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ट्रांसलेशनल स्वास्थ्य विज्ञान
एवं प्रौद्योगिकी संस्थान

TRANSLATIONAL HEALTH SCIENCE
AND TECHNOLOGY INSTITUTE

ANNUAL REPORT

2016 - 2017

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, scientists and engineers 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.

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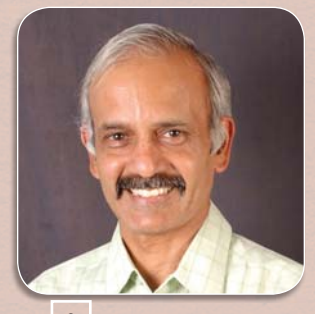

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FROM THE EXECUTIVE DIRECTOR'S DESK

The past year has been an interesting one in the life of a young institution. The Department of Biotechnology undertook several levels of institutional and programmatic reviews, and the high-powered committees that were charged with the task challenged DBT's institutions to demonstrate how they were fulfilling and going beyond their mandates. Within THSTI, the completion of the first phase of several centres led to a consideration of the role of the centres vis-à-vis the institution as a whole, and what shape the future of the centre programmes should take. In the past eight years, the THSTI has grown from an idea to an institution that is ready to take its place with leading science institutions in the country, but differentiates itself by being aimed beyond discovery research.

THSTI has unique foundational elements to support its mission. With enthusiastic, well-trained interdisciplinary young faculty who have a spectrum of scientific strengths that bridges clinical, basic and applied sciences; their commitment to focus on practical science and technology and the building and strengthening of academia-industry networking promote an institutional architecture and environment to support translation. The strong clinical links and collaboration and the support of clinical development feasible through CDSA distinguish THSTI among all DBT institutions.

Altruism, ambition and accountability must define the future of THSTI. As an autonomous institute of DBT established with the mandate of finding solutions for large and unique public health problems, we cannot lose sight of the fact that we exist to serve society through science. Therefore, we must take on problems that may be complex and large but where our inter-disciplinary skills are necessary for solutions.

In discussion with faculty and advisors, during the past year, THSTI has focused on the opportunities available to chart a future course. Five areas have been identified as 'star' projects where we will develop world-class research and translational programmes. These are i) vaccines, ii) maternal and child health, iii) point-of-care diagnostics, iv) metabolic diseases and nutrition, and v) training in clinical and product development. All of these will be pursued in parallel with the creation of an inter-institutional ecosystem in the NCR Biotech Science Cluster focused on the development of an academia-biotech-industry collaboration

modeled on the science research parks that are nested within major innovation hubs.

In the past year, a strategy charting a course towards a major engagement in the development of vaccines has been developed. In training, we have decided to narrow our efforts to focus on areas where we can develop high quality programmes and we have developed a new partnership with the Indian Council for Medical Research. In parallel, we have begun to consider how best to strengthen and expand our activities in maternal and child health and in point of care diagnostics, particularly through collaborations and support from philanthropic organizations and the World Health Organization.

Given the investments that the Government of India has made in infrastructure, personnel and resources so far, even as the institution continues to grow to fulfill its mandate, our responsibility as stewards of what we have been given needs to be front- and centre of our activities. The building of an institute focused on translation in health is no small commitment by the government, and it is important to recognize that our own efforts should both work towards the goals established for THSTI, but also attract partners and resources that further support our mission.

This year, we have also reformatted the Annual Report, organizing it by themes that align broadly with the areas that we have identified as our 'star' programmes, with vaccines, infectious diseases and diagnostics under communicable diseases, while pediatric biology and several extramural projects are under maternal and child health. In each area, there are examples of discovery science, early and late translation, and we look forward to feedback on the structure and suggestions for how we can improve both our science and its presentation.

There are many highlights to the year in science, and the publications which are listed here will demonstrate the caliber of our scientists, but an important endeavor for the coming year is going to be the evolving of mechanisms to evaluate contributions to translation, which are unlikely to be publication alone. This is a challenging task, but we have the support of excellent partners and advisors within and outside academia.

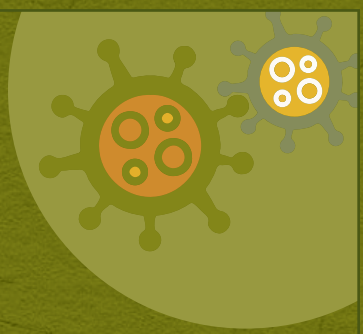
Changes in senior staffing included Dr. Vrati, the first member of the faculty of THSTI leaving to head the Regional Center for Biotechnology, Dr. Bimal Chakraborti who had led the HIV Vaccine Translational Research programme returning to the US while Dr. Jonathan Pillai moved from a faculty position to adjunct faculty, and Dr. Nitya Wadhwa joined the faculty. We hope to make more faculty appointments during the coming year, including at the senior level.

Finally, it is our privilege to have a team of bright and committed scientists who work on human health challenges that are unique to developing countries. It is our responsibility to develop a translation and innovation strategy that can maximize the value that can be generated from the science at THSTI and elsewhere. Opportunities for new and improved therapies, for diagnosis and prevention strategies informed by our understanding of human and population biology offer routes to innovation that can and must be seized by THSTI. The past year has been one where we were able to think together about these opportunities and also identify constraints to be addressed.

