary units (A.U.) at 37°C in the presence of fetal bovine serum for upto 3 hrs assessed by Native PAGE and densitometric analysis. (F) Percentage infectivity estimated from intracellular CFU count obtained from THP-1 cells infected with Mtb H37Rv (10:1 MOI) 2 hrs post-infection, following pretreatment with HupB-4T and HupB-13T aptamers and control oligonucleotides (Scrambled, Control oligos 2 and 3) relative to untreated (100%). (*$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$).

present on the surface of *Mtb* and block its entry into THP-1 monocytic cells ($p < 0.0001$) indicating the potential to develop novel inhibitory molecules against HupB (Figure 8).

Designing vaccines against tuberculosis

As of today, the only TB vaccine in use is Bacillus Calmette Guerin (BCG) that is administered to all neonates at birth. Though it protects infants from TB meningitis, it is poorly protective against pulmonary TB in children, adolescents and adults. Therefore, there are no TB vaccines available to vaccinate healthy and/or latently infected and/or diseased children and adults.

Consequently, several groups across the world are developing and testing superior alternates to BCG. Several other groups are currently exploring novel subunit vaccine candidates for their protective value. They are made from either (a) purified *Mtb* proteins (3-4 max) embedded into liposomes, or (b) nucleic acid-based vaccines that express 2-10 *Mtb* proteins/proteins fragments. However, thus far both of these have failed in human trials.

Dr. Krishnamohan Atmakuri

In this regard, **Dr. Krishnamohan Atmakuri**'s group is **exploring the use of mycobacterial membrane vesicles (MVs) as a way to extend and boost BCG's protective ability**. Their long-term goal is to find subunit vaccines that can (i) extend BCG's protective timelines, (ii) arrest progression from latent to active TB state, and (iii) shorten the treatment course duration by acting as therapeutic vaccines especially in multidrug and/or extremely drug resistant TB patients.

The group's approaches and progress during the last year are as below:

A] Exploration of membrane vesicles of mycobacteria as a subunit vaccine candidate: They have been working towards the identification of diverse contents present in MVs of pathogenic mycobacteria and if these MVs might promote protection against future mycobacterial infections/ exposure especially when administered as vaccines in humans. While they were at it, another research group from USA reported that MVs from a virulent mycobacterial strain (primarily adopted to laboratory conditions) contain virulence molecules that promote sustenance of the pathogen (at least in mice). This would mean that MVs from such laboratory-conditioned virulent mycobacteria cannot serve as a subunit vaccine candidate. However, the question remains whether MVs from clinical isolates of pathogenic mycobacteria are protective.

In the past year, his group had set out to compare MV contents between the laboratory virulent strain and the clinical isolates (both pulmonary and extra-pulmonary mycobacteria) (Figure 9) and evaluate if MVs from clinical isolates could provide any protection. Interestingly, they found that the proteome content in MVs from clinical isolates was significantly different from that observed in MVs from laboratory virulent strain, and that of MVs enriched from extrapulmonary over the pulmonary isolates. Most importantly, they found fewer virulence proteins inside MVs from clinical isolates. They

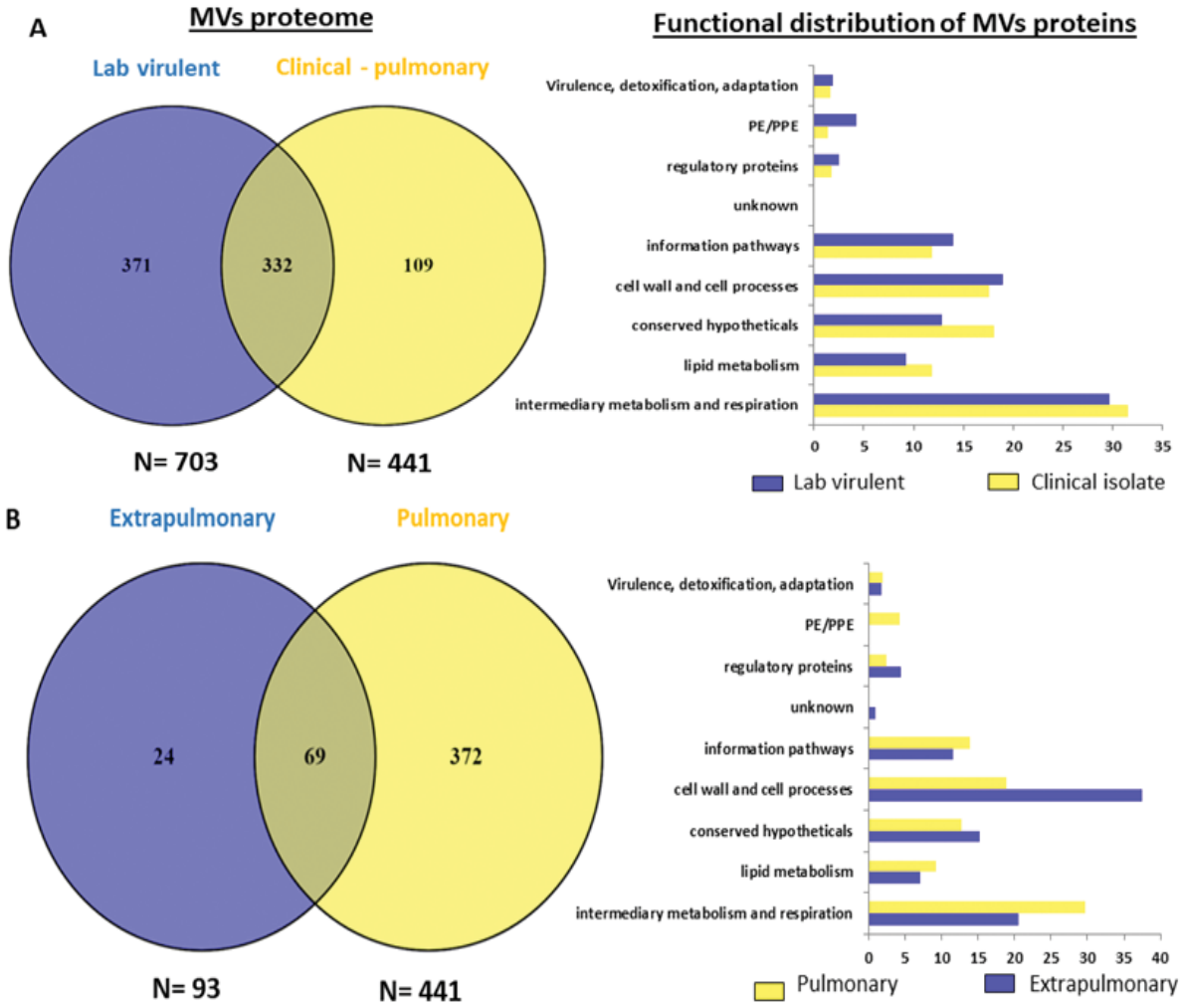
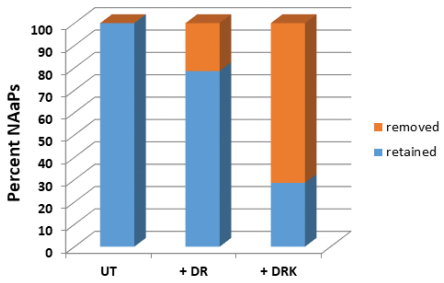


Figure 9: Comparative proteome analyses of mycobacterial MVs. MVs were enriched (as reported earlier) and their proteome identified through tandem LC-Mass Spectrometry. Comparative MV proteome analyses between A] lab virulent and clinical pulmonary isolate and B] pulmonary and extrapulmonary isolates from TB patients were performed. Proteins falling into different functional groups are represented to the right while the common and distinct proteins in each mycobacterial isolate are depicted on the left as Venn diagrams. N: number of total proteins.

speculate that since the laboratory virulent strain (H37Rv) is well conditioned for *in vitro* growth conditions (of the laboratory), perhaps it uses MVs as 'trash bags' to channel out virulent and pathogenesis-associated proteins that are no more necessary for its continued *in vitro* growth (in rich media).

Their group previously reported that while enriching for mycobacterial MVs, they constantly observed portions of mycobacterial Nucleic Acids (NAs) getting simultaneously enriched that localize not inside but outside of MVs. It turns out that ~20 to 30% of mycobacterial MV proteome that constitutes nucleic acid-associating proteins (NAaPs) often localizing only to cytoplasm, is identified because of its association with the enriching NAs (Figure 10). Interestingly, the MV proteins fall into several functional categories (Figure 10) with almost one-third of total proteins being involved in diverse respiration and intermediary metabolism functions. The role of these proteins towards TB pathogenesis is yet unknown. They will soon test

A



	NAaPs before T	NAaPs after T	NAaPs removed	%
Nonpathogenic	196	56	140	71.4
Lab attenuated	219	95	124	56.6
Lab virulent	122	34	88	72.1
Pulmonary	74	2	72	97.3
Extrapulmonary	14	3	11	78.6

B

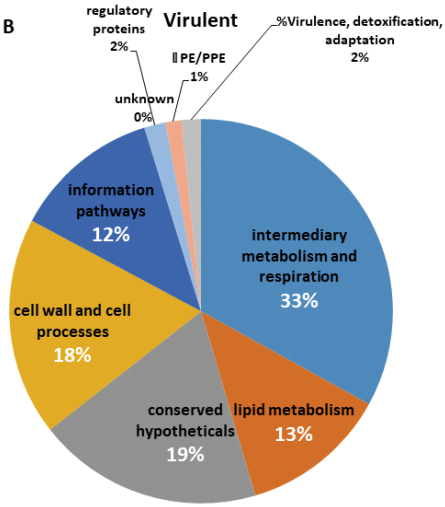
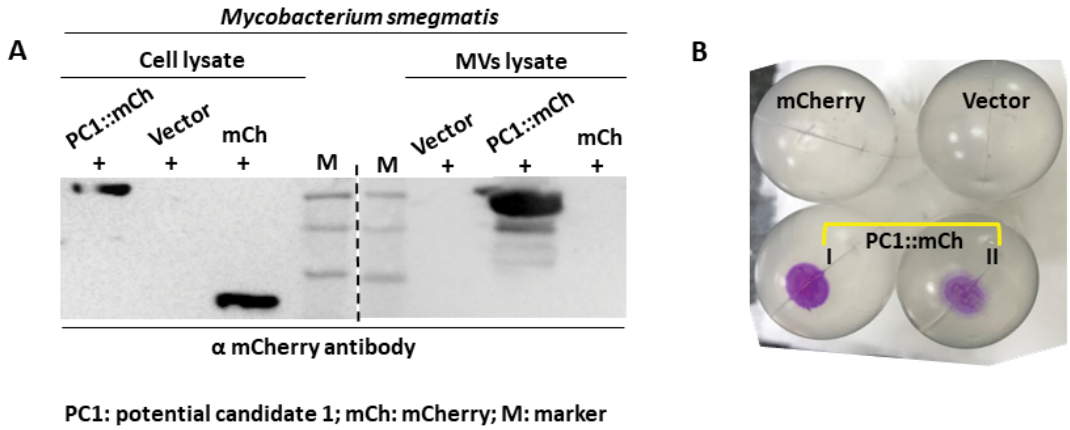


Figure 10: Treating MVs removes 80% of NAaPs: A] Nonpathogenic and pathogenic mycobacterial MVs were enriched and treated with contained amounts of nucleases and Proteinase K. B] Representative functional groups of MVs proteins from virulent mycobacteria. UT: untreated MVs; T: Treated MVs (with nucleases and Proteinase K); D: Dnase I; R:Rnase A; K: Proteinase K.

if MVs from clinical isolates of mycobacteria (from human TB patients) can stimulate immune response and promote protection against *Mtb* challenges in guinea pig model.

B] Design and development of recombinant MVs: Literature indicates that MVs from non-pathogenic (eg. *Mycobacterium smegmatis* (*Msmeg*)) mycobacteria are comparatively less immunogenic. Hence, they need to be packed with avirulent but immunogenic vaccine antigens of virulent mycobacteria for exploring their use as subunit vaccines. Thus, to generate recombinant MVs (rMVs), the research team shortlisted 50 *Msmeg* proteins that abundantly and consistently accumulate in *Msmeg* MVs. Around 20 of these proteins could tolerate a 3X FLAG tag at their N- or C-terminus and continued to accumulate into MVs of *Msmeg*. Based on their abundance of accumulation (despite-being tagged), pI and charges, the size of the proteins, and the availability of quartenary structures, the *Msmeg* MV proteins were further shortlisted to 10. Of them, randomly, they genetically fused two with a red fluorescent reporter protein at their N- and C-terminal ends and tested for their ability to accumulate in MVs of *Msmeg*. Interestingly, only one among them retained its ability to localize into MVs (Figure 11). This is the first time ever a genetic strategy has been successfully devised to generate rMVs from mycobacteria. While this is being currently prepared for patent application, the group is excited about the possibilities of engineering rMVs with various vaccine antigens and testing them in different animal models for protection against future TB infections.

C] Deciphering *Mycobacterium* artillery: It is well known that TB patients contain antibodies and T-cells against abundantly secreted pathogen proteins but still become susceptible to reinfections and resurgence. Consequently, Dr. Atmakuri's group is pursuing a hypothesis that pathogens deliver both 'decoy' and 'effector' molecules into the host environment



PC1: potential candidate 1; mCh: mCherry; M: marker

Figure 11: Construction of rMVs from nonpathogenic mycobacteria. A] Western blot depicting presence of reporter protein (mCh: mCherry) in MVs only when fused to C-terminus end of PCI, a potential candidate protein identified from Msmeg MVs. B] Image of bottom portion of ultracentrifuge tubes showing enriched MVs from different samples. Only PCI when fused at its C-terminus end with mCherry continues to localize the fusion protein to MVs. Concentrated mCherry is seen as purple (because of camera).

to subdue host cellular pathways. They speculate that some of the most abundantly secreted proteins that are good immunogens are infact decoys that deliberately divert host attention to them. In this array of decoys are hidden the less abundant, poorly immunogenic effectors that truly subvert host cellular pathways. They speculate that until the right combination of pathogen effectors/immunogens are exploited, new vaccine candidates will continue to fail expectations. To identify such decoy and effector pathogen proteins that access host macrophages, this group had reported earlier a genetically-based novel assay system developed in their laboratory to fluorescently identify secreted *Mtb* proteins that access host macrophages.

In the last year, they have made several hundreds' (~300) of gateway destination constructs and transformed some (~120) into the virulent pathogenic strain to monitor translocation of the fusion proteins into the host macrophages. They have also harvested sufficient femur and tibia from the reporter mice, and differentiated monocytes (from bone marrow) into macrophages which are currently stored in liquid nitrogen for translocation experiments. The infection experiments will soon be performed. They intend to express different combinations of decoy and effector proteins through their rMVs and test for the best possible ones that can be taken forward towards translation.

In another attempt, **Dr. Amit Pandey**'s laboratory is **exploring the potential of using a recombinant *M. bovis* BCG strain as a live attenuated vaccine against TB**. The recombinant BCG is a deletion mutant of a gene hypothesized to be involved in the down regulation of immune-dominant antigens: an essential process by which *Mtb* is able to hide form a robust host immune-surveillance mechanism. They believe increasing the antigenicity of *M. bovis* BCG might increase its efficacy against preventing TB.

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Flavivirus Infections

Flaviviruses are globally emerging and cause significant human disease in the form of encephalitis or haemorrhagic fever. The medically important flaviviruses are dengue, zika virus, yellow fever, Japanese encephalitis, St. Louis encephalitis, tick-borne encephalitis and West Nile viruses. Flaviviruses account for approximately 400 million infections annually, with billions at risk and no specific therapy available. In humans, the majority of WNV and DENV infections are subclinical, with severe illness occurring in only a subset of individuals. Disease diagnosis can be difficult as all flaviviruses are antigenically and genetically closely related. There are no effective antiviral therapies that exist for any flavivirus so the main approach to disease control is through vaccination and vector control.

Dengue

Dengue is a major public-health concern throughout tropical and sub-tropical regions of the world. The incidence of dengue has increased 30-fold over the last 50 years. Up to 50-100 million infections are now estimated to occur annually in over 100 endemic countries, putting almost half of the world's population at risk. Moreover, there is no specific treatment for dengue fever. Research at THSTI is focused on understanding the role of host factors in severe dengue development, identification of potential biomarkers for disease progression, and development of dengue diagnostic assays and therapeutics.

Understanding Dengue Pathogenesis: Role of Host Factors in Disease Progression

Dr. Arup Banerjee

Severe dengue is a potentially deadly complication due to increased vascular permeability and consequent plasma leakage, leading to circulatory collapse and shock. During severe conditions, many of the critical dengue patients have low virus titer suggesting that viral load is not an only determinant factor for disease severity. **Dr. Arup Banerjee's** research **investigates the mechanism of viral pathogenesis in *in vitro* and clinical settings through understanding the function of dysregulated non-coding RNAs and genes in inflammation and disease manifestation**.

Over the last three years, his team has been working towards understanding the basis of the development of dengue severity. They have recently completed a small-RNA sequencing analysis of 48 plasma samples obtained from different categories of dengue patients. The levels of circulating miRNAs have been analyzed in patients with uncomplicated Dengue Infection (DI; n=9), Dengue with a Warning Sign (DWS; n=14), and Severe Dengue (DS; n=16). They have also used plasma from nine dengue patients followed up at two-time points (day 0 and day 5) for small RNA sequencing.

A total of 89 microRNAs have been detected in all three groups in at least two-third of the samples. These miRNAs could target 77 genes in peripheral blood mononuclear cells (PBMCs) significantly differentially expressed

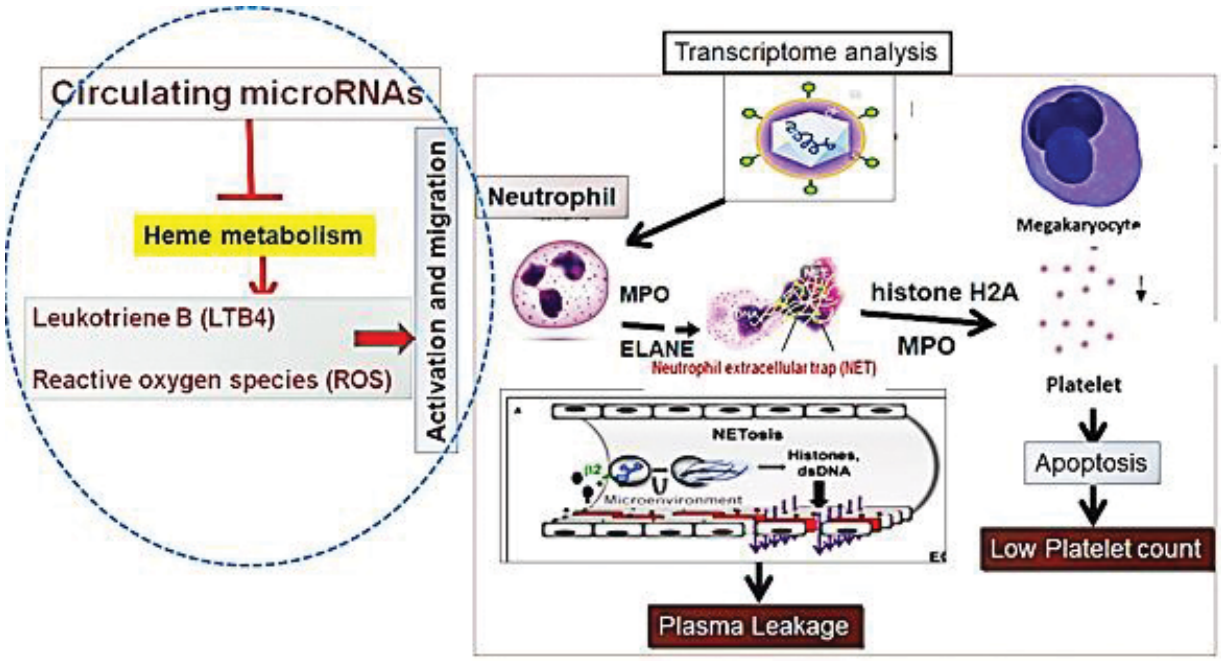

Figure 12: Schematic representation of Neutrophil activation process in the development of severity in Dengue-infected patients.

in DS cases. Through pathway enrichment analysis, they discovered that 'Hallmark Heme Metabolism' was one of the highly enriched pathways that could be affected by the dysregulated microRNAs. Altered heme metabolism can induce Leukotriene 4 (LTB4) and reactive oxygen species (ROS) that can activate neutrophil and facilitate neutrophil migration and activation (Figure 12). From the previous RNA-Seq study as well as through meta-analysis, they could identify signature genes involved in neutrophil activation and neutrophil extracellular trap (NET) formation process, a novel mechanism that may explain plasma leakage and platelet depletion events resulting in the release of histone-dsDNA in the circulation. Circulating dsDNA can activate platelets and induce apoptosis resulting in lower platelet count. Deposition of NET on the blood vessel may increase capillary damage and haemorrhagic lesions, thereby causing severe neutropenia and leading to poor prognosis. The circulating miRNA data also points towards the involvement of neutrophil activation process in the development of dengue severity. By comparing this miRNA profile with follow-up samples, they were able to identify four potential microRNAs (miR-486, miR-92, miR-26a, and miR-191) as disease progression markers. A validation of these signature microRNAs in a significant number of patients plasma samples as well as follow-up samples will provide insights into the use of microRNA level as a potential marker for dengue disease progression.

In future, the team aims to identify the immune components (subtypes of neutrophils) from the dengue-infected cohorts and understand their contribution towards the development of severe dengue complication. They are also working towards the development of a specific inhibitory molecule (peptide against NET-inducing enzymes) that could control the neutrophil activation process.

Dr. Guruprasad Medigeshi

Dr. Guruprasad Medigeshi's research group focuses on **identifying host factors that associate with severe dengue disease and play a role in dengue virus life-cycle**. They use epithelial and endothelial cells as model systems and ongoing efforts are focused on the link between zinc homeostasis, virus infection and permeability barrier functions. Dr. Medigeshi is currently running cohort studies with the Department of Pediatrics, All India Institute of Medical Sciences, New Delhi and ESIC-Faridabad to look into the role of specific subsets of blood cells and their zinc status in dengue and respiratory syncytial virus infection. The team aims to explore the role of zinc homeostasis in viral infections and identify the cellular pathways that are affected due to changes in zinc homeostasis. They hope to generate information that could be harnessed to design zinc supplementation studies for specific viral infections. In addition to these studies, the group is also characterizing viral isolates from dengue patients to gain insights into the sequence and phenotype of circulating dengue isolates. In the last year, they have identified and characterized the role of DDX3X, a DEAD-box helicase, as a dengue capsid-interacting

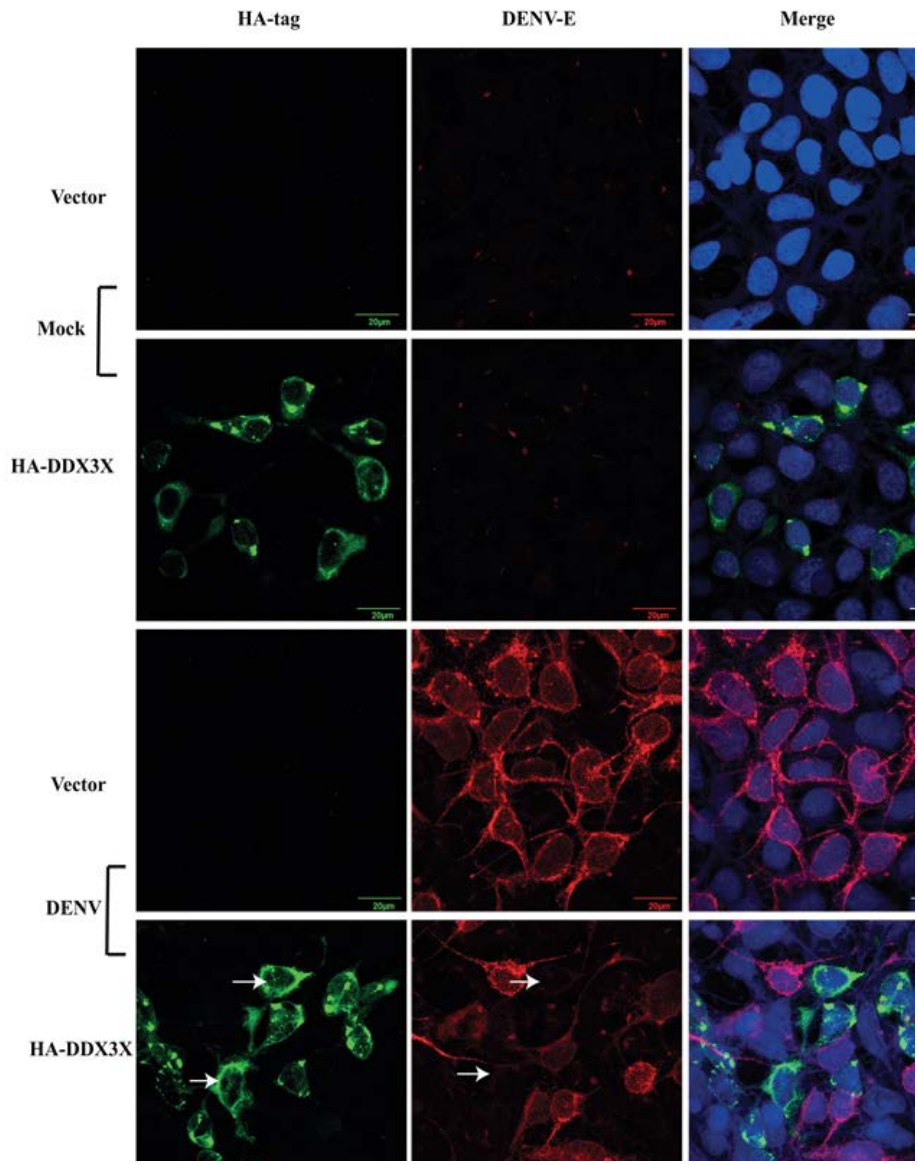

Figure 13: DDX3X over-expression suppresses dengue infection. HA-DDX3X plasmid or the vector was transfected in HEK293T cells. 24 hrs post-transfection cells were infected with DENV at a multiplicity of infection of 5 plaque forming units/cell. Cells were fixed at 24 h post-infection and stained with antibodies against dengue envelope and HA-tag followed by secondary antibodies. Nuclei were stained with DAPI. Arrows indicate absence of envelope staining in cells expressing HA-DDX3X.

partner (Figure 13). Using quantitative proteomics approaches, they have also identified plasma proteins associated with severe dengue. Their collaborative work has contributed to the generation of a serotype-specific dengue diagnostic assay.

Dr. Sankar Bhattacharyya

Dr. Sankar Bhattacharyya's group is steering efforts to **understand the tropism of dengue virus in specific cell types found in bone marrow**. Using an *in vitro* model of megakaryocyte formation, they have suggested that the replication of dengue virus is favored by differentiation of megakaryocyte progenitors. In addition, they are elucidating the cellular and molecular mechanisms of function of traditional medications available in India for management of dengue haemorrhagic fever. They hope to contribute to the discovery of either novel or repurposed drugs for use as antivirals against dengue virus. In this regard, they have preliminary evidence suggesting that a novel small molecule, discovered in collaboration with computational and synthetic chemists at THSTI, is capable of inhibiting dengue virus replication at low micromolar concentrations.

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Japanese Encephalitis

Japanese Encephalitis (JE) is a serious neurological disease characterized by extensive inflammation in the central nervous system. JE virus is the main cause of viral encephalitis in many countries of Asia with an estimated 68,000 clinical cases every year, with approximately 13,600 to 20,400 deaths. 24 countries in the WHO South-East Asia and Western Pacific regions have endemic JE virus transmission, exposing more than 3 billion people to the risk of infection.

There is no cure for the disease. At THSTI, research on JE involves:

- Identification and validation of molecular targets for development of antiviral drugs and therapies
- Development of strategies to enhance immune responses and improve vaccine efficacy

Molecular Targets for Drug Development and Vaccine Efficacy Improvement

Dr. Manjula Kalia

Virus infections such as those caused by Japanese Encephalitis and dengue viruses are transmitted by mosquito bites and are major health burdens for India with high morbidity and mortality. As no effective antivirals are available for any of these viruses, the treatment is at best supportive. Further, even though vaccines for JE exist, the numbers of JE cases and associated deaths have not decreased. The major reason for this is that the existing vaccines do not confer long-term protection and also do not provide cross-protection against other circulating highly pathogenic genotypes. **Dr. Manjula Kalia**'s research is focused upon the **identification and validation of molecular targets for development of antiviral drugs and therapies**. Her research group has identified potential druggable targets that can block JEV replication which are currently being validated and are being tested in *in vitro* primary human monocyte derived dendritic cells and in animal model of disease (Figure 14). Their research has advanced on understanding the host-pathogen interactions with a focus on cellular autophagy pathway and immune response. They are currently investigating the potential of modulating this pathway to enhance immune responses and improve vaccine efficacy.

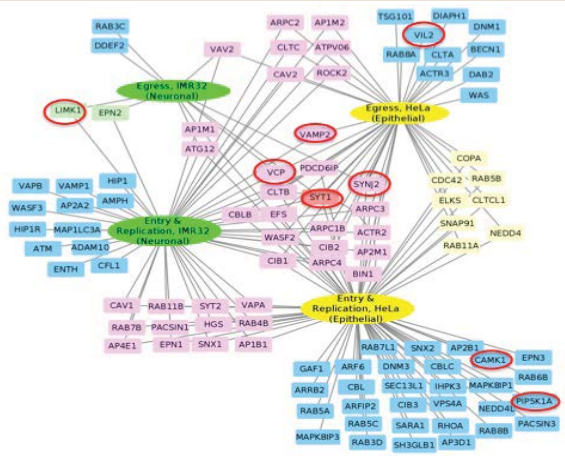

Figure 14: Molecular targets that block JEV replication.

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Viral Hepatitis

Hepatitis E is found worldwide with an estimated 20 million HEV infections annually, contributing to an estimated 3.3% mortality due to viral hepatitis. The disease prevalence is highest in East and South Asia. Prevention is the most effective approach against the disease as there is no specific treatment capable of altering the course of acute hepatitis E. Research at THSTI is pivotal to understanding multiple aspects of Hepatitis E Virus (HEV) biology in an attempt to identify and develop disease interventions.

Dr. Milan Surjit

Dr. Milan Surjit's laboratory is inclined to **generate sufficient knowledge/ resources for in depth molecular understanding of the HEV lifecycle** to facilitate (a) the development of a mouse model that mimics HEV infection in humans, (b) understanding the host-pathogen interactions involved in HEV pathogenesis, (c) understanding the mechanism of viral translation, replication and release, (d) the identification of novel anti-HEV compounds that can be used as therapeutic drugs, and (e) the development of a recombinant vaccine against HEV. They aim to employ these resources to develop efficient prophylactic and therapeutic products against the pathogen. Recently, they have generated human hepatoma cell-derived stable lines which constitutively produce infectious HEV as well as EGFP replicons of HEV. These cell culture models would be a useful tool to investigate the HEV life cycle and validate potential antivirals. In another study, they have identified the ability of zinc to block HEV replication by inhibiting the activity of viral RNA-dependent RNA polymerase. They have also identified a cyclic peptide inhibitor of HEV release. These are significant steps towards development of specific antivirals against HEV. In the near future, they not only plan to continue investigating the molecular details of HEV life cycle but also emphasize on various approaches towards the development of novel antivirals and a recombinant vaccine against HEV.

COLLABORATORS

Dr. Milan Surjit

Dr. Ranjith Kumar, Indraprastha University, New Delhi, and THSTI, Faridabad
Drs. Baibaswata Nayak and Shalimar, All India Institute of Medical Sciences, New Delhi
Dr. Manidipa Banerji, Indian Institute of Technology, New Delhi

Acquired Immunodeficieny Syndrome

The Human Immunodeficiency Virus (HIV) continues to be a major global public health issue, having claimed more than 35 million lives so far. In 2017, 940 000 people died from HIV-related causes globally. There were approximately 36.9 million people living with HIV at the end of 2017 with 1.8 million people becoming newly infected in 2017 globally. The WHO African Region is the most affected region, with 25.7 million people living with HIV in 2017. The African region also accounts for over two-thirds of the global total of new HIV infections. In India, more than 1 million people per year are infected with HIV.

HIV targets the immune system and results in increased susceptibility to a wide range of infections, cancers and other diseases that people with healthy immune systems can fight off. There is no cure for HIV infection.

Dr. Jayanta Bhattacharya

The HIV Vaccine Translational Research (HVTR) laboratory carries out early translational research and development under the joint partnership program between THSTI and the International AIDS Vaccine Initiative (IAVI) that follows the principles of a center of excellence with unique strengths towards accelerating the efforts towards development of broadly neutralizing antibodies (bnAbs) to HIV-1, and characterizing antigenic properties of HIV-1 envelope proteins (Env) for their suitability in informing immunogen design and antibody isolation.

The HVTR laboratory comprises an interdisciplinary team that possesses expertise in distinct disciplines and has been addressing its research goals through partnering with other laboratories and clinical research centres, both globally and locally. The overall goals of the THSTI-IAVI HIV Vaccine Design Program are:

1. Screening, isolation and characterization of Broadly Neutralizing Antibodies (bnAbs) from donors of Indian origin.
2. Screening, identification and selective modifications of HIV-1 Envelope (Env) antigens obtained from Indian patients towards examining their suitability for bnAb isolation and inform immunogen design.

A. Characterization of neutralizing antibody response in individuals chronically infected with HIV-1 and efforts in isolation of bnAbs from elite neutralizers of Indian origin

Investigators:
Drs. Huma Qureshi, Suprit Deshpande, Rajesh Kumar, Ranajoy Mullick, Sweety Samal, and Jayanta Bhattacharya

The HVTR laboratory has been working on understanding the neutralizing antibody response mounted in patients chronically infected with HIV-1 in absence of antiretroviral therapy (ART). This has led to the identification of rare individuals who have elicited potent and bnAb antibodies in the course of infection. With that information, their laboratory has been working to isolate bnAbs from such individuals by antigen-specific single B cell sorting. They have successfully built capacity in isolation and characterization of bnAbs from HIV-1 infected elite neutralizers in close

collaboration with their partners at the IAVI Neutralizing antibody center at The Scripps Research Institute, La Jolla, California.

Isolation of broadly neutralizing antibodies from HIV-1 Indian subtype C infected elite neutralizers

Their research focus is to isolate and characterize bnAbs from HIV-1 Indian subtype C-infected elite neutralizers using antigen specific single cell sorting strategy. Towards standardizing the technology for the isolation process, they have carried out single cell sorting of memory B cells from one known HIV -1 infected donor provided by the IAVI NAC, enrolled under the global IAVI Protocol G study. This was done in close collaboration with the NAC team under the guidance of Dr. Devin Sok at the Scripps Research Institute, La Jolla, California. Following PBMC staining, they sorted CD19+/IgG+/ antigen+ single memory B cells into 96 well plates (Figure 15). They further amplified and cloned variable heavy and light chains gene fragments into antibody expression vectors. Sequencing of variable heavy and light IgG chains data revealed closely comparable sequences to that of PGT121-PGT124 bnAbs

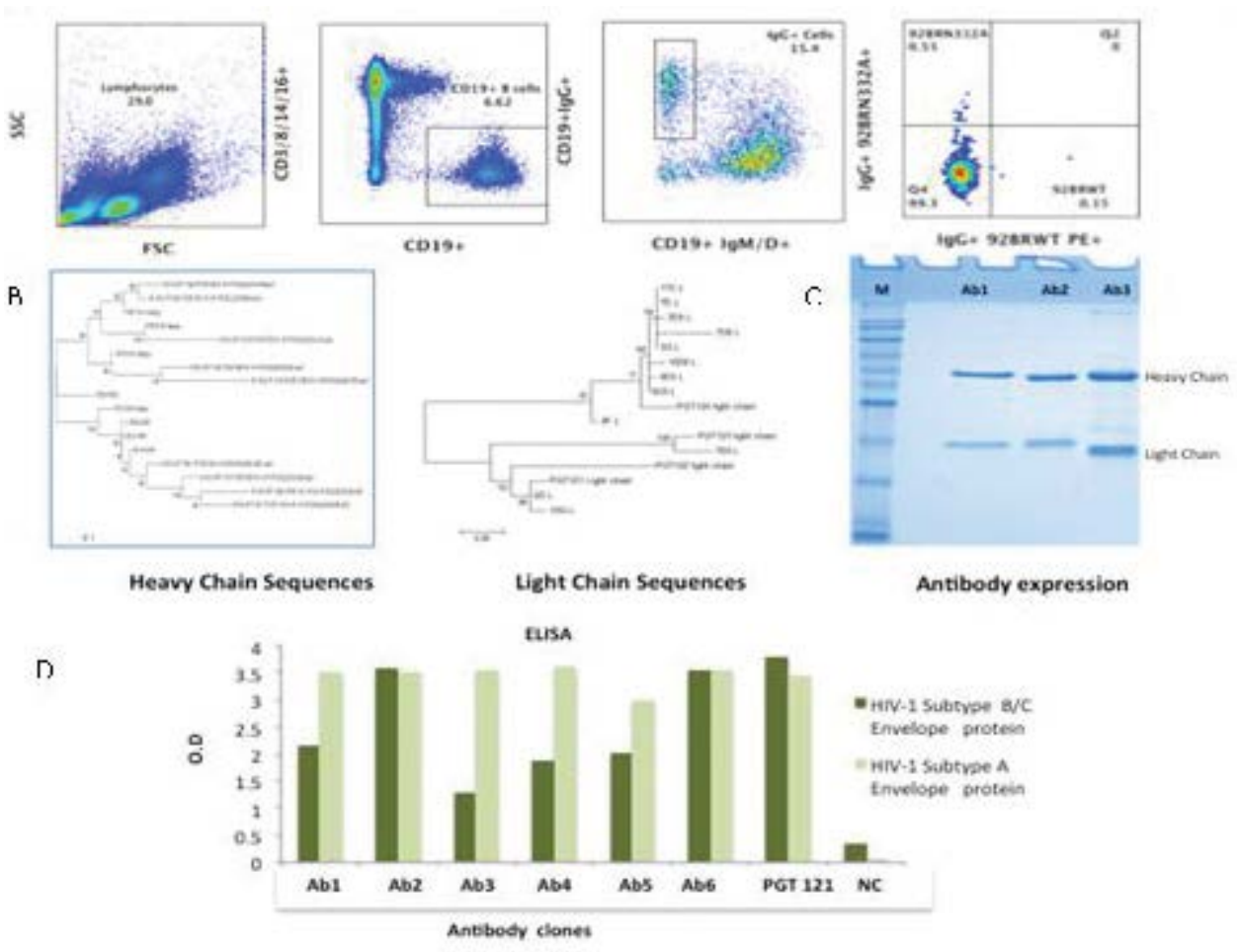

Figure 15: Isolation of monoclonal antibodies from HIV-1 infected donor using multicolor flow-cytometry platform A; Frequency of HIV-1 envelope specific memory B cells (CD19+IgG+Env+) cells, B; Phylogenetic analysis of the PGT 121-124 heavy and light chain sequences isolated from envelope specific single memory B cell from Donor 17, C; Representative SDS PAGE showing expression of IgGs, D: HIV-1 specificity of the monoclonal antibodies was confirmed by indirect ELISA using HIV-1 envelope proteins of Subtype A and B/C recombinant.

reported earlier. In addition, they obtained functional monoclonal antibody clones (bnAbs) that showed comparable genetic property and neutralization potency to that of PGT121. Through this exercise, the HVTR laboratory successfully established capacity in isolation of bnAbs from PBMCs by single B cell cloning and high throughput functional screening. Towards isolation of bnAbs from India Protocol G donors, they have substantially mapped the serum neutralizing antibody specificities through antibody depletion methodologies and, mutant virus constructs of one of the elite neutralizers and plan to initiate isolation and characterization of bnAbs from this donor during the 2018-2019 reporting period.