We expect to see significant innovation emerge over time. In partnership with the government, academia and industry, we are creating an environment that enables innovation and drives the translation of research into clinical settings and commercial enterprises as services and products that will improve public health in India.

Gagandeep Kang
Executive Director

RESEARCH ON INFECTIOUS DISEASES



TUBERCULOSIS

BACTERIAL SEPSIS

FLAVIVIRUS INFECTIONS

VIRAL HEPATITIS

HIV/AIDS

ANTIMICROBIAL RESISTANCE OF BACTERIAL PATHOGENS

DIAGNOSTICS FOR INFECTIOUS DISEASES

TUBERCULOSIS

Intensified Research and Innovation is one of the components of WHO's END TB strategy. At THSTI, the research foci on tuberculosis (TB) research are on new understanding the molecular mechanisms of TB pathogenesis, emergence of persisters, identification of drug targets, drug screenings and development of novel vaccines against tuberculosis.

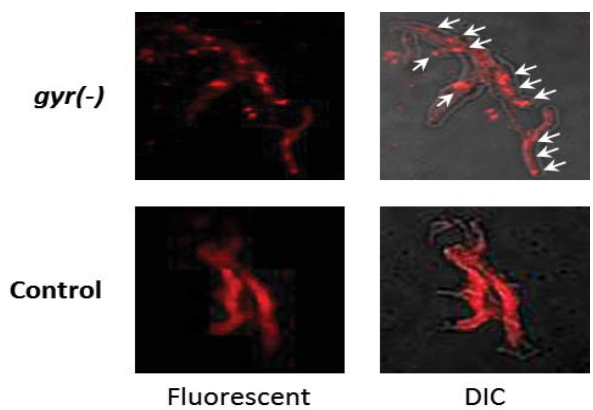
UNDERSTANDING THE MOLECULAR MECHANISMS OF TB PATHOGENESIS

1. *Host-Pathogen interactions upon infection by Mycobacteria*
2. *Characterization of essential metabolic pathways in Mycobacteria*

Dr. Nisheeth Agarwal's team works on a systems approach to analyze **global post-translational modifications of the host proteins following mycobacterial infection**. Towards this they are (1) analyzing the effect of mycobacterial infection on total proteome and post-translational modifications of host proteins, and (2) characterizing the *in vivo* functioning of **DNA gyrase in *Mycobacterium tuberculosis* (*Mtb*) and understanding the mechanism of proteostasis by emphasizing the role of Clp proteases**.

Through the host proteome and phospho-proteome analysis studies, Dr. Nisheeth Agarwal proposes that mycobacterial infection alters the cell cycle of host macrophages and primes the machinery for production of interferons. His group has identified many interesting host proteins that undergo differential expression and phosphorylation upon infection. Some of these proteins are currently being studied to better understand their role in mycobacterial infection.

His team has found that DNA gyrase in *Mtb* is involved in attributing differential resistance to clinical drugs such as rifampicin and isoniazid possibly by promoting the emergence of persister population. The results also reveal that genetic suppression of DNA gyrase results in accumulation of lipid bodies-a hallmark of persisters.

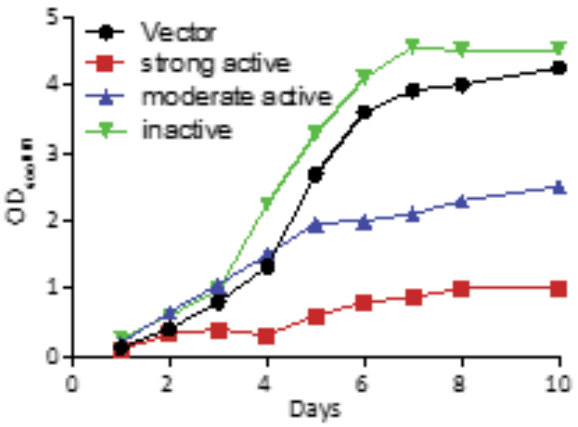


Dr. Krishnamohan Atmakuri's lab understands the **host-pathogen interactions** by developing and using a novel genetic screen that exploits Cre-recombinase from bacteriophage P1 as a reporter. The open reading frames of pathogenic *Mtb* are fused to Cre, a recombinase. This modified *Mtb* is used to infect macrophages harboring lox sites flanking a promotorless fluorescent marker. The proteins that gain entry into the host are tracked by expression of fluorescence because of recombination into the lox sites. One of the potential hits from this screen, a pathogen-encoded aminopeptidase has been well characterized by his group (manuscript in preparation). The preliminary analyses indicate that this protein might be involved in controlling host-mediated antigen presentation or cellular communication by accessing the host endoplasmic reticulum. In addition, specific open reading frames of *Mtb* in fusion with Cre-recombinase reporter has been constructed and transformed into pathogenic *Mycobacteria*. They will be used to infect macrophages (derived from loxP knockin mice) to test for translocation of Cre-fusion *Mtb* proteins.

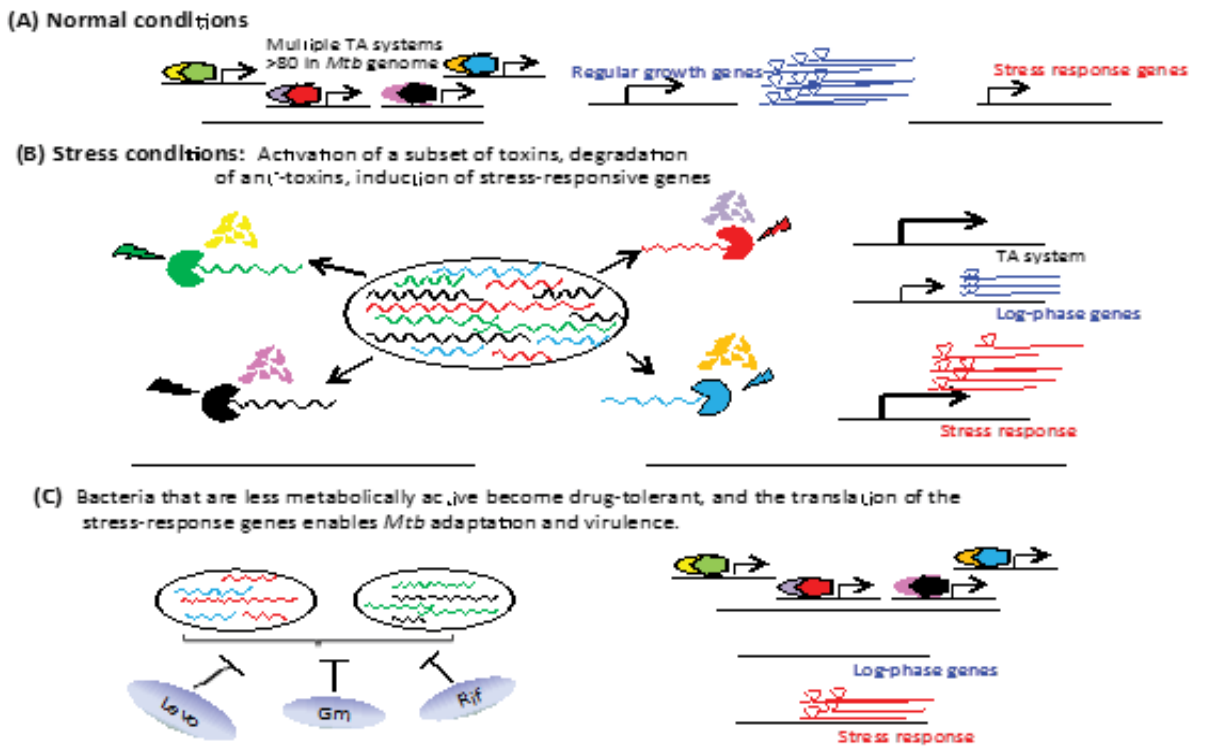
Toxin-antitoxin (TA) systems are present in multiple copies and widely distributed in the genome of prokaryotes. *Mtb* genome encodes for 88 putative TA systems and these are considered to be associated with either bacterial

genome stability or adaptation to unfavorable environment. Among these, 48 TA systems belong to the Virulence associated proteins B and C (VapBC) family.

Dr. Ramandeep Singh and his team explored this TA system in *Mtb*. In order to assess the effect of overexpression of these toxins, genes encoding for *vapC* homologs were overexpressed in *M. bovis*. The growth was monitored spectophotometrically by measuring $OD_{600nm.}$ They observed that based on the magnitude of growth inhibition, phenotypes could be classified as either strong growth inhibition or moderate growth inhibition or no growth inhibition. Numerous type II TA systems have been implicated to play an essential role in genome stabilization and bacterial adaptation in conditions such as nutrient starvation, DNA damage, oxidative stress, persistence and biofilms. qPCR studies indicated that exposure to different stress conditions resulted in induction of multiple ribonucleases in *Mtb*. The team found that post-transcriptional cross-activation existed between TA systems from *Mtb*. Since, these TA modules were induced upon exposure to nutrient limiting, low oxygen and levofloxacin, the role of these TA systems in *Mtb* physiology and pathogenesis was investigated. Mutant strains were found to be dispensable for growth of *Mtb in vitro*. Interestingly, VapC toxins were essential for *Mtb* pathogenesis in both acute and chronic stage of infection. This attenuation was more pronounced in chronic stage of infection indicating that these systems enable



Effect of overexpression of VapC toxins on the growth of *M. bovis* BCG. The expression of toxins was induced by the addition of 50 ng/ml Atc and based on growth patterns obtained, these toxins have been classified as either strongly active, moderately active or inactive.



Under normal physiological conditions, the TA complex binds and represses the transcription of its self-promoter. Under stress conditions, antitoxins are cleaved by cellular protease, and the presence of free toxins leads to the induction of genes belonging to the stress regulon. These bacteria, which have reduced metabolism and altered gene expression profiles, become drug-tolerant and are able to persist in the host.