B. Characterization of antigenic and immunogenic properties of HIV-1 Env obtained from individuals of Indian origin

Investigators:
Drs. Supratik Das, Shubbir Ahmed, Tripti Shrivastava, Sweety Samal, Rajesh Kumar, Jayanta Bhattacharya, Bimal Chakrabarti

The HVTR laboratory has adopted a strategy to design a soluble, native-like, trimeric form of the Env that conformationally resembles the Env protein present on the viral surface as immunogen. This native-like Env trimer can also be used as antigenic bait for isolation of bnAbs from the PBMC of elite neutralizers. Given the genetic diversity of HIV Envs, a sequence-specific design and modulation of each Env is needed to create a panel of antigenic baits from different subtypes of HIV Env.

Identifying HIV-1 Envs suitable for designing immunogens

Lead Investigator: Dr. Supratik Das

The HIV-1 Env glycoprotein is the target of bNAbs which otherwise spontaneously develop in about 15-20% of HIV-1 infected patients. The team has previously used efficient cleavage property of Envs into its constituent subunits to identify Envs suitable for immunogen design. Efficient cleavage of Envs into the gp120 and gp41 subunits which then rearrange to form native Env spikes on the viral surface is correlated with specific binding to bNAbs and poor binding to non-NAbs (non-neutralizing antibodies), properties desirable in Env-based immunogens. They had previously identified efficiently cleaved Envs with desirable antigenic properties from clades A, B and C which make up about 75% of global infection. The laboratory had reported that soluble B/C recombinant protein LT5.J4b12C SOSIP shows trimeric, native-like propeller structure in Electron Microscopy (EM) studies and specifically binds to bNAbs but poorly to non-NAbs. Besides, it binds weakly to sCD4 suggesting that this Env is in its pre-fusion form. These properties are desirable towards designing an immunogen. In this reporting period, they have studied the properties of the membrane-bound form of this Env in order to investigate whether this Env can be used for DNA priming. They observe that the clade B/C recombinant, chimeric Env LT5.J4b12C is efficiently cleaved on the plasma membrane and has requisite antigenic properties on the cell surface suitable for DNA priming and also for designing immunogens to be delivered by other methods as explained above (Figure 16).

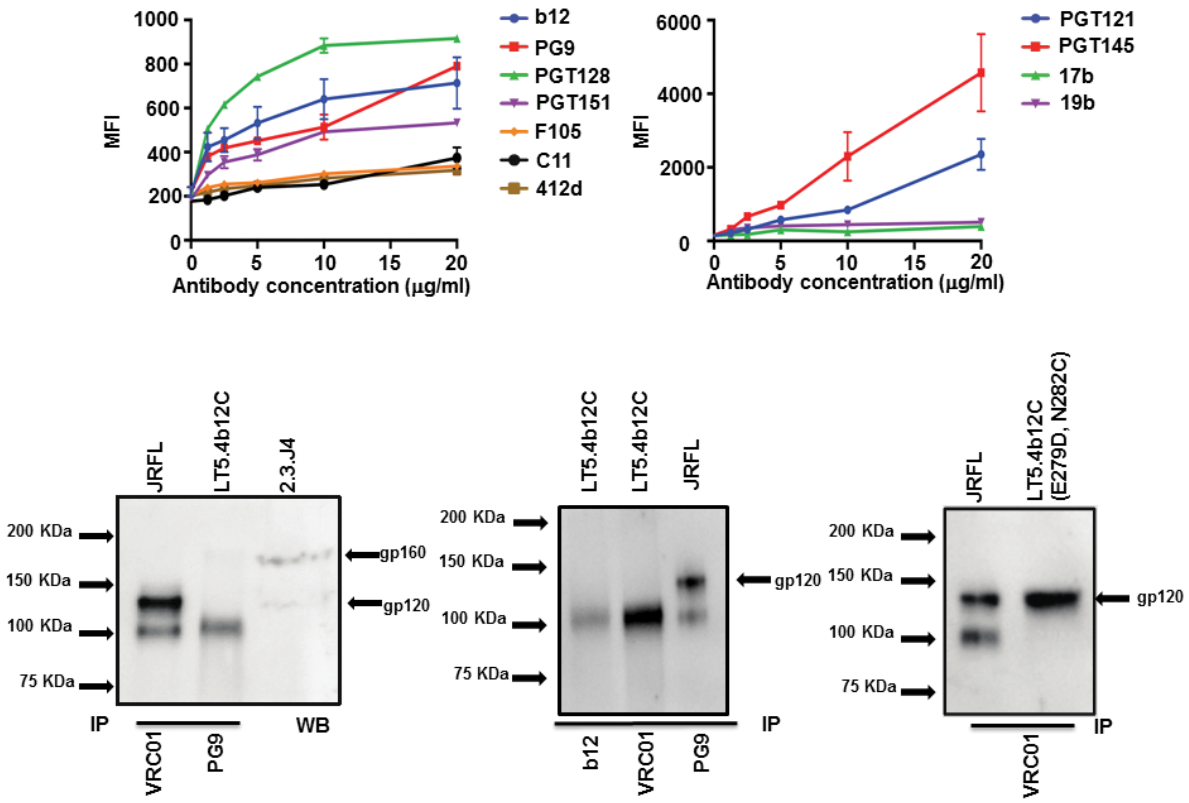

Figure 16: The chimeric, B/C recombinant Env LT5.J4b12C is efficiently cleaved and displays specifically bNAb epitopes suitable for immunogen design. Top panel: FACS-based cell surface assay of the Env LT5.J4b12C with a panel of bNAbs and non-NAbs; Bottom panel: Immunoprecipitation studies of plasma membrane fractions of JRFL, LT5.J4b12C, LT5.J4b12C (E279D, N282C) mutant with bNAbs as shown. Env 2-3.J4 western blot was used as control. Position of gp120 and gp160 bands are shown.

Designing soluble stable HIV-1 clade C Env of Indian origin towards targeting germline antibody repertoire

Lead Investigator: Dr. Shubbir Ahmed

Designing a stable, soluble, native-like, trimeric HIV-1 envelope glycoprotein (Env) is a challenging task due to high sequence diversity, heavy glycosylation and inherent meta-stability of Envs. They attempted to design novel Env to target and isolate antibodies with unique and different specificities and also as potential immunogen candidates for vaccine development. In the past year, the focus was on designing HIV Env trimer with glycan holes at potentially immunogenic locations. Recently, they have created few deglycosylated forms of the Env trimer of clade A (BG505) and Indian clade C (4-2.J41) origin to understand the impact of deglycosylation on the structural and functional integrity of Envs and its influence on their antigenicity particularly for germ line antibodies (Figure 17).

The specially designed stable, soluble, native-like trimeric Env with glycan holes at strategic locations will be used as antigenic bait to target and isolation of antibodies with unique class and specificity that may be present in clinical samples. They will also help in improved induction of the germ line B-cells due to better exposure of the immunogenic regions. Subsequent

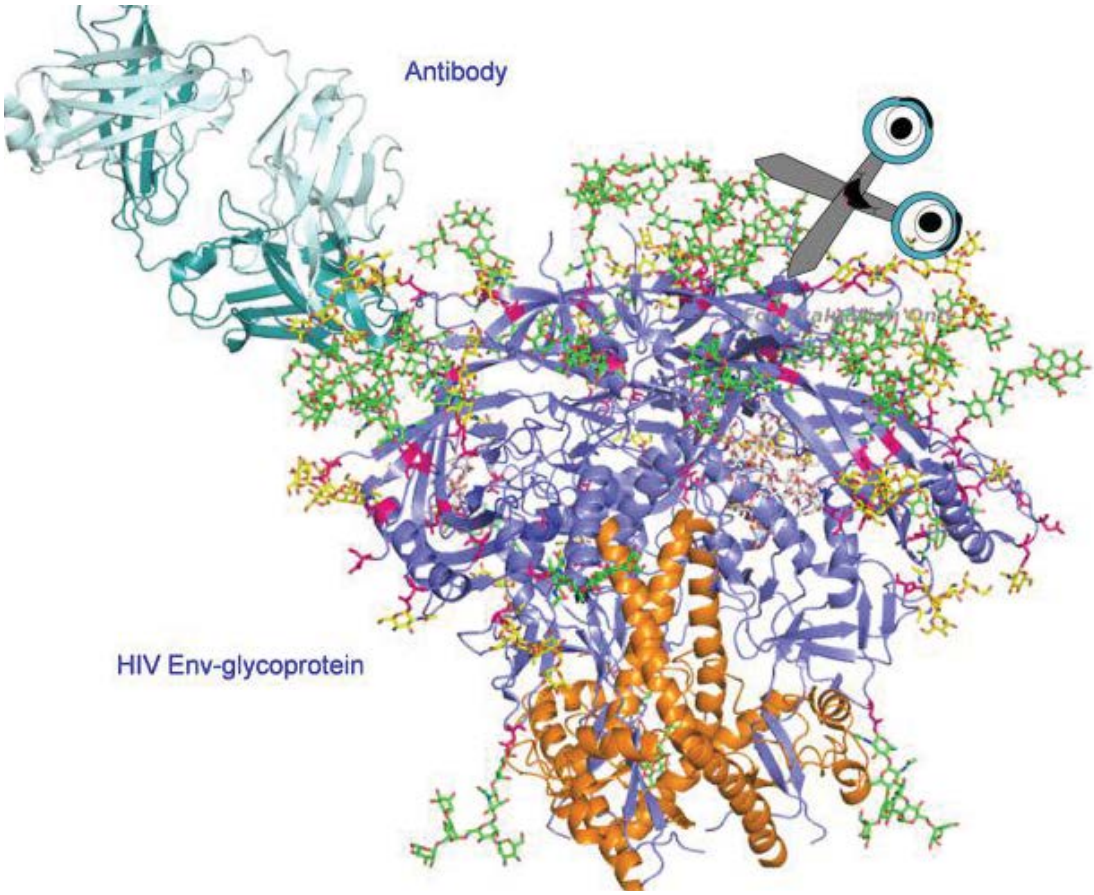

Figure 17: Assisted immuno-focusing by targeted deglycosyaltion.

immunization with wild-type (with all glycans present) Env will help in affinity maturation of induced B-cells to produce bnAbs with reasonable titre and breadth.

Designing, development and characterization of HIV-1 Envs obtained from elite neutralizers for their suitability towards informing immunogen design and use as antigen baits for bnAb isolation

Lead Investigator: Dr. Rajesh Kumar

Recently, they have shown that escape from potent autologous humoral response of circulating HIV-1 clade C in an elite neutralizer was associated with mutations in V1 loop (Patil et al, J. Virol, 2016). Towards characterization of antigenic properties of patient Env, they have prepared a stable and soluble trimeric protein of one of the autologous Env that is sensitive to its autologous plasma antibodies *i.e.* HVTR-PG80v1.eJ19-SOSIP.664 (Figure 18). 2D. Negative EM studies reveal that most of the trimers have closed native like conformation. The clade C trimeric Env protein appears to undergo minimal conformational change in the presence of CD4 compared to other SOSIP Envs when examined under the same experimental conditions. In addition, the clade C trimeric Env binds to several known bNAbs including those elicited in HIV-1 clade C-infected Indian patients with unknown specificities. However, it does not bind to V3 and CD4i-epitope directed antibodies

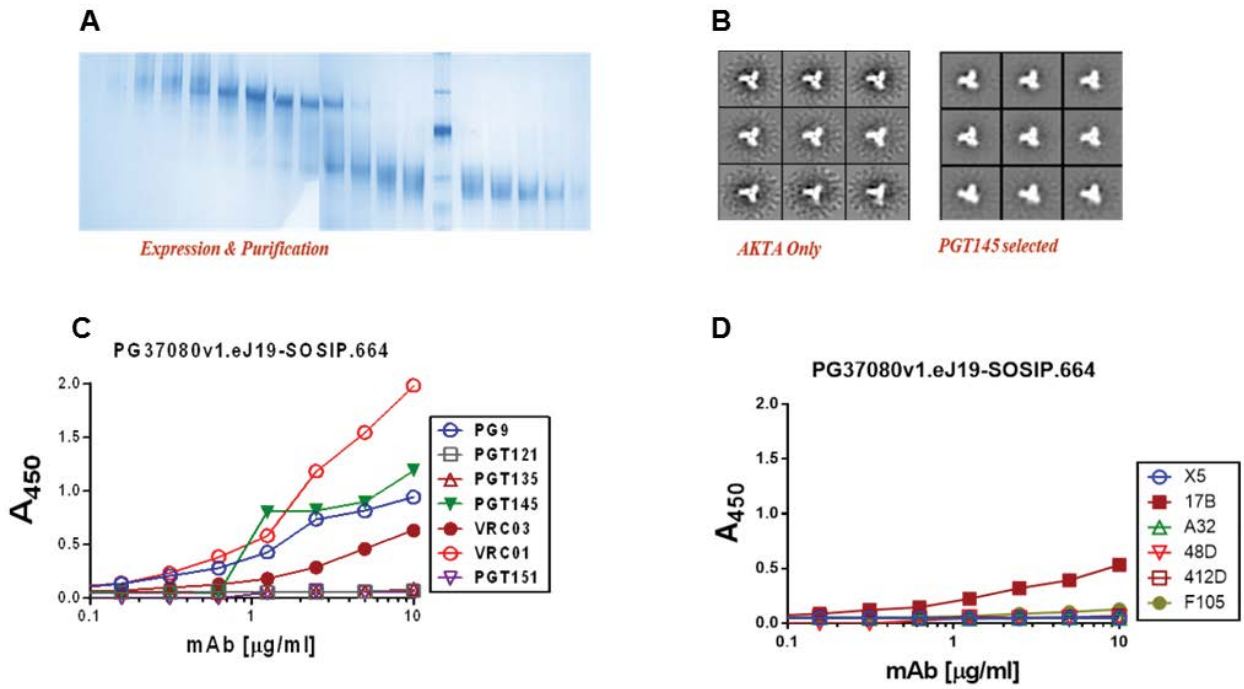

Figure 18: A) Blue native-PAGE profile of E19 SOSIP Trimer. B) 2D-Negative Stain -EM of purified trimeric Env shows presence of well-formed closed native like trimers. C) ELISA binding analysis of E19 SOSIP trimer with selected broadly neutralizing antibodies (bnAbs) & D) non-neutralizing antibodies.

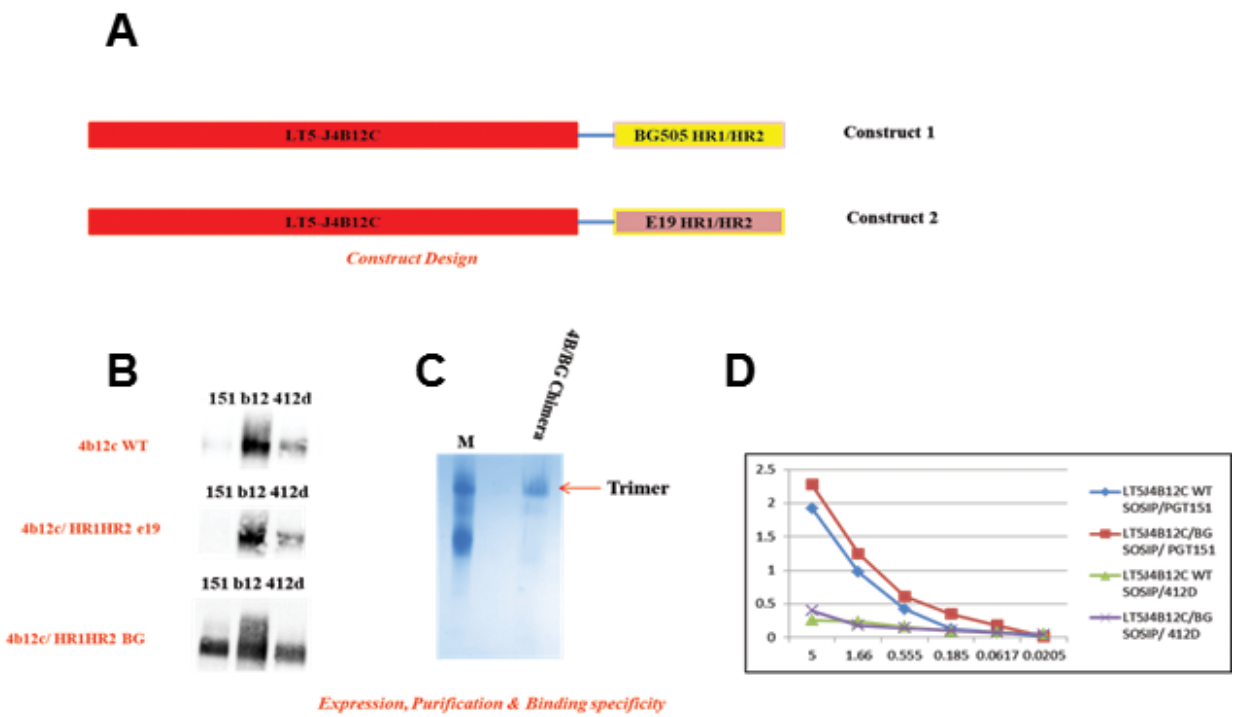

Figure19: A) Design of LT5-J4b12c Domain swap construct with gp120 (Red) of LT5-J4b12c & gp41 region from BG505 (Yellow), E19 (Brown). B) Screening of designed constructs with mAbs. The Env swapped with BG505 gp41 showed improved binding with cleavage specific antibodies in Co-IP/Western blot. C) Expression & purification of LT5-J4b12c/BG construct. D) Comparative ELISA binding analysis of wild type LT5.J4b12C & LT5-J4b12C/BG505 construct.

indicating its excellent antigenic properties. Rabbit immunogenicity study using this Env SOSIP is ongoing.

In addition to the work described above, they have also made suitable modification towards enhanced expression of a stable HIV-1 B/C recombinant Env, LT5.J4b12C SOSIP.664 that they published previously (Kumar, R et al., J Biol. Chem., 2017) essentially following the protocol established in their own laboratory (Ahmed, S et al., J Biol. Chem., 2017) without altering its native antigenic and conformational properties (Figure 19). They are currently assessing its suitability for use as antigenic bait for broadly neutralizing antibody isolation as well as its immunogenicity in rabbit model.

Understanding structure-function aspect of HIV-1 Env protein towards strategic immunogen design

Lead Investigator: Dr. Tripti Shrivastava

The envelope glycoprotein is the major target for HIV-1 bNAbs and harbors the conserved epitopes that are targeted by bNAbs. The conserved primary receptor, CD4 binding site, is the prime target for the bNAbs, however its conformational orientation and flanking N-linked glycans limit antibody access to this site. The team employed two independent approaches to address the accessibility of CD4: first, targeting a patch of conserved sequence in close proximity to CD4 binding site and using this sequence as an epitope through scaffold to elicit antibodies that can block the entry of virus through steric hindrance (previously reported ongoing research project) and second, an approach of development of an Outer Domain (OD)-based immunogen prepared via *Escherichia coli*-expression system. The OD of the gp120 is an important target for vaccine design as it contains a number of conserved epitopes including the CD4 binding site. Glycan coat, which other than acting as target site of bNAbs, also protects the virus from neutralizing antibodies. Designing of non-glycosylated HIV Env immunogen encounters enormous challenges pertaining to protein expression and aggregation. They employed a strategy of identification of exposed hydrophobic residues on the interface of outer domain-inner domain and mutated them to generate a hydrophilic surface. A SCHRODINGER-based surface analysis was done and nine identified hydrophobic amino acids were experimentally mutated to generate a hydrophilic surface. The resultant sequences were further cloned into SUMO-fusion protein-based expression vector and purified as soluble homogeneous fractions. Outer domain of Env glycoprotein contains conserved epitopes for neutralizing and non-neutralizing antibodies. They plan to examine the biochemical, biophysical, structural as well as immunogenic potential of these non-glycosylated soluble OD constructs.

Characterization of Indian clade C HIV-1 Envelope to understand the role of specific domains in envelope conformational and functional integrity

Lead Investigator: Dr. Sweety Samal

The unusual 150 amino acid long cytoplasmic tail (CT) of Env contains several motifs that are highly conserved across different HIV-1 clades and

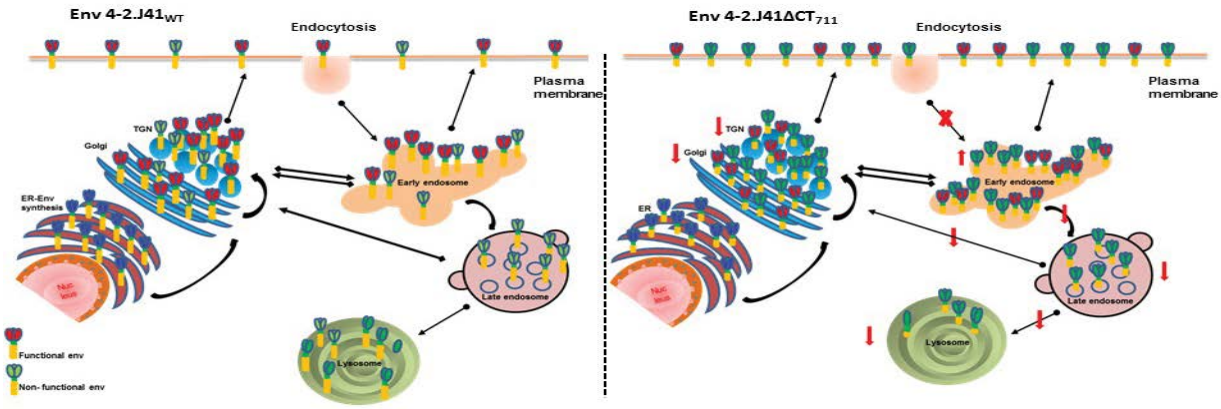

Figure 20: Graphical abstract model of HIV-1 Env intracellular trafficking: (Left panel) HIV-1 Indian clade C 4-2.J41 wild type Env sub cellular localization in different cellular compartments. (Right panel) 4-2.J41 Env cytoplasmic tail deleted protein showing differential accumulation of del-CT Env proteins in cellular compartments.

play critical roles in modulating multiple Env functions. One of the strategies that have been widely used for enhancing the surface expression of the Envs is to remove the CT-containing specific internalization motifs. Their previous studies have shown that Envs from different clades maintain their cleavage property upon CT deletion, however they have CT-dependent ectodomain conformational changes and bind to both neutralizing and non-neutralizing antibodies. Furthermore, they had demonstrated for the first time that a conserved hydrophilic domain in CT can restore the conformation. In continuation, they have studied the mechanism by which the CT-deleted Envs are modulating the conformational changes. A series of CT-truncated Envs were characterized by various biochemical and FACS based assays. Transport of Envs inside different cellular compartments was studied by confocal microscopy and cell biology techniques. They studied naturally occurring, efficiently cleaved, membrane-bound Envs from three major clades (Env A-clade A5, JRFL and JRCSF-clade B, and 4-2. J41 clade-C) that show change in antigenicity/conformation in a subset of C-terminal tail deleted Envs. Their results suggest that retrograde transport of a subset of naturally occurring efficiently cleaved Envs depends on their CT. These studies have been done by expressing Envs on various cell lines. These findings demonstrate the relevance of CT in modulating HIV-1 Env ectodomain conformation, a property hitherto unknown, which will help in illuminating the role of components of CT in Env structural integrity, thus facilitating Env-based immunogens designing and development (Figure 20).

The various engineered constructs of HIV-1 Env in the stable, soluble, native-like trimeric form with glycan holes, outer domain of Env glycoprotein or non-glycosylated soluble outer domains will be characterized for their suitability as potential immunogens or as antigenic bait for antibody isolation. Various biochemical and biophysical as well as immunogenic properties of these constructs will be tested for the development of a platform to understand the sequence-structure-functional relationship from genetically diverse Env sources for elucidating the complexities in HIV Envs.

COLLABORATORS

The Scripps Research Institute, La Jolla, California, USA
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Antimicrobial Resistance in Bacteria

Antimicrobial Resistance (AMR) has become a global threat, and the situation is particularly alarming in developing countries like India. It has crippled advancements in the treatment of infectious diseases, organ transplantation, cancer chemotherapy, and major surgeries further resulting in increased healthcare costs, prolonged illness, disability, and death.

Although, prevalence of AMR genes among pathogenic bacteria is widely studied for the interest of infectious disease management, the resistance profile and the genetic traits that encode resistance in the commensal microbiota living in the gut of healthy humans are not well studied.

Molecular Insights into AMR Traits of Commensal Human Gut Microbiota

Dr. Bhabatosh Das

Dr. Bhabatosh Das's team is working to **understand the mechanisms that connect the human gut microbiota to the efficacy and toxicity of xenobiotics, including antimicrobial drugs and how gut microbiota contribute in the dissemination of AMR traits in enteric pathogens.** The genes encoding antibiotic resistance in gut microbiota are physically linked with mobile genetic elements that are widespread in the genomes of both commensal and gut microbiota. These genes could disseminate vertically to the progeny and laterally to the distantly related microbial species. Consequently, the AMR genes present in the chromosome of gut commensals could be a potential source of resistance acquired by the enteric pathogens. His team has characterized AMR phenotypes of dominant commensal enteric bacteria isolated from the gut of healthy Indians. The whole genome sequence analysis of multidrug resistant commensal gut microbiota revealed that like pathogenic bacteria, enteric commensals are also multidrug resistant. The genes encoding antibiotic resistance are physically linked with mobile genetic elements and could be a potential source of resistant traits in the enteric pathogens (Figure 21).

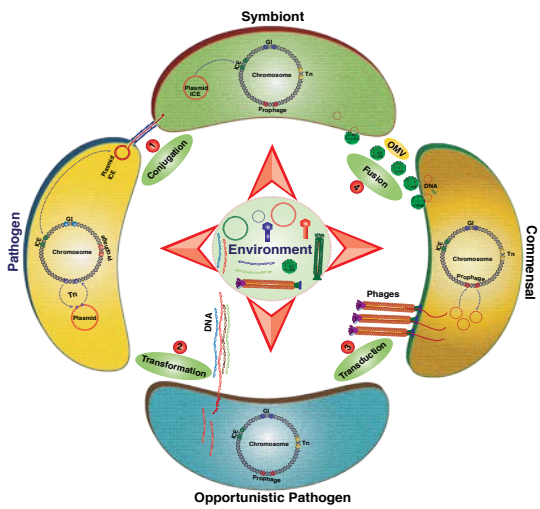

Figure 21: AMR genes could disseminate from gut commensals to enteric pathogens.

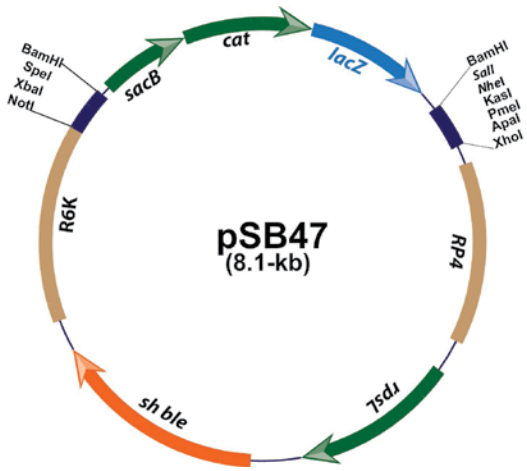

Figure 22: Vector map.

Currently, there is a lack of suitable DNA vectors to study the dynamics of chromosomal and extrachromosomal mobile genetic elements in the genomes of bacterial species. Dr. Das's team has **engineered a novel genetic tool to study the mobility of antibiotic resistance genes linked with mobile genetic elements.** In order to investigate the stability of genomic islands in *V. cholerae* genome, they constructed a novel vector pSB47, which has two selectable (*cat* and *sh ble*), two counter selectable (*rpsL* and *sacB*), one chromogenic marker (*lacZ*), and two multiple cloning sites (Figure 22). The *sh ble* gene encodes a small acidic protein (14 kDa) that inhibits DNA damage by the glycopeptide bleomycin and the *cat* gene confers resistance against chloramphenicol by transferring an acetyl group to the antibiotic scaffold. The selective markers will help to monitor the presence of vector in the bacterial genome and the counter selectable markers and chromogenic enzyme will be useful to monitor the loss of vector in the presence of sucrose, streptomycin and *5-bromo-4-chloro-3-indolyl β-D-galactopyranoside*. The vector carrying two multiple cloning sites will allow to introduce required size of DNA fragments on both the sides of the *sacB-cat-lacZ* allele and consequently label the genetic elements of interest by allelic exchange methods.

COLLABORATORS

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Diagnostics for Infectious Diseases

Tuberculosis

Sputum smear microscopy is the oldest and the most common method of TB diagnosis used around the world. However, it has many limitations. It relies on sputum, which is difficult by people (especially children) to produce and is the wrong sample for diagnosing TB outside of the lungs (extrapulmonary TB). Moreover, it has low sensitivity, especially among people living with HIV and among children. By far, there is no Point-Of-Care Test (POCT) that can be used in low-level health facilities. This contributes in delays for diagnosing and treating TB, worsening our fight against the disease.

Dr. Tarun Sharma

Dr. Tarun Sharma's team is working towards the **development of an aptamer-based rapid assay for Pulmonary Tuberculosis (PTB) detection** which could circumvent the limitations posed by smear microscopy-based diagnosis of PTB. Towards this, they have developed a same day Aptamer Linked Immobilized Sorbent Assay (ALISA) for direct detection of HspX, a potent TB biomarker, in sputum using a high affinity aptamer generated in-house against HspX. They compared its performance with the anti-HspX polyclonal antibody-based ELISA. In a blinded study of 314 sputum specimens, HspX ALISA displayed 94% (CI 86.8-98.1%) sensitivity compared to 68% (CI 86.8-98.1%) sensitivity of anti-HspX antibody-based ELISA using culture as the reference standard (***p *value* < 0.0001), and both assays exhibited 100% specificity (Figure 23). The high sensitivity of the same day

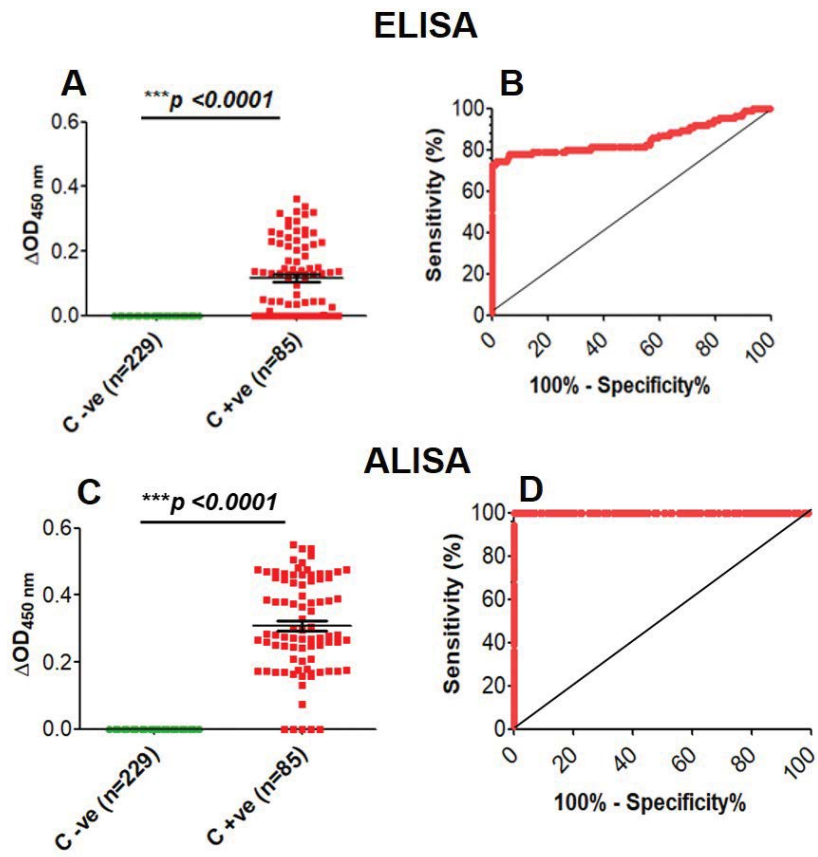

Figure 23: ELISA (A and B) and ALISA (C and D) based detection of the HspX antigen in pulmonary TB sputum samples. (A and C) Anti-HspX antibody and aptamer-based detection of HspX antigen by ELISA and ALISA respectively. (B and D) ROC curve of anti-HspX antibody-based ELISA and ALISA respectively. C-ve and C+ve refer to culture negative and culture positive specimens, respectively.

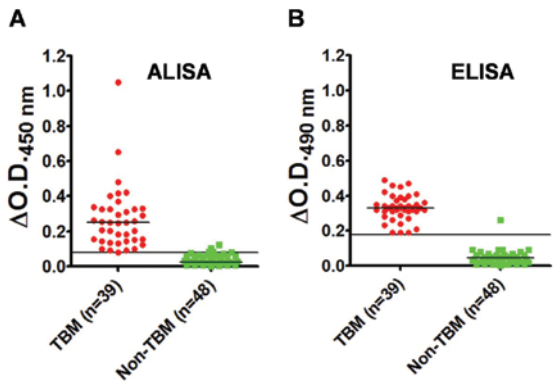

Figure 24: (A) H63 SL-2 M6 aptamer-based ALISA. Archived CSF samples were obtained from TBM patients (n=39) and Non-TBM patients (n=48). (B) Anti-HspX antibody-based antigen detection. Aptamer evinced comparable performance with that of anti-HspX antibody.

assay suggests that aptamer-based HspX detection in sputum by ALISA is superior to antibody-based ELISA and holds promise for developing a rapid screening tool for TB. In future, they plan to adapt the developed aptamer to a paper-ALISA format so that it could be used in an instrument-less manner.

They also aim to **develop an aptamer-based rapid diagnostic test for the detection of Tuberculous Meningitis** (TBM), one of the most severe manifestations of extrapulmonary TB that results in irreversible neurological damage. The diagnosis of TBM remains a challenge due to paucibacillary condition (low bacterial load). HspX antigen of *Mtb* has been previously established as a reliable diagnostic biomarker for TBM in an Enzyme Linked ImmunoSorbent Assay (ELISA) test format using anti-HspX polyclonal antibodies. However, antibodies usually evince batch-to-batch variation and this problem poses a great challenge for scalability of antibody-based diagnostic assays. To overcome this, his group has utilized Systematic Evolution of Ligands by EXponential enrichment (SELEX) to develop high affinity DNA aptamers against HspX as an alternative diagnostic reagent. Post-SELEX optimization of the best-performing aptamer candidate, H63, has established its derivative H63 SL-2 M6 to be superior to its parent. Notably, it could differentiate between cerebrospinal fluid specimens from TBM and non-TBM subjects (n=87, ***p<0.0001) with ~100% sensitivity and ~91% specificity (Figure 24). Being a synthetic molecule, it can be synthesized on a large scale with uniform quality.

A much larger study is in progress and they are planning to adapt these aptamers to a more potable diagnostic platform so that it can be used as point-of-care test.

COLLABORATORS

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Dr. Niraj Kumar and Dr. Susmita Chaudhury
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Drs. V. Singh and S. Aneja, Kalawati Saran Children's Hospital, New Delhi
Drs. S. Bhatnagar and N. Wadhwa, THSTI, Faridabad
G.B. Nair, World Health Organization office, New Delhi
Dr. R. Pathak, Gurgaon General Hospital, Gurugram

Tropical Fevers

Acute Febrile Illness (AFI) is common in the tropics and sub-tropics and can be caused by very diverse pathogens. Every year different parts of India are hit by seasonal fevers in the post monsoon period. These fevers include dengue, malaria, scrub typhus, leptospirosis, typhoid fevers etc. leading to very high morbidity and mortality. A large number of these patients require intensive care unit care due to single or multiorgan failure. The availability of a reliable POCT that can quickly identify a pathogen from a group of pathogens causing similar symptoms is of paramount importance for patient treatment, surveillance and prevention of anti-microbial resistance.

Dr. Gaurav Batra

Despite the strong need, commercially available POCTs (singleplex) for these infections are of poor quality. Moreover, no multiplex POCT is available in the market that can be used in resource-limited settings for the detection of multiple etiologies of tropical fevers.

Dr. Gaurav Batra's team is working on the **development of improved POCTs for different tropical febrile illnesses including malaria, dengue, chikungunya, scrub typhus** etc. During the last year, they have made the following developments:

A) Second generation dengue NS1 antigen detection assays for routine diagnosis and surveillance

Using antibody phage library, his team had earlier generated a large repertoire of 75 unique synthetic recombinant antibodies against dengue NS1 antigen with a wide specificity profile e.g. serotype-specific, pan-dengue, pan-flavi NS1 etc. Now, they have further characterized these antibodies in different formats to differentiate the affinity, binding to different genotypes and other binding properties in the presence of different biological matrices (human serum and plasma: different anticoagulants). They have generated a new mouse monoclonal antibody specific for DENV-2 NS1 to compensate for poor affinity observed with DENV-2-specific recombinant monoclonal antibodies. Immunoassay optimization work is under progress.

B) Ultrasensitive rapid diagnostic assay for malaria

Earlier, his group had developed a prototype ultrasensitive rapid Lateral Flow Assay (LFA) utilizing fluorescent nanoparticles for the detection of Pf-HRP2 antigen with analytical sensitivity equivalent to less than 5 parasites/µl. The rapid LFA assay has been further optimized which results in batch-to-batch consistency in the performance, stability of more 30 days at 45oC and improved analytical sensitivity of 1 parasite/µl in spiked whole blood panel.

C) Antibody detection assay for scrub typhus

Earlier, they had produced recombinant antigens derived from two strains of *Orientia tsutsugamushi*. Last year, the group has produced recombinant antigens from three other strains of *O. tsutsugamushi* to cover the diversity. Work is underway to utilize the cocktail of recombinant antigens for the development of ELISA and a LFA for the detection of antibodies against *O. tsutsugamushi*.

In future, the team plans to develop a large panel of clinical specimens from children and adults positive for different acute febrile illness causing pathogens. These would be further utilized to test the performance of the new diagnostic assays for different acute febrile illnesses.

Blood-Borne Infections

Blood-borne infections are a concern of patients, family members, and health care providers alike. Individuals may be exposed to these infections through the transfusion of banked blood products or through blood-contaminated injuries. A development of high sensitivity multiplex POCT system for detection of blood-borne infections such as those caused by Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and HIV is the need of the hour. The commercially available rapid POCTs have a poor performance compared to central laboratory tests and a multiplexed POCT for simultaneous detection of antigen and antibody markers for HIV, HBV and HCV is altogether lacking.