Mtb to adapt to changes associated with the onset of host adaptive immunity. Accordingly, reduced pathology and tissue damage was seen in sections from Δ*vapC* infected guinea pigs in comparison to sections from wild type and complemented strains infected guinea pigs. However, growth characteristics of these mutant strains was similar to the wild-type strain in liquid cultures, suggesting that attenuation *in vivo* is not associated with *in vitro* replication rates. *Mtb* pathogenesis is a complex interplay of host-pathogen interactions, any of which could be disrupted during Δ*vapBC3* or Δ*vapBC4* infection. Based on the findings, Dr. Ramandeep Singh proposed that overexpression of VapC toxins induced **bacteriostasis**-although VapC toxins inhibited protein translation by tRNA or rRNA cleavage, these were under different regulatory controls and a subset of VapC toxins were induced in a particular stress condition and might function in a coordinated manner.

Further studies would involve identification of biochemical processes that lead to TA system activation in host. The future plan is to study the contribution of remaining VapBC TA systems alone or in combination with other systems in *Mtb* pathogenesis.

One of the most challenging aspects of TB treatment is the presence of a slow-growing, non-replicating, metabolically inactive "persister" population of bacilli inside host cells that requires extremely long treatment regimen. Clinical and experimental evidences show that the capacity of *Mtb* to enter a dormant state leading to latent infection is the key for its survival inside the host, thus delaying the efficacy of currently available therapies. **Dr. Amit Kumar Pandey's** team works **on inhibiting the dormancy or altering the metabolic state of dormant *Mtb* as a way to increase effectiveness of antibiotics and shorten treatment duration.** They hypothesize that differentially regulated critical metabolic pathways triggered by the intracellular nutrient availability and requirements contribute significantly towards the generation of *Mtb* persisters. His team earlier demonstrated that *Mtb* could metabolize and survive on media containing cholesterol as a sole carbon source and that cholesterol metabolism is very critical for *Mtb* persistence. This would require *Mtb* to actively modulate the host biosynthetic machinery for the generation of nutrients required for its own survival. Utilizing genetic and high dimensional informatics approach, they have identified and characterized critical mycobacterial genes required for cholesterol-mediated mycobacterial persistence.

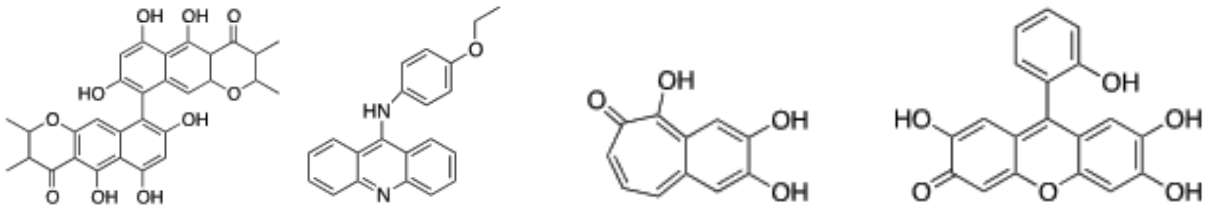
IDENTIFICATION OF DRUG TARGETS

Inorganic polyphosphate (PolyP) is a linear polymer of inorganic phosphate linked by phosphoanhydride bond. PolyP is ubiquitously present in all domains of life (archaea, bacteria and eukarya) and plays an important role in various cellular physiological functions. These functions include processes such as substitute for ATP in enzymatic reactions, chelator of divalent metal ions, phosphate reservoir and microbial adaptation to numerous stress conditions. In bacterial pathogens, polyphosphate kinase-1 (PPK-1) catalyzes the reversible transfer of the terminal phosphate group of ATP to form long chain polyphosphates and the exopolyphosphatase (PPX) enzyme cleaves the phosphoanhydride bonds of PolyP to generate inorganic phosphate. *Mtb* genome harbors enzymes involved in both PolyP synthesis (PPK-1, Rv2984) and its utilization (PPK-2, Rv3232c and PPX, Rv0496 and Rv1026). *In vitro* quantification experiments have revealed that *Mycobacteria* accumulates PolyP at a later stage of growth upon exposure to oxidative, nitrosative, nutrition, and low oxygen stress and drugs such as rifampicin (Rif), levofloxacin (Levo), isoniazid (Inh) and gentamycin (Gm).

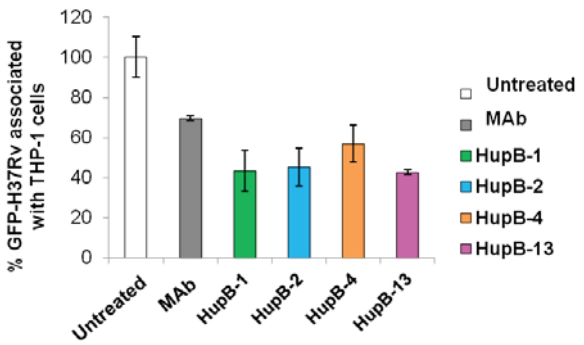
Dr. Ramandeep Singh's lab had previously shown the importance of *ppk-2* for *Mtb* survival. To further characterize its role, his team found that (1) PPK2 exhibited NdkA-like activity using PolyP as phosphate donor (2) In contrast to purified PPK-1 enzyme, MBP-PPK-2 also utilized small chain polyphosphates such as $PolyP_3$ as the phosphate donor, however, its activity increased in the presence of long chain polyphosphates $PolyP_{17}$ or $PolyP_{45}$ (3) PPK-2 activity increased in the presence of ADP in a dose-dependent manner (4) *ppk-2* mutant strain-infected guinea pigs had significantly reduced bacterial loads and tissue pathology in comparison to wild-type-infected guinea pigs at later stages of infection (5) *ppk-2* mutant strain was more tolerant to isoniazid

and impaired survival in THP-1 macrophages in comparison to wild-type strain. The results presented in this study demonstrated that PPK-2 is an *in vivo* drug-target that contributed to the ability of *Mtb* to cause disease in guinea pigs. The future plan is to identify more potent PPK-2-specific non-cytotoxic inhibitors.

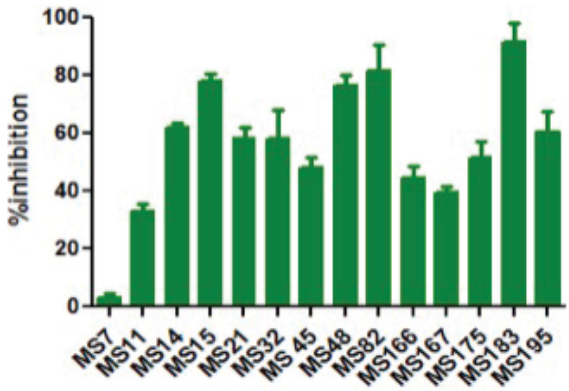
Dr. Tarun Sharma's team developed aptamer against malate synthase G (glcB) and histone-like protein (hupB) of *Mtb*.



Four chemical entities that specifically inhibited *ppk-2* by >80% at 100μM concentration in a dose-dependent manner have been identified.



The high affinity aptamers against HupB, a protein that facilitates *Mtb* invasion in cells, were tested to block *Mtb* invasion in THP-1 cells. The results demonstrated that the aptamer could block *Mtb* invasion in these cells.



ssDNA aptamers were isolated with sub-picomolar and nanomolar affinities that showed robust inhibition of catalytic activity of GlcB *in vitro*. The best aptamer candidate MS183 evinced ~90% inhibition of catalytic activity of GlcB.

DRUG SCREENING AGAINST DRUG-RESISTANT AND SENSITIVE MYCOBACTERIA

The outcome of TB treatment is hampered due to the ability *of Mtb* to switch to a phenotypically drug-tolerant dormant state. This situation is further aggravated due to emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) *Mtb* strains. New chemotherapeutic agents with novel mechanisms of action are urgently required to combat the challenge imposed by the emergence of drug resistant *Mycobacteria*. Phenotypic or target-based screening have led to identification of various scaffolds, that possess activity against drug-resistant TB. Dr. Ramandeep Singh's team has screened >10,000 compounds for activity against *Mtb* and identified approximately 30 molecules that are active against drug-resistant and drug-susceptible bacteria in low micromolar range. 5-Nitro-1,10-phenanthroline (5-NP) is one such candidate that has been identified in whole cell-based screens. 5-NP has been earlier reported to inhibit *Mtb* growth *in vitro* and in macrophages but its mechanism of killing is still unknown. The team has performed mechanistic studies to understand the mechanism of action of this scaffold. In a detailed SAR study, they have synthesized derivatives that are more potent than the parent compound (manuscript under preparation). The lead compound is able to clear *Mtb* in infected mouse tissues. In addition to whole cells based screening, the group has also performed target-based screening against various metabolic enzymes that have been shown to be essential for *Mtb* growth *in vivo*. These enzymes include those involved in PolyP metabolism and amino acid biosynthesis. These studies have also led to identification of small molecule libraries that are non-cytotoxic and possess whole cell activity.

Dr. Nisheeth Agarwal's team is standardizing substrate protein degradation assay by Clp protease to enable *in vitro* assay for screening of small molecule inhibitors. In addition, the newly identified host proteins and metabolic pathways that exhibit differential regulation and post-translational modification upon *Mtb* infection are under investigation as new targets for screening of FDA-approved drugs.

Dr. Amit Kumar Pandey's group has identified a novel broad-spectrum antimicrobial compound, diphenyleneiodonium chloride (DPIC), to have potent anti-microbial activity against drug-resistant *Mtb* (manuscript under preparation).