LFA format is the most widely used POCT format which often suffers from problems including poor assay sensitivity, subjectivity in reading the test results, and limited multiplexing possibilities. To circumvent these, **Dr. Gaurav Batra**'s team has replaced the colloidal gold (used for signal generation in traditional LFA) with upconverting phosphor nanoparticles (UCNPs) as a tracer, with optimized flow properties. UCNPs are very stable and provide very high signal amplification that can be easily quantified. During the last year, they have generated a UCNPs-based LFA for the detection of anti-HCV antibody, anti-HIV antibody and Hepatitis B surface antigen with initial sensitivity and specificity of >95% for these analytes compared to high performance central laboratory immunoassays. Work is underway to further optimize the assay to improve its performance. The team is also working on the generation of monoclonal antibodies against HCV core suitable for LFA format.

COLLABORATORS

Dr. Gaurav Batra

Dr. Navin Khanna, International Centre for Genetic Engineering and Biotechnology, New Delhi
Dr. Urpo Lamminmäki and Prof. Kim Pettersson, University of Turku, Finland
Prof. Rakesh Lodha, All India Institute of Medical Sciences, New Delhi
Prof. John Antony Jude Prakash, Christian Medical College, Vellore

Pneumonia

Pneumonia is a major cause of childhood mortality and morbidity, especially in resource-poor countries. It is primarily caused by bacterial and viral acute lower respiratory infection and is the single largest cause of deaths (27.5%) among children in post-neonatal period in India, with an incidence of 0.03-0.52 episodes per child per year. Pneumonia can be difficult to diagnose because it shares many symptoms with other conditions such as common cold, bronchitis, and asthma.

Dr. Niraj Kumar

Of the currently available diagnostics for pneumonia, nucleic acid-based methods have shown highest sensitivity (70-90%) and specificity (60-90%). However, these tests do not differentiate between colonizing and invading pathogens and also fail to provide information about the presence of any drug-resistant pathogens. To address this problem, the research groups of **Dr. Susmita Chaudhuri** and **Dr. Niraj Kumar** are **designing species-specific probe(s) for all bacterial pathogens commonly known to be associated with childhood pneumonia in India using a pan-genomic approach and plan to evaluate their potential in diagnosis as uniplex and multiplex tests** (Figure 25). They also aim to evaluate the performance of a number of potential targets already reported to enable efficient differential diagnosis of bacterial pneumonia.

Towards this, the groups have started to enrol patients at the Kalavati Saran Children Hospital, New Delhi. They have set up an in-house molecular assay for the panel of bacterial etiology of pneumonia and pathogen identification in the clinical samples using reference standard tests is in progress. They are also working towards the characterization of unique pathogens identified from culture-positive pneumonia cases.

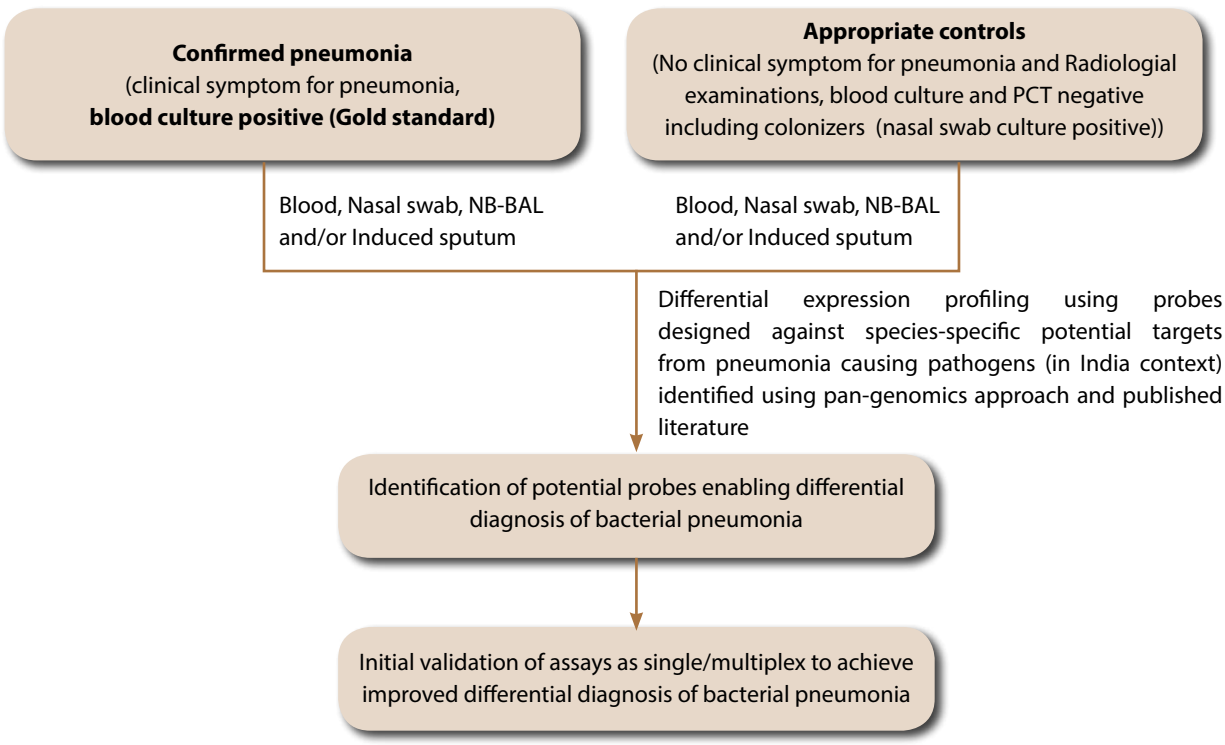


Figure 25: Overall diagrammatic representation of the research plan

Antimicrobial Susceptibility/Resistance Diagnosis for Bacterial Pathogens

AMR is a serious global health threat that is undermining our ability to effectively prevent, detect, and treat infections. Although, culture-based susceptibility test is still the 'gold standard', several culture-independent molecular techniques are now available to detect the presence of pathogens with resistance traits. Despite this, the implications of molecular diagnostics in public health setups are still insufficient due low-availability, high turn-around time, resource requirement and ultimately high cost. Therefore, the need of the hour is a rapid phenotypic susceptibility/resistance test which holds immense promise to evolve as the future gold-standard diagnostics for AMR. This test would immensely help clinicians to take decisions and avoid inappropriate use of antimicrobials.

Dr. Susmita Chaudhuri

Dr. Susmita Chaudhuri and **Dr. Niraj Kumar**'s teams have been working to **develop and optimize process and products for facilitating quality yet affordable rapid diagnostics** for the purpose. Initially, they aim to develop the same for ESKAPE group of pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) that are known to contribute major portion of AMR in India. In collaboration with Dr. Amit Yadav, they have started a project targeted to identify pathogen-specific peptides, protein and/or nucleic acid sequences so that pathogen-specific high affinity binders can be developed and utilized for establishing pathogen identity. They have already created a list of potential pathogen-specific peptides and proteins using bioinformatics-based approaches which need to be evaluated for their specificity. They are testing different tracer molecules comprising of chemicals, fluorescence molecules, luminescence molecules, metal nanoparticles etc., for developing these protocols into a rapid Antimicrobial Susceptibility Test (AST). They are further optimizing AST profiling-compatible protocols for rapid growth of low-density bacterial cultures to achieve minimal number of pathogens in the sample to allow successor technology to establish pathogen identity and AST profiling (Figure 26).

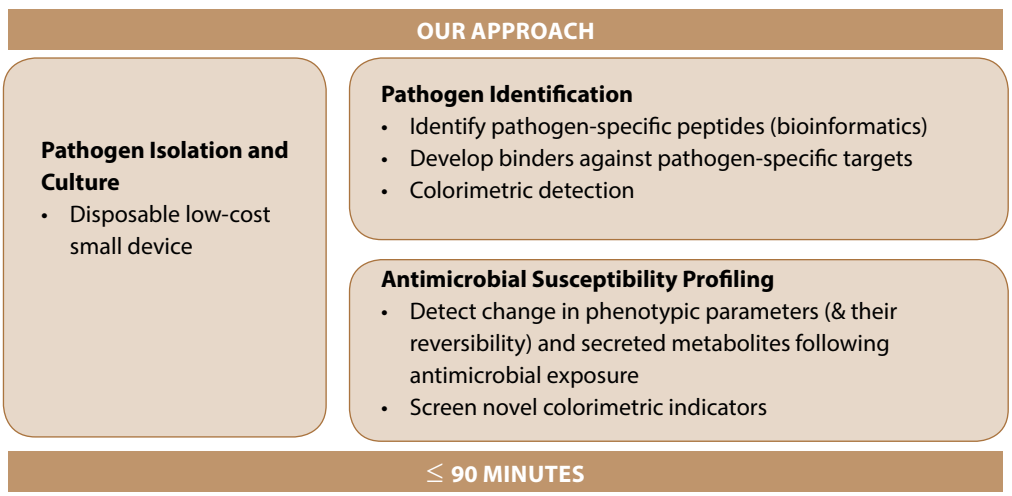
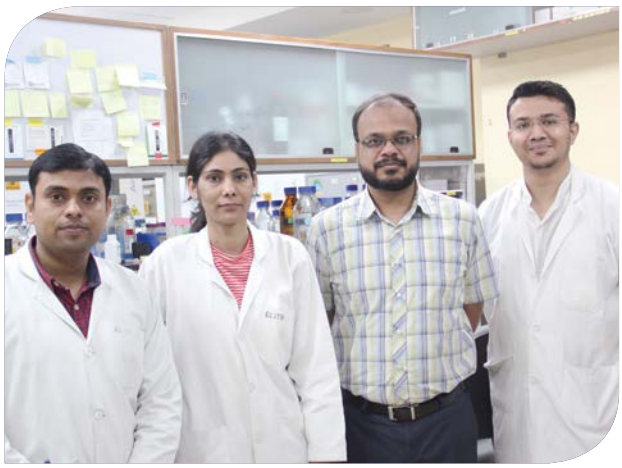


Figure 26: Overview of the research plan

Research teams



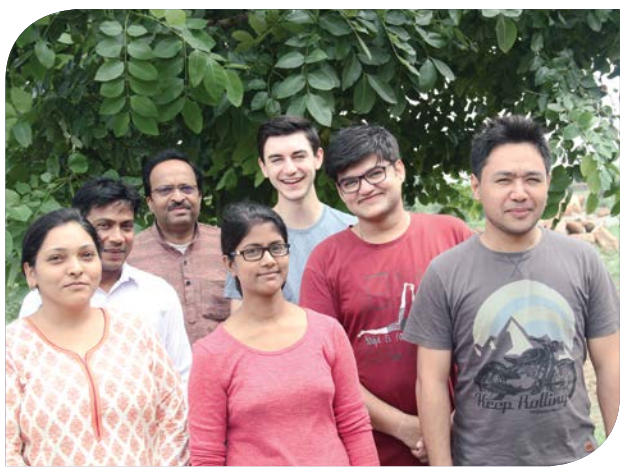
L-R: Rishabh Sharma, Eira Choudhary, Nisheeth Agarwal, Ajitesh Lunge

L-R: Naina Soni, Aarti Tripathi, Alok Singh, Arup Banerjee, Ashok, Ravi, Sandeep Goswami

L-R: Deepika Choudhary, Rania Bouzeyen, Saakshi Agarwal, Harleen Khurana, Arun Sharma, Ramandeep Singh, Cheepurupalli Lalitha, Neeraj Chauhan, Saruchi Wadhwa, Saqib Kidwai, Rajesh Kumar

L-R: Priyanka Bahree, Sakshi Talwar, Amit Pandey, Surjeet Yadav, Shaifali Tyagi

L-R: Soon Jyoti Das, Tarun K. Sharma, Anjali Anand



L-R: Ritu Gaur, Surjeet Kumar, Krishnamohan Atmakuri, Niti Singh, Ben Allwein, Nishant Sharma, Mohd. Ilyas

L-R: Yogita Rawat, Vishal Gupta, Sankar Bhattacharyya, Jaskaran Kaur

L-R: Shiv Kumar, Amit Kumar, Milan Surjit, Smita Hingane, Saumya Anang, Jyoti Gupta

L-R: Jyoti Verma, Taroshi Senapati, Bhabatosh Das, T. Ramamurthy, Pawan Kumar, Naveen Sharma, Bipasa Saha, Archana Pant

L-R: Pooran Singh, Souvick Chattopadhyay, Navdeep Batra, Suresh Kumar, Neha Kaushik, Gaurav Batra, Jitendra Kansana, Sarla Yadav, Akshay Binayke, Shirlie Roy Chowdhury, Suresh Goswami, Sangita Sinha

L-R: Niraj Kumar, Shrikant Kumar

L-R: Subhash Chandra Tanwar, Susmita Chaudhuri, Shailesh Kumar

RESEARCH ON NON-COMMUNICABLE DISEASES

AUTOIMMUNE DISORDERS

METABOLIC DISORDER: DIABETES

CONGENITAL HEART DISEASE

Autoimmune Disorders

Autoimmune disorders result when immune system produces antibodies that attack healthy cells, tissues and organs. There are around 80 different autoimmune disorders and their causes remain largely unknown. Some autoimmune diseases are life-threatening, and most are human immune system debilitating and require a lifetime of treatment. There are treatments available to reduce the symptoms and effects from many autoimmune diseases, but cures are yet to be discovered. Since most autoimmune diseases are rare, patients can often spend years seeking a proper diagnosis. Research at THSTI is focused to delineate the role of immune T cells in the development and progression of various autoimmune diseases. The focus is also to understand the interrelationship between genetic and environmental factors which is crucial to gaining insights into the etiopathogenesis of these diseases.

Interplay of Immune Cells in Autoimmune Disorders

Dr. Amit Awasthi

The focus of the immunobiology laboratory led by **Dr. Amit Awasthi** is to **understand the molecular pathways that define the generation and functions of effector and regulatory T cells, primarily Th9 and Th17 cells, in various disease conditions such as IBD, asthma, and cancer**.

Interleukin (IL)-17- producing Th17 cells comprise the dominant effector T cell population during tissue inflammation in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, psoriasis and Inflammatory Bowel Disease (IBD). Accumulating data has shown the existence of both pathogenic and non-pathogenic Th17 cells, and in fact, both non-pathogenic and protective Th17 cells have been described. Using the whole genome microarray profiling, his group has shown that Th17 cells generated by TGF-β3 are functionally and molecularly distinct from TGF-β1-induced Th17 cells. A comparative gene-profiling analysis of these two subsets of T_h17 cells reveals a molecular signature that defines pathogenic and non-pathogenic Th17 cells. They have elucidated that non-pathogenic Th17 cells express high levels of IL-9 compared to the pathogenic Th17 cells. Further, they have identified for the first time that Foxo1, a forkhead family transcription factor, reciprocally regulates the expression of IL-9 and IL-17 in Th17 cells (Figure 1).

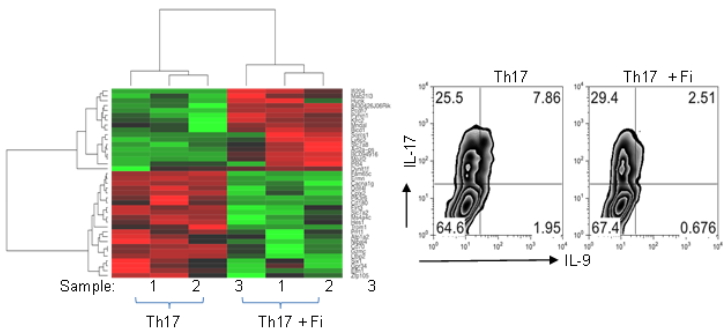


Figure 1: Foxo1 inhibition enhanced Th17 cells signature while suppressed IL-9 in Th17 cells.

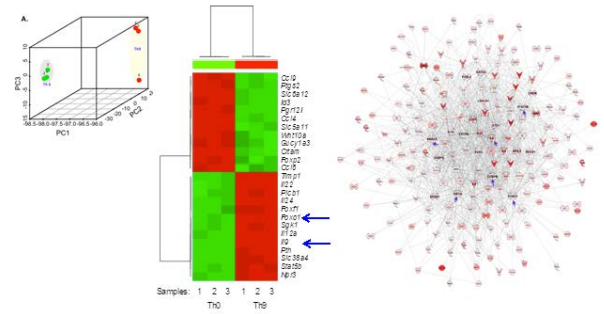


Figure 2: Global RNAseq analysis identified Foxo1 differentially expressed in Th9 cells.

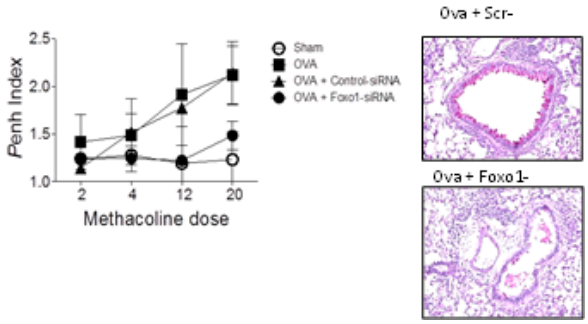


Figure 3: Foxo1 inhibition suppressed IL-9 and allergic inflammation in mouse model of asthma.

Their research has evidenced that Foxo1 is also required for the induction of IL-9 in Th9 and Th17 cells (Figure 1, 2). They have identified the Foxo1 DNA binding motif in IL-9 promoter and CNS2 region of IL-9 locus. Mechanistically, Foxo1 binds and transactivates IL-9 and IRF4 promoters in Th9 and Th17 cells. Furthermore, a loss of Foxo1 suppresses IL-9 production in mouse and human Th9 and Th17 cells, and substantially ameliorates allergic inflammation in asthma (Figure 3). Their findings, thus, reveal that Foxo1 is essential for the induction of IL-9 in Th9 and Th17 cells.

Urinary Potassium as a Potential Biomarker of Ulcerative Colitis

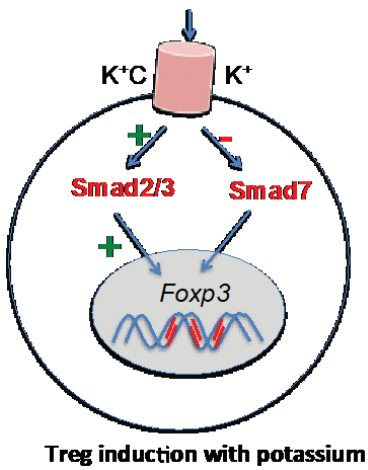


Figure 4: Potassium induces the Foxp3+ T cells. Extracellular potassium enhances TGF-b1 signaling by inducing smad2/3 activation and decreasing smad7 activation (based on our published reports in Frontiers in Immunology, 2016)

Crohn's disease (CD) and Ulcerative Colitis (UC), that constitute IBD, are caused by an imbalance between Th1 and Th17 immune cells, and Foxp3+ T-regulatory immune cells.

Salt (sodium) is known to alter the balance between pathogenic Th17 and Treg cells. Dr. Awasthi's research group has identified that extracellular potassium not only induces the generation of Foxp3+ Treg cells in humans by enhancing TGF-β1-signaling but also inhibits the generation of Th1 and Th17 cells (Figure 4).

They have translated these findings in a prospective cohort of nearly 170,000 US women who have been followed up for over 20 years. With a total of 194,711 women over a follow-up of 3,220,247 person-years, they have documented 273 cases of CD and 335 cases of UC. They found that the dietary intake of potassium (*P*trend = 0.005) but not sodium (*P*trend = 0.44) was inversely associated with the risk of CD. Although, both dietary potassium and sodium were not found to be significantly associated with risk of UC, there was a suggestion of an inverse association with dietary potassium (*P*trend = 0.08). The association of potassium with risk of CD and UC appeared to be modified by loci involved in the Th17 pathway that have previously been associated with susceptibility to CD, particularly SNP rs7657746 (*IL21*). They speculate that the dietary potassium is inversely associated with the risk of CD by regulating immune tolerance through its effect on Tregs and Th17 pathway. They further continued this work and have identified urinary potassium as a potential biomarker in UC patients in India.

COLLABORATORS

Dr. Amit Awasthi
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Dr. Balram Ghosh, Institute of Genomics and Integrative Biology, New Delhi

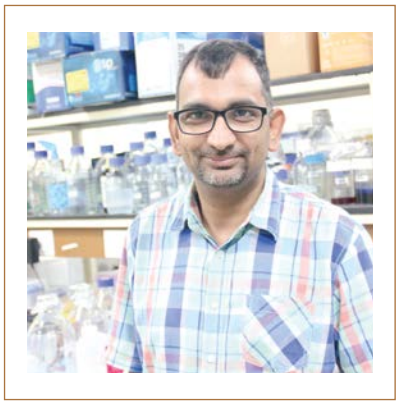
Metabolic Disorder: Diabetes

Diabetes is a chronic disease resulting in increased concentrations of glucose in the blood, which in turn damages many of the body's vital systems. About 422 million people are living with diabetes worldwide. Diabetes prevalence has been rising more rapidly in middle- and low-income countries. Almost half of all deaths attributable to high blood glucose occur before the age of 70 years. In 2015, an estimated 1.6 million deaths were directly caused by diabetes. WHO projects that diabetes will be the seventh leading cause of death in 2030. At THSTI, scientists aim to study gut microbiota in healthy and diabetic subjects, and progression of cardiovascular complications in diabetes.

Identification of Disease-Specific Microbial Signatures

The human gastrointestinal tract (GIT), the major site of nutrient assimilation and micronutrient production, is populated with trillions of microbial cells from all the domains of life (*Archaea*, *Bacteria* and *Eukarya*). A healthy immune system and balanced community of gut microbiota are crucial for human health. **Dr. Bhabatosh Das'**s laboratory is investigating gut microbiota of patients suffering from PreDiabetes (PD), Type 2 Diabetes (T2D) mellitus and IBD in an attempt to **identify disease specific microbial signatures, and develop genetically-defined microbial consortia for potential therapeutic applications**.

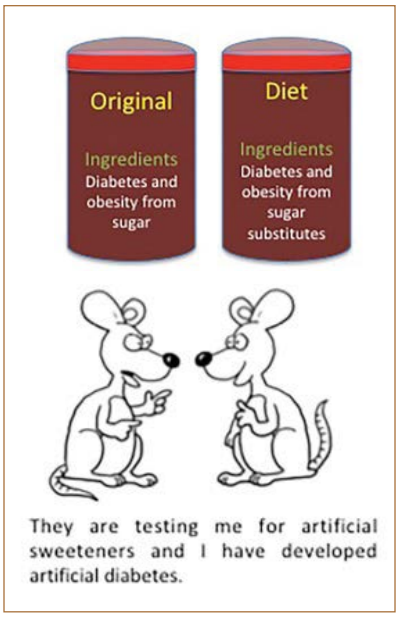
PD, a condition where blood glucose levels are higher than normal but lower than the diabetic range, is an extremely important indication to prevent rapid progression to T2D mellitus. Till now, limited information is available for possible association between the gut microbiome composition and PD. With an aim to find gut microbial signatures in prediabetic subjects, the group, in collaboration with Madras Diabetes Research Foundation (MDRF), Chennai, Tata Consultancy Services (TCS), Pune and Novo Nordisk Foundation Center for Basic Metabolic Research, Denmark, is investigating the gut microflora in adults with normal glucose tolerance (NGT) compared to those with PD in two countries (Denmark and India), which have entirely different ethnic, cultural, climatic and socio-demographic patterns. They have adopted 16S rRNA-based targeted metagenomics to investigate gut microbiome of 259 Danish subjects (NGT=138, PD=121) and 278 Indian subjects (NGT=137, PD=141). A total of 1897 Operational Taxonomic Units (OTUs) have been assigned to the gut microbiota of subjects from both the countries. Although, no significant differences in alpha diversity have been observed between microbiomes belonging to the NGT and PD groups, the gut microbiomes of Danes are found to be significantly (t-test, $p<0.05$) more diverse. A search for 'core' genera in the NGT and PD gut microbiomes has revealed that *Blautia*, *Collinsella*, *Coprococcus*, *Faecalibacterium*, *Lachnospira*, *Oscillospira*, *Ruminococcus*, and *Roseburia* are present ubiquitously in subjects from both the groups, irrespective of their geographical origin. However, *Megasphera* is one genus which could be identified as a core microbiota exclusively in the Indian PD gut microbiomes. Considering



Dr. Prabhanshu Tripathi

grouping of the samples based on their geographical origin, they have found that *Parabacteroides* and *Sutterella* are present in a higher proportion of the Danish population as compared to Indians, whereas *Megasphaera* and *Lactobacillus* are mostly specific to the Indian samples. Currently, the team is investigating richness and diversity of microbial species in T2D subjects of both the countries. In future, they aim to sequence isolate whole genome and identify microbial functions that may induce disease progression.

Dr. Prabhanshu Tripathi is **studying the role of environmental factors including diet, medications and other therapies in shaping gut microbiome and health**. Specifically, his research group is looking at the **effect of artificial sweeteners on gut microbiome and their consequences on type 2 diabetes**. To circumvent the negative impact of sugar-sweetened beverages on weight and other health outcomes, many people consume artificial sweeteners like aspartame, sucralose, and saccharin in their diets. However, many upcoming evidence suggest that these artificial sweeteners may also increase the risk of excessive weight gain, metabolic syndrome and type 2 diabetes. Very less information is available in the literature on the effect of diet, malnutrition, artificial sweeteners and medication on bacterial composition.



To shed light on the same, Dr. Tripathi's research group is exploring the role of artificial or non-caloric sweeteners on Caco 2 cells (human epithelial colorectal adenocarcinoma cells). They treat monolayer of Caco 2 cells with different concentrations of commonly used FDA-approved artificial sweeteners (aspartame, saccharin, acesulfame) for different time points and find that some of these artificial sweeteners reduced transepithelial resistance, thereby, producing leaky guts that could increase access of the gut bacteria to inner layers of the epithelial lining resulting in detrimental effects. They also observe significant changes in mRNA and protein levels of glucose transporters and PYY (also known as peptide tyrosine tyrosine or pancreatic peptide YY) in artificial sweetener-treated cells. Animal experiments are underway to find the effect of these artificial sweetners on gut microbiome and disease severity in type 2 diabetes model.

Cardiac Complications in Diabetes

Dr. Sanjay Banerjee

The study of the **progression of cardiovascular complications in diabetes** is the focus of **Dr. Sanjay Banerjee's** laboratory. His group is working to generate animal models of human diseases and identify novel targets for validation. Towards this, they have identified Toll-like receptor 4 (TLR4), Sirtuin-1 (SIRT1) and Vitamin D Receptor (VDR) as potential targets for cardiac hypertrophy and cardiac complication in diabetes. Last year, they found that inhibiting TLR4 in cardiac hypertrophy is beneficial in terms of reducing inflammation and fibrosis. For this, they developed cardiac hypertrophy in rats after administration of isoproterenol (ISO 5mg/kg/day, sc) for 14 days. Either TLR4 receptor inhibitor, a lipopolysaccharide from the photosynthetic bacterium *Rhodobacter sphaeroides* (RS-LPS), or TLR4 receptor agonist, a lipopolysaccharide from *E.coli*, were administered through osmotic pump along with isoproterenol. Cardiac hypertrophy

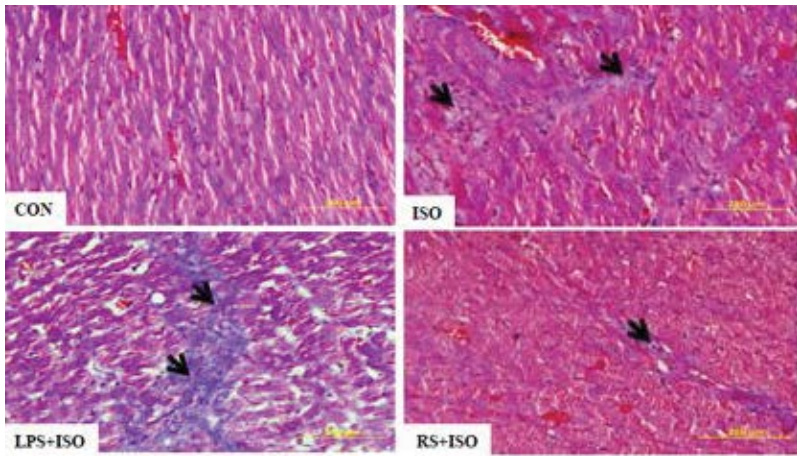


Figure 5: Masson's trichrome staining of rat heart tissue. Arrows in figures represent the presence of fibrosis.

was confirmed with an increased heart weight/body weight ratio, cardiac fibrosis (Figure 5) as well as assessment of hypertrophic markers in heart. They found a marked increase in the TLR 4 expression and oxidative stress along with mitochondrial dysfunction in the ISO group. TLR4 agonist along with ISO administration (LPS-ISO group) further exaggerated the oxidative stress in heart and, hence, accelerated disease development and progression. On the other hand, inhibition of TLR4 (RS-ISO group) attenuated cardiac hypertrophy, inflammation, mitochondrial dysfunction and oxidative stress. Together, their data showed that TLR4 inhibition could be a promising target to attenuate inflammation associated with cardiac hypertrophy.

His group is also working to identify a set of inflammatory and metabolic markers that distinguish diabetes from different cardiovascular complications i.e., hypertension, coronary artery disease and diabetic cardiomyopathy. They aim to discern serum biomarkers (cytokines, adipokines and hormones) for identification of T2D conditions likely to develop coronary artery disease.

Congenital Heart Disease

Congenital heart disease (CHD), a major cause of serious morbidity and mortality, is common. It is usually defined as clinically significant structural heart disease present at birth. The birth prevalence of CHDs is estimated to be eight per 1000 live births. The burden of CHDs in India is likely to be enormous, because of a very high birth rate. It is estimated that over 1,80,000 children in India are born with CHDs every year. As only a very small proportion get required intervention, the number of young adults with CHDs is steadily increasing. This heavy burden emphasizes the importance of the study of CHDs in India. Research at THSTI is focussed to shed light on the genetic factors leading to CHD.

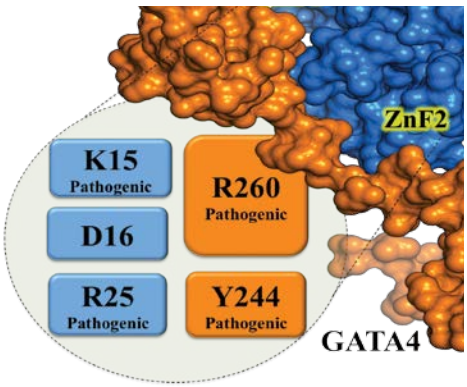


Figure 6: Interaction of NKX2.5 with GATA4 at atomic level.

Dr. **Sanjay Banerjee**'s group is trying to **understand the molecular defects that lead to congenital heart disease**. Several studies have reported that mutations in genes encoding NKX-2.5 and GATA4 transcription factors result in different types of CHD. However, very few studies on the atomic level have been conducted to find the genetic causes of CHD. Previous findings have evidenced that both the transcription factors bind to the promoters/enhancers of downstream targets as homo-hetero multimeric complexes and regulate their function through protein-protein interactions. In collaboration with Dr. Shailendra Asthana, his group has uncovered the importance of protein-protein interactions that perturb the disease state. A novel non-synonymous D16N mutation in NKX-2.5 gene, associated with Tetralogy Of Fallot (TOF) and Ventricular Septal Defects (VSD) in South Indian patients, was found to form a strong hydrogen bond with the pathogenic variation R260 of GATA4 (Figure 6). Genetic variation at D16N induced a conformational change due to loss of polar contacts, indicating that D16 mutation might lead towards the disease state. They have identified two binding regions on which NKX-2.5 and GATA4 were zipped together by a series of hydrogen bonds. Altogether, this study underscores the importance of protein-protein interactions for phenotype development during the early stages of heart development and identifies several possible mutations that may cause congenital heart disease.

COLLABORATORS

Dr. Sanjay Banerjee

Prof. Sandeep Seth, Prof. S. K. Maulik, and Dr. Sudheer Arava, All India Institute of Medical Sciences, New Delhi
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Drs. N.C. Talukdar and Rajlakshmi Devi, The Institute of Advanced Study in Science and Technology, Guwahati
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Dr. Charu Lata Mahanta, Tezpur University, Tezpur

Research teams

L-R: Jyoti Verma, Taroshi Senapati, Bhabatosh Das, T. Ramamurthy, Pawan Kumar, Naveen Sharma, Bipasa Saha, Archana Pant

L-R: Prabhanshu Tripathi, Manisha Tyagi

L-R: Parmeshwar Bajirao Katare, Hina Lateef Nizami, Bugga Parmesha, Sima Kumari, Parul Kamboj, Md. Jahangir Alam, Ubaid Tariq Bhat, Soheb Anwar Mohd., Sankarsan Bhattacharya, Amit Tanwar, Gowtham Annarapu, Sanjay Banerjee, Jasmine Sethi

TOOLS AND TECHNOLOGIES FOR DRUG, VACCINE AND DIAGNOSTIC RESEARCH

TOOLS FOR DRUG DISCOVERY RESEARCH AND DEVELOPMENT

COMPUTATIONAL TOOLS FOR SMALL MOLECULE DESIGN

CRISPR/CAS9-BASED GENOME EDITING TOOLS

ADENOVIRUS-BASED VECTOR SYSTEMS

PROTEOMICS IN DISEASE: MASS-SPECTROMETRY-BASED TOOLS

HIGH THROUGHPUT TOOLS FOR STUDYING DISEASE DEVELOPMENT

MATHEMATICAL TOOLS FOR STUDYING DISEASE PROCESSES

BIOPROCESS IMPROVEMENT

Tools for Drug Discovery Research and Development

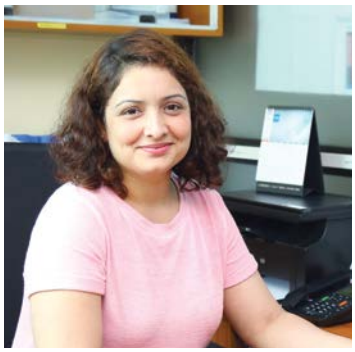
The drug discovery research programme at THSTI is focused on new drug development. To this end, innovative approaches for dissecting disease mechanisms are employed to identify novel drug targets. Currently, efforts are being channelized to develop lead candidates for three diseases: AIDS (Principal investigator: **Dr. Dinesh Mahajan**), Non-Alcoholic SteatoHepatitis (NASH; Principal investigator: **Dr. Shilpa Jamwal**), and cardiac hypertrophy (Principal investigator: **Dr. Sameena Khan**).

mTOR-Independent Autophagy Regulators: Potential Drug Targets in Diseases

Dr. Dinesh Mahajan

Dr. Dinesh Mahajan and his research group are **focused on medicinal chemistry and pharmacology studies pertaining to pre-clinical drug lead development**. Last year, the team had identified three drug-like leads with a novel pharmacology possessing inhibition of **HIV** replication and growth activities. The new molecules developed under this program have a dual mode of action i.e. autophagy induction in host cells and inhibition of viral integrase activity. Inhibition of viral integrase is an approved anti HIV therapy and there are drugs in clinical development based on integrase inhibition (Dolutegravir and Elvitegravir). Importantly, autophagy induction is also found to play a role in disease control and has been clinically observed/validated but with no drug approved so far. The project team has identified three drug-like leads after intensive medicinal chemistry efforts, *in-vitro* screening by the high-content screening team, and initial Drug Metabolism and Pharmacokinetic (DMPK) analysis. His group has designed and synthesized around ~80 new chemical entities around the initial hits to optimize the Structure-Activity Relationship (SAR). These efforts have not only increased the *in vitro* potency significantly, but also enhanced the drug-like properties resulting in the development of new drug leads having very good plasma exposure in rats when administered orally. The newly identified molecules under this project are not only very potent virus integrase inhibitors but also are strong autophagy inducers at nanomolar concentrations. Because of this novel mode of action, the identified leads managed to demonstrate antiviral replication effect in integrase-resistant strains also. The project team is presently focused on the evaluation of the drug leads in animal (rat/mice) pharmacokinetic and toxicity studies. Later, this will set the stage for proof of concept studies in Macau disease model.

Project Co-coordinator and Principal Investigator: *Dr. Dinesh Mahajan*
Co-Investigators:
Dr. Debashis Mitra, National Centre for Cell Science, Pune; Dr. Shilpa Jamwal, Dr. Sameena Khan, and Dr. Shailendra Asthana, THSTI, Faridabad



Dr. Shilpa Jamwal

Non-Alcoholic Fatty Liver/ Non-Alcoholic SteatoHepatitis (NAFL/NASH) represents a serious liver disease under the Non-Alcoholic Fatty Liver Disease (NAFLD) spectrum. NASH constitutes 40% of total liver diseases, and is anticipated to hike tenfold in 50 years. In India alone, NASH accounts for 30% of total liver diseases. This condition is defined by excess fat accumulation, inflammation and injury in liver. NASH is a potential risk factor to develop liver cirrhosis or hepatocarcinoma. Currently with no FDA-approved drug against NASH, it is the second major reason for liver transplant across globe.

Autophagy induction is a potential therapeutic approach for chronic liver diseases such as NASH. Last year, the medicinal chemistry group has synthesized around 120 new molecules that could act as potential autophagy inducers in cells. These newly synthesized molecules were **screened for autophagy induction and lipid lowering effect in a primary screening** by **Dr. Shilpa Jamwal** and her team, who also **developed an improved disease model representing NASH**. A series of small molecules were selected for further evaluation based on their high efficacy in an *in vitro* disease model where they were shown to decrease the accumulation of lipids as well triglyceride loads. Additionally, these molecules have a strong positive effect on overall cell health parameters such as reduction in mitochondria and ER stress. The project team is planning to perform detailed pharmacokinetic analysis and dose-tolerance studies in rats to determine a suitable dose for animal efficacy study.

Additionally, Dr. Jamwal's interests encompass developing methods for high content phenotypic screening, in addition to generation of 3D models of mammalian cell lines as screening tools for the shortlisted hit molecules (Figure 1). Her future plans would involve the development of *in vitro* disease models representing advanced stages of NASH and co-culture cell models representing liver diseases. She also aims to optimize these cell-based models for screening activities.

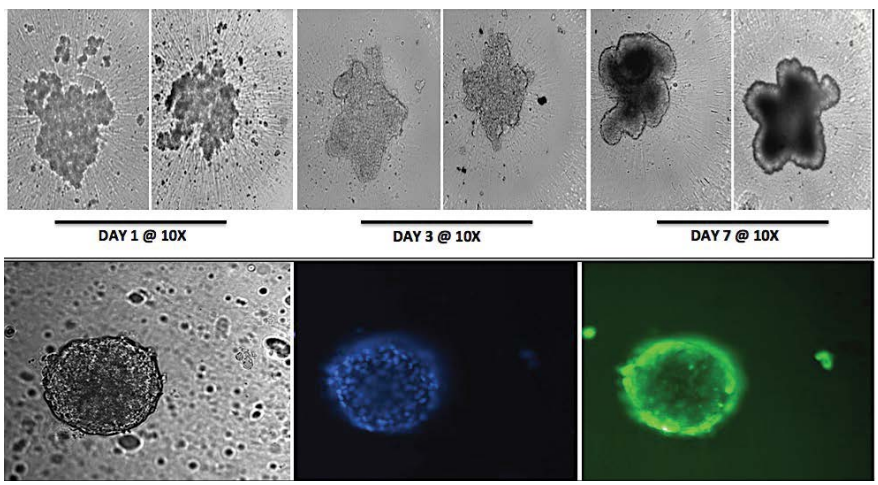


Figure 1: Upper panel shows representative images of optimization and culture conditioning of 3D-model of Human Hepatocytes (HepG2) at different days of culturing. Lower panel showing 3-D model in Human Hepatocytes (HepRG) as DIC, Hoechst and CMFDA stained respectively.

Project Co-coordinator and Principal Investigator: *Dr. Shilpa Jamwal*
Co-Investigators:
Dr. Dinesh Mahajan, Dr. Sameena Khan, Dr. Shailendra Asthana, THSTI, Faridabad

Dr. Sameena Khan

Cardiovascular disease (CVD) has acquired the scale of a global pandemic with India contributing prominently to this figure. No effective therapies are currently available for heart failure with acute decompensated hypertrophy. The only therapeutic agents available are diuretics and vasodilators that reduce the pressure and volume overload, thereby providing symptomatic relief. Novel pharmacological agents targeting important pathophysiological features in the failing heart are the need of the hour. **Dr. Sameena Khan**'s research team and her collaborators at the institute have **generated a potent compound, DR0000 (compound DR-X, henceforth) that stimulates cellular autophagy (EC50 = 10 nM) and inhibits both stress-induced apoptosis and hypertrophy in human and rat primary cardiomyocytes.**

In the past year, they have performed proof-of-concept experiments in the rat model for cardiac hypertrophy. They found that treatment of diseased rats with DR-X yielded significant therapeutic benefits in terms of suppression of cardiac hypertrophy, improvement in cardiac function, and prevention of cardiomyocyte death. Importantly, their findings suggest that the efficacy of compound DR-X is comparable to that of carvedilol, a drug currently in use for severe congestive heart failure.

In a preliminary pharmacokinetic analysis, DR-X displayed limited oral exposure in both mice and rats, which demanded further improvements. Therefore, efforts were focused on the synthesis of close analogues of DR-X and ~30 new molecules were synthesized having different chemical variations around DR-X. The final structure and purity of these molecules were assigned based on various analytical methods such as NMR spectroscopy, mass spectrometry and HPLC. The group screened these molecules in autophagy induction and in vitro cardiac hypertrophy and apoptosis assays for efficacy evaluation. They identified few new leads having in vitro potency equivalent or better than the original lead DR-X. These experiments are under reinvestigation for final validation.

Collectively, their findings suggest that induction of autophagy is a novel strategy for treatment of cardiac hypertrophy and heart failure. They have identified an initial lead, DR-X, as an exciting chemical tool to achieve autophagy induction and hence therapeutic benefits in an animal model of disease. In future, research from her laboratory would focus around developing a better orally available lead with potency and efficacy better or equivalent than the original lead compound, DR-X.

Project Co-coordinator and Principal Investigator: *Dr. Sameena Khan*
Co-Investigators: *Dr. Dinesh Mahajan, Dr. Shilpa Jamwal, Dr. Shailendra Asthana, THSTI, Faridabad*
Collaborator: Dr. Sagartirtha Sarkar, University of Kolkata

New Synthetic Process Development for Approved Drugs, Active Pharmaceutical Ingredients and Molecules of Commercial Importance

Dr. Dinesh Mahajan is steering **efforts to fill the gap towards having cost/resource-efficient and environment-friendly synthetic and manufacturing processes for molecules of commercial interest with a major focus on drugs and Active Pharmaceutical Ingredients** (APIs). This is of great national interest as raw material import dependency and pollution from industrial waste are two national challenges. Almost all of the key raw materials and molecules of commercial interests are being imported from China and other countries by all Indian manufacturing industries. His laboratory is pursuing a small program for development of new chemical technologies, processes and reagents. As an initial outcome, they have developed few proprietary synthetic methodologies (provisional patent filed) for chemical transformation in a cost-effective, environment friendly way. Work is underway to demonstrate the utility of these synthetic methodologies for cost-effective and cleaner synthesis of existing approved drugs, new APIs and other molecules of commercial importance.

Computational Tools for Small Molecule Design

Dr. Shailendra Asthana

Dr. Shailendra Asthana is focused to **identify small molecule modulators for broad therapeutic applications by exploring protein-protein interaction interfaces through multiple computational techniques like computational biophysics, peptidomimetics and virtual screening** (Figure 2). His research group is working to develop a multipurpose database of drug-like molecules which can be used to screen against disease-specific targets, and design peptide-based small molecules for different types of protein-protein complexes. They have developed a substantially large virtual library (more than 2.5 lakh compounds) of small molecules, FDA-approved compounds (for reposition) and fragment compounds. They have generated an integrated platform of modeling-docking-dynamics for identification of computationally active peptides from protein-protein interaction interface. They are also attempting to determine structure-function-dynamics relationship for the mechanistic understanding of inhibition at molecular level. Towards this, they have generated docking approaches with/without water for thermodynamic profiling at compound

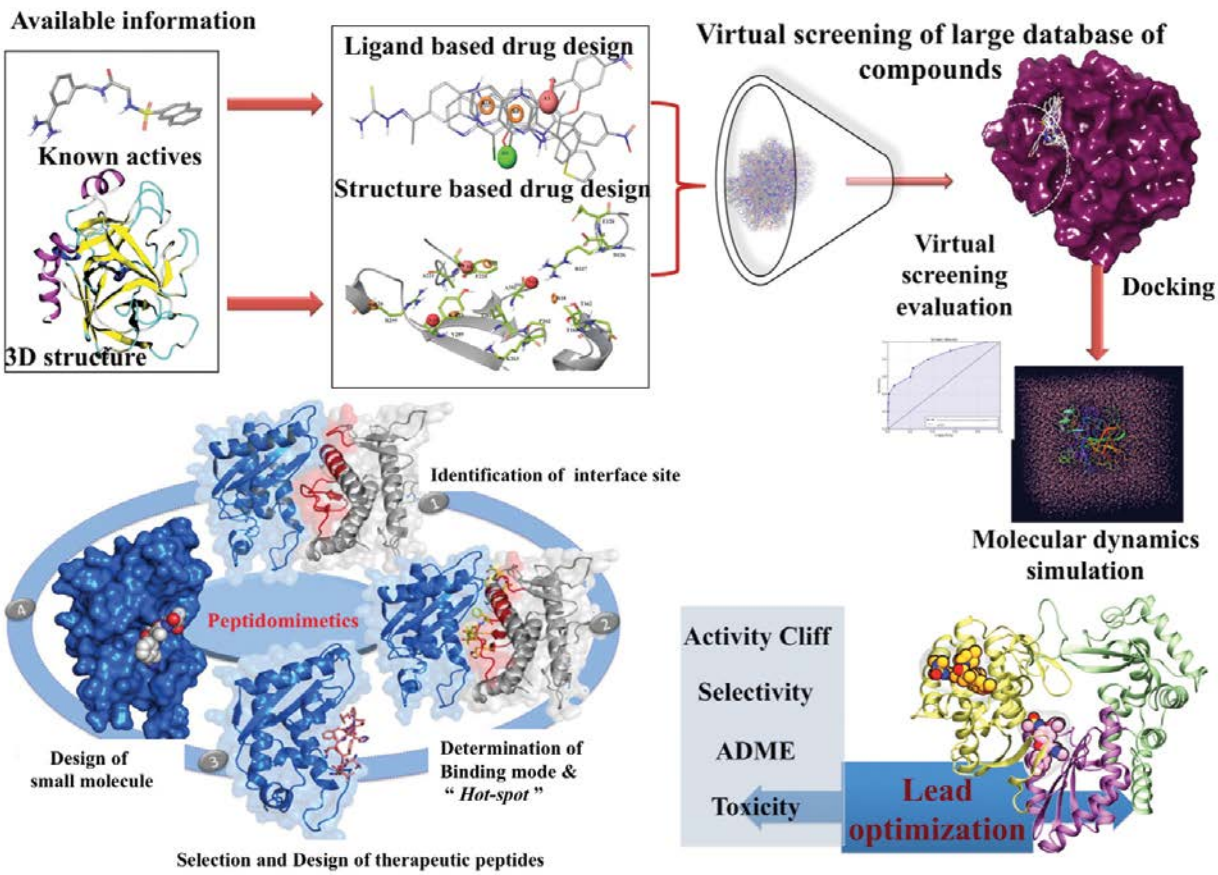


Figure 2: Computational strategies for identification of small molecule through different approaches and prediction of ADME (Absorption, Distribution, Metabolism, and Excretion) properties.

screening level as water dynamics is essential for better understanding of protein structure-function-dynamics behavior.

In future, they aim to establish a robust computational platform as an approach to understand protein dynamics and residue-wise translation of the conformational nature of binding sites into small molecule designing. Additionally, they plan to utilize protein-protein interaction surfaces for the identification and design of active peptides, and peptide-based peptidomimetics to modulate the interaction between two proteins. They see this platform as an informative tool useful in multiple therapeutic areas spanning infectious diseases and metabolic disorders.

COLLABORATORS

Dr. Shailendra Asthana

Dr. B. Ravindran, Institute of Life Sciences, Bhubneswar
Dr. Mohan Wani, National Centre for Cell Science, Pune
Drs. Nisheeth Agarwal, Ramandeep Singh, Krishnamohan Atmakuri, Sankar Bhattacharyya, Milan Surjit, Amit Awasthi, Shilpa Jamwal, Sameena Khan, Dinesh Mahajan, and Manjula Kalia, THSTI, Faridabad

CRISPR/CAS9-Based Genome Editing Tools

Dr. Ajay Kumar

CRISPR/Cas9 is emerging as a key genome-editing tool in research and holds great promise in discovery/validation of therapeutic targets in disease. The primary focus of **Dr. Ajay Kumar**'s laboratory is to **develop an in-house expertise in designing CRISPR-Cas9-based genome editing tools and use them in drug target discovery and validation**. Last year, they had successfully generated a Cas9-stable HEK293 cell line. Expression of Cas9 was validated using western blotting over a range of protein concentrations. This Cas9-expressing cell line was targeted with specific guide RNAs to target a set of genes for their knockout and subsequent knock-in. They have also designed vectors containing a fluorescent marker which would eventually tag endogenous expression of the targeted protein. Standardization of reaction conditions to validate knock-out of the targeted genes using CRISPR primers in Cas9 expressing cells is currently underway.

Dr. Nisheeth Agarwal has initiated a **nationwide program to facilitate the TB research in the country by creating a resource of defined CRISPRi-based knockdown plasmid constructs and mutant strains**. In a joint proposal with the CSIR-Institute of Microbial Technology submitted to the Department of Biotechnology, he envisages to create a repository of ~120 *Mtb* mutant strains targeting various genes having potential for new drug targets such as those regulating *Mtb* virulence and TB pathogenesis, dormancy in *Mtb* clinical isolates, peptidoglycan biosynthesis, type III polyketide synthesis, emergence of drug resistance in *Mtb*, protein acetylation, and respiratory metabolism. Importantly, this project would initially serve 12 TB researchers across different institutions in India.

Adenovirus-Based Vector Systems

Dr. Mohan Appaiahgari

Human Adenovirus type 5 (HAdV5)-based vector platform, though is well studied and has been demonstrated to be highly effective in preclinical studies and/or early clinical trials, has been found to be associated with certain safety and efficacy issues in advanced phase trials. Therefore, animal adenovirus-based vector systems are being explored as suitable alternatives for HAdV5-based vector systems for the development of safe and efficacious recombinant vaccines and therapeutics. However, these novel vectors are protected under intellectual property rights and therefore cannot be used freely for the development of interventions that are important in the Indian context. **Dr. Mohan Appaiahgari**'s laboratory is working to **develop novel animal adenovirus-based vector systems, protect their IP rights, and subsequently develop recombinant vaccines and therapeutics against diseases of medical and veterinary importance in India**. They have initiated a program to isolate novel adenoviruses from Indian livestock and to characterize them for their suitability as candidates for vector development. In collaboration with Dr. Sudhanshu Vrati and Dr. Gerald Both, they have recently constructed a recombinant Ovine Adenovirus expressing JEV envelope protein (OAdVEs). They have evaluated the immunogenicity and the protective efficacy of this recombinant in mice models both in the presence and absence of pre-existing neutralizing immunity to HAdV5 as well as against a lethal intracerebral JEV challenge. Data from these studies suggest that the ovine adenovirus recombinant, when given at an equivalent dose, induces significantly lower neutralizing immunity compared to that induced by the human adenovirus 5-based recombinant and results in lower protection rates in mice groups immunized with the ovine adenovirus recombinant, irrespective of the pre-existing adenovirus 5 neutralizing immunity.

In future, he aims to generate more such data using different animal adenovirus-based vector systems expressing a variety of antigens. Data from these studies will be helpful in understanding the pros and cons of animal adenovirus-based vector systems and will also form the basis for identification of ideal vectors for clinical development.

COLLABORATORS

Dr. Mohan Babu Appaiahgari
Dr. Sudhanshu Vrati, Regional Centre for Biotechnology, Faridabad
Dr. Gerald Both, Broadvector Limited, Melbourne, Australia

Proteomics in Disease: Mass Spectrometry-Based Tools

Dr. Amit Yadav

Post-Translational Modifications (PTMs) play a crucial role in mediating biological functions through protein-protein interactions, structural binding, aiding enzyme activity, subcellular localization and their crosstalk drives disease development and progression. **Dr. Amit Yadav**'s group broadly focuses on the **development of mass spectrometry-based tools and techniques for large-scale proteomics and PTM analyses**. They develop statistical tools, algorithms, software pipelines, and next generation visualization applications for high throughput analyses**.** They also integrate data from disparate sources like omics studies and public databases for discerning the emergent properties of biological systems.

PTM Analysis of Sirtuin Interaction Landscape in Cardiovascular Diseases

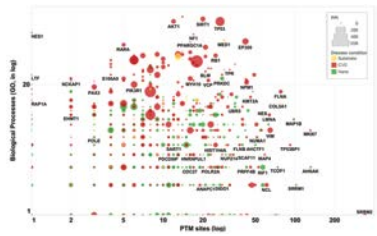


Figure 3: PTMs and protein-protein interactions have a strong association with CVDs in functionally diverse sirtuin interactors.

To understand the role of acetylation and related PTMs in cardiovascular diseases, they studied protein-protein interactions of sirtuins from BioGRID database. Sirtuins are a family of deacetylases that remove acetyl group from their substrates to modulate their function in distinct cellular compartments. By studying various properties of these interactors like subcellular localization, disease involvement, number and types of PTMs, association with SNPs, and disorder and substrate specificity, one could understand the mechanisms more deeply leading to a better prediction of markers for diagnosis or treatment of cardiovascular diseases. His group observed a strong association of interactors with cardiovascular diseases and also role of closely found PTM types which may be indicative of PTM crosstalk in regulating cellular processes by regulating the PPIs that they mediate. The analysis of the amino acid sequence motifs around the validated substrates enabled the prediction of yet unknown substrates for specific sirtuin isoforms (Figure 3).

Modification Search Tool: Blind Mode Mapping of PTMs from Human Plasma

In another pilot study, Dr. Yadav's group has completed a blind mode mapping of PTMs from a human plasma dataset. **For automated analyses of PTMs on a large scale, they have developed and copyrighted ModST (Modification Search Tool) to process data in parallel on commodity hardware**. They have analyzed human plasma data to show that several proteins occur only in modified form (Figure 4). In general, researchers are able to identify only the unmodified part. This analysis has also revealed the challenges of site localization and confidence assessment by false discovery

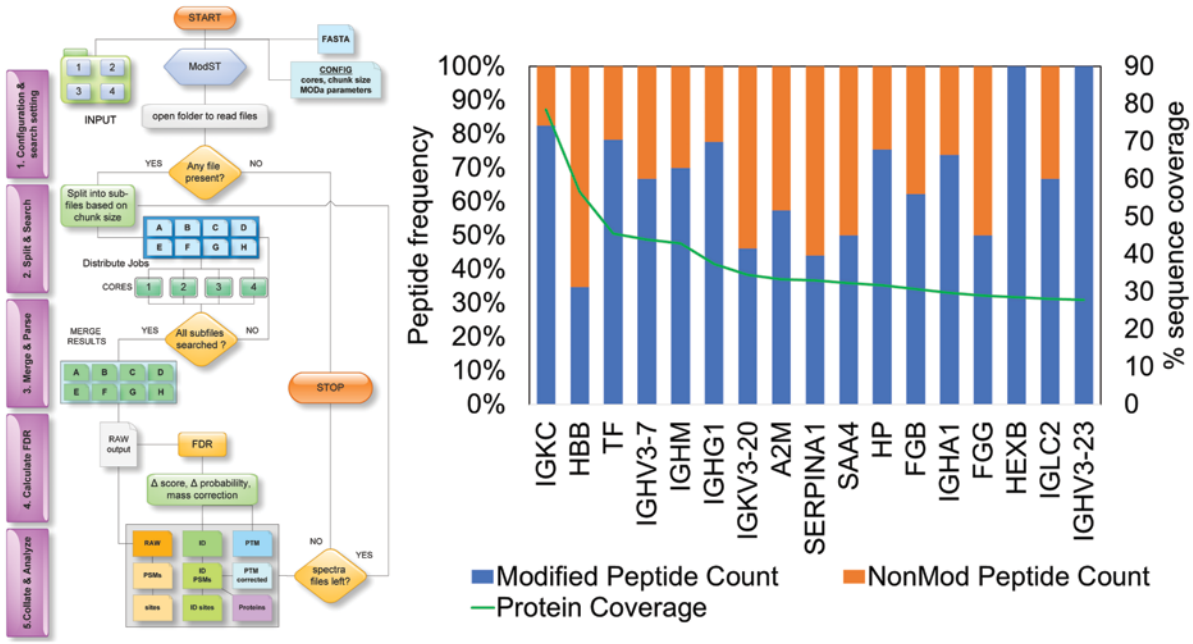


Figure 4: ModST tool for parallel mode blind PTM search reveals modified proteins in human plasma.

rate and false localization rate. Using the knowledge gained from this analysis and benchmarking, they are currently testing automated annotation of modifications using the Unimod database of PTMs, along with a *post search* PTM site localization for faster and more accurate PTM identification and annotation. In future, they also plan to address the challenges of PTM masses corresponding to a combination of modifications.

Bonplex – A Tool For Large-Scale Secretome Analysis Of Newly Synthesized Proteins

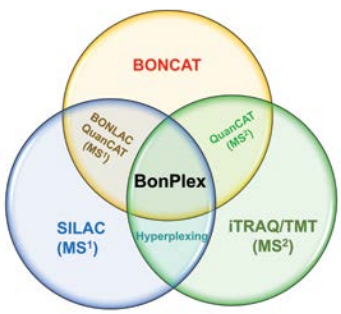


Figure 5: BonPlex technique combines the best of BONCAT, SILAC and iTRAQ for large-scale secretome analysis of newly synthesized proteins.

In an attempt to expand the quantitative capacity of proteomics, they have developed a new method–**BONPlex for studying newly synthesized and secreted proteins in 18 conditions/samples in a single run of mass spectrometer** (Figure 5). This has made the statistical analysis and reproducibility within reach for the proteomics community which had otherwise been elusive due to run-to-run variation, high dimensionality, and the volume of generated mass spectrometry data.

Further, they have applied this method to study the temporal effects of virulent/avirulent *Mtb* infection on the secretome of macrophages. They observe that while most of the secretory processes are dampened during infection by a virulent strain, many other proteins (cytokines, interleukins, proteases etc.) are also downregulated as compared to the uninfected cells. The expression profiles across various time points are shown in Figure 6.

Upon categorizing the mapped proteins according to the cellular locations reported in Uniprot, they have found several novel secretory proteins which have not been reported as secretory earlier (Figure 7). These proteins were likely never found in the secretome due to their very low

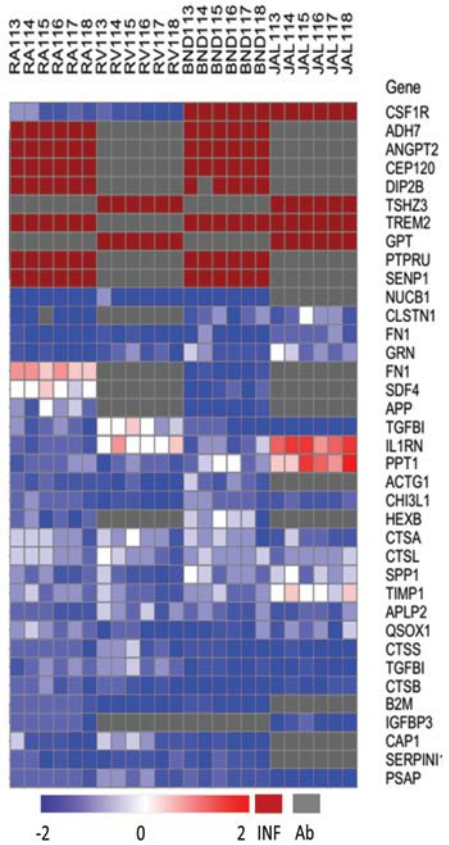


Figure 6: Temporal proteome expression patterns of immune cell (THP-1) secreteome after infection with avirulent (*Mtb* H37Ra) and virulent (*Mtb* H37Rv, BND433, JAL2287) strains of *Mycobacterium tuberculosis.*

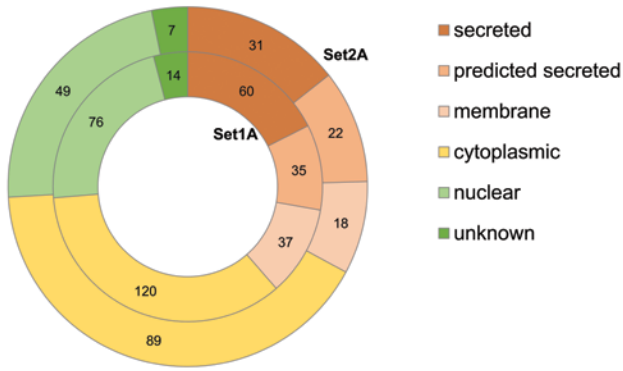


Figure 7: Subcellular localization revealed several low abundance proteins, newly reported to be in secretome using BonPlex technique.

abundance. However, it has been made possible due the depth and sensitivity of their method. Their enrichment protocol and hyperplexing method could mine the low abundance secretome fraction to identify these proteins with statistical confidence and reproducibility. The known cellular localizations are similar for the two sets of experiments i.e. set 1 (Mtb H37Ra; avirulent and Rv; virulent) and set 2 (BND433; virulent slow-growing and JAL2287; hyper-virulent fast growing) of the conducted experiments suggesting that the fraction of known to unknown secretory proteins remains the same in the two sets of experiments and there is no technical bias in identifying the novel secretome.

Pepuniverse: A Universal Peptide Database

Microbes have molecular signatures hidden in their genomes that define their pathogenicity, virulence, host adaptation, resistance to drugs and evolutionary information. These can be exploited as unique identification markers for diagnostic purposes in microbe- borne diseases. However, using knowledge from protein sequences of bacteria for disease diagnosis and evolutionary sequence analyses is a challenge due to the size and complexity of data. Dr. Yadav's group has created a tool, **UniPEPtor**, to cleave all bacterial proteomes of interest into k-mers of length 7-20 amino acids. Low complexity peptides and repeats are common in bacterial proteomes hindering facile analysis and cause database inflation without adding much analytical value. They have **created a sequence complexity calculation method encompassing mono-, di- and tri- amino acid frequency that is used to filter out peptides with less than 50% sequence complexity**. The tool creates tables of peptides, proteins and rank-wise taxonomy lineage (from NCBI) and filters the peptides with low sequence complexity (<50%). Using this tool, his group has created a database of all possible peptide fragments for ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas*

aeruginosa, Enterobacter). The data tables were uploaded into a relational database and indexed for efficient data retrieval and analysis for the billions of peptides created. From the data, fetching unique peptides would require billions of sequence comparisons and ranked taxonomy wise classification would assist in finding unique taxon wise signature peptides. So far, they have pilot results for 22 organisms from the ESKAPE group of pathogens for which they have retrieved unique (distinct) peptides not overlapping with other species in the set. Currently, they are analyzing them further to select diagnostically important peptides for validation experiments.

Proteomic Approaches for Disease Parameter Study

Dr. Renu Goel

Dr. Renu Goel is inclined to study **disease parameters using mass spectrometry-based proteomic approaches**. Last year, she embarked on a clinical biomarker study along with Dr. Guruprasad Medigeshi where Isobaric Tags for Relative and Absolute Quantitation (iTRAQ) followed by mass-spectrometry analyses was carried on plasma samples from dengue patients with different clinical symptoms (Figure 8A & B). Her group has observed significant modulations in the expression of many proteins which play a significant role in dengue progression, thereby indicating their potential for use as biomarkers of disease severity.

In collaboration with Dr. Nisheeth Agarwal, she has studied the effect of YidC induction on the global expression profile of membrane proteins in *M. smegmatis*. YidC is a translocase whose induction down-regulates expression of proteins involved in cell wall lipid biosynthesis affecting the strength of mycobacterial cell wall. Her research has identified 2558 and

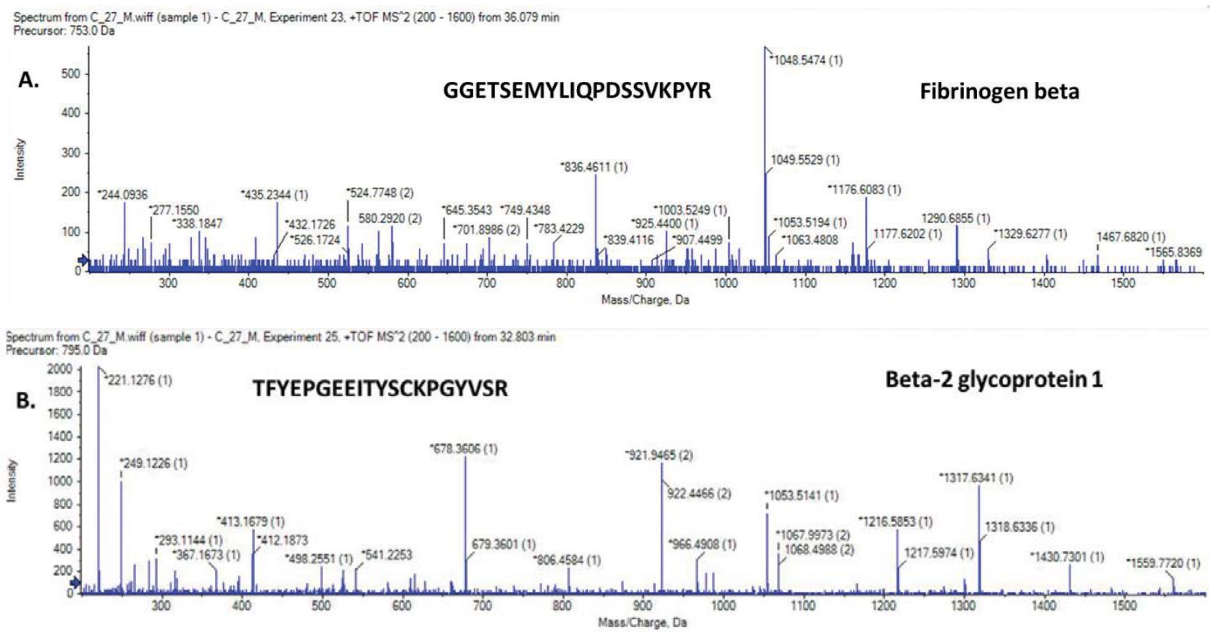


Figure 8: Representative MS/MS spectra of known proteins in dengue fever identified in this study. A) Peptide GGETSEMYLIQPDSSVKPYR belongs to fibrinogen-beta. B) Peptide TFYEPGEEITYSCKPGYVSR belongs to beta-2-glycoprotein I (APOH).

2220 proteins from two biological replicates with 1% false discovery rate. Interestingly, they have found 359 proteins being differentially expressed with >1.5-fold change in mycobacterial cell membrane upon YidC induction, of which ~55% are downregulated and the remaining are upregulated. Their observations strongly propose screening of small molecule inhibitors against YidC to feed the ongoing anti-TB drug discovery pipeline.

Akt1 Signaling in Cell Cycle Regulation

To delineate the bridging protein(s) between cell growth and cell cycle progression, **Dr. Ajay Kumar** and his team extracted the interacting partners of Akt1 as well as Rb protein from HEK293 cells. HEK293 cells were arrested in different cell cycle stages and selective labeling of amino acids in cell culture (SILAC) was used to distinguish cells in different stages as well as for quantitative analysis of the identified interactors. Affinity purification coupled with mass spectrometry revealed the unique interactors for the two target proteins. Multiple proteins presented altered association with Akt1 and Rb at the G1/S checkpoint, compared to when cells were arrested at the G0 phase. Functional analysis, using siRNA-mediated gene silencing, revealed that a significant proportion of the G1/S-specific interactors played key role in contributing either to cell survival and/or the cell cycle. Overall results revealed some novel protein-protein linkages through which Akt1 executes its function in driving cell division. Functional association studies for Rb interactors are underway which will subsequently be evaluated together with Akt1 results. Their preliminary findings provide a framework for mechanistic investigations to gain novel insights into functions of Akt1 and Rb, as well as on the nature of interactions between them.

COLLABORATORS

Dr. Amit Yadav

Drs. Guruprasad Medigeshi, Krishnamohan Atmakuri, Dinesh Mahajan, Shilpa Jamwal, Manjula Kalia, Sanjay Banerjee, Ajay Kumar, Sameena Khan, Niraj Kumar, and Susmita Chaudhury, THSTI, Faridabad

Dr. Gagan Dhawan, Delhi University, New Delhi

Dr. Yumnam Silla Devi, CSIR-North East Institute of Science and Technology, Jorhat

Dr. Renu Goel

Dr. Anupam Kumar, Institute of Liver and Biliary Sciences, New Delhi

Dr. Girish Mishra, University of Delhi-South Campus, New Delhi

Dr. Sumit Rungta, Kings George Medical College, Lucknow

Dr. Neeloo Singh, Central Drug Research Institute, Lucknow, India

High Throughput Tools for Studying Disease Development

Dr. Yashwant Kumar

Dr. Yashwant Kumar's group works on **disease biomarker discovery using high throughput metabolomics and lipidomics approaches**. Their analysis pipeline includes sample preparation, data acquisition, data analysis using various regression and classification approaches and statistical validation of biomarker panels. Based on untargeted metabolomics and machine learning approaches, they **have developed and patented a tool that can predict future diabetic susceptibility outcomes**. In future, they aim to develop a robust and translatable biomarker for early identification of the diabetic susceptibility.

In collaboration with Dr. Sanjay Banerjee, his group is also aiming to understand various metabolic syndromes developed because of diabetic conditions. A combination of metabolomics and random forest classification analysis on 12 control subjects, 48 Diabetes Mellitus (DM) subjects, 46 Coronary Artery Disease (CAD) subjects, and 40 Diabetes Mellitus with Coronary Artery Disease (DMCD) subjects revealed that branched amino acids play a very important role in developing metabolic syndromes such as CAD and DMCD (Figure 9-11).

Further, random forest classification could accurately classify the control, DM, CAD and DMCD with cumulative out of bag error 0.0959.

	CAD	Control	DM	DMCD	Class error
CAD	44	0	0	2	0.0435
Control	3	8	0	1	0.333
DM	0	0	48	0	0
DMCD	3	0	5	32	0.2

In the past year, the group also developed an in-house metabolite library of 800 metabolites from different metabolic pathways involved in disease conditions. Additionally, they have established a high throughput lipidomics platform at THSTI which will be a useful tool to study lipid metabolism and its role in disease.

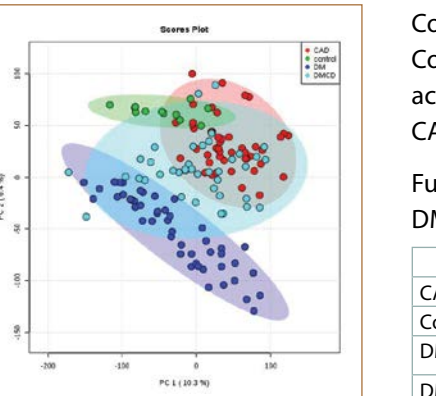


Figure 9: Principal component analysis (PCA) of control, DM, CAD, and DMCD subjects showed changes in metabolome after onset of disease.

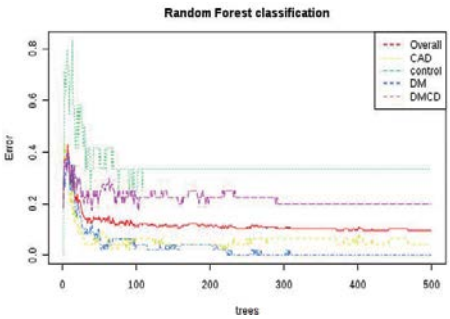


Figure 10

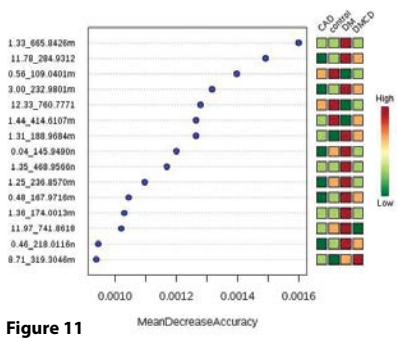


Figure 11

Figure 10: Cumulative error rates by Random Forest classification. The overall error rate is shown in red; other lines represent error rates for each class.

Figure 11: Significant features identified by Random Forest classification. The features are ranked by the mean decrease in classification accuracy when they are permuted.

COLLABORATORS

Dr. Yashwant Kumar

Drs. Sanjay Banerjee and Samrat Chatterjee, THSTI, Faridabad

Dr. Nikhil Tandon, All India Institute of Medical Sciences, New Delhi

Dr. Chitranjan Yajnik, KEM Hospital, Pune

Mathematical Tools for Studying Disease Processes

Model Using Machine-Learning Algorithm for Predicting the Susceptibility to Type 2 Diabetes

Dr. Samrat Chatterjee

Dr. Samrat Chatterjee's research is dedicated to **develop methodologies that could pre-diagnose the susceptibility of an individual to T2D**. To achieve this, they take advantage of the fact that the serum metabolite composition of an individual is a reflection of her/his health state. In the last year, they have reported the successful development of an artificial intelligence algorithm that analyzes the serum metabolome of an individual, and predicts the likelihood of s/he succumbing to T2D in the future. This algorithm uses machine learning for training, and takes the high-resolution mass spectrometric profile of serum metabolites of humans as input to predict the susceptibility with high accuracy. To develop the algorithm, the team profiled the serum of healthy human subjects and analyzed the metabolite composition against the fasting blood glucose levels measured 6 years later in those subjects. The data was processed to give the intensity/ concentration of each metabolite in each of the sample. This resulted in a matrix with rows as samples, columns as metabolites, and values as the intensity/ concentration of a given metabolite in the respective sample. This matrix, along with the future diabetic state of sample/patient, was fed through a classification algorithm that trained the classifier to distinguish samples/ patients either into future diabetic or future non-diabetic groups, based on the metabolite patterns (Figure 12). The performance of this algorithm was determined by testing it on an unknown dataset, and quantifying accuracy of the results obtained. A very high accuracy of prediction was obtained. The model was transformed in the form of software that they got copyright licensed and have applied for the patent. In future, they plan to extend the same concept to other diseases like cancer.

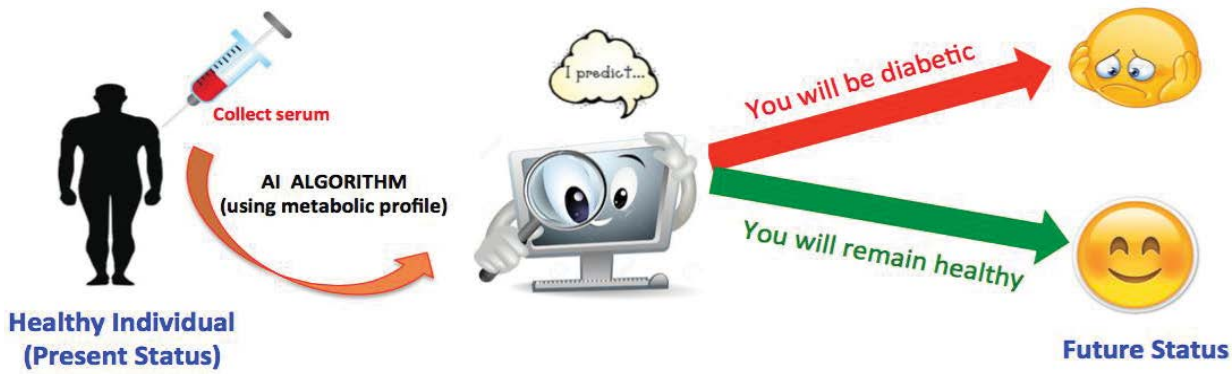


Figure 12. A schematic outlining the development of machine learning-based model for predicting susceptibility to T2D.

Tracking Disease Progression by Searching Paths in a Temporal Network of Biological Processes

Metabolic disorders such as obesity and diabetes are diseases that develop gradually over time through perturbations of biological processes. These perturbed biological processes usually work in interdependent ways. Dr. Chatterjee's research team has **developed an algorithm to capture the interlinking between different biological processes that work together to regulate the disease phenotype**. Through microarray data analysis in obese and diabetic mice, they have developed methods to establish a link between these perturbed biological processes (Figure 13). They have derived a mathematical formula to score genes and identified a significant set of genes regulating a complex process network. The methods developed in their study are applicable to a broad array of data types. They have used this data along with an available protein-protein interaction network to find a network of interactions between proteins which would reproduce the next time point data from the previous time point data. Their results suggest that the resulting network could be mined to identify critical nodes involved in the temporal progression of perturbations. Further, published algorithms could be applied on such a connected network to mine important proteins and to show an overlap between outputs from published and their algorithms. The critical proteins identified from algorithms could be hypothesized to play important role in temporal progression of the data. His group has developed a tool to connect temporal proteomics data which could be expanded to any temporal high-throughput data. In parallel to testing this in future, they would be adding more factors like protein functionality to their algorithm so that it could further dissect and extract more information from the obtained data.