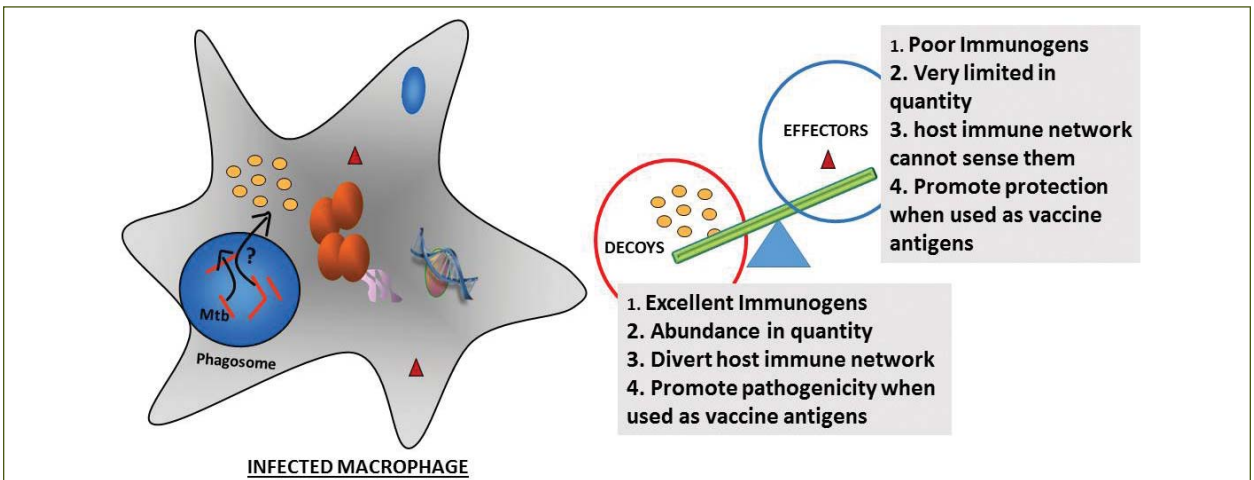
NOVEL VACCINES FOR PROTECTION AGAINST TUBERCULOSIS

In endemic settings for TB (including India), Bacillus Calmette–Guérin (BCG), the current TB vaccine, poorly protects infants, children and adults against pulmonary TB. To address this issue and to simultaneously prevent latently-infected individuals turn active (as TB patients), attenuated strains superior to BCG, DNA- and protein-based subunit vaccines are being evaluated worldwide.

Globally, Membrane Vesicles (MVs) of few gram negative pathogens are currently under evaluation for their potency as vaccine candidates (against their cognate diseases). Dr. Krishnamohan Atmakuri's laboratory works on a long-term aim to design and generate recombinant MVs from non-pathogenic *Mycobacteria* containing few pathogenic mycobacterial proteins that are not only excellent immunogens but also drive host immune system towards protection from infection. His lab is testing the hypothesis that pathogens deliver both decoys and effectors molecules into host to subdue host cellular pathways. Some of the most abundant secreted proteins that are also good immunogens are perhaps decoys and hence deliberately divert host attention to them, while the less abundant ones are not only poorly immunogenic but also the true host cellular pathways modulators. The right pathogen effectors/immunogens, if identified, could be a novel vaccine candidate. Towards that, they have first set out to compare the proteome content of MVs from both pathogenic and non-pathogenic *Mycobacteria*. To identify pathogen proteins that access host macrophages, they are using a genetic-based novel assay system developed in their laboratory.

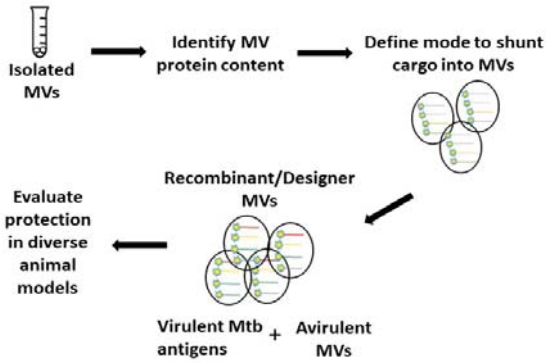
In the last year, they have identified the protein content of MVs from both pathogenic (lab and clinical) and non-pathogenic *Mycobacteria* (manuscript in preparation) but also consistently observed few proteins to be either present or missing in both. There were few proteins that were always present in either pathogenic or non-pathogenic MVs but never in both. This is despite some proteins being 90% homologous and constitutively expressed with possible identical functions (manuscript under preparation).

They are currently evaluating what drives this dichotomy and if packing is all that passive as believed. Their data also suggests the possibility that mycobacterial MVs also contain nucleic acids



Decoy-Effector Hypothesis-Dr. Krishnamohan Atmakuri's lab is evaluating the hypothesis that decoys pose as excellent immunogens, get recognized by host immune surveillance, hence diverting immune system away from the effectors to establish infection.

(NAs). Further analysis of MV preps containing NAs indicates that NAs are in fact outside the MVs. Their initial results indicate that significant amount of NAs are outside MVs in several Gram negatives (manuscript in preparation). The results also indicate that only 1-2% cells get lysed during the entire protocol for enrichment and that the quantity does not reflect amount of NAs accumulating during the MV enrichment protocols. The team is currently evaluating the reasons behind NAs being on the surface of the MVs and looking for any horizontal gene transfer at the host level.