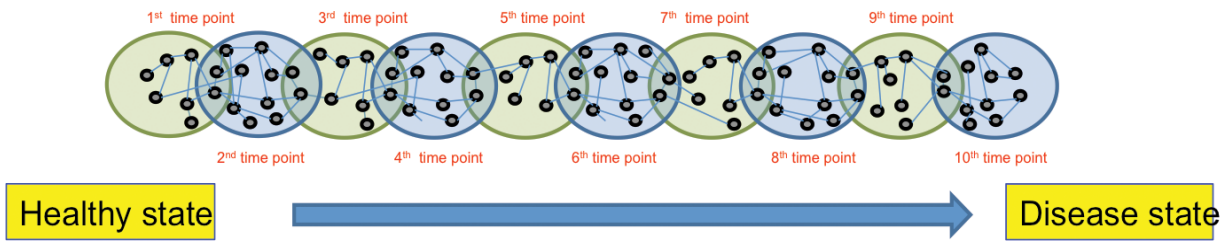


Figure 13: A diagram showing temporally connected network capturing disease progression

Understanding the Architecture of Biological Networks to Identify Points of Sensitivity Under Perturbations

His research group is also focussed to **understand the architecture of biological networks to identify points of sensitivity under perturbations**. Understanding these sensitive nodes could affect the progression of diseases like diabetes and obesity. They aim to obtain a mathematical formula (derived from SDE models) to identify perturbation-sensitive

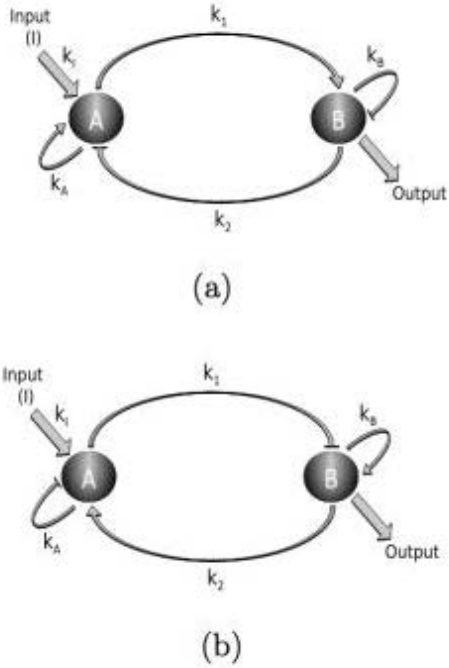


Figure 14: A schematic represention of two-node motifs showing rich dynamical behaviour and sensitivity to perturbation.

nodes under stochastic perturbation in large-scale networks. The obtained sensitive nodes could then be exploited to identify potential candidates for drug targets. The strategy developed would be especially useful in diseases causing complex perturbations in cellular signalling networks such as cancer, diabetes, and obesity. They have started with all possible two-node structures. After studying 32 structures in detail, they have identified two structures showing rich dynamical properties under perturbation. They have built stochastic differential equation (SDE) models for these two motif structures (Figure 14) and observed that the range of output signal is dependent on the structure but the sensitivity of the parameter is not. In both the structures, it is the downstream node which is more sensitive in the outcome of output signal. They also observe that under random perturbation with high noise intensity, the system loses its stability and the bistable points scatter leading to an undesirable output signal. This is a small study focusing on only two specific structures, nevertheless it shows the importance of the structure and noise in the signaling mechanism. The group is presently working on higher dimension models.

Understanding the Role of Calcium in Cardiomyocyte Functioning

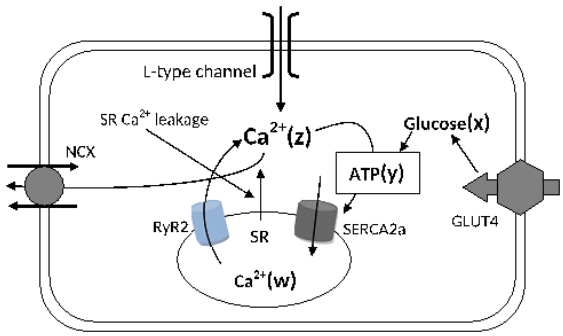


Figure 15. A schematic of the ODE model system

Calcium homeostasis is a key factor in the regulation of cardiac excitation–contraction coupling. Calcium dynamics in cardiomyocytes is governed by ATP which depends on insulin-dependent glucose concentration, via the glucose transporter type 4 (GLUT4). **Dr. Samrat Chatterjee**'s group is interested to see **how calcium dynamics changes in a cardiomyocyte under diabetic conditions**. Towards this, they have proposed and analyzed a four-dimensional Ordinary Differential Equation (ODE) model (Figure 15) to capture the interdependency of calcium dynamics on glucose uptake and ATP generation. Through parameter perturbation, they have captured the role of different parameters in maintaining normal calcium oscillation (frequency 40 to 180 beats per minute and amplitude >= 0.4 μM) and hence normal cardiac function. They observe that any divergence in the GLUT4 activity (especially a decrease in the glucose uptake rate) might cause abnormal calcium oscillation, leading to Cardiac Dysfunction (CD). Their study hypothesizes that a regulated sarcoplasmic reticulum (SR) calcium flux could be a possible therapeutic strategy to maintain normal calcium dynamics in a diabetic heart, thereby preventing CD.

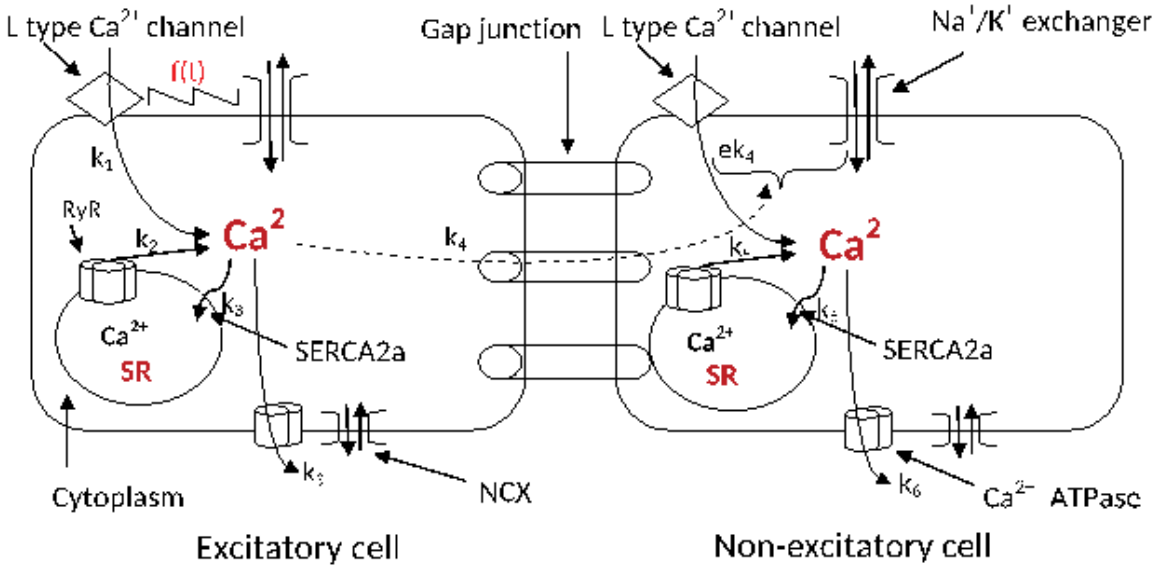


Figure 16: A model system to study calcium dynamics in different types of cardiac cells.

To further understand the cardiac calcium homeostasis, they have elucidated calcium dynamics in different types of cardiac cells. They have developed a model to capture the calcium dynamics in excitatory cells (EC) and non-excitatory cells (NEC), taking into consideration the gap junction-mediated calcium ion transfer from an EC to a NEC (Figure 16). Their study reveals that the gap junction coupling between an EC and a NEC plays an important role in the calcium dynamics. Any reduction in the functioning of gap junction could result in abnormal calcium oscillations in NEC, even when the calcium dynamics is normal in EC cell. The sensitivity of gap junction is independent of the pacing rate and hence a careful monitoring is required to maintain normal cardiomyocyte condition. They also highlight that sarcoplasmic reticulum may not be always able to control the amount of cytoplasmic calcium under the condition of calcium overload. Together, they have identified some critical factors responsible for cardiac dysfunction. In future, they plan to collaborate with biologists and clinicians to validate and refine the result of their model.

Host-Pathogen Interactions During *Mycobacterium tuberculosis* Infection

The current scenario of TB has worsened due to a lack of good understanding of the host-pathogen interactions and the emergence of drug- resistant TB. To fill this void, **Dr. Samrat Chatterjee**'s group has **constructed Genome Scale Metabolic Models (GSMMs) using proteomics/ metabolomics data from macrophages infected with different laboratory and clinical *Mtb* strains** (Figure 17). Using these GSMMs, they would identify novel targets that, upon modulation, might result in clearance of intracellular bacteria. In

the last year, they have identified some critical host factors and regulatory points manipulated by the pathogen for its survival. The model result is under *in vitro* validation.

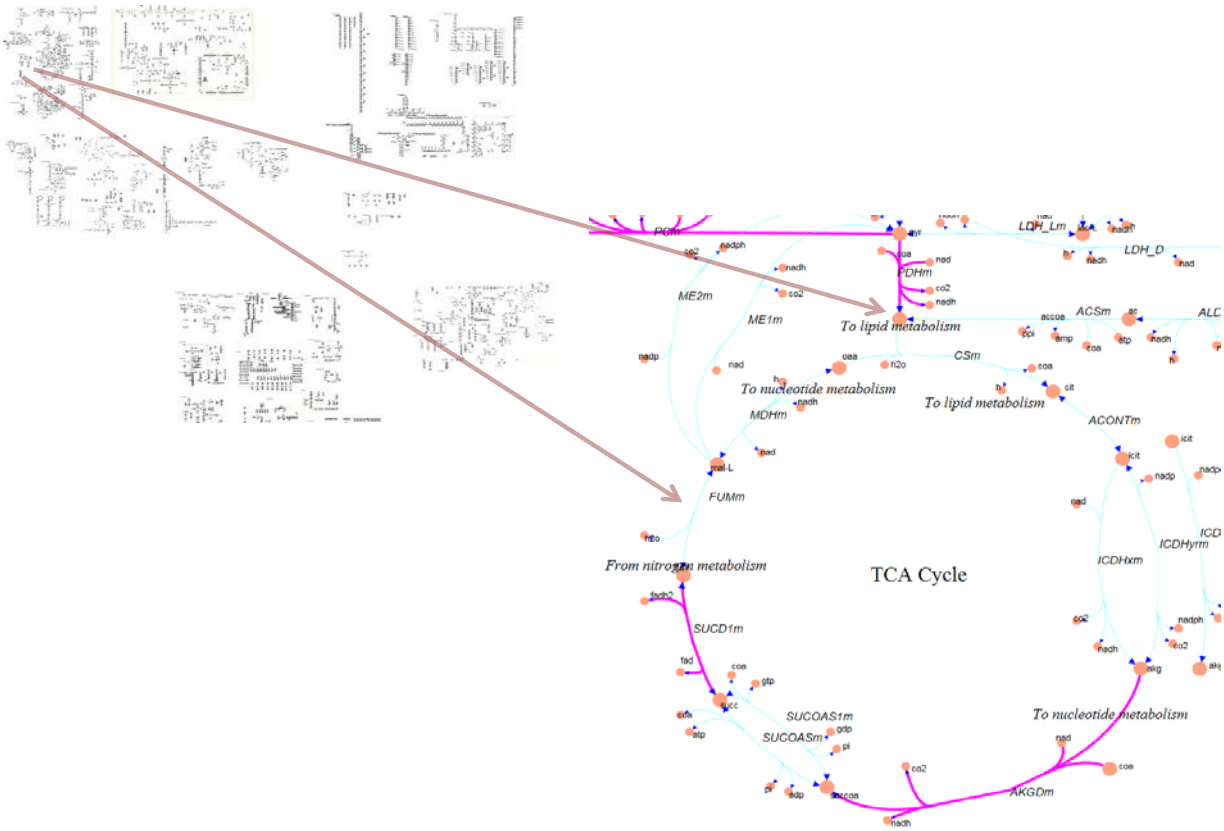


Figure 17: A schematic representing Genome Scale Metabolic Model (GSMM) consisting of 1700 metabolites and corresponding 1200 enzymatic proteins. The network was overlaid with proteomics data to identify the perturbed pathways. The TCA cycle is zoomed out to show how it looks after putting the data on the network (marked in pink colour).

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Bioprocess Improvement

High-quality mammalian recombinant proteins are extensively used in research, pathological diagnostics as well as in therapy and are among the most profit-generating market products in the biopharmaceutical industry. The cost of these products remains high due to complex and challenging industrial scale multi-step production process. Efforts are being made to improve the performances of the mammalian cell based production process; and by today, it is possible to achieve >10g/L. However, further improvements in the production capabilities of bioactive recombinant proteins are of eminent importance to meet the global demand at low- or at least affordable-cost.

Dr. Niraj Kumar's and **Dr. Susmita Chaudhuri**'s research teams are **working to improve the yields of recombinant protein products from mammalian cell-based industrial bioprocess**. Towards this, they are steering efforts to improve the production capability of cells in culture, minimize product degradation and heterogeneity, and improve the product purification process.

Last year, they found that the availability of few selected metals in culture media and supplementation of microvesicles collected from early-log phase of culture in growth media improved cell growth in culture. This knowledge would help to reduce lag phase and quickly achieve maximal viable cell density in culture. Since availability of viable producer cells in culture is directly correlated with the yield, it is expected to significantly impact the overall yield from production culture with reduced lag phase and increased culture longevity. They have also tested a few frugal-innovation-based prototypes of 'exoRemove' (a proposed product for online removal of proteolytic enzymes enriched microvesicles secreted in stationary phase of culture) and still working for the purpose. exoRemove would also enable the collection of the microvesicles in sterile conditions for bioprocess, medical, research use or other related purposes.

In future, they aim to develop and optimize host cell and its feeding strategy for achieving optimally improved production from Chinese Hamster Ovary (CHO)-based bioprocess along with developing a functional prototype of exoRemove and collaborations with potential large-scale developers and users of the product.

Research teams

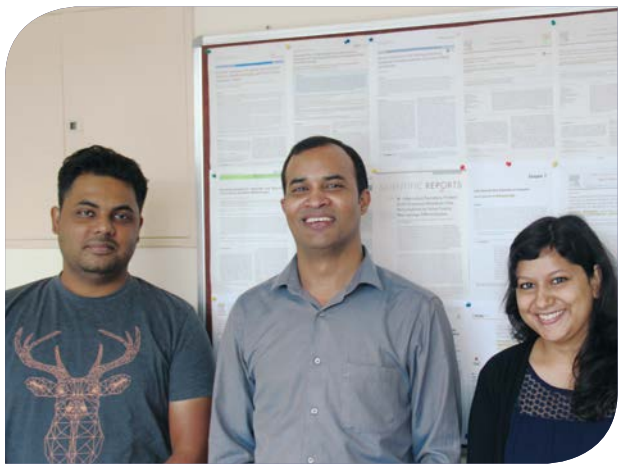
L-R: Nidhi Sharma, Naveen Kumar, Vikas Phagna, Dinesh Mahajan, Lata Tiwari, Bhuvesh Kumar, Arun Kumar

L-R: Sandeep Singh, Ghanshyam Sharma, Deepika Kumari, Shilpa Jamwal

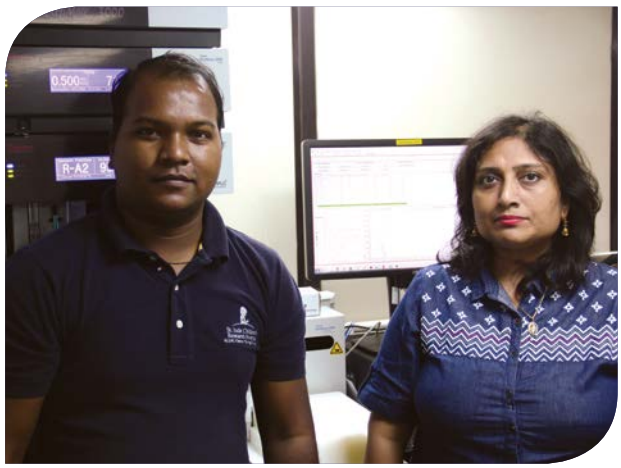
L-R: Ankit Gupta, Sameena Khan, Sudha

L-R: Anvita Chaudhary, Ajay Kumar, Shweta Duggal, Ganga Sagar

L-R: Mrityunjay Singh, Mitul Srivastava, Shailendra Asthana, Lovika Mittal, Charu Suri, Anita Kumari



L-R: Puneet Kumar Kadimi, Amit Kumar Yadav, Suruchi Aggarwal,



L-R: Ankur Kumar, Renu Goel

L-R: Sonu Kumar, Yashwant Kumar, Neema Bisht

L-R: Shivam Kumar, Surender Rawat, Ganga Sagar, Samrat Chatterjee, Sonali Porey Karmakar, Rajat Anand, Anuradha Yadav, Krishan, Dipanka Tanu Sarma

RESEARCH ON MATERNAL AND CHILD HEALTH

GARBH-INI: A PREGNANCY COHORT TO STUDY MULTIDIMENSIONAL CORRELATES OF PRETERM BIRTH IN INDIA

ADVERSE PREGNANCY OUTCOMES: MOLECULAR CHARACTERIZATION STUDIES IN PERINATAL BIOLOGY

MATERNAL NUTRIENTS AND CHILD HEALTH

CHILDHOOD DISEASES

NEONATAL SEPSIS

B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

MINIMAL CHANGE DISEASE NEPHROTIC SYNDROME

GARBH-INI: A Pregnancy Cohort to Study Multidimensional Correlates of Preterm Birth in India

It is a unique collaborative interdisciplinary program between research institutes (THSTI, Faridabad; National Institute of Biomedical Genomics (NIBMG), Kalyani; Regional Centre for Biotechnology (RCB), Faridabad; and district Gurugram Civil Hospital (GCH), Gurugram and tertiary care hospitals (Safdarjung Hospital, Maulana Azad Medical College (MAMC), New Delhi); **coordinated by Pediatric Biology Centre, THSTI**).

GARBH-INI (Interdisciplinary Group for Advanced Research on BirtH Outcomes-a DBT INdia Initiative): A Pregnancy Cohort to Study Multidimensional Correlates of Preterm Birth in India

Dr. Shinjini Bhatnagar

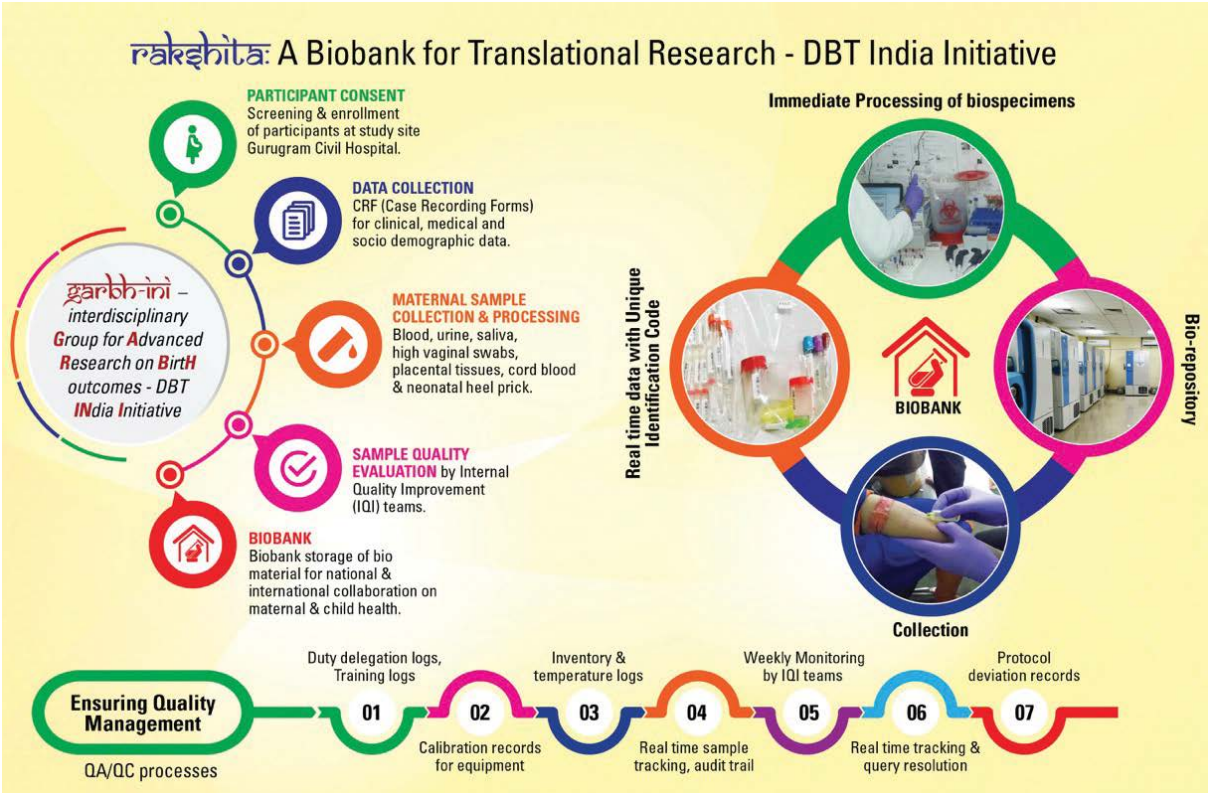
Preterm Birth (PTB) is a major public health problem globally. In India, annually about 13% (3.6 million of 27 million) of all babies born are preterm. About 300,000 of preterm babies die each year because of complications contributing to 25% of the overall global preterm-related deaths. The adverse consequences of preterm birth extend beyond early infancy with substantial consequences later in life. Effective solutions have not been possible because PTB is a complex syndrome with multiple etiologies that include interacting biological, psychosocial and environmental factors. Risk stratification of women based on multidimensional risk factors assessed during pregnancy is critical for prevention of preterm birth.

To address this, an interdisciplinary **G**roup for **A**dvanced **R**esearch on **B**irt**H** outcomes – a DBT **IN**dia **I**nitiative (**GARBH-INI**) has been established across DBT autonomous research institutes and hospitals. **A cohort (GARBH-INI-cohort) of pregnant women was started in May 2015 at the civil hospital in Gurugram, Haryana, India with the objectives to identify the clinical, epidemiological, genomic, epigenomic, proteomic and microbial correlates, discover molecular risk-markers by using an integrative omics approach, and generate a risk-prediction algorithm for preterm birth**.

Study Overview

Women are enrolled within 20 weeks of gestation and are followed until delivery and once post-partum. A dedicated research team of physicians, nurses, clinical technicians, field workers, and project managers ensures that all study procedures are followed according to standard procedures at the clinical research infrastructure established at the GCH and the Safdarjung Hospital. They are responsible for documenting all relevant exposures and pregnancy outcomes as per protocol. The serially collected human biospecimens across pregnancy, at delivery, and post-partum are processed immediately in the research laboratory established at GCH and transported by the study laboratory technicians to the biorepository at THSTI using validated standard operating protocols.

The biorepository established at THSTI has liquid cryo-vessels, dry shippers (temperatures at -196°C for 10 days), and deep freezers (-75°C) with continuous power supply and electronic remote alerts for



temperature monitoring. A dedicated, trained technical team maintains storage and retrieval of biospecimens according to the protocols developed according to the global guidelines of the International Society for Biological and Environmental Repositories. Over the last year, the biorepository has been expanded to cover an area of 2766 sq. feet with increase in its capacity to store a total of ~ 14 lakh biospecimens. An online laboratory monitoring system enables real time tracking of each collected and processed biospecimen using a unique identification code for each participant. It anonymizes the collected biospecimen. Relevant biospecimens are further transported to the respective institutions for specific bioassays (NIBMG: genomics and epigenomics, RCB: proteomics, THSTI: microbiome, micronutrient, immunophenotyping, placental exosomes and metabolomics).

The Internal Quality Improvement team maintains rigorous quality control and assurance for all study procedures.

Serial abdominal and transvaginal ultrasound scans are taken by a dedicated study radiologist on a GE Voluson E8 Expert (General Electric Healthcare, Chicago, Illinois, USA) ultrasound machine to document the Period Of Gestation (POG), fetal growth and well-being, serial changes in cervical length, and placental location and morphology.

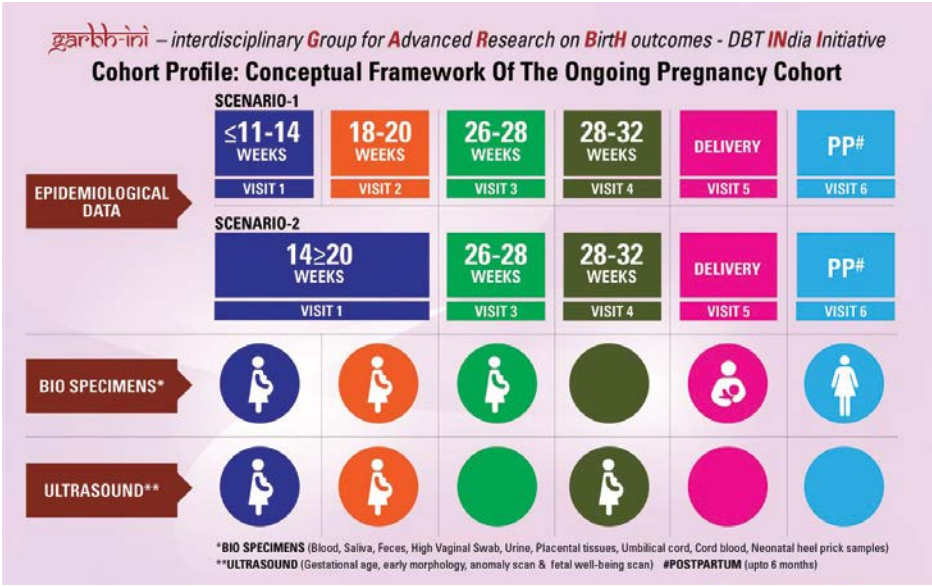
Virtual ultrasound images and the de-identified clinical, epidemiological and laboratory data are stored in the repository at the Data Management Centre at THSTI. All data collected is linked through the unique identification code. The database is anonymized and can be accessed from the server (Dell PowerEdge R720, Dell Inc., Texas, USA) at THSTI. The front-end of the application is on C#/.NET (Microsoft Inc., Washington, USA) and the backend in the MS-SQL server (Microsoft Inc., Washington, USA). Quality control is performed at regular intervals on data of $\sqrt{n}$ +1 (n= participants), or 20% participants, whichever is less. All data is protected and confidential and has adequate backups.

A Steering Committee of international and national experts reviews the progress, guides the scientific strategy and policies on data and biospecimen sharing.

Current Status of the GARBH-INI Cohort

The research group started enrolling women in May 2015 and a total of 14,433 women were screened till March 2018 (5,257 from April 2017 to March 2018)**.** Among them, 4,326 (1,044 from April 2017 to March 2018) were enrolled after ultrasound documentation of uterine pregnancy of <20 weeks POG and confirmation of all eligibility criteria. Nearly 60% of the participants in the cohort were enrolled within 14 weeks POG. The current attrition rate is 12.3% and has decreased from 22% in the initial period of the study.

The participants have a median (interquartile range; IQR) age of 23 (21, 25) years and more than a fourth are underweight (BMI < 18.5). Interestingly, over 10% are overweight or obese. History of preterm birth, a known risk



Timelines for implementation: 2015-2018

Enrollments - 4800

Outcomes determined - 3200

PTB - 14% Still birth ~ 2%

LBW - 23% SGA - 38%

Maternal anemia - 88%

EARLY FINDINGS

- *Indoor pollution associated with early birth*
- *Early shortening of the cervix - risk factor for PTB*
- *3 distinct microbial community state types in maternal vagina*
- *Distinct proteomic profiles in longitudinal collected maternal saliva & HVS*
- *Few proteins are central proteins ('the hub') that are modulated with the progression of pregnancy*
- *Epigenomic alterations between term and PTB in maternal blood*

factor for PTB, was documented as recall data in 7.8% of the participants, emphasizing that PTB is a common problem in our setting.

A total of 2935 outcomes have been documented in the enrolled participants till March 2018 (1657 from April 2017 to March 2018). Table 1 describes the pregnancy outcomes till now.

TABLE 1. Summary of pregnancy outcomes till March 2018

Pregnancy outcomes	N (%)
Outcomes documented	n=2935[a]
Live births	2792 (95.1)
Abortions	85 (2.9)
Medical termination of pregnancy	6 (0.2)
Stillbirths	51 (1.7)
	n= 1662
Preterm births[b]	391 (14.0)
Preterm birth by clinical severity	n=391
Extremely preterm (< 28 weeks)	7 (2.8)
Very preterm (28 - < 32 weeks)	14 (5.7)
Moderate preterm (32 - <35 weeks)	64 (25.9)
Late preterm (35 - <37 weeks)	162 (65.6)

An Integrative OMICS Approach to Discover Molecular Risk Markers for Preterm Birth

The research group has demonstrated the longitudinal maternal quantitative proteome profile in saliva and high vaginal swab in normal pregnancy by using high throughput mass spectrometry-based proteomics. The findings suggest that 38 proteins from saliva are central proteins ('hub') that are modulated with the progression of pregnancy; there are six broad clusters with distinctive patterns of expression that alter with gestation. The results provide a conceptual framework for understanding the molecular mechanisms governing the progression of normal pregnancy and will help to compare the proteome profile of the preterm birth with that of normal pregnancy. Temporal alterations of the DNA landscape that occurs during the course of pregnancy in maternal peripheral blood might be indicative of preterm birth outcomes. The preliminary results have shown changes in genome-wide alterations in DNA methylation in the maternal peripheral blood collected during the course of pregnancy (sampled at three trimesters during pregnancy and one at delivery) in a subset (n=20) of women who had delivered preterm compared to those delivered at term (n =20). These changes are now being correlated with changes in the gene expression levels by performing RNA-Seq with the RNA obtained from whole blood stored in PAXgene Blood RNA tubes (preanalytic) in a subset of samples.

In future, risk stratification of pregnant women for preterm birth will be done using traditional statistical methods like multivariable regression models, data mining techniques by Classification and Regression Trees, and novel technologies using machine learning methods like Artificial Neural Networks. Correlation-based analysis of the multidimensional data sets will be performed to integrate clinical outcomes and other associated demographic data. Enrichment analysis will be undertaken to provide biological interpretation by integrating biochemical pathways and processes with gene expression results. The biological networks (complex interactions between diverse types of cellular components such as genes, proteins, and metabolites) will be used to integrate the experimental results obtained from multiple platforms to identify biological alterations, which do not depend on any predefined biochemical pathways. The same will also be used for visualization and functional enrichment analysis. The ultimate goal of this multi-omics analysis is to identify an effective model that predicts a phenotype or traits and outcomes. This model will facilitate an effective tool for prediction of preterm delivery.

This ongoing large cohort of pregnant women from early pregnancy is the only such cohort in India that uses an interdisciplinary approach comprising methodologies of clinical, epidemiological, statistical, genetic, proteomic, and imaging sciences to study PTB-a major global public health problem with significant immediate and long-term implications in low- and middle-income countries. The high proportion of 14% preterm birth reported in the preliminary analysis is remarkable. It is envisaged that this cohort and the repository will become a national and global resource to answer important questions around pregnancy and birth outcomes.

MEMBERS OF GARBH-INI

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Adverse Pregnancy Outcomes: Molecular Characterization Studies in Perinatal Biology

Dr. Pallavi Kshetrapal

Dr. Pallavi Kshetrapal's research team is studying adverse pregnancy outcomes using candidate and agnostic approaches. Specifically, they are **analyzing Single Nucleotide Polymorphisms (SNPs) in HLA- G gene and their association with adverse pregnancy outcomes**. HLA-G, a non-classical Major Histocompatibility Complex class I molecule, is expressed in the extra-villous trophoblasts lining the maternal-fetal side of the placenta. It plays an important role in the prevention of fetal cell cytolysis by regulating the uterine NK cells and T cells. Apart from that, HLA-G also plays an important role in regulating other mechanisms operating at the maternal-fetal interface that are critical for maintaining pregnancy.

They aim to identify SNPs at the 5` URR region of the HLA- G gene between two categories, Small for Gestational Age (SGA) vs Appropriate for Gestational Age (AGA) neonates and understand how these polymorphisms lead to changes in expression patterns of this protein, if any. SGA neonates are smaller than 90% of all other babies of the same gestational age and are at greater risk for stillbirth, birth hypoxia, neonatal complications, impaired neurodevelopment, and possibly type 2 diabetes and hypertension in adult life. Despite evidence for HLA-G playing an important role during pregnancy, the precise relationship between genetic variation in HLA-G and the associated pregnancy outcome, i.e. birth of SGA/AGA neonates remains unresolved.

The cases (SGA) and controls (AGA) have been selected from the pregnancy cohort population being enrolled in the GARBHINI study cohort. The DNA isolated from umbilical cord blood samples from the consented enrolled participants is being stored along with curated clinical data on the medical history of the participating mothers. The neonates are categorized as SGA or AGA on the basis of Fenton Growth Charts 2013.

As a preliminary step, the obtained sequences from the promoter region of the HLA-G gene are being aligned and compared using online tools MUSCLE (MUltiple Sequence Comparison by Log- Expectation), and HapMap to identify the differences between the two groups. Later, these molecular results will be correlated with the clinical data using statistical tools and multivariate models to identify the correlation between the SNPs in HLA-G to birth of SGA neonates.

The placenta is a transient organ that provides nutrition and functions as an immuno-tolerant zone for the fetus. There is limited data on longitudinal development of the growing placenta, due to unobtainability of the tissue. Use of surrogate markers of placental growth and function such as multi-vesicular bodies in the maternal circulation could help identify new markers of fetal well-being and the biology of the placenta. In another study, her research group is **elucidating the biochemical and molecular signatures**

of placental exosomes in adverse pregnancy outcomes. They aim to (i) perform metabolome, proteome and microRNA profiling on placental-specific exosomes derived from longitudinally-collected maternal sera/ plasma to identify molecular signatures of placental growth, (ii) analyze the metabolite profile obtained at various time points of pregnancy using a combination of mathematical and computational tools to identify temporal patterns that may correlate to the pregnancy outcome.

In the past year, they carried out both total exosome and placental-specific exosome isolation from maternal plasma samples obtained at three different time points in pregnancy, and at delivery from term and preterm delivering mothers. Further, they acquired and analyzed the miRNA and protein cargo present in the isolated exosomes. The preliminary data obtained from this longitudinal study have identified specific exosomal miRNA changes in term and PTB as a function of gestational age during pregnancy. This data was subjected to an innovative approach of linear mixed modelling so as to determine exosomal miRNA expression as a function of gestational age in term and PTB pregnancies. The bioinformatic analysis established that the differences in the miRNA profile are targeting signaling pathways associated with TGF-β signaling, p53, and glucocorticoid receptor signaling, respectively.

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Maternal Nutrients and Child Health

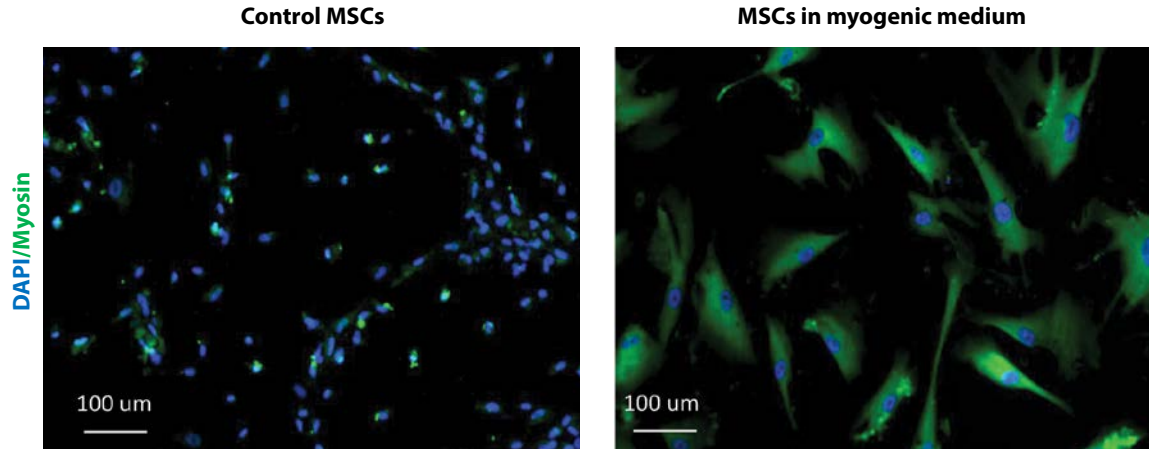
Dr. Suchitra Gopinath

Dr. Suchitra Gopinath's research is focused on **understanding how maternal micronutrient levels affect fetal skeletal muscle growth and eventually the fetal growth index**. She is working towards the identification of molecular mechanisms regulating fetal skeletal muscle mass, particularly in the context of micronutrient deprivation (specifically vitamin D), with an added focus on how muscle stem cells contribute to this process.

Her team has begun enrolling pregnant women in their second trimester from Northern India with the intention of isolating mesenchymal stem cells (MSCs) from umbilical cord blood (uMSCs). They have used the uMSCs to transdifferentiate them into skeletal muscle cells within a time span of 14 days using a combination of dexamethasone and hydroscortisone (Figure 1). The group aims to assess the myogenic differentiation potential of these populations derived from women with different vitamin D levels to investigate whether there is a link between muscle mass in fetal growth and maternal vitamin D levels.

Further, preliminary experiments in mice lacking vitamin D receptor indicate that mitochondrial gene expression and function are directly regulated by receptor activity. At the level of protein synthesis and translation, atrophying muscle observed in vitamin D receptor-lacking mice is, surprisingly, not due to a decline in global protein synthesis, as revealed by polysomal profiling experiments, but due to rapid protein degradation rates. Whether synthesis of specific proteins is affected by the absence of vitamin D signaling, is being investigated using RNA-sequencing and ribosomal profiling technologies. These mechanistic studies in mice might provide insights into the role of maternal vitamin D levels in fetal skeletal muscle formation and growth in humans.

Figure 1: Myogenic differentiation of umbilical cord-derived mesenchymal stem cells. MSCs obtained from umbilical cord blood were cultured in control or myogenic differentiation media for 14 days, fixed, and stained with a Fast Myosin antibody (MY32, in green) and DAPI (in blue) for the nucleus.



COLLABORATORS

Dr. Suchitra Gopinath
Dr. Shinjini Bhatnagar, THSTI, Faridabad
Dr. Sunita Sharma, Gurugram Civil hospital, Gurugram
Dr. Aneeshkumar A.G., National Institute of Immunology, New Delhi

Childhood Diseases

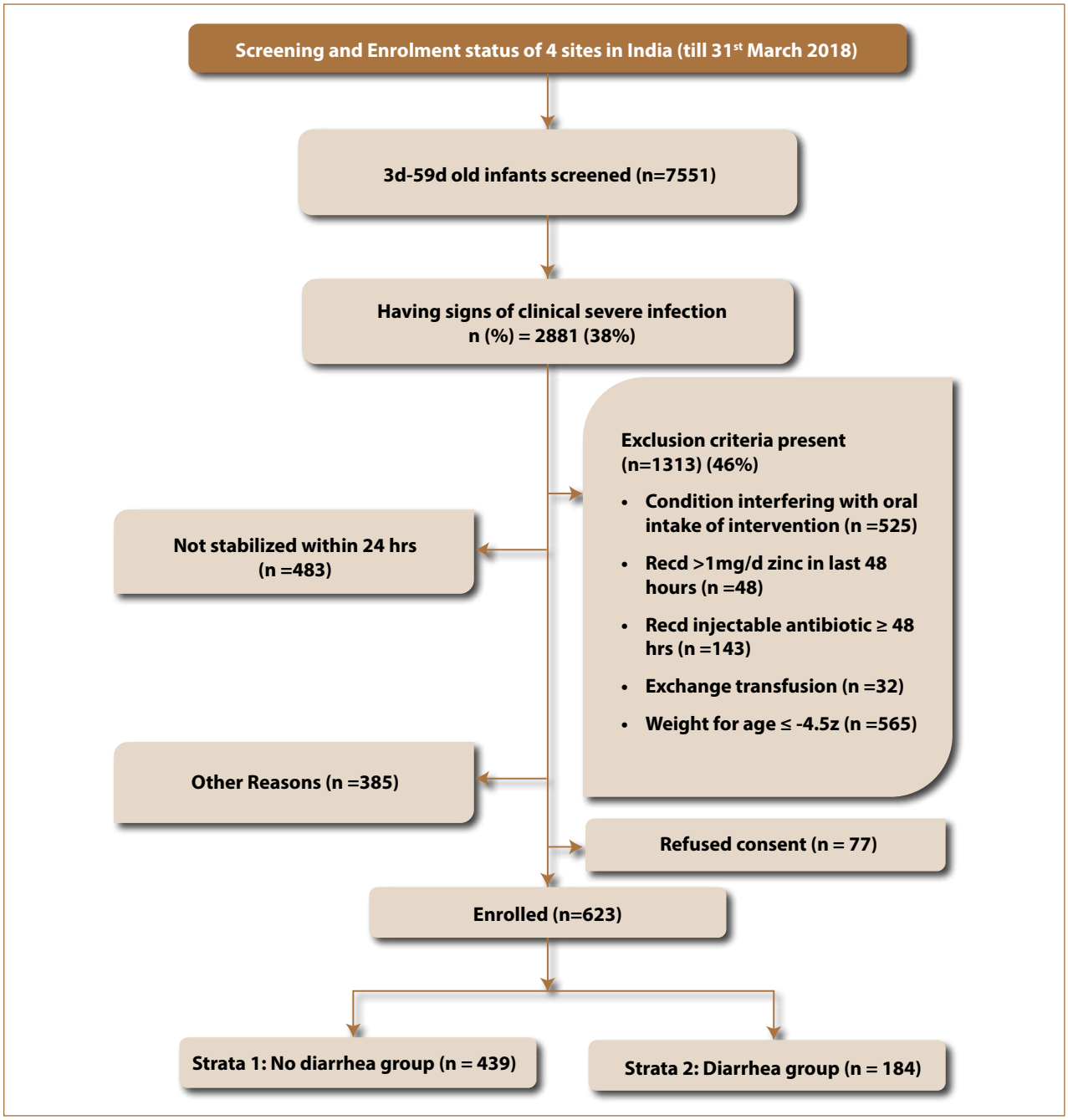
Neonatal Sepsis

Almost half of the 6.3 million deaths in children under 5 years of age occur in the first month of life (neonatal period) and about three-quarter of these deaths occur in the first week of life. More than 70% of the neonatal deaths occur in Africa and South East Asia. In India, more than a quarter of the annual 1 million neonatal deaths result from serious infections like pneumonia, sepsis, and meningitis. These illnesses are a major cause of death and hospitalization also in Nepal. While appropriate antibiotics are available in many hospitals in low and middle income countries, second-line antibiotics are unavailable or are prohibitively expensive in peripheral health facilities. It is important to develop inexpensive, effective, and accessible interventions that can be added to standard therapy for severe infections to improve treatment outcome and reduce case fatality.

Dr. Nitya Wadhwa

Dr. Nitya Wadhwa's research group is **attempting to evaluate the role of zinc as an adjunct to standard antibiotic therapy for clinical sepsis in reducing mortality and treatment failure in young infants, particularly in settings where resources are limited and second line antibiotics may not be readily available.** In a previous randomized placebo-controlled trial conducted in three tertiary hospitals in New Delhi, they found that 10 mg of elemental zinc given daily to 7- to 120-days old infants treated with antibiotics for probable serious bacterial infection (PSBI) carried a 40% (95% CI 10% to 60%) efficacy against treatment failure. The absolute risk reduction was 6.8% (95% CI 1.5% to 12.0%) indicating that 15 (95% CI 8 to 67) infants would need to be treated with zinc in addition to antibiotics to prevent one treatment failure. The point estimate for the efficacy of adjunct zinc therapy against death was the same as that against treatment failure (43%), albeit with poorer precision (95% CI -23% to 73). The study was not designed or powered to measure an effect on death, and therefore is not a strong driver for policy change. Based on the promising results of the above-mentioned trial, a large, multi-center study powered to examine the effect of zinc on case fatality from clinical sepsis would contribute evidence towards revising treatment recommendations for low resource settings in South Asia and elsewhere. Further, as they propose to identify young infants with clinical sepsis using an adaptation of the Integrated Management of Childhood Illnesses (IMCI) criteria, it would be easier to justify the introduction of zinc in the national programs where IMCI/ IMNCI are followed.

The group is in the process of conducting a multi-country (India and Nepal) multi-center (6 hospitals) individually randomized double-blind placebo-controlled parallel group clinical trial. The trial was initiated in a phased manner in February 2017. As of March 2018, the study enrolled a total of 758 young infants across the 6 sites. The 4 sites in India have enrolled 623 young infants with clinical severe infection. The study is ongoing and the group proposes to complete the enrolments by August 2020.



Project Investigator: *Dr. Nitya Wadhwa*
Co-Project Investigators:
Dr. Shinjini Bhatnagar, THSTI, Faridabad
Dr. Sudha Basnet, Tribhuvan University, Nepal
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B-Cell Acute Lymphoblastic Leukemia (B-All)

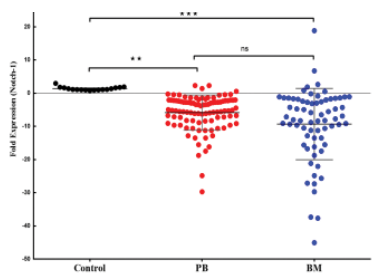

Figure 2: Gene expression analysis using quantitative Real-time PCR (qPCR) on Pediatric B-ALL patients, peripheral blood (PB) and bone marrow (BM) and compared to pediatric healthy controls. (unpaired, non-parametric {Mann-Whitney test} Student's t-test was used for comparison between control vs. patients samples for Notch-1 expression. Statistical significance was assessed ($p < 0.001–0.05$).

Childhood Acute Lymphoblastic Leukemia (ALL) is an aggressive hematologic malignancy that results from malignant transformation of normal developing B cells. **Dr. Pallavi Kshetrapal** is trying **to understand the molecular mechanisms in pediatric B-All, with a focus on studying the relation of the master regulator Notch and its synergies in B-All**.

To test the hypothesis that Notch plays a crucial part in progression of pediatric B-All, her group collected peripheral blood and bone marrow samples from consented enrolled pediatric patients who came to the AIIMS hospital for standard care. They performed expression analysis using quantitative real-time PCR (qPCR) on samples from precursor B-All (N=103) and healthy donors (N=22). The qPCR data revealed a marked down-modulation of Notch 1 transcript in 70% of the cancer patient samples (Figure 2).

Using statistical tools and multivariate models, they are in the process of analyzing their molecular results with the clinicopathological data to identify the correlation of the Notch1 expression profiles to symptoms, severity, progression, remission, and prognosis of the disease. In future, they aim to understand the mechanism these genes adopt in the progression of the disease using *in vitro* cell culture approaches.

Minimal Change Disease Nephrotic Syndrome

Dr. Shailaja Sopory

Minimal Change Disease Nephrotic Syndrome (MCDNS) is the most common cause of nephrotic syndrome in children. CD80, a T-cell costimulatory molecule, has been shown to be upregulated in podocytes and also excreted in the urine of patients with active disease. Some research groups have demonstrated CD80 expression in kidney biopsies of patients with focal segmental glomerulosclerosis and also successfully used abatacept, an inhibitor of CD80, to induce partial or complete remission in these patients. On the contrary, there is some controversy in the field regarding the detection of CD80 in human biopsy samples and whether abatacept can be used in all cases of nephrotic syndrome. **Dr. Shailaja Sopory**'s research is targeted to **understand the mechanism of CD80-mediated proteinuria in nephrotic syndrome and the causes and consequences of CD80 upregulation in the podocyte**.

In the past year, her group demonstrated that TNFα treatment of murine podocytes leads to an increase in CD80, actin derangement and poor wound healing. Podocytes stably expressing CD80 show actin derangement and co-localization with Neph-1. CD80 and Neph-1 interaction was confirmed by pulldown assays of CD80 and Neph-1 transfected in HEK293 cells. They show that this interaction was via the extracellular domain of both proteins and suggest that binding of CD80 to Neph-1 precludes Neph-1 from oligomerizing, thus physically disrupting the structure of the slit diaphragm and interfering with the signaling pathways involved in actin

polymerization (Figure 3). Moreover, it also implies the possible use of small molecules that disrupt CD80-Neph-1 interaction as a potential treatment of nephrotic syndrome associated with CD80 upregulation. One such molecule, abatacept (a fusion protein composed of the Fc region of IgG1 and the extracellular domain of CTLA4) that binds to CD80 has shown positive effects in some cases of nephrotic syndrome.

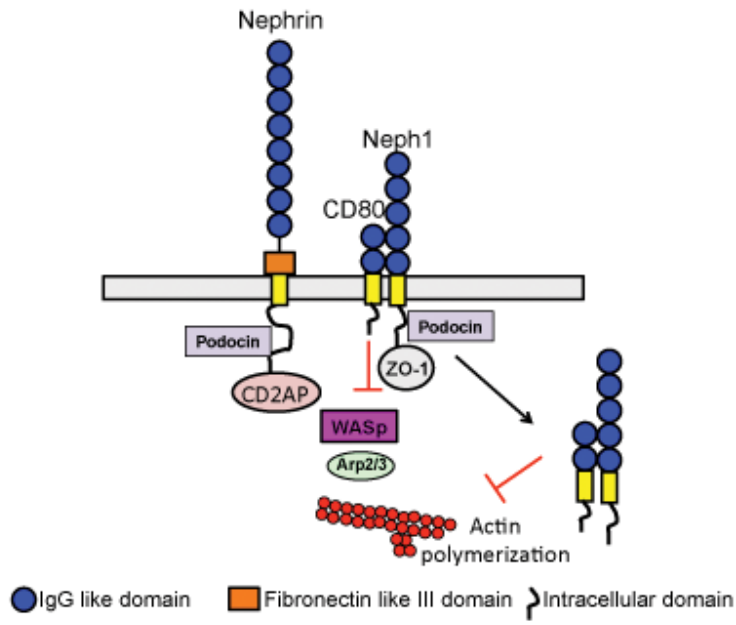

Figure 3: Illustration to show disruption of Neph-1 Nephrin signalling at the Slit Diaphragm by CD80. Binding of CD80 to Neph-1 can trap Neph-1 in the cell preventing it from targeting to the cell surface for oligomerization with itself or nephrin, thereby disrupting the signalling processes required for actin organization

COLLABORATORS

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Research teams

L-R: Rashmi, Ajay, Archana, Shilpi Sehgal, Savita, Dr. Pallavi Kshetrapal, Dr. Mukesh Kumar Singh, Vijayakumar P., Himanshu, Nitin Kumar, Amit, Uttam Saini, Amitab Bachan

L-R: Dinesh Chauhan, Ramesh Kumar, Sagar Singh, Mamta Rai, Sachin Baloni, Rakesh Kumar, Satish, Ashu Sharma, Ritesh Ranjan, Shrichand Pandey, Manish Sethi, Mukesh Juyal, Rahul Sharma, Amanpreet Singh, S. S. Suresh, Nitya Wadhwa, Veenu Kumar Mani, Debjani Purakayastha, Rajkumar Tanwar, Shilpa Chopra, T. Ramachandran, Sandeep, Priyanka Sharma

L-R: Ashish Tyagi, Yamini Goswami, Raj Kumar Tanwar, Khushboo Kaushal, Anubhuti Gupta, Saimah Raza, Shailaja Sopory, Deepa Nair, Anita Chaudhary, Gaurav Singh, Manoj Mahato

POLICY RESEARCH

FLAGSHIP PROGRAM ON DIAGNOSTICS

FLAGSHIP PROGRAM ON CHOLERA

FLAGSHIP PROGRAM ON MATERNAL AND CHILD HEALTH

NEGLECTED TROPICAL DISEASES

ONE HEALTH

A key goal of THSTI is to provide policy support for health care in India. As a part of this endeavour, the policy research group provides inputs in the form of reviews and landscaping to identify technology needs and gaps in the public health system. It engages with multidisciplinary stakeholders both nationally and internationally to create networks of investigators, consultants, funding agencies and industries in specific areas. Briefly, the activities range from collation and analysis of evidence for decision-making, creation of a technology-push and demand generation for socially relevant interventions for public health in the country.

Flagship Program on Diagnostics

Prof. N.K. Ganguly

Dr. Bratati Mukhopadhyay

This program aimed at mapping resource requirements for basic sciences and biomedical research for development of diagnostics. Consequently, a "diagnostics dashboard" was created based on the gaps and unmet needs in India.

As a part of flagship program of point of care diagnostics for infectious diseases in India, a landscaping exercise of the current diagnostics technologies in TB was carried out. The gap analysis identified mechanisms to facilitate introduction of appropriate technologies at different levels of health care systems. The work also focused upon identification and mitigation of challenges associated with TB diagnostics through partnerships. Based on the current recommendation of World Health Organization (WHO) for replacement of microscopic culture method for TB test, the policy programme conceptualized a multi-centric validation study of Loop Mediated Amplification (LAMP) test at community health centers under some of the established processing laboratories across selected geographical representations in India. Collaboration was initiated with a Germany-based diagnostic company and few Indian investigators to facilitate its prospective introduction in the national program.

Likewise, the challenges of current diagnostics for visceral leishmaniasis were identified and the feasibility of a large-scale validation for novel and indigenous diagnostics for elimination program of Kala azar in India was attempted in collaboration with Rajendra Memorial Research Institute of Medical Sciences, Patna.

In addition, a situation analysis for novel diagnostics platforms was created for AMR. Innovators of indigenous diagnostics for TB, pneumonia, sexually transmitted diseases, and typhoid were supported for getting their products validated. An attempt was also made to supplement the knowledge on use of cholera diagnostics in laboratories across India identified through the pan-India Biosafety project.

Contributors: Dr. Bratati Mukhopadhyay and Prof. N.K. Ganguly

Flagship Program on Cholera

Sanjukta Sen Gupta

India leads the world in the number of cases as well as deaths due to cholera. It is presumably the cause of recent major cholera outbreaks in countries like Haiti and Yemen. The Indo-Gangetic plain has been the locus of global spread of cholera in six out of seven pandemics of the disease. Even within the country, cholera is now reported from 14 states and union territories.

Funded by the Bill and Melinda Gates Foundation in 2015, an initiative under policy research was to create a roadmap for prevention and control of cholera in India. In the process of creating this roadmap, trends and distribution of cholera from 2010-2015 were reported and the gaps that existed in surveillance and reporting of cholera were identified. Based on available evidence, an effort was made in collaboration with DOVE project at Johns Hopkins University (JHU) to map the hotspots of cholera in India.

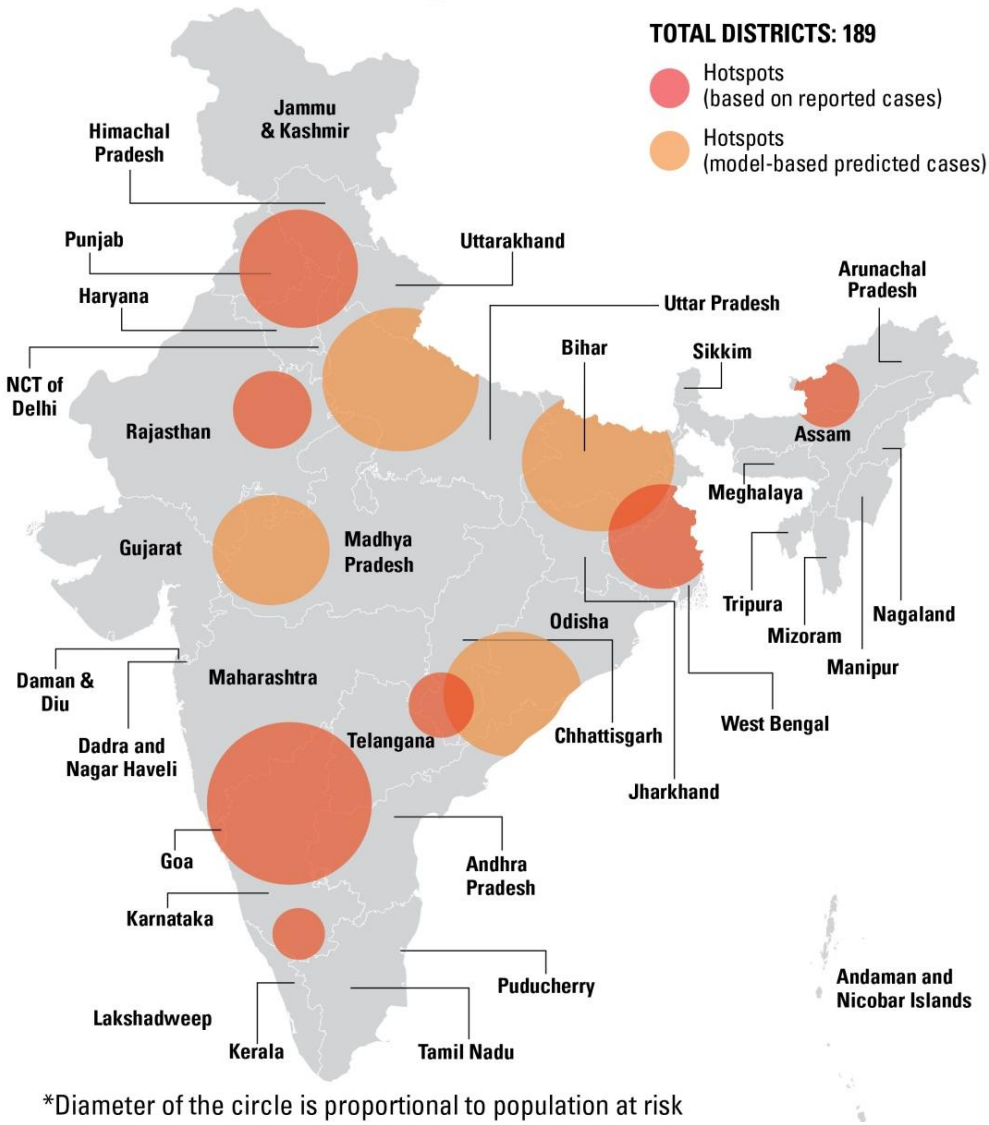

Figure 1: Hotspots of Cholera.

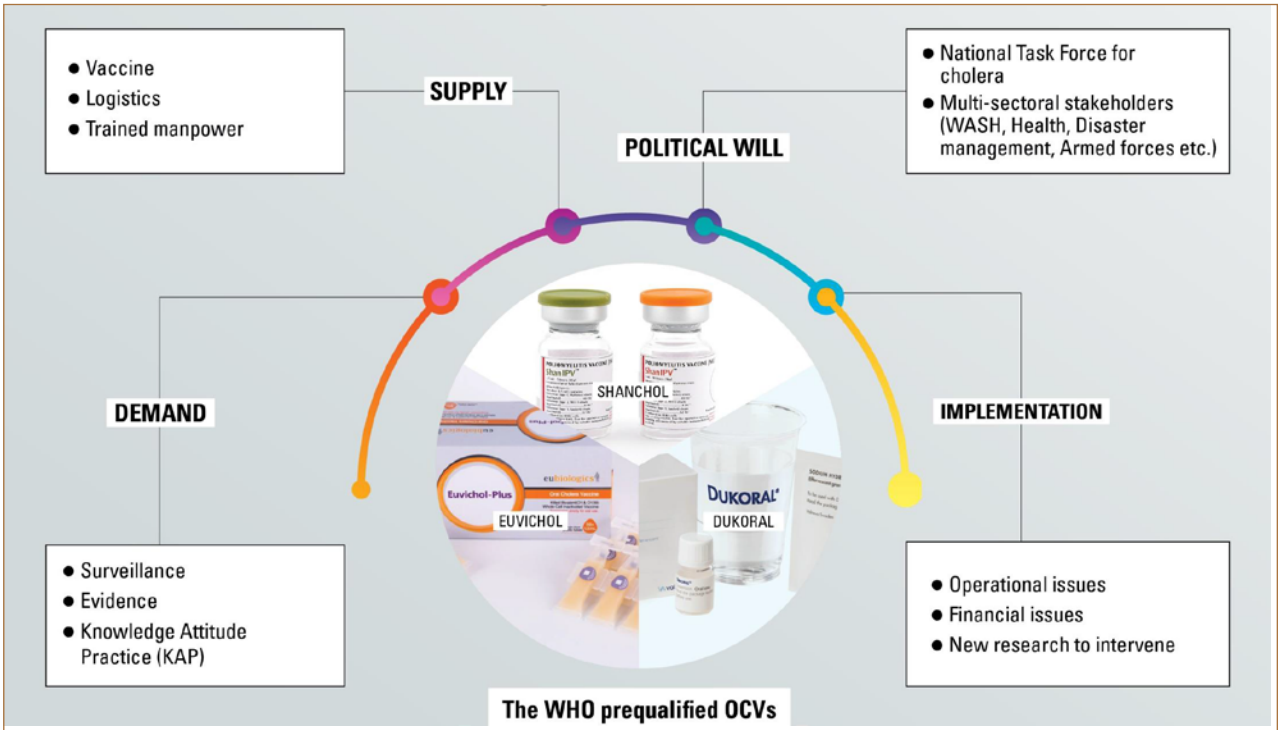

Figure 2: Bottleneck in decision making for use of Oral Cholera Vaccines in India.

7 hotspots, spread across 111 districts were found based on cases reported to the Integrated Disease Surveillance Program whereas 4 hotspots, spread across 178 districts were reported from model-based predicted cases. The latter included states of Uttar Pradesh, Bihar and Chattisgarh (Figure 1). Ironically, India also happens to be the producer of a vaccine for cholera, Shanchol, which is the first of the three vaccines to be WHO prequalified. Despite having good safety and immunogenicity profile and being used in 29 countries worldwide, the vaccine is still not being used in India through a public program ((Figure 2). According to their research, a whopping 375 million people in the country were estimated to be at risk for cholera, a population far beyond the reach of the currently available vaccine doses.

The policy programme at THSTI has also provided support towards introduction of new vaccines in India. It created a discussion platform for multidisciplinary stakeholders from government, academia, industry, global NGOs and funding agencies on specific vaccines that were being developed/ slated to be introduced. This activity was done in collaboration with the International Vaccine Access Center (IVAC) and Global Health Strategies (GHS), New Delhi. Two such meetings for Pneumococcal Conjugate Vaccine (PCV) were conducted in 2012 and 2015. Several decisions that emerged during these meetings were taken cognizance of when the PCV was introduced in the Expanded Program for Immunization (EPI) in April 2017. Since 2012, a series of meetings were conducted in partnership with ICMR to develop the Pneumococcal Etiology Surveillance Program, which finally got funded in July 2017.

Contributors: Dr. Sanjukta Sen Gupta and Prof. N.K. Ganguly

Flagship Program on Maternal and Child Health

Dr. Dibyakanti Mandal

The global burden of infectious diseases affecting neonates is very high. Since neonates are too young to be vaccinated, there is a considerable interest in studying ways of preventing maternal and infant morbidity with immunisation of the mother during pregnancy. Respiratory diseases that fall under this category are pertussis, respiratory syncytial virus, Group B Streptococcus, pneumococcus and influenza virus infections.

Global data on influenza burden where high degree of morbidity and mortality was observed in pregnant women was analysed by the policy research scientists at THSTI. In view of lack of systematically collected data on influenza in pregnant women from India, the scientists partnered with SOMAARTH – Demographic Development and Environmental Surveillance Site (DDESS) set up by the INCLEN trust International at Palwal, to collect baseline data on the prevalence and incidence of influenza in pregnant women prospectively for two seasons. A vaccine manufacturer has agreed to donate vaccine doses for the study. The work will not only identify a target group for influenza vaccination but will move towards building a policy of maternal immunization against influenza in India.

Contributors: Dr. Dibyakanti Mandal and Prof. N.K. Ganguly

Neglected Tropical Diseases

Dr. Gautam K. Saha

In partnership with WHO-SEARO and the Special Programme for Research and Training in Tropical Diseases at the WHO (WHO-TDR), the scientists mapped and documented the institutes, scientists, ongoing research and publications etc. on neglected tropical diseases in India. This initiative formed the basis of partnerships with global and national funding agencies, investigators and industry in the area of NTDs slated for elimination, namely, leishmaniasis, filariasis and soil-transmitted helminthiasis. They worked closely with the principal investigators of four vaccines for leishmaniasis, namely, Dr. Simon Croft, London School of Hygiene and Tropical Medicine, UK; Dr. Hira Nakhashi, US Food and Drug Administration, MD; Dr. A. Selvapandian, Jamia Hamdard, New Delhi; and Dr. Steeve Reed, Infectious Disease Research Institute, USA), and provided support to vaccine manufacturers who have absorbed some of the above mentioned technologies, namely Gennova Biopharmaceuticals Ltd., Pune; and Zydus Cadilla Pvt. Ltd., Ahmedabad.

Contributors: Dr. Gautam K. Saha and Prof. N. K. Ganguly

One Health

The rise of zoonotic diseases in the recent past and outbreaks of SARS, Ebola and Zika virus have underscored the importance of disease surveillance and need for educating the community about effective response against the outbreak as well as preventive measures for future calamities. The Millennium Development Goals 4 and 5 are key to progressing towards the Sustainable Development Goals for which a framework needs to be developed that could aid in promoting and implementing the concept of "One health", paving way for achieving sustainable heath and development goals. A proposal for engaging with different partners across disciplines for "One health concept" has been submitted for approval from the One Health Commission. This will enable creation of a One health forum to bring together educationists and researchers from different fields of science: human and animal health, environment, social sciences etc. to bring about the desired change.

Contributors: Dr. Gautam K. Saha, Dr. Sanjukta Sen Gupta and Prof. N. K. Ganguly

CLINICAL DEVELOPMENT SERVICES: A FOCUS ON CLINICAL DEVELOPMENT SERVICES AGENCY

TRAINING

REGULATORY AFFAIRS

CLINICAL STUDY SUPPORT SERVICES

COMPREHENSIVE NATIONAL NUTRITION SURVEY

MEDICAL AFFAIRS AND MEDICAL WRITING

CLINICAL DATA MANAGEMENT

Clinical Development Services Agency (CDSA) was launched in September 2009 as an extramural unit of THSTI. It was created to facilitate development of affordable healthcare products for public health diseases. Registered in September 2010 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 ecosystem for training and learning, and work with public sector institutions, and small and medium enterprises (SMEs) to translate innovative technologies into medical products for public good.

The main objectives of CDSA and work done so far have been as a:

- Training academy, building capacity and capability in the area of clinical development and translational research through training programs for young clinical researchers, ethics committee members and other personnel in becoming an efficient clinical research professional
- Monitoring agency for public health studies for compliance to Schedule Y regulations, ICMR, CDSCO-GCP guidelines, study protocol and other requirements
- Clinical study support services agency for academic investigators and SMEs through, project management, clinical and medical monitoring, audit, data management and regulatory consultation

CDSA with 5 Centers of Excellence (CoE), has formed a collegium of Centers of Clinical Research Excellence for collaboration in all the three areas listed above. The institutions are Center for Chronic Disease Control (CCDC), Gurugram; Centre for Health Research and Development (CHRD)-Society for Applied Studies (SAS), New Delhi; Christian Medical College (CMC), Vellore; Jagadguru Sri Shivaratreeswara (JSS) University, Mysuru; and King Edward Memorial (KEM) Hospital, Pune.

Training

CDSA has worked in the last year with the Indian drug regulators, Central Drugs Standard Control Organisation (CDSCO) and Indian Council of Medical Research (ICMR) in training biomedical researchers, clinicians, scientists, and ethics committee members. Key areas covered included Good Clinical Practice (GCP), Good Clinical Laboratory Practice (GCLP), Good Laboratory Practice (GLP), and ethics in clinical research and clinical research methodology (CRM) (Table 1).

TABLE 1: Summary of training courses conducted by CDSA

	2009-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	Total
Number of training cources undertaken	3 (1 CRM)	10 (1 GP; 1 RM)	14 5 GCP; 2 GLP)	17 (2 GCP)	21 (4GCP; 1 GLP)	29 (10 GCP; 3 GCLP; 1 GLP; 3 CRM)	17 (5 GCP; 1 GCLP; 1CRM)	111
Cities	2	5	10	10	9	15	12	63
Faculty	11	112	146	175	233	236	120	1033
Participants	41	436	894	1241	1906	1510	3376	10504
Institutions involved	10	117	222	428	536	391	439	2113

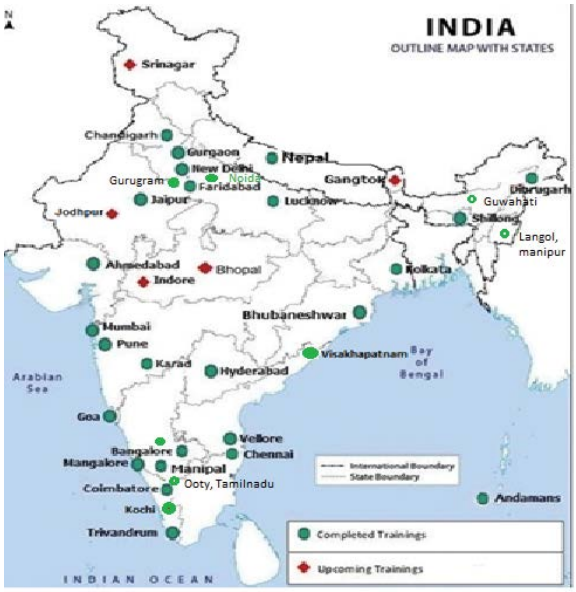

Figure 1: Training programs undertaken (green) and planned (red) across India.

Figure 2: Photographs from our various training programs across India.

Dissemination of National Guidelines 2017: CDSA, in association with ICMR Bioethics Unit, National Centre for Disease Informatics and Research had conducted a nationwide dissemination series on the ICMR-DBT National guidelines for stem cell research (2017), ICMR National ethical guidelines for biomedical and health research involving human participants (2017), and ICMR National ethical guidelines for biomedical research involving children (2017). During 2017-18, four programs were conducted at Ahmedabad, Vishakhapatnam, Kochi, and Guwahati which were attended by approximately 4000 participants.

Programs with our Centres of Excellence (COEs) partners: A new initiative was introduced to reach out to more target audience by working with our CoE partners in coming out with CDSA co-branded programs. Three such programs were conducted last year (2 with JSS, Mysuru; and 1 with CCDC, Gurugram). The topics covered were Research Methodology and Biostatistics using SPSS (JSS), Public Health Nutrition Research Methods and Policy Course (CCDC) and Critical thinking and GCP (JSS).

Capacity and capability building in clinical research: A two-day residential clinical research methodology course was delivered at CDSA for 33 clinicians and research scientists awarded with Wellcome Trust-DBT fellowships and project grants. This program was very well received by all attending participants.

National series on Laboratory Quality Management System (LQMS): This series was initiated in 2016-17 in collaboration with National Institute of Biologicals (NIB), Noida. Last year, a three-day residential hands-on LQMS course was conducted on diagnostics which was attended by 45 participants, representing 34 institutes and industry. A handbook developed from this program is being taken up by CDSCO for national implementation as a way forward.

Delivering training to far off and unrepresented areas: India is a vast country and we make special efforts to reach out to more distant regions and unrepresented areas like North East Region and tier 2 or 3 cities. Last year, we covered Langol (Manipur) and Guwahati (Assam).

The various cities where the team had conducted training sessions in 2017-18 are detailed in Figure 1**.** Our program photographs are presented in Figure 2.

Other contributions by the CDSA training team

Indian Institute of Management (IIM), Ahmedabad

Dr. Sucheta Banerjee Kurundkar, Director, Training, CDSA was a member of the International Programme Committee of the 3rd Conference on Advances in Healthcare Management Services (three years in a row) at IIM Ahmedabad held from December 9-10, 2017. CDSA contributed in designing the program format, bringing faculty and getting national experts with main focus on innovation, and regulation and evidence-based policy decision making.

National Institute of Training for Standardization, Bureau of Indian Standards (BIS), Noida

Dr. Sucheta Banerjee Kurundkar, Director, Training, CDSA was the key faculty to the 8th International training programme on Laboratory Quality Management System from February 05-23, 2018 at NITS, BIS, Noida.

Regulatory Affairs

In 2017-18, CDSA provided regulatory advisory services for the development and registration of new drugs, medical devices, diagnostics, phytopharmaceuticals, biopharmaceuticals, and biosimilars including vaccines to SMEs and public funded pre-clinical and clinical stage research projects. Example: Regulatory inputs for ongoing clinical trials in CDSA (OPV-BIBCOL, GLSE).

Figure 3: GLSE study: Joint RSG-DSMB-Investigators Meeting, AIIMS, New Delhi, January 11, 2018.

Figure 4: GLSE study: Monitoring at site, AIIMS, New Delhi, June 02, 2017.

Figure 5: Guidelines for evaluation of nanopharmecuticals in India.

Highlights:

- CDSA contributed to the development of 'Guidelines for evaluation of nanopharmecuticals in India' which was formally released on December 6, 2017 (Figure 5).
- CDSA, along with National Institute of Biologicals (NIB), developed 'Laboratory Quality Management System (LQMS) in Diagnostics' (as Blue and Green Book). This was formally released by Drugs Controller General of India (DCGI) in February 2017. Second version of the same was released by DCGI in September 2017 ((Figure 6).
- CDSA was the lead auditor for external audit (technical)-Quality Management System of Pharmacovigilance Programme of India (PVPI) which is the National Coordination Centre at Indian Pharmacopoeia Commission (IPC) on September 1, 2017. Other auditors were represented from CDSCO and ICMR.

Figure 6: Laboratory Quality Management System in Diagnostics (Blue and Green Book) written by NIB and CDSA and released by DCGI.

Clinical Study Support Services

The Department of Clinical Portfolio Management (CPM) manages projects, supports investigators in preparing sites for conducting research, and independently monitors clinical data for quality. During the past year, CDSA had successfully created a robust institutional platform and a governance structure, developed a performance-based contract career path to attract talented professionals, recruited high quality professionals, developed an ecosystem for training- and capacity-building in clinical research, and provided support services to several ongoing projects.

CDSA provided specialized clinical study support services to the following projects and programs listed in the Table 2.

TABLE 2: Summary of specialised clinical study support services provided by CDSA

Sl. No:	Project Title (Funding Agency)	Principal Investigator / Institute	CDSA Role	Contribution
1.	Inter-Institutional Program for Maternal, Neonatal and Infant Sciences: A translational approach to studying preterm birth (DBT)	Prof Shinjini Bhatnagar, THSTI; other collaborating institutes: RCB, THSTI, NIBMG, AIIMS, SJH, MAMC, CDSA, General Hospital Gurgaon	• Study start-up support • Quality Management • Clinical and laboratory monitoring	• GCP-compliant study documents, ICD, CRF, SOPs and data collection tools. • Site set-up as per project requirements • GCP and GLP training of project team.
2.	Post marketing study to assess the safety & tolerability and immunogenicity bOPV in healthy Indian infants (DBT)	Mr. SK Tyagi, BIBCOL (05 sites across India)	• Co-applicant/ Co-PI • Regulatory advisory • Project management • Clinical operations • Data management • Medical writing • Quality monitoring • Biostatistics support	• Regulatory compliance approvals (approval for protocol, amendments, study progress, Safety reporting) • GCP-compliant study documents, ICD, CRF, SOPs and data collection tools. • Site set-up
3.	Efficacy and Safety of an Innovative and Affordable Goat Lung Surfactant for the treatment of RDS) in preterm neonates (Wellcome Trust)	Dr. Ramesh Agrawal, AIIMS, Delhi	• Co-applicant/ Co-PI • Regulatory advisory • Project management • Medical writing • Medical monitoring • Clinical operations • Site Management • Data management	• Successful grant receipt for the project • Regulatory compliance approvals (approval for protocol, amendments, study progress, Safety reporting) • GCP and CDSCO compliant study documents, ICD, CRF, SOPs and data collection tools. • Site set-up as per project requirements • GCP trained project team
4.	Zinc as an adjunct for the treatment of clinical severe infection in infants younger than 2 months (Research Council of Norway through GLOBVAC and CISMAC)	Dr. Nitya Wadhwa & Dr Shinjini Bhatnagar, THSTI	• Study start-up support • Quality Management • Clinical monitoring	• GCP compliant study documents, ICD, CRF, SOPs and data collection tools • Site set-up as per project requirements • GCP trained project team
5.	Immediate Skin-to-Skin Contact (Immediate Kangaroo Mother Care) Study (WHO/BMGF)	Dr. H. Chellani, Safdarjung Hospital, Delhi	• Co-applicant/ Co-PI • Study start-up support • Internal Quality Management	• Successfully supported TOT workshop for all participating countries • GCP compliant study documents • Site set-up as per project/ WHO requirements • GCP trained project team
6.	Investigation Of Rheumatic Atrial Fibrillation Using Vit K Antagonists, Rivaroxaban or Aspirin (PHRI)	Dr. Karthikeyan, AIIMS, Delhi (12 sites across India)	• Study start-up support	Successfully activation of 9 sites across India
7.	Accelerating the application of stem cell technology in human disease – ADBS Study (DBT)	Dr. Sanjeev Jain, NIMHANS, Bengaluru	• Quality Management	Quality management initiated
8.	Iron Supplement in Infant Phase 2 Clinical Trial (NIH)	Dr. Sanjiv Amin, Rochester University	• Co-applicant/ Co-PI • Clinical operations • Medical monitoring	Local coordination for study clearances and project execution planning
9.	An open-label, non-randomized, two-stage, dose-finding study of Verapamil [IR] tablet formulation in adult tuberculosis patients in Continuation phase of anti-tuberculosis treatment (ICMR/ DBT)	Dr. Padmapriya Darsini, National Institute for Research in Tuberculosis (NIRT), Chennai (02 sites across India)	• Medical monitoring and writing support • Quality Management	• Regulatory compliance and approvals • GCP and CDSCO compliant study documents, ICD, CRF, SOPs and data collection tools. • Site set-up as per project requirements
10.	Efficacy and Safety of a Combination regimen in Adults with Pre-extensive (Pre-XDR) and Extensively Drug-resistant Pulmonary Tuberculosis (XDR-TB) (USAID)	Dr. Padmapriya Darsini, National Institute for Research in Tuberculosis (NIRT), Chennai (05 sites across India)	• Medical monitoring • Quality Management	• Regulatory compliance and approvals • GCP and CDSCO compliant study documents, ICD, CRF, SOPs and data collection tools. • Site set-up as per project requirements

Comprehensive National Nutrition Survey

Figure 7: CDSA monitoring pan India (Phase I: Orange; Phase II: Green; Phase III: Violet; Unmonitored: Yellow).