Dr. Amit Kumar Pandey's team has conducted preliminary studies on the potential of a recombinant *Mycobacterium bovis* BCG strain as a live attenuated vaccine against tuberculosis. The recombinant BCG strain is a deletion mutant of a gene hypothesized to be involved in the downregulation of immune-dominant antigens: an essential process by which *Mtb* is able to hide from a robust host immune-surveillance mechanism. They believe that increasing the antigenicity of *M. bovis* BCG might increase its efficacy against preventing tuberculosis.

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Dr. Manjula Kalia, THSTI
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Dr. Raghavan Vardarajan, Indian Institute of Science
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Dr. Rohan Dhiman, National Institute of Technology Rourkela
Dr. ILL-Young Lee, Korean Research Insitute of Chemical Technology
Dr. Amita Gupta, Delhi University
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BACTERIAL SEPSIS

In India, neonatal sepsis is the number one killer that haunts most neonatal units. The clinical syndrome is characterized by systemic signs of infection-accompanying bacteremia in the first month of life. This clinical entity includes systemic infections like septicemia, pneumonia, meningitis, urinary and bone/joint infections. The disease exhibits two distinct patterns-the early onset sepsis (EOS; onset within first 72 hours of life) and the late onset sepsis (LOS; onset after 72 hours of life).

Dr. Krishnamohan Atmakuri's team, together with the neonatal group at the All India Institute of Medical Sciences, New Delhi and the genomics group, Bengaluru at the National Centre of Biological Sciences, has initiated work on understanding bacterial sepsis.

Research Involving Human Participants

Population: Inborn neonates with clinical sepsis.

Comparison: Healthy neonates.

Objective: Identification of potential pathogenic determinants behind bacterial septicemia and exploration of host signatures from infected children.

Progress: Across several laboratories working on bacterial sepsis, pathogens have been cultured *in vitro* from blood, their numbers significantly amplified, their DNA and RNA extracted, whole genome and RNA sequence performed (respectively) and data analyzed to understand pathogen genomes and trancriptomes. The approach taken to understanding their transcript signature correctly requires blood-infecting bacteria are isolated without multiplying them *in vitro* and then obtain RNA for transcriptome and protein for proteomic signatures study (*in situ* analysis).

Isolating bacteria from small volume of neonates' blood is quite challenging in the absence of available kits. Literature predicts that only 1-100 bacteria reside per ml of infected blood. Dr. Krishnamohan Atmakuri's team has done extensive analysis of storage conditions of infected blood before lysis sets in, time at which to perform isolations, options/methods employed for isolation, and blood fractions used for isolation. The analysis also indicates that bacteria distribute across several components of blood, the distribution varies with time of sampling blood and thus isolation efficiency of pathogen dramatically reduces. Pilot experiments are on to efficiently extract pathogen RNA without isolating the pathogen from blood. Together with this project, the future plan of this group lies in identifying diagnostic markers from both pathogen and host that would aid in rapid and accurate diagnosis. They also aim to garner additional funds to explore transmission dynamics and evaluate appropriate molecular tools for both EOS and LOS caused by nosocomial infections in Indian hospital settings.

COLLABORATORS

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FLAVIVIRUS INFECTIONS

DENGUE

The year 2016 was characterized by large dengue outbreaks worldwide. Dengue is a fast emerging pandemic-prone viral disease in many parts of the world.

UNDERSTANDING DENGUE PATHOGENESIS

The basis of development of dengue severity is addressed by **Dr. Arup Banerjee** through exploring the transcriptional signature in Peripheral Blood Mononuclear Cells (PBMCs) of a significant number of clinically and virologically well-characterized patients with mild and severe dengue infection. To obtain a global landscape of dysregulated gene signatures, genome-wide transcriptome profiling was performed using high throughput RNA sequencing from samples obtained from human participants.

Research Involving Human Participants

Population: Dengue suspected individuals.

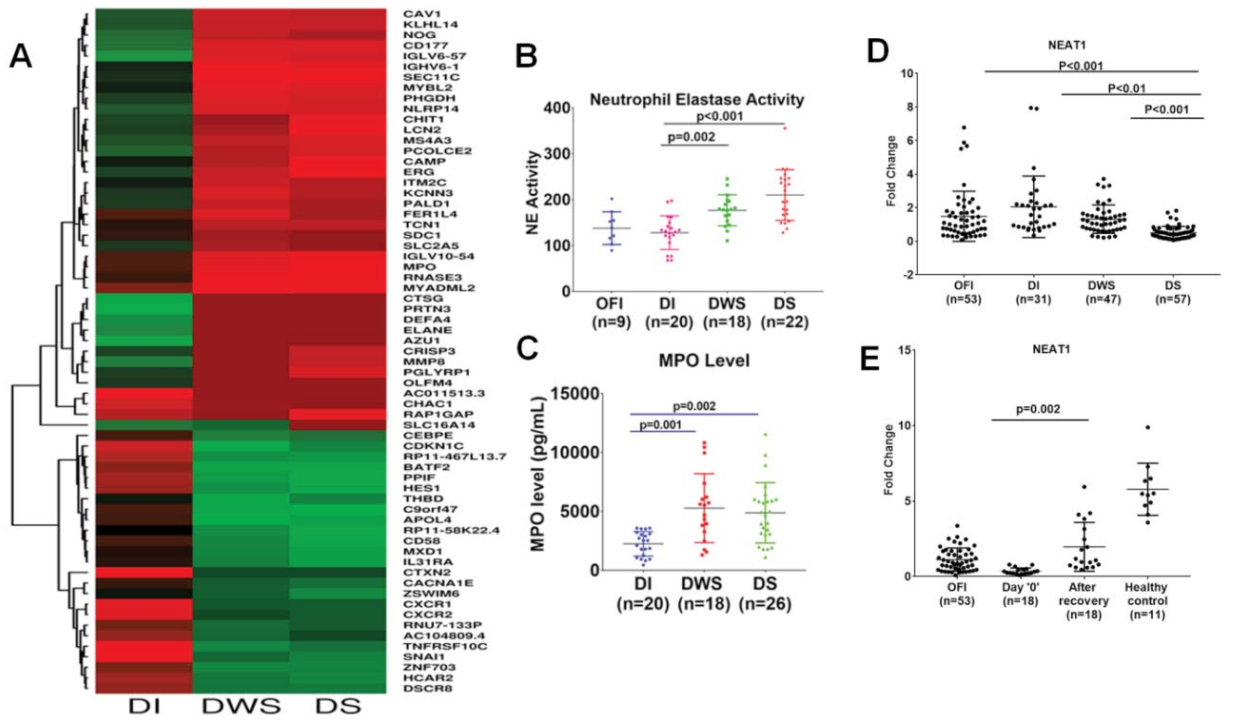
Comparison: Other Febrile Illness (OFI, dengue-negative) patients and healthy donors, as controls for comparison. Further, for validation and disease association studies, follow-up patients and patients with Dengue Severe (DS) who ultimately recovered from the infection were included.

Objective: Identification of disease-associated genes that may play a significant role in DS pathophysiology.

Progress: High-throughput RNA sequencing was done on 31 dengue-infected and 8 dengue-negative patients. A total of 137 PBMC samples were used for validation of gene expression: Dengue Infection; DI (n=20), Dengue with Warning Sign; DWS (n=47), and DS (n=70). The rest were OFI group (n=24), and apparently healthy individuals (n=11).

The comprehensive study has identified unique transcriptional signature associated with dengue severity. Several upregulated genes in the inflammatory process (MPO, DEFA4, ELANE, AUZ1, CTSG, OLFM4, SLC16A14, and CRISP3) that were associated with the dengue disease progression are known to facilitate leukocyte-mediated migration, and neutrophil activation and degranulation process. High activity of MPO and ELANE in the plasma samples of the follow-up and recovered dengue patients as well as the presence of a larger amount of cell-free dsDNA in the DS patients suggested an association of neutrophil-mediated immunity with dengue disease progression. Further, some progress has been made in identifying disease-associated non-coding RNA as possible prognostic marker. **NEAT1** was identified as one of the differentially expressed lncRNAs. Analysis of NEAT1 expression in healthy and dengue infected patients (during the acute and convalescent phases) further confirmed its potential association in dengue pathogenesis. This data would be helpful in clinical research pointing to future strategies for guiding prognosis.

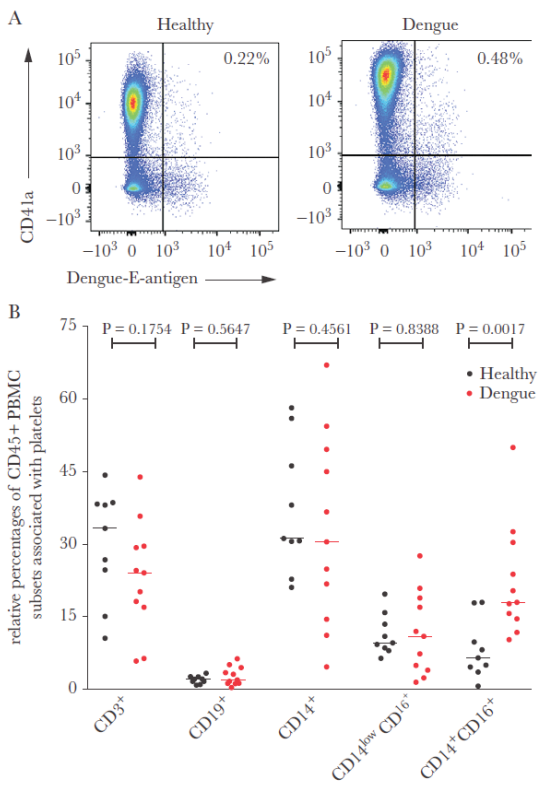
Based on the results obtained from the study of patients, their work plan is to understand dengue virus (DENV)-mediated disease progression at the molecular level. The discovery of miRNA circulating in the blood or body fluid of infected patients has become a powerful non-invasive tool to identify biomarker for diagnosis or disease progression during infection. His team is also working to identify circulating miRNAs from plasma of dengue infected