Figure 8: Photographs from pan India monitoring.

Comprehensive National Nutrition Survey (CNNS), a cross-sectional, household survey covering more than 1,20,000 children and adolescents (0-19 years) in both urban and rural areas across all 30 states of India, is being conducted by the Ministry of Health and Family Welfare (MoHFW), Government of India in partnership with UNICEF. It aims to assess the national prevalence of biological indicators (micronutrient deficiencies, subclinical inflammation, and worm infestation) and prevalence of overweight/obesity, along with information on body composition, cardio-metabolic risk, muscular strength, and fitness.

CDSA was selected as the national monitoring agency to conduct concurrent monitoring of CNNS biological samples (blood, urine and stool). This monitoring includes, but not limited to primary sample collection at PSUs, processing at collection centres, shipment, and analysis at a central laboratory. CDSA provides ongoing feedback to the central laboratory team and informs lead survey agency and UNICEF on the quality of biological data collection, processing, transportation, analysis, and reporting.

Figure 9: CNNS Project: Biological sample collection, Sheetla Mata Colony, Gurugram, June 01, 2017.

Figure 10: Data Logger Device: Training under CNNS project, CDSA, Faridabad, January 05, 2017.

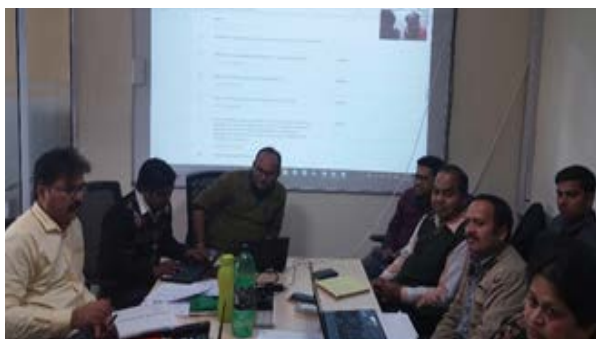

Figure 11: CNNS Project Meeting, CDSA, Faridabad, February 01, 2017.

CDSA'S IMPACT IN CNNS PHASE I AND II

1. Introduction of temperature data loggers as evidence based monitoring tool for ensuring biological sample integrity (*cradle to grave*).
2. Implementation of approx. cent percent data logger activities for all monitored & unmonitored samples to ensure sample integrity in Phase II was due to CDSA's findings from Phase I.
3. Complete cold chain maintenance through use of deep freezer and proprietary tool at every PSU was deployed in Phase II based on CDSA's recommendations.
4. Rejection of invalid primary samples and test reports by CDSA led to significant improvement in the quality of laboratory data.
5. Notification of critical parameters (critical call out) to the beneficiaries resulted in positive social impact.
6. Better Coordination and communication between the Field teams ensured compliance to best industry practices related to:
   - Cold Chain Maintenance
   - Phlebotomy
   - Sample collection, packaging, shipment and disposal of biohazard material.
   - Completeness and accuracy of primary data collected.
7. Feedback at pre-determined frequencies from field monitoring significantly enhanced the quality of primary sample (Blood/Stool/Urine/BP).
8. Laboratory validation exercises with various variables (temperature, time, quality, precision and accuracy) were suggested & undertaken at AIIMS New Delhi. All 22 CNNS biochemical parameters were under the purview of this study.

Medical Affairs and Medical Writing

CDSA supports researchers in the areas of medical monitoring, safety reporting, protocol writing, and clinical study report writing.

The Medical Department has successfully provided the following services:

S. No.	Project	Task Accomplished
1.	An Open-Label, Non-Randomized, Two-Stage, Dose-Finding Study Of Verapamil Tablet Formulation In Adult Tuberculosis Patients In Continuation Phase Of Anti-Tuberculosis Treatment	Stage 1: Preparation and submission of Clinical study Report to DCGI Successfully coordinated for obtaining the regulatory approval for stage 2. Stage 2: Revision of all the study documents (ICD, CRF, Protocol)
2.	Evaluating the efficacy and safety of an innovative and affordable Goat Lung Surfactant for the treatment of respiratory distress syndrome in preterm neonates: a multi-site randomized clinical trial	Medical Monitoring, review of safety narratives Preparation and submission of Clinical study Report to DCGI

S. No.	Project	Task Accomplished
3.	A Phase IV, Interventional, Open Label, Multicentric, Single Arm Clinical Trial to Assess the Safety, Tolerability and Immunogenicity of Bivalent Oral Polio Vaccine (bOPV) in Healthy Indian Infants.	Medical Monitoring, review of safety narratives, DSMB Charter preparation and coordination for DSMB. Reviewed and prepared study document(ICD,CRF, Study logs, SAP) DSMB Report preparation

Clinical Data Management

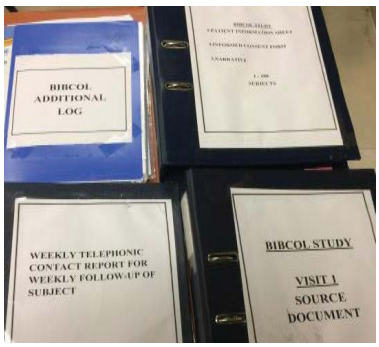

Figure 12: Data management, subject data maintained at site.

CDSA provides specialized Clinical Data Management services to government and non-government innovators, SMEs, and academic institutions to ensure consistent data quality and quicker turnaround. CDSA offers CDM through Promasys v7.2 that has been installed in a secure and validated IT environment, ensuring quick and smooth transition of database build to database lock with operational cost advantage.

COLLABORATORS

- *United Nations Children's Fund (UNICEF)*
- *World Health Organization (WHO)*
- *Wellcome Trust, UK*
- *Bill and Melinda Gates Foundation (BMGF), USA*
- *National Institute of Health (NIH), USA*
- *Indian Council of Medical Research (ICMR), India*
- *Centre for Intervention Science in Maternal and Child Health (CISMAC), Norway*
- *Population Health Research Institute (PHRI), Canada*
- *All India Institute of Medical Sciences (AIIMS), India*
- *National Institute for Research in Tuberculosis (NIRT), India*
- *National Centre for Disease Informatics and Research (NCDIR), India*
- *Safdarjung Hospital (SJH), India*
- *Biotechnology Industry Research Assistance Council (BIRAC), India*

ACHIEVEMENTS

PEER-REVIEWED PUBLICATIONS

EXTRAMURAL GRANTS

PATENTS

HONORS AND AWARDS

SEMINARS AND CONFERENCES

INVITED TALKS AND PANELS

Peer-Reviewed Publications

1. Khullar B, Balyan R, Oswal N, Jain N, Sharma A, Abdin MZ, Bagga A, Bhatnagar S, Wadhwa N, Natchu UCM, George A, Rath S, Bal V, Sopory S. Interaction of CD80 with Neph1: a potential mechanism of podocyte injury. Clin Exp Nephrol 2017; 22(3):508-516.

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BOOKS AND BOOK CHAPTERS

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2. Ganguly NK, Saha GK. Change management: Identifying the need and taking proper steps towards implementing change. Essential of Health Management; Chapter 17.

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Extramural Grants

DR. GAGANDEEP KANG

Project: Indian surveillance and impact studies: New state roll-out
Funding agency: Bill and Melinda Gates Foundation
Duration of sanction: 2017-2020
Amount: USD 2,966,102
Collaborators:
Christian Medical College
CDC Foundation
National Institute of Epidemiology
Indian Council of Medical Research
24 site hospitals

Project: Building the clinical research ecosystem in India
Funding agency: Bill and Melinda Gates Foundation
Duration of sanction: 2017-2020
Amount: USD 1,840,000
Collaborators:
University College London
National Centre for Disease Informatics and Research
St. John's Research Institute
Sree Chitra Tirunal Institute for Medical Sciences and Technology
Clinical Development Services Agency

DR. SHINJINI BHATNAGAR

Project: A "bench to bedside" model for clinical and translational science between academic research institutes and hospitals focused on fetal growth restriction and preterm birth.
Funding agency: Department of Biotechnology
Duration of sanction: 2018-2021
Amount: INR 6,81,90,800
Collaborators:
Dr. Tushar Kanti Maiti, Regional Centre for Biotechnology, Faridabad
Dr. Sunita Sharma, Gurgaon Civil Hospital, Gurugram

Project: CALOPUS - Computer Assisted LOw-cost Point-of-care UltraSound
Funding agency: Global Challenges Research Fund
Duration of sanction: 2018-2021
Amount: £1,013,662
Collaborators:
Dr. J. Alison Noble, University of Oxford, United Kingdom

Project: Maternal micronutrient and genetic associations with pregnancy outcomes in North India
Funding agency: Bill and Melinda Gates Foundation
Duration of sanction: 2017-2019
Amount: INR 5,56,00,000
Collaborators:
Dr. Partha P Majumder, National Institute of Biomedical Genomics, Kalyani

Project: Validation of a metabolite panel for postnatal assessment of gestational age on cord blood and neonate heel dried blood spot in low and middle-income resource settings in India
Funding agency: Bill and Melinda Gates Foundation
Duration of sanction: 2017-2019
Amount: INR 1,66,80,170
Collaborators:
Dr. Siddharth Ramji, Maulana Azad Medical College, New Delhi
Dr. Seema Kapoor, Lok Nayak Hospital and Maulana Azad Medical College, New Delhi
Dr. Yashwant Kumar, THSTI, Faridabad

Project: Studies on placental regulatory mechanisms in abnormal pregnancies and exosome specific metabolomic signatures in adverse pregnancy outcomes
Funding agency: Department of Biotechnology
Duration of sanction: 2017-2019
Amount: INR 30,00,000
Collaborators:
Dr. Ramkumar Menon, The University of Texas Medical Branch, USA

DR. AMIT YADAV

Project: Integrating multiple proteomics database search algorithms in a unified framework for time efficient large scale analyses
Funding agency: Department of Biotechnology
Duration of sanction: 2018-2021
Amount: INR 39,85,600

DR. PRABHANSHU TRIPATHI

Title: Effect of environmental factors including diet and artificial sweeteners on gut microbiome and their consequences on type 2 diabetes

Funding agency: Department of Biotechnology
Duration of sanction: 2016-2020
Amount: INR 88,00,000

DR. SAMRAT CHATTERJEE

Project: Improving the resolution of protein-protein interaction network
Funding agency: Department of Biotechnology Duration of sanction: 2017-2020
Amount: INR 79,91,200
Collaborators: Dr. Shailendra Asthana, THSTI, Faridabad

DR. ARUP BANERJEE

Project: Understanding the therapeutic role of adult stem cell-derived exosome in combating virus-induced neurodegenerative disease
Funding agency: Department of Biotechnology
Duration of sanction: 2018-2021
Amount: INR 81,38,600
Collaborators:
Dr. Sujata Mohanty, All India Institute of Medical Sciences, New Delhi
Dr. Anirban Basu, National Brain Research Centre, Manesar

DR. NISHEETH AGARWAL

Project: Understanding the roles of ClpX and ClpC1 components of Clp proteolytic machinery in *Mycobacterium tuberculosis*
Funding agency: Department of Biotechnology
Duration of sanction: 2018-2021
Amount: INR 72,35,000

DR. SANJAY BANERJEE

Project: Characterization of high value phytochemicals of anti-diabetic and immunomodulatory properties in North Eastern banana varieties
Funding agency: Department of Biotechnology
Duration of sanction: 2018-2021
Amount: INR 30,00,000
Collaborators:
Dr. CP Suresh, North-Eastern Hill University, Shillong
Dr. M Mayilvaganan and Dr. P Suresh Kumar, National Research Centre for Banana, Thiruchirapalli
Dr. Rajlakshmi Devi, Institute of Advanced Study in Science and Technology, Guwahati
Ananya Kashyap, Assam Down Town University, Assam

DR. SANKAR BHATTACHARYYA

Project: Study effect of dengue virus infection on *in vitro* megakaryopoiesis
Funding agency: Science and Engineering Research Board, Department of Science and Technology
Duration of sanction: 2018-2021
Amount: INR 30,00,000

Project: Mechanism of rapid propagation of dengue virus during infection
Funding agency: Department of Biotechnology
Duration of sanction: 2018-2021
Amount: INR 1,00,10,000

DR. TARUN SHARMA

Project: Aptamer based rapid test to differentiate venomous snake bites from non-venomous and dry snake bites
Funding agency: Biotechnology Industry Research Assistance Council
Duration of sanction: 2018-2019
Amount: INR 50,00,000
Collaborator: Dr. Robin Doley, Tezpur University, Tezpur

DR. JAYANTA BHATTACHARYYA

Project: Isolation and characterization of monoclonal antibodies from HIV-1 subtype C infected individuals
Funding agency: Department of Biotechnology, and Department of Science and Technology
Duration of sanction: 2017-2020
Amount: INR 1,31,01,536
Collaborators:
Prof. Kalpana Luthra, Prof. Kunzang Chosdol, and Dr. Bimal Kumar Das, All India Institute of Medical Sciences, New Delhi
Dr. Kailapuri G Murugavel and Mr. Aylur S Krishnan, YRG Center for AIDS Research and Education, Chennai

DR. MOHAN APPAIAHGARI

Project: Development of a live, attenuated fowl adenovirus 4-based candidate poultry vaccine against hepatitis-hydropericardium syndrome
Funding agency: Biotechnology Industry Research Assistance Council
Duration of sanction: 2018-2019
Amount: INR 50,00,000

Patents

Title: Flow-cytometry based rapid method of testing antimicrobial drug susceptibility and resistance in biological fluids
Application number: 201711046980
Filing date: 28 December 2017
Inventors: Niraj Kumar, Chandresh Sharma, Susmita Chaudhuri, Deepak Kumar Rathore, Shrikant Kumar, Sagarika Haldar, Jonathan Pillai, Shinjini Bhatnagar

Title: Method of hyperplexing in mass spectrometry to elucidate temporal dynamics of proteome
Application number : PCT/IN2017/050369
Filing date: 31 August 2017
Inventors: Ajay Kumar, Shilpa Jamwal, Suruchi Aggarwal, Kanury VS Rao, Amit Kumar Yadav

Title: Method of predicting diabetes outcome susceptibility
Application number: 201711041969
Filing date: 23 November 2017
Inventors: Samrat Chatterjee, Kanury VS Rao, Rajat Anand, Shivam Kumar, Yashwant Kumar, Ravi Chandra Beeram

Title: Novel compounds for liver disorders
Application number: 201711031441
Filing date: 5 September 2017
Inventors: Kanury VS Rao, Dinesh Mahajan, Shailendra Asthana, Shilpa Jamwal, Sameena Khan, Debashis Mitra

Title: A novel nucleophilic acyl substitution method of carboxylic acid and its anhydride derivatives catalyzed by novel reagents
Application number: 201711019482
Filing date: 2 June 2017
Inventors: Dinesh Mahajan, Varun Kumar, Anil Rana, Chuttan Lal Meena, Nidhi Sharma, Anamika Thakur, Lata Tiwari

Title: Chemical processes utilizing carbon dioxide as a source of carbon
Application number: 201711036319
Filing date: 12 October 2017
Inventors: Dinesh Mahajan, Varun Kumar, Anil Rana

Title: A cyclic peptide and pharmaceutical composition comprising the same for inhibiting proliferation of HEV
Application number: 201811004996
Filing date: 9 February 2018
Inventors: Milan Surjit, Saumya Anang

Title: Novel DNA aptamers against nucleoid-associated protein HupB of *Mycobacterium tuberculosis* and uses thereof
Application number: 201711001246
Filing date: 12 January 2018
Inventors: Tarun Kumar Sharma, Priya Kalra, HK Prasad, Jaya S Tyagi

Honors and Awards

AWARD

Dr. Bhabatosh Das received the Japan Society for the Promotion of Science (JSPS) Invitational Fellowship Award from the Govt. of Japan, 2017.

MEMBERSHIP

Dr. Shinjini Bhatnagar was elected as the Fellow of the Indian National Science Academy, 2017.

Dr. Tarun Kumar Sharma received the membership of American Chemical Society, 2018.

TRAVEL GRANTS

Dr. Ajay Kumar received a travel grant from THSTI, Faridabad to attend the EMBL course on Quantitative Proteomics: Strategies and Tools to Probe Biology organized by European Molecular Biology Laboratory (EMBL) held at EMBL headquarters, Heidelberg, Germany, 2017.

Dr. Bhabatosh Das received the Bill and Melinda Gates Foundation travel grant to present his research findings at the 52nd US-Japan Joint Panel Conference on Cholera and Other Bacterial Enteric Infections held at Hat Yai, Thailand, 2018.

Seminars and Conferences

1. Bag S, Verma J, Mehta O, Ramamurthy T, Das B. Molecular insights into antimicrobial resistance traits of multidrug-resistant commensal human gut microbiota. International Conference on Antimicrobial Resistance, National Institute of Pharmaceutical Education and Research (NIPER) and ICMR-National Institute of Cholera and Enteric Diseases, Kolkata, 2018.

2. Das B, Verma J, Bag S, Ramamurthy T. Molecular insights into evolving genome of extensively drug resistant *Vibrio cholerae*. United States-Japan Cooperative Medical Science Program: 52nd Joint Panel Conference on Cholera and Other Bacterial Enteric Infections, Hat Yai, Thailand, 2018.

3. Ghosh TS, Ahuja A, Das B. Gut microbiome in inflammatory bowel disease: A comparative analysis in the Indian population. Cardiovascular Research Convergence, THSTI, Faridabad and All India Institute of Medical Sciences, New Delhi, 2017.

4. Bag S, Ghosh TS, Das B. The genomic enzymology of *Prevotella copri* Indica. Cardiovascular Research Convergence, THSTI, Faridabad and All India Institute of Medical Sciences, New Delhi, 2017.

5. Kumar A, Bag S, Koley H, Das B. Engineering a novel vector containing selectable and counter-selectable markers to study the stability of genomic islands. Foundation Day event, THSTI, Faridabad, 2017.

6. Pant A, Das B. Filamentous integrative bacteriophages: Outstanding tool for genomic manipulation in prokaryotes. Foundation Day event, THSTI, Faridabad, 2017.

7. Halder S, Bairagi N, Chatterjee S. Unravelling the sensitivity of two motif structures under random perturbation. The conference BIOMAT 2017-International Symposium on Mathematical and Computational Biology, Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow, Russia, 2017.

8. Banerjee A, Pandey AD, Singh A, Pandey P, Bandyopadhyay B, Ramachandran V, Vrati S. Circulating microRNA profiles of dengue virus infection. RNA viruses: immunology, pathogenesis, and translational opportunities, India-EMBO Symposium, New Delhi, 2018.

9. Singh K, Gupta I, Khan S. Understanding the cellular and regulatory role of human protein degradation machinery key players. 10th Young Investigator Meeting, Kerala, 2018.

10. Singh K, Sarkar A, Dubey VD, Mahajan D, Jamwal S , Asthana S, Rao K, Sarkar S, Khan S. Preclinical development of a novel class of drug-like molecules that trigger autophagy leading to therapeutic value against cardiac hypertrophy. Indian International Science Festival, Anna University, Chennai, 2017.

11. Awasthi A, Malik S, Khalili H. Identification and characterization of a novel association between dietary potassium and risk of Crohn's disease and ulcerative colitis. Annual meeting of American Association of Immunologists, Washington DC, USA, 2017.

12. Aggarwal S, Yadav AK. Next-generation spatio-temporal proteomics data analysis and visualization. 10th Young Investigator Meeting, Trivandrum, Kerala, 2018.

13. Shrivastava T, Samal S, Tyagi AK, Goswami S, Kumar N, Ozorowski G, Ward AB, Chakrabarti BK. Foldon domain stabilized Indian clade C HIV-1 Env, 4-2.J41 trimer displays quaternary epitope: A promising vaccine target. 8th THSTI Foundation day event, THSTI, Faridabad, 2017.

14. Samal S, Shrivastava T, Tyagi AK, Goswami S, Kumar N, Chakrabarti BK. Native HIV-1 envelope protein conformation-directed antibody response induced by Indian clade C Env. 16th European AIDS Conference, Milan, Italy, 2017.

Invited Talks and Panels

2017

Dr. Shinijini Bhatnagar delivered a talk on 'Development of a biorepository for enhanced applications in human research' at the Healthy Birth Growth Development Knowledge Integration-India workshop, New Delhi.

Dr. Shinijini Bhatnagar delivered a talk on 'How to write a winning research proposal' at the Pediatric Conference of North India and 1st National Conference on Research in Child Health, New Delhi.

Dr. Shinijini Bhatnagar delivered a talk on 'Objectives and expected outcomes of the workshop' at the Indo-US Workshop on Genomics and Bioinformatics to Explore Human Microbial Ecology in Health and Disease, THSTI, Faridabad.

Dr. Amit Yadav delivered a talk on 'Next-generation spatio-temporal proteomics data analysis and visualization' at Pondicherry University, Pondicherry.

Dr. Samrat Chatterjee delivered a talk on 'Regulation of host metabolic network by *Mycobacterium tuberculosis*' at the National Symposium on Multidrug Resistant Tuberculosis: Challenges and Strategies, Amity University, Gurgaon.

Dr. Samrat Chatterjee delivered a talk on 'Mathematical and computational biology for drug target discovery and disease pre-diagnosis' at the SPARC (Sunpharma research) office, Vadodara.

Dr. Samrat Chatterjee delivered a talk on 'Studying host-pathogen interaction under the influence of *Mycobacterium tuberculosis* through mathematical models' at the National Conference on Mathematical and Theoretical Biology, Jadavpur University, Kolkata.

Dr. Bhabatosh Das delivered a talk on 'Insights into gut microbiome of Indian population in health and diseases' at Osaka University, Japan.

Dr. Bhabatosh Das delivered a talk on 'Human microbiome research in THSTI: Understanding and challenges' at the Indo-US Workshop on Genomics and Bioinformatics to Explore Human Microbial Ecology in Health and Diseases, THSTI, Faridabad.

Dr. Bhabatosh Das delivered a talk on 'Diversity, stability and resilience of human gut microbiota' at the Cardiovascular Research Convergence, THSTI, Faridabad, and All India Institute of Medical Sciences, New Delhi.

Dr. Bhabatosh Das delivered a talk on 'Dysbiosis: How to measure it and its association with various diseases' at the Kalinga Institute of Industrial Technology (KIIT)/ Kalinga Institute of Medical Sciences (KIMS) Faculty Development Programme, KIIT University, Bhubneswar.

Dr. Bhabatosh Das delivered a talk on 'Microbiome in liver diseases' at the Institute of Post-Graduate Medical Education and Research, Kolkata.

Dr. T. Ramamurthy delivered a talk on 'Global epidemiology of enteric pathogens: the role of WGS' at the National Communicable Diseases meeting, Johannesburg, South Africa.

Dr. T. Ramamurthy delivered a talk on 'Perspectives of *Clostridium difficile* infection' at the Training Program on Isolation and Molecular Characterization of Pathogenic Anaerobes from Sheep, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu, Kashmir.

Dr. T. Ramamurthy delivered a talk on 'Role of WGS in global epidemiology of enteric pathogens' at the 14th Asian Conference on Diarrhoeal Disease and Nutrition (ASCODD), Kochi.

Dr. T. Ramamurthy delivered a talk on 'Modern science in health and environment' at the DST-INSPIRE Science Camp for School children, SASTRA University, Thanjavur, Tamil Nadu.

Dr. Gaurav Batra delivered a talk on 'Point-of-care diagnostics for resource poor settings: from acute febrile illness to blood borne infections' at the Guru Gobind Singh Indraprastha University, New Delhi.

Dr. Guruprasad Medigeshi delivered a talk on 'Dengue virus infection in India' at the 4th National Institutes of Health-International Collaborations in Infectious Disease Research meeting, International Centre for Genetic Engineering and Biotechnology, New Delhi.

Dr. Ramandeep Singh delivered a talk on 'Understanding mechanisms of persistence and validation of new drug

targets against *Mycobacterium tuberculosis*' at the Microbiology in the New Millenium: From Molecules to Communities conference, Bose Institute, Kolkata.

Dr. Amit Awasthi delivered a talk on 'Adaptive immune responses with examples of causation of various diseases' at the UGC-KIIT/KIMS Faculty Development Program, KIIT University, Bhubaneswar.

Dr. Amit Awasthi delivered a talk on 'Using FACS as a tool to understand T cell differentiation pathway' at the National Workshop on Advancement in Immunology, Vallabhbhai Patel Chest Institute, New Delhi.

Dr. Amit Awasthi delivered a talk on 'Molecular pathway in generation of pathogenic Th17 cells' at the 86th Congress of Society of Biological Chemists, Jawaharlal Nehru University, New Delhi.

Dr. Amit Awasthi delivered a talk on 'Understanding the transcriptional regulation of Th9 and IL-9-producing T cells in allergic inflammation' at the National Research Scholars Meet, ACTREC, Tata Memorial Centre, Mumbai.

Dr. Amit Awasthi delivered a talk on 'Role of Foxo1 in IL-9-IL-17 plasticity in Th17 cells' at the Annual meeting of Indian Immunology Society, Nirma University, Ahmedabad.

Dr. Nitya Wadhwa delivered a talk on 'Roles and responsibilities of an investigator' at the Workshop on Good Clinical Practices, Safdarjung Hospital, New Delhi.

Dr. Manjula Kalia delivered a talk on 'Interactions between host autophagy machinery and Japanese encephalitis virus: Implications for pathogenesis' at the India-EMBO symposium-Autophagy: Cellular mechanisms and significance in health and disease, Institute of Life Sciences, Bhubaneshwar.

Dr. Pallavi Kshetrapal delivered a talk on 'Functional properties of neonate immune system and its clinical implications' at the National Seminar on Diarrhoeal Disease Burden and Management: Special Reference to North Eastern India, Tezpur University, Assam.

Dr. Pallavi Kshetrapal delivered a talk on 'Winter School on Minimally Invasive Biopsy in Cancer' at the National Institute of Biomedical Genomics, Kalyani, West Bengal.

Dr. Nisheeth Agarwal delivered a talk on 'Implementation of CRISPR interference approach for silencing the expression of genes in *Mycobacterium tuberculosis*' at the Society of Biological Chemists meeting, Jawaharlal Nehru University, New Delhi.

Dr. Nisheeth Agarwal delivered a talk on 'Understanding the host-*Mycobacterium tuberculosis* interaction' at the Indian Network for Soil Contamination Research International Conference, Department of Zoology, Delhi University, New Delhi.

Dr. Amit Awasthi delivered a talk on 'Transcription factor Foxo1 is essential for IL-9 induction in T helper cells' at the School of Biomedical Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong.

Dr. Amit Awasthi delivered a talk on 'Role of Foxo1 in IL-9-producing T cells' at the Indian Institute of Science, Bangalore.

Dr. Sanjukta Sen Gupta and **Prof. NK Ganguly** presented the India data as a part of the global coalition against cholera at the Ending cholera: A global Road map for 2030 meeting, Annecy, France.

2018

Dr. Shinijini Bhatnagar delivered a talk on 'Bridging the Gap between Evidence and Policy' at the 10th Young Investigators Meeting, Trivandrum, Kerala.

Dr. Amit Yadav delivered a talk on 'Using mass spectrometry to understand disease mechanisms' at the XXIV Quality Improvement Program on Current Updates in Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi.

Dr. Samrat Chatterjee delivered a talk on 'Algorithms analyzing temporal omics data to track disease progression' at the CDAC Symposium on Accelerating Biology 2018: Digitizing life, Indian Institute of Science Education and Research Pune, Pune.

Dr. Samrat Chatterjee delivered a talk on 'Studying host-pathogen interaction under the influence of *Mycobacterium tuberculosis* through mathematical models' at the 8th Workshop on Bioinformatics and Molecular Modeling in Drug Design, Ambedkar Centre for Biomedical Research, Delhi University, New Delhi.

Dr. Arup Banerjee delivered a talk on 'Understanding dengue pathogenesis: Recent discoveries and translational research' at the National Seminar on Role of Basic Sciences in Translational Research Applied on Biological Sciences and Human Health, Midnapore City College, West Bengal.

Dr. Bhabatosh Das delivered a talk on 'Genomics of commensal and pathogenic enteric bacteria: AMR perspectives' at the Current Trends in Genomics meeting, Aligarh Muslim University, Aligarh.

Dr. Bhabatosh Das delivered a talk on 'Microbiome and metabolic diseases' at the NASH-Context and Research meeting, Indian Institute of Liver and Digestive Sciences, Kolkata.

Dr. T. Ramamurthy delivered a talk on 'Antibiotic-associated diarrhoea and *Clostridium difficile* infection' at the International Conference on Antibiotic Resistance, SASTRA University, Tamil Nadu.

Dr. T. Ramamurthy delivered a talk on 'Challenges in curing *Clostridium difficile* infections' at the Ram Lal Anand College, University of Delhi, New Delhi.

Dr. T. Ramamurthy delivered a talk on 'Implications of antibiotics on gut microbes' at the International Conference on Antibiotic Resistance, National Institute of Cholera and Enteric Diseases, Kolkata.

Dr. Guruprasad Medigeshi delivered a talk on 'Host factors in Dengue virus life-cycle' at the Workshop on Advanced Microscopy and Imaging Techniques, Central University of Rajasthan, Ajmer.

Dr. Krishnamohan Atmakuri delivered a talk on 'TB vaccines: Discovery and challenges – where do we stand globally' at the World TB Day symposium, All India Institute of Medical Sciences, New Delhi.

Dr. Nitya Wadhwa delivered a talk on 'Study documents: protocols, manuals, case report forms, and databases' at the Workshop on Principles and Practice of Clinical Research**,** Indo-US Vaccine Action Programme and National Biopharma Mission of DBT-BIRAC, Hyderabad.

Dr. Tarun Sharma delivered a talk on 'Harnessing aptamer technology for the detection of tuberculous meningitis' at the Society of Young Scientists Conference**,** All India Institute of Medical Sciences, New Delhi.

Dr. Pallavi Kshetrapal delivered a talk on "Molecular studies of human blood cancer and its implications in clinical research" at SASTRA University, Thanjavur, Tamil Nadu.

Dr. Rajesh Kumar delivered a talk on 'HIV Vaccine Design and How Far We Are' at the National Conference on Current Research and Innovations in Biotechnology, Nanotechnology and Environmental Science, Suresh Gyan Vihar University, Jaipur.

Dr. Nisheeth Agarwal delivered a talk on 'Optimization and implementation of CRISPR interference approach for gene silencing in mycobacteria' at the National Symposium and Faculty development Program on Genome Editing: Tools and Applications, Miranda House, Delhi University, New Delhi.

RESEARCH INFRASTRUCTURE

SMALL ANIMAL FACILITY

EXTERNAL RELATIONS AND INSTITUTIONAL DEVELOPMENT OFFICE

Small Animal Facility

Small Animal Facility Building

SAF Team

The Small Animal Facility (SAF) at THSTI breeds and maintains laboratory animals. The facility strives to provide support to the scientific community of NCR biotech science cluster. The SAF has been established in compliance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment, Forest and Climate Change, Government of India and registered with CPCSEA vide registration number 1685/GO/ReBi/S/2013/CPCSEA for 'Research for education and breeding in-house use of small animals i.e. guinea pigs, mice, rat and rabbit.' All animal research is being done after approval by the Institutional Animal Ethics Committee (IAEC). The main objectives of the facility are to:

A) breed and maintain genetically defined inbred strains of mice and rat

B) provide sufficient space and infrastructure to the investigators for conducting animal research work

C) create a specialized animal biosafety containment facility for undertaking animal research for infectious disease

Layout of the facility

The facility has a total built up area of ~ 4939.69 square meters spread over ground plus three floors. There are defined routes for material, animal and human movements to prevent cross contamination. The ground floor mainly serves as a support area. The remaining three floors are dedicated for animal housing and animal-related work. Each floor can house approximately 20,000 to 25,000 mice or 10,000 to 17,500 rats at a given point of time. These floors have a central clean corridor and two dirty corridors for the movement of personnel and related animal supplies. The facility also has dedicated procedure rooms equipped with necessary equipment to perform animal-related procedures. Environmental conditions are being maintained in the animal quarters in accordance with the CPCSEA guidelines.


BALB/c Mice


C57BL/6 Mice


Sprague Dawley Rats

Current Status

SAF started its operations in September 2016. Initially, the breeding program was initiated with two genetically defined strains of mice viz. C57BL/6 and BALB/c. At present, the facility houses 15 mice strains and 1 rat stock in its breeding and experimental colonies. The animal import permits have been received and subsequently mice strains were imported from overseas animal suppliers. The animal rooms are equipped with biosafety cabinets and laminar airflow units for cage changing and animal handling. Individually Ventilated Caging (IVC) systems are in place for housing the mice and rats to reduce the contamination chances. Sterilized feed, water and bedding material are being used to maintain the animals in healthy state. Appropriate standard operating procedures are followed for animal handling, supplies and animal-related procedures. The animal facility records are being maintained in accordance with the CPCSEA guidelines.

The standard quality control measures are being followed to ascertain the quality of the animals. An in-house quality control laboratory has been set up at the facility for health, genetic and environment monitoring-related activities. The facility also conducts trainings on animal care, handling and experimental techniques for staff and students from THSTI and RCB.

In order to develop animal models to carry out research on infectious diseases, an Infectious Disease Research Facility (IDRF) is being built up as an integral part of SAF. IDRF will become operational in due course of time.

In-vivo Imaging System

IVC Systems

Wash and Autoclave Area

Future plan

THSTI is in the process of implementing a plan of upgradation of the existing facility to the applicable national and international standards related with animal research and animal facility management. It will help in optimal utilization of the built up area of the SAF building, generation of resources related to animal research in the country as well as facilitate connection with international resources of small animal research in partnership with highly credible international organizations. Following upgradation of the SAF with validation, a fully integrated management and operations model will be developed which will be handed over to THSTI for sustainable long-term execution. It is aimed to develop SAF as a national resource and nodal centre for collaborative work utilizing small laboratory animals within India.

External Relations and Institutional Development Office

External Relations and Institutional Development (ERID) office continues to provide support to the researchers in the areas of grants management, regulatory compliance for ethics committees, communications, and science outreach. **Ms. Vidhya Krishnamoorthy** is responsible for the grants support and ethics secretariat functions of the ERID. **Dr. Divya Khatter** and **Dr. Siuli Mitra** are in charge of the science communication and outreach programs at THSTI.

THSTI is a part of the India Research Management Initiative (IRMI), launched by the Wellcome Trust/ DBT India Alliance and aimed at strengthening institutional ecosystems.

Dr. Siuli Mitra, Ms. Vidhya Krishnamoorthy and Dr. Divya Khatter

ACADEMIA

DOCTORAL PROGRAM

POSTDOCTORAL PROGRAM

SHORT-TERM TRAINING PROGRAM

Doctoral Program

THSTI is a recognized R&D institute of the Jawaharlal Nehru University, New Delhi that offers doctoral programs in biomedical and clinical research.

The broad domains of ongoing research at THSTI are:

- Vaccines and infectious diseases
- Translational research in maternal and child health
- Drug discovery and mathematical modelling to understand disease biology
- Human microbial ecology
- Diagnostics, devices and biodesign

Courses offered in Ph.D.

Clinical Research Methodology
Biomedical Research
Research Internship
Essentials of Regulatory Trials
Infectious Disease Biology
Infectious Disease Epidemiology
Introduction to Biodesign
Topics in Epidemiology
Immunology and Immunotech
Health Policy and Decision Analysis
Essentials of Clinical Trials

THSTI is also recognized by the Jadavpur University, Kolkata for a Ph.D. program in Mathematical Biology and Systems Biology.

Ph.D. students that joined in 2017-18

Abhijit Paul
Suvankar Halder
Pramila Pal
Alok Singh
Amit Kumar
Mohd. Ilyas
Pawan Kumar
Srikant Sadhu
Surendra Kumar Prajapat
Jaskaran Kaur
Nikita Mangla
Shaifali Tyagi
Akshay Anil Binayke
Khushboo Kaushal
Rohit Verma
Saurabh Chugh
Ayushi Purohit

Postdoctoral Program

THSTI offers training to young researchers through various postdoctoral research awards and programs as under:

- 'Innovation Award' scheme in Biodesign
- Translational Research Award in Infectious Diseases (TRAIN)
- Early Career Medical Research Award (ECMRA)
- SERB-National Postdoctoral Fellowship
- DBT-Research Associateship

Postdoctoral researchers that joined in 2017-18

Komal Agrawal
Harleen Khurana
Md. Jahangir Alam
Mukesh Kumar
Pratibha Gupta
Vasudha Singh
Neeraj Kumar Chauhan
Gowtham Kumar Annarapu

Short-term Training Program

The academic committee manages the short-term training program for external students seeking to complete their Bachelor's or Master's thesis at a research laboratory in THSTI. Under this program, 10 undergraduate students were trained in the last year.

ACADEMIC HIGHLIGHTS

- **Ms. Preeti Thakur** was awarded her Ph.D. degree from Jamia Hamdard (Hamdard University).
- **Sakshi Malik** received GP Talwar Young Scientist Award from Indian Immunology Society for her Ph.D. work.
- **Suyasha Roy** got selected for Newton-Bhabha Ph.D. placement program at the University of Oxford, United Kingdom.
- **Suruchi Aggarwal** won first prize in poster presentation at THSTI Foundation day, 2017.
- **Suruchi Aggarwal** won appreciation award for poster presentation in Cardiovascular Research Convergence, 2017.
- **Hina Lateef Nizami** won third prize in poster presentation at THSTI Foundation day, 2017.
- **Hina Lateef Nizami** bagged the best poster presentation award at the 5th Annual Conference of the ISHR (Indian Section), 2018.
- **Shilpi Sehgal** received the ICMR Travel Award for participating in International Conference titled 'Keystone Symposia: Maternal–Fetal Crosstalk: Harmony vs. Conflict' held in Washington DC, 2017.
- **Shilpi Sehgal** presented a poster titled "Human Leukocyte Antigen-G: A predictor for the birth of small for gestational age neonates?" in International Conference titled "Keystone Symposia: Maternal–Fetal Crosstalk: Harmony vs. Conflict" held in Washington DC, 2017.
- **Dr. Anshu Agarwal** was awarded the DST-WOS: a fellowship for women scientists for the period of 3 years from year 2017 onwards.

ADMINISTRATION

Mr. M.V. Santo

The THSTI administration provides unstinted support for the smooth functioning of the institute in compliance with the Government of India rules. Information on some of the administrative functions is provided below.

THSTI Governance

On the governance front, THSTI conducted one Society, two Finance Committee, and three Governing Body meetings. All the decisions taken were implemented.

THSTI Internal Committees

In order to provide support to the Executive Director in decision-making, various internal committees have been constituted. THSTI also has various statutory committees like Institutional Ethics Committee (Human Research), Institutional Ethics Committee (Animal Research), Institutional Biosafety Committee, and Internal Complaints Committee. The constitution of all committees is given in the later part of this report.

Joint RCB-THSTI Committee

The existing two partners of the NCR Biotech Science Cluster, namely, THSTI and RCB had jointly constituted a Committee of Operational Protocols which continues to make recommendations regarding common requirements in the new campus.

Right to Information

During the period 2017-18, THSTI received 24 applications under the RTI act. Among these applications, 15 were with respect to THSTI-related activities and the information was disseminated under the provisions of RTI act. The rest were applications transferred from DBT seeking general information. The Parliament questions, references from DBT and other organizations were responded to within the stipulated deadlines.

Human Resource Management

During this financial year, THSTI posted 38 recruitment notices for filling 156 positions. The rolling positions were continued to be advertised.

Finance and Accounts

Finance and Accounts section of the institute attends to the day-to-day financial matters, payments to contractors/ suppliers, payment of salaries to staff etc. The section is also responsible for preparing the annual statement of accounts which is provided in the later part of this report.

Stores and Purchase

The Stores and Purchase section is responsible for purchase of scientific equipment, chemicals, reagents, and consumables from overseas and local markets. THSTI has invested INR 1816.01 Lacs on consumables and INR 1613.19 Lacs on equipment and furniture during this financial year.

Information Technology

The IT team has built a modern Data Center Infrastructure which primarily ensures physical security, adequate cooling and power for the hosted equipment. During the last fiscal year, the team had initiated a phase of indigenous development in terms of website and portals. They developed a blogging platform, on-line vendor registration portal, Advanced Equipment Facility portal, home grown cloud platform and other applications. The network reach has widened by reaching to the faculty residence and PRRC building, and the internet speed has reached upto 1Gbps.

Engineering and Estate Management

The Engineering section develops and maintains the physical infrastructure of the institute. The primary responsibility of this section is to ensure that all the equipment and infrastructure is kept functional.

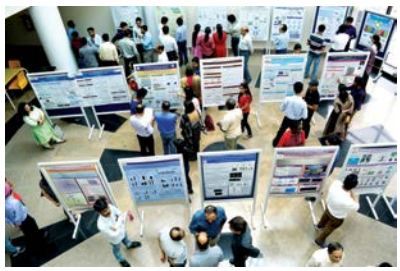
Intellectual Property Protection

THSTI screens outcomes from projects on routine basis to identify the intellectual property vested in it. During this financial year, THSTI filed eight patent applications, two out of which are outcomes of collaborative research.

Events at THSTI

9th Foundation day

THSTI celebrated its 8th foundation day with great zeal and enthusiasm on July 15, 2017. Among the people who graced the occasion with their presence were officials from the Department of Biotechnology, collaborators and well-wishers.



Independence day

THSTI celebrated 71st Independence Day on August 15, 2017. The day comprised events like painting competition, rangoli competition, and cultural events with large participation from the THSTI community.

Hindi Saptah Samaroh

Hindi week was observed from September 14-21, 2017. As part of the celebrations, various competitions were organized in Hindi such as poem recital and essay competition. Dr. Sudha Singh, Professor, Delhi University was the chief guest for the valedictory function, who relentlessly emphasized the importance of Hindi and its use in our country.

Vigilance awareness week

THSTI observed Vigilance Awareness Week from October 30 – November 4, 2017. The week commenced with the administration of integrity pledge by Dr. Guruprasad Medigeshi, Chief Vigilance Officer. Members of THSTI community pledged in large numbers to fight against corruption and to promote integrity, transparency, and accountability in public life.

Sports competitions and the family get-together

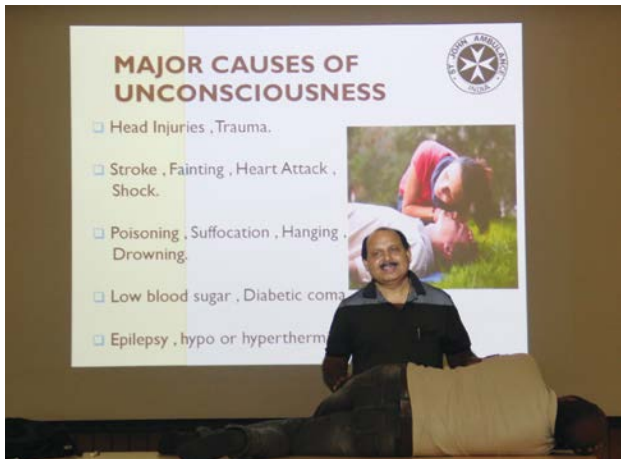
THSTI organized various sports competitions, fun activities and games on March 10, 2018. The institute faculty and staff participated warmly in the events with their family members.

International Yoga day

THSTI observed the 3rd International Yoga Day on June 21, 2017 at the NCR Biotech Science Cluster, Faridabad. The event received enthusiastic participation of people who practiced various asanas and meditation during the hour-long session.

First aid training

THSTI, along with St. John's Ambulance Association, Delhi organized a two-day training programme on first aid for the benefit of its employees. The programme was organized on August 24-25, 2017 and a total of 33 people participated in the training. Dr. R.K. Sharma, Sr. Lecturer & Examiner, St. John's Ambulance Association, shed light on the fundamentals of first aid, dressings and bandages, and how to deal with fractures, wounds, burns, animal bites, asphyxia, shock, cardio-pulmonary resuscitation, stroke, to name a few. Along with the learning on the various first aid measures, the participants went home with a guidebook to first aid and a certificate in hand.



Finance and Account Statements

TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE,FARIDABAD

BALANCE SHEET AS AT 31ST MARCH, 2018

Amount (In Rs.)

LIABILITIES	Schedule	31.03.2018	31.03.2017
Corpus / Capital Fund	1	1,58,48,12,511	1,55,06,53,102
Reserves and Surplus	2	11,40,76,493	12,53,16,862
Earmarked/Endowment Funds	3	-	-
Secured Loans and Borrowings	4	-	-
Unsecured Loans and Borrowings	5	-	-
Deferred Credit Liabilities	6	-	-
Current Liabilities and Provisions	7	44,82,98,120	27,28,80,968
TOTAL		**2,14,71,87,124**	**1,94,88,50,932**
ASSETS			
Fixed Assets	8	1,60,37,86,179	1,53,41,01,018
Investment From Earmarked/Endowment Funds	9	-	-
Investment-Others	10	2,700	-
Current Assets, Loans, Advances etc.	11	54,33,98,245	41,47,49,914
Miscellaneous Expenditure (to the extent not written off or adjusted)		-	-
TOTAL		**2,14,71,87,124**	**1,94,88,50,932**
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 Kumar Vijay Gupta & Co
Chartered Accountants

(C.B.YADAV)	(M.V.SANTO)	(Dr.GAGANDEEP KANG)	(M.L.AGRAWAL)
FINANCE & ACCOUNTS OFFICER	*HEAD ADMINISTRATION*	*EXECUTIVE DIRECTOR*	*PARTNER*

M No.086469

Place: Faridabad

Date: 24/09/2018

एम. वी. सैंतो / M. V. Santo
प्रभाग - प्रशासन / Head - Administration
ट्रांसलेशनल स्वास्थ्य विज्ञान एवं प्रौद्योगिकी संस्थान
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TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE

INCOME AND EXPENDITURE ACCOUNT FOR THE YEAR ENDED 31st MARCH, 2018

Amount (in Rs.)

INCOME	Schedule	31.03.2018	31.03.2017
Income from Sales/ Services	12	1,25,08,532	33,91,229
Grants/Subsides	13	21,50,00,000	22,00,00,000
Fees/Subscriptions	14	68,000	69,500
Income from Investments	15	-	-
Income from Royalty, Publication etc.	16	-	-
Interest Earned	17	80,51,229	59,14,358
Other Income	18	25,61,477	29,43,876
Increase/(Decrease) in stock of Finished goods and works in progress	19	-	-
Deferred Income-Fixed Assets		9,16,34,124	8,73,83,256
TOTAL (A)		**32,98,23,362**	**31,97,02,219**
EXPENDITURE			
Establishment Expenses	20	8,40,09,924	5,86,75,196
Other Administrative Expenses etc.	21	14,52,50,684	12,60,93,066
Expenditure on Grants , Subsidies etc.	22	-	-
Interest	23	-	-
Depreciation (Net Total at the year-end-corresponding to Schedule 8)		9,16,34,124	8,73,83,256
Prior period Adjustment A/c (ANN-A)		-	-
TOTAL(B)		**32,08,94,732**	**27,21,51,518**
Balance being excess of Income Over Expenditure (A-B)		**89,28,630**	**4,75,50,701**
Transfer to special Reserve(Specify each)		-	-
Transfer to /from General Reserve		89,28,630	4,75,50,701
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 Kumar Vijay Gupta & Co
Chartered Accountants

(C.B.YADAV)	(M.V.SANTO)	(Dr.GAGANDEEP KANG)	(M.L.AGRAWAL)
FINANCE & ACCOUNTS OFFICER	*HEAD ADMINISTRATION*	*EXECUTIVE DIRECTOR*	*PARTNER*

Place: Faridabad

Date: 24/09/2018

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प्रधान - प्रशासन / Head - Administration
ट्रांसलेशनल स्वास्थ्य विज्ञान एवं प्रौद्योगिकी संस्थान
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TRANSLATIONAL HEALTH SCIENCE & TECHNOLOGY INSTITUTE (THSTI)
Faridabad

CONSOLIDATED RECEIPTS AND PAYMENTS ACCOUNT FOR THSTI,PROJECTS & FELLOWSHIP FOR THE YEAR ENDED 31ST MARCH, 2018

AMOUNT-IN-RUPEES

RECEIPTS	31.03.2018		31.03.2017	
OPENING BALANCE:-				
Fellowship	(1,34,98,813)		(1,65,480)	
Projects	29,18,07,010		33,46,40,661	
THSTI	11,81,78,864		3,30,69,216	
Grant-in Aid Received:-				
Fellowship	2,59,94,119		2,10,13,738	
Projects	58,12,99,022		54,57,02,086	
THSTI	29,48,31,000		30,00,00,000	
Other Receipts -THSTI				
Application Fees	68,000		69,500	
Earnest Money Deposit	67,17,779		79,60,012	
Guest House Receipt	2,32,852		-	
Income from Sales and Services	1,24,46,132		32,29,728	
Income Tax Refund Received	17,56,920		7,62,577	
Interest Received from Banks	78,95,639		58,64,795	
Interest Received from Income Tax	1,55,590		49,563	
Miscellaneous Receipts	83,500		-	
Other Receipts	35,772		27,81,090	
Penalty Receipt	1,62,599		-	
Recruitment Fee	4,300		35,100	
Donation	2,700		-	
HRA Recovery	18,43,404		-	
Vendor Registration Fee	67,000		-	
RTI Receipt	122		186	
Sales of Scrap	62,400		1,61,500	
Security / Hostel Deposit Received	33,54,093		6,83,526	
Tender Fee	1,65,000		1,27,500	
Accrued Interest Received	7,43,954		44,32,367	
Decrease in advances	1,08,85,103		2,86,95,798	
Govt. Dues Payable	18,78,974		5,57,722	
Other Liabilities/Payable	1,12,78,635		70,91,381	
TOTAL		**1,35,84,51,670**		**1,29,67,62,566**

AMOUNT-IN-RUPEES

Particulars	31.03.2018		31.03.2017	
Fellowship	**2,03,57,816**		**3,43,47,071**	
Projects	**46,54,80,725**		**58,85,35,737**	
THSTI				
Work -in- Process- Building	3,00,00,000		4,00,00,000	
Fixed Assets	8,30,63,424		2,87,30,390	
Administrative Expenses	10,10,78,759		8,28,32,841	
Manpower	7,52,50,121		5,44,59,034	
Consumables	4,66,28,655		3,72,36,911	
Advances , Receivables & Liabilities	1,60,77,602		3,41,33,521	
Closing Cash & Bank Balance				
Fellowship	**(78,62,510)**		**(1,34,98,813)**	
Projects	**40,76,25,305**		**29,18,07,010**	
THSTI	**12,07,51,771**		**11,81,78,864**	
TOTAL		**1,35,84,51,670**		**1,29,67,62,566**

AS PER OUR SEPARATE REPORT OF EVEN DATE ATTACHED.
For KUMAR VIJAY GUPTA & CO.
CHARTERED ACCOUNTANTS

(C.B. YADAV)	(M.V SANTO)	(DR. GAGANDEEP KANG)	(M.L.AGRAWAL)
FINANCE & ACCOUNTS OFFICER	HEAD ADMINISTRATION	EXECUTIVE DIRECTOR	PARTNER

PLACE: Faridabad
DATE:24/09/2018

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AUDITOR'S REPORT

To
Executive Director
TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE
FARIDABAD

1. We report that we have audited the Balance Sheet of "TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE" as at 31 March 2018 and the relative Income & Expenditure Account & Receipt & Payment Account for the period ended on that date, annexed there to. These financial statements are responsibilities of the society management. Our responsibility is to express an opinion on these financial statements based on our audit.

2. We conducted our audit in accordance with auditing standards generally accepted in India. These 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 amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

3. Further to our comments as follows, we report that:

   a) We have obtained all the information and explanations, which, to the best of our knowledge and belief, were necessary for the purpose of our audit.

   b) In our opinion, proper books of account have been kept as required by law so far, as appears from our examination of those books.

   c) The Balance Sheet and Income & Expenditure Account and Receipt & Payment Account dealt with by this report are in agreement with the books of accounts.

   d) In our opinion, the balance sheet and the Income & Expenditure account and Receipt & Payment Account deal with by this report comply with the Accounting Standards issued by the Institute of Chartered Accountant of India, to the extent applicable.

   e) In our opinion and best to the information and according to the explanation given to us, the said account a true and fair view in conformity with the accounting principles generally accepted in India

   i. In the case of the balance sheet, of the state of affairs of the Institute as at 31"March 2018;and
   ii. In the case of Receipt & Payment Account, of the receipt for the period ended on that date.
   iii. In the case of Income and expenditure Account, excess of Income over Expenditure for the period ended on that date.

For Kumar Vijay Gupta &Co.
Chartered Accountants

CA M.L. Agrawal
(Partner)
M.No:086469
Place: Faridabad
Date:24/09/2018

Scientific Events and Outreach

First Annual Asia-Pacific Meeting on Rotavirus and Rotavirus Vaccines

The first Annual Asia-Pacific Meeting on Rotavirus and Rotavirus Vaccines was held in New Delhi on October 12-13, 2017. The meeting was jointly organized by the Christian Medical College, Vellore and the South-East Asia Regional Office of the World Health Organization.

The purpose of this meeting was to:

- Review data generated by rotavirus surveillance systems and disease burden estimates in the region.
- Consider methods and data needs for country cost-effectiveness studies.
- Share global data on rotavirus vaccine introduction, impact assessment and safety monitoring.
- Provide support for research on disease burden, cost-effectiveness and impact assessment by facilitation of interactions with WHO and global leaders.

The participants included leading rotavirus researchers in the region and globally, EPI programme managers, chairs or members of national immunization technical advisory groups and WHO country focal points.

Workshop on Chikungunya Vaccines - Challenges, Opportunities and Possibilities

On 5-6 February 2018, a workshop was organized by the Translational Health Science and Technology Institute and the Coalition for Epidemic Preparedness Innovations with support from the Department of Biotechnology, U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases and PATH on Chikungunya Vaccines - Challenges, Opportunities and Possibilities. This workshop brought together international delegates for two days of intense dialogues on ideas, data, challenges and opportunities related to Chikungunya and Chikungunya vaccine development. The main aim of the workshop was to identify the key bottlenecks and challenges faced by vaccine developers and facilitate dialogues around solutions and opportunities to rapid development of a Chikungunya vaccine.

Representatives from the vaccine industry, the research community involved in Chikungunya research, regulatory organizations (FDA, DCGI), government organizations (MoH, DBT, ICMR), independent consultants, public health officials, non-governmental and funding organizations (Wellcome Trust, GAVI etc.) presented data and participated in discussions on the epidemiology of Chikungunya, disease burden, vaccines in the pipeline, and challenges, bottlenecks and possible solutions to foster vaccine development for the disease.

Indo-US Vaccine Action Program on Dengue meeting

A meeting was organized on January 14-15, 2018 for the Department of Biotechnology in New Delhi under the aegis of the Indo-US Vaccine Action Program, a bilateral program between the Indian Department of Biotechnology and the US National Institute of Allergy and Infectious Diseases (NIH) with a focus on developing and evolving joint R&D projects towards development of safe and efficacious vaccines. The Steering Group on Epidemiological Preparation for Flavivirus Vaccine Trials, comprising of both US and Indian experts led by Dr. M.K. Bhan and Dr. Gagandeep Kang, met to review vaccine studies underway and provide expedited guidance on epidemiology studies and capability assessments and to help in site identification for clinical trials of candidate Dengue vaccines in India.

5th Global Forum on TB vaccines

The 5th Global Forum on TB Vaccines took place in New Delhi, from 20 – 23 February 2018. It was convened under the auspices of the Stop TB Partnership Working Group on New TB Vaccines. Organizing partners were Aeras, the TuBerculosis Vaccine Initiative (TBVI), Indian Council on Medical Research (ICMR), Department of Biotechnology (DBT), and the THSTI.

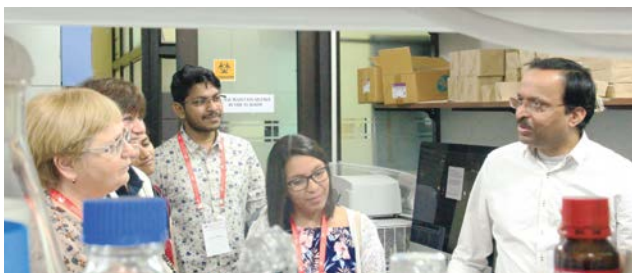
The main goals of the Global Forum on TB Vaccines are to:

- Review progress and share the latest research and data.
- Identify and promote innovative and transformative approaches to TB vaccine R&D.
- Encourage partnerships and collaboration to accelerate TB vaccine R&D.
- Increase global recognition of the critical role vaccines will play in global efforts to end TB.

The 5th Global Forum brought together 347 participants from 31 countries, making it the largest Global Forum on Vaccines to date. The program included over 60 speakers in 12 special, plenary and breakout sessions, 72 posters, and several networking opportunities, and it covered the full spectrum of TB vaccine R&D activities.

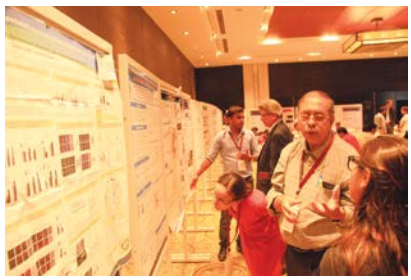
Site visits to four local institutions and TB care providers were organized, offering participants a first-hand look at how TB research and care are conducted in India. These were:

- International Centre for Genetic Engineering and Biotechnology
- National Institute for Tuberculosis and Respiratory Diseases
- Operation ASHA
- THSTI



India | EMBO Symposium on "RNA viruses: Immunology, pathogenesis and translational opportunities"

Dr. Guruprasad Medigeshi received a grant from the Wellcome Trust/DBT India Alliance and EMBO to organize a symposium entitled "RNA viruses: Immunology, pathogenesis and translational opportunities" from March 27– 30, 2018 at Faridabad. The symposium was intended to bring together RNA virus experts of national and international repute to assess and provide a roadmap for RNA virus research in India. Five sessions were organized with talks overarching epidemiology, disease burden and risk factors associated with RNA viruses, pathogenesis and evolution of RNA virus infections, viral and immunological determinants, novel strategies for vaccine development targeting new markets, clinical trials and models to test therapies and vaccines. Prof. Maharaj Kishan Bhan, National Science Professor, IIT Delhi delivered the keynote lecture elaborating on the importance of RNA viruses and the gaps in knowledge and challenges for RNA virus research in India.



Indo-US workshop on Genomics and Bioinformatics to explore human microbial ecology in health and diseases

In collaboration with the National Institutes of Health, THSTI organized a workshop with an aim to understand different aspects of human microbiome research and its implications in public well-being. The three day event from September 6-8, 2017 was focused on providing hands-on-training to the participating scientists for analyses of high throughput sequencing data.

Cardiovascular Research Convergence

THSTI organized a two-day meeting aimed at exchanging research views between clinicians and basic scientists on translational research in cardiovascular medicine on August 12, 2017 at THSTI and on August 20, 2017 at the All India Institute of Medical Sciences, New Delhi. The meeting at THSTI primarily focused on (i) understanding cardiovascular complication in diabetes and identify newer therapeutic strategies to reduce disease complication, (ii) understanding heart failure in clinic and finding its treatment, and (iii) role of gut microbiome on cardiovascular and metabolic diseases. Distinguished cardiologists and scientists who were present discussed their views on identifying cardiovascular problems in clinic and finding solutions to prevent the disease.

Liquid biopsy in precision medicine

With support from the Wellcome Trust/ DBT India Alliance, Dr. Amit Awasthi co-organized an intense day-long brainstorming meeting on liquid biopsy in precision medicine on August 26, 2017. Participants included clinicians and industrial experts who are in process of drafting a white paper as a multi-institutional effort to describe the current status of liquid biopsy in India and propose ways for its wider and uniform adoptability in clinics.

Lecture and Workshop series

THSTI organized a Lecture and Workshop series on December 13-14, 2017 at THSTI and the National Institute of Immunology, Delhi. Day 1 was themed around big data science and its management. Prof. Alexander Hoffmann from University of California Los Angeles (UCLA) who was the distinguished speaker of the day provided a system biologist's perspective of immune compartments. Day 2 was focused upon education outreach efforts using research as a tool. Prof. Tracy Johnson shared her experiences about leading education and outreach activities at UCLA. Later in the day, she also talked about mechanisms underlying transcriptional regulation by splicing machinery. The event observed enthusiastic participation of students and scientists from the NCR Biotech Science Cluster.

Ethics of Human Challenge Studies meeting

A meeting was organized by THSTI in collaboration with the Department of Biotechnology and the Indian Council of Medical Research to discuss the feasibility and the ethical issues associated with Controlled Human Infection Models (CHIM) studies. The meeting was held on January 7-8, 2018 at the Tata Institute of Social Sciences, Mumbai. The meeting was attended by a diverse group of participants including lawyers, researchers, social scientists, ethicists, vaccine manufacturers and media personnel. THSTI is working with ICMR to develop guidelines for such studies, and this meeting was the first in a series that we anticipate will continue for several months.

Immunology Training Course

A course on Overview of Cellular and Molecular Immunology was taught at the institute from February 1-4, 2018 by Dr. Shiv Pillai, Professor of Medicine and HST, Harvard Medical School. The course was attended by research fellows, post-doctoral fellows and scientists at the NCR-Biotech Science Cluster.

Grand Challenges Canada Vice President's visit

Dr. Karlee Silver, Vice President (Programs) of Grand Challenges Canada accompanied by her team of researchers visited the Gurugram Civil Hospital and THSTI to learn about the ongoing studies on preterm birth, the associated stress outcomes on pregnancy and fetal growth, and creation of a biorepository being pursued by the host teams. The meeting was also used as a platform to exchange views on similar programs across the globe.

Workshop on Chromatography

A workshop on chromatographic techniques was organized in collaboration with GE healthcare on November 14-15, 2017. The program comprised lectures and hands-on-training sessions on AKTA chromatography system and UNICORN software.

THSTI open day

THSTI organized an open day on September 22, 2017 as a pre-event of the 3rd India International Science Festival. More than hundred students and faculty members from eight colleges of Delhi NCR participated in the event. The students visited various laboratories and interacted with faculty and students during the day.

THSTI Committees

S.No.	Committee	Members
1.	**Scientific Advisory Committee**	Dr. Partha Majumder Dr. Raghavan Varadarajan Dr. Rajesh Gokhale Dr. Ashok Venkitaraman Prof. Judi Allen Dr. Sujata Srinivasan
2.	**THSTI Management Committee**	Executive Director and Heads of all the centres **Chairperson – Executive Director**
3.	**Finance Committee**	Financial Advisor, Department of Biotechnology Executive Director, THSTI Deputy Secretary (Finance), Department of Biotechnology Advisor/Scientist-G, Department of Biotechnology, and Scientific Coordinator-THSTI Executive Director, Regional Centre for Biotechnology Dr. B. Ravindran, Emeritus Professor, Institute of Life Sciences Dean, THSTI Administrative Officer (Finance and Accounts), THSTI Head-Administration, THSTI
4.	**Maintenance Committee**	Dr. Ramandeep Singh Dr. Bhabatosh Das Dr. Uma Chandra Mouli Natchu Dr. Niraj Kumar Dr. Shailendra Asthana Mr. G.R. Agarwal Mr. Vishal Gupta Mr. Narender Sharma Mr. C.B. Yadav **Chairperson – Dr. Ramandeep Singh / Dr. Bhabatosh Das**
5.	**Purchase Committee**	Dr. Nisheeth Agarwal Dr. Sanjay Banerjee Dr. Amit Awasthi Dr. Gaurav Batra Dr. Shailaja Sopory Mr. Manoj Kumar Mr. C.B. Yadav **Chairperson- Dr. Nisheeth Agarwal / Dr. Sanjay Banerjee**
6.	**IT and Communication Committee**	Dr. Guruprasad Medigeshi Mr. M.V. Santo Dr. Samrat Chatterjee Dr. Amit Yadav Mr. G.R. Agarwal Mr. Tushar Sharma **Chairperson – Dr. Guruprasad Medigeshi / Mr. M.V. Santo**

S.No.	Committee	Members
7.	**Institutional Ethics Committee-Human Research**	Prof. Satinder Aneja Prof. Subir Kumar Maulik Dr. Ujjayini Ray Mr. Munawwar Naseem Ms. Jasmine Singh Ms. Vidhya Krishnamoorthy Mr. D. Raghunandan Dr. Ashutosh Tiwari Dr. Suvasini Sharma Dr. Sarmila Mazumder Dr. Tarun Batra Prof. Rajiv Janardhanan Dr. Sivaram Mylavarapu **Member Secretary – Ms. Vidhya Krishnamoorthy**
8.	**Institutional Ethics Committee-Animal Research**	Dr. Sudhanshu Vrati Dr. Neeraj kumar Dr. Krishnamohan Atmakuri Dr. Amit Awasthi Dr. Amit Pandey Shri. M.T. Sambandam Mr. Ranvir Parashar Prof. Harbans Lal Dr. J.P.Mittal **Chairperson - Dr. Sudhanshu Vrati**
9.	**Institutional Committee for Stem Cell Research** (under reconstitution according to the National Guidelines for Stem Cell Research, 2017)	Prof. Narinder K. Mehra Dr. Sujata Mohanty Dr. Ujjayini Ray Mr. Munawwar Naseem Dr. Prasenjit Guchhait Dr. Shailaja Sopory Prof. Nalin Mehta **Chairman- Prof. Narinder K. Mehra**
10.	**Biosafety Committee**	Dr. Nisheeth Agarwal Dr. Susmita Chaudhuri Dr. Shailaja Sopory Dr. Vinay Kumar Nandicoori Dr. Uma Chandra Mouli Natchu Dr. Anirban Basu **Chairperson – Dr. Nisheeth Agrawal**
11.	**Academic Committee**	Dr. Guruprasad Medigeshi Dr. T. Ramamurthy Dr. Uma Chandra Mouli Natchu Dr. Manjula Kalia Dr. Amit Awasthi Dr. Samrat Chatterjee Mr. Joby Cyriac **Chairperson – Dr. Guruprasad Medigeshi**

S.No.	Committee	Members
12.	**RTI Act Committee**	Dr. Krishnamohan Atmakuri – Public Information Officer Dr. Shinjini Bhatnagar – Appellate Authority Mr. M.V. Santo – Nodal Officer Executive Director – Public Authority
13.	**Internal Complaints Committee**	Dr. Shinjini Bhatnagar Dr. Nita Bhandari Dr. Manjula Kalia Dr. Monika Bahl Ms. Amandeep Kaur Ahuja (external member) Dr. Shobha Broor (external member) Mr. M.V. Santo **Chairperson – Dr. Shinjini Bhatnagar**
14.	**Student Welfare and Hostel Committee**	Dr. Amit Kumar Pandey Dr. Nitya Wadhwa Dr. Sankar Bhattacharyya Dr. Sucheta Kurundkar Mr. M.V. Santo Two student representatives **Chairperson – Dr. Amit Pandey / Dr. Nitya Wadhwa**
15.	**Tender Opening Committee**	Mr. Satish Kumar Mr. Alok Kumar Gupta Mr. Abhishek Sharma
16.	**Building Committee**	Dr. V.S. Chauhan Executive Director, THSTI Executive Director, Regional Centre for Biotechnology Director, National Institute of Immunology Director, National Institute of Plant Genome Research Director, National Brain Research Centre Dean, Clinical Research, THSTI Dr. Alka Sharma, Advisor, Department of Biotechnology Mr. Shrikumar Suryanarayan, Director-General, Association of Biotechnology Led Enterprises Dr. Partha Majumder, Professor, Indian Statistical Institute **Chairman -Dr. V.S. Chauhan**
17.	**Grievance Redressal Committee**	Dr. Chandrashekar Dr. Niraj Kumar Mr. M.V. Santo – Member and Nodal officer – SC/ST **Chairperson - Dr. Chandrashekar**
18.	**Vigilance Officer**	Dr. Guruprasad R. Medigeshi

Chair and Honorary Faculty

Biotechnology Chair

Prof. John David Clemens
Professor, Department of Epidemiology
Founding Director, Centre for Global Infectious Diseases, UCLA School of Public-Health, California

National Chair

Dr. T. Ramamurthy
THSTI, Faridabad

Visiting Professor of Eminence

Prof. N.K. Ganguly
Former Director-General, Indian Council of Medical Research, New Delhi

Honorary International Visiting Faculty

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

Prof. Salman Azhar
Associate Director of Research, Geriatric Research Education and Clinical Center (GRECC), USA

Adjunct Faculty/ Honorary Visiting Professor

Dr. Satyajit Rath
Agharkar Chair, Agharkar Research Institute, Pune

Dr. Vineeta Bal
Visiting Faculty, Biology Division, Indian Institute of Science Education and Research, Pune

Prof. Anil K. Tyagi
Vice Chancellor, Guru Gobind Singh Indraprastha University, Dwarka

Dr. Navin Khanna
Group Leader, International Centre for Genetic Engineering and Biotechnology, New Delhi

Dr. Nita Bhandari
Director, CHRD-Society for Applied Studies, New Delhi

Dr. Amit Sharma
Group Leader, International Centre for Genetic Engineering and Biotechnology, New Delhi

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

Dr. Partha Majumder
Professor, Indian Statistical Institute , Kolkata

Dr. Ankur Mutreja
Senior University Lecturer, Department of Medicine, University of Cambridge, United Kingdom

Dr. Ranjith Kumar C.T.
Associate Professor, University School of Biotechnology,
Guru Gobind Singh Indraprastha University, New Delhi

Dr. Jonathan D. Pillai
Project Lead, Jiva Sciences Pvt. Ltd.
Center for Cellular and Molecular Platforms, National Centre for Biological Sciences Campus, Banglaore

Dr. Suchitra Devi Gopinath
Innovative Young Biotechnologist Award Fellow, THSTI

Dr. Amit Singhal
Principal Investigator, Singapore Immunology Network, Singapore

Dr. Harshpal Singh Sachdev
Senior Consultant,
Paediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, New Delhi

Dr. Usha Menon
Professor and Group Leader,
Gynaecological Cancer Research Centre, Faculty of Population Health Sciences
University College London, United Kingdom

Dr. Sagarika Haldar
Assistant Professor, Department of Experimental Medicine and Biotechnology,
Postgraduate Institute of Medical Education and Research, Chandigarh

Seminars and Meetings

Date	Title	Speaker
3/23/2018	Role of Osteopontin, a Chemokine in Breast Tumor Microenvironment: A New Paradigm in Cancer Therapy	Dr. Gopal C Kundu, Scientist G, National Centre for Cell Science, Pune
3/21/2018	Shape does matter: Cell-geometry regulates the response to TNFα-signaling	Dr. Aninda Mitra, IFOM Research Fellow, FIRC Institute of Molecular Oncology Foundation (IFOM), Milan, Italy
3/12/2018	Public Health Engineering: Restoring the Synergy	Prof. David M. Gute, Dept. of Civil and Environmental Engineering, Tufts University
2/22/2018	Proactive approaches to technologies in public health	Dr. Biju Soman, Additional Professor, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum
2/19/2018	What's so essential about essential genes?	Prof. Eric Rubin, M.D., Ph.D. , Department of Immunology and Infectious Diseases Harvard Medical School Boston, MA, USA
1/10/2018	Measuring the impact of Arbovirus infections in humans	Dr. Irene Bosch, Research Scientist, Massachusetts Institute of Technology
1/3/2018	Autoimmunity and Cancer: Yin and Yang of T cell exhaustion?	Prof. Vijay Kuchroo, Director, Evergrande Center for Immunologic Diseases, Harvard Medical School and Brigham and Women's Hospital
12/19/2017	C-CAMP: A BIG Partner	Dr. Papri Banerjee, Program Manager-Bio Entrepreneurship Program C-CAMP
12/4/2017	Optimization and troubleshooting for IHC/WB techniques	Dr. David A. Grotsky, Scientific Support Specialist-Epigenetics, Abcam
7/17/2017	SERINC: A novel family of antiretroviral genes	Dr. Ajit Chande, Assistant Professor, IISER Bhopal
7/12/2017	Change the face of medicine starting from diabetes: Unrevealing the role of glucagon in diabetes and beyond	Dr. Jibin Chi, Managing Director Asia Pacific, Mercodia AB
5/31/2017	Point-of-care Drop-based Microfluidics Platform using Isothermal Amplification for the Quantitative Detection of Malaria	Neil Davey, Harvard School of Engineering and Applied Sciences, Cambridge, MA, USA
6/6/2017	Drosophila development under nutritional stress: a role for IP3R mediated intracellular Ca2+ signalling in neuroendocrine cells	Dr. Megha, Wellcome Trust/DBT India Alliance Early Career Fellow NCBS(TIFR) Bangalore
5/24/2017	The Cell Metabolism Revealed	Dr. Siva Kumar, Product Manager, Labmate (Asia) Pvt Ltd.

Date	Title	Speaker
4/24/2017	Discovery of segregating infertility alleles in humans	Dr. Priti Singh Co-Director, Genome Editing component of Cornell stem cell and transgenic core facility Cornell University, Department of Biomedical Sciences, Ithaca, New York
4/5/2018	Omics approaches to newborn traits and diseases	Prof. Jeffrey Murray, Deputy Director in Family Health, Bill and Melinda Gates Foundation
5/24/2018	Targeting Antimicrobial Resistance	Prof. Annelies Verbon, Associate Professor, Department of Medical Microbiology, Maastricht University, Netherlands
5/24/2018	Immunology & Genetics of Chronic Viral Infections	Dr. Andre Boonstra, Associate Professor, Erasmus MC, Netherlands
5/24/2018	Modelling and cost effectiveness of antiretroviral based HIV prevention strategies	Dr. David van de Vijver, Scientist, Department of Virology, Erasmus MC, Netherlands
5/24/2018	Post-transcriptional regulation of cytotoxic CD8+ T cells	Prof. Peter Katsikis, Professor and Head of the Department of Immunology, Erasmus MC, Netherlands
4/23/2018	T and B cell signatures in preclinical islet transplant studies in non-human primate preclinical models	Dr. Amar Singh, Schulze Diabetes Institute, Department of Surgery, University of Minnesota
11/27/2017	Programmed fetal membrane senescence and exosome-mediated signaling: A mechanism associated with timing of parturition	Dr. Ramkumar Menon, Associate Professor, Department of Obstetrics and Gynecology, The University of Texas Medical Branch at Galveston, USA
7/26/2017	Epigenetic regulation of the immune system as a driver of human disease	Dr. Shiv S Pillai, Director, Harvard Immunology Graduate Program, Harvard Medical School
12/19/2017	Understanding molecular mechanisms of virus-membrane interaction and virus disassembly	Dr. Manidipa Banerjee, Assistant Professor, Kusuma School of Biological Sciences, IIT Delhi
10/31/2017	Neurovascular targets for Alzheimer's disease and stroke	Dr. Itender Singh, Assistant Professor at the Department of Neurological Surgery, Washington University, St. Louis
8/28/2017	Rapid detection, differentiation and identification of multiple vector-borne pathogens including dengue virus, Zika virus, and *Mycobacterium tuberculosis* complex	Mr. Teh Bao Ju, Veredus Laboratories Pte Ltd, Singapore
8/9/2017	3D bioprinting for patient-specific constructs and *in vitro* model systems	Dr. Swati Midha, Dept of Textile Technology, IIT Delhi
7/11/2017	Doxper: Digitalizing health care data	Dr. Randeep Singh, Chief Scientific Officer, InformDS Technologies Pvt. Ltd.

Faculty Scientist Presentation Series

Date	Title	Speaker
8/3/2018	The role of Unfolded protein response in flavivirus replication	Dr. Sankar Bhattacharyya
7/6/2018	Rapid pathogen identification and antimicrobial susceptibility testing	Dr. Niraj Kumar
4/27/2018	Molecular insights into antimicrobial resistance of human gut microbiota	Dr. Bhabatosh Das
4/20/2018	Curtailing viral infections; T cell immunity or Neutralizing antibodies?	Dr. Huma Qureshi
4/6/2018	Vitamin D signaling in skeletal muscle mass maintenance	Dr. Suchitra Devi Gopinath
3/16/2018	Insights into activities of Tuberculosis Research Laboratory	Dr. Ramandeep Singh
3/9/2018	Role of microRNA in viral pathogenesis	Dr. Arup Banerjee
2/9/2018	Understanding the Cardiovascular Apoptosis through Protein Degradation System	Dr. Sameena Khan
1/19/2018	Understanding the complexity of Envelope protein-HIV conundrum	Dr. Sweety Samal
1/12/2018	Studies on Childhood diseases and Perinatal Biology	Dr. Pallavi Kshetrapal
1/5/2018	Faculty-Scientists Presentation Series:Towards Finding a Therapy to Prevent HIV-1 Infection	Dr. Supratik Das
12/22/2017	Chemistry Group at THSTI- strength and focused area	Dr. Dinesh Mahajan
12/15/2017	Childhood diseases, immunity, inflammation and growth	Dr. Shailaja Sopory
12/8/2017	Immunity, Nutrition and Child Health - INCHing towards better childhood health and growth	Dr. Uma Chandra Mouli Natchu
12/1/2017	Engineering tools for immunogen design & monoclonal antibody isolation	Dr. Rajesh Kumar
11/17/2017	Whole genomes in the epidemiology of enteric pathogens	Dr. T. Ramamurthy
11/3/2017	My Scientific Pursuits	Dr. Nisheeth Agarwal
10/27/2017	Novel insight on HIV immunogen designing: a structure-function guided path	Dr. Tripti Shrivastava
10/6/2017	Understanding the generation of effector T cells in autoimmune and allergic inflammation	Dr. Amit Awasthi
9/15/2017	Insights into dengue biology	Dr. Guruprasad Medigeshi
7/28/2017	Protein Engineering as a Tool for Immunogen Design	Dr. Shubbir Ahmed
5/22/2017	Diagnostics for tropical fevers and blood borne infections: my vision and progress so far	Dr. Gaurav Batra
4/10/2017	Research on Hepatitis E virus: my vision and progress so far	Dr. Milan Surjit
4/3/2017	Targeting "persisters": A new paradigm for tuberculosis drug development	Dr. Amit Pandey

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एवं प्रौद्योगिकी संस्थान

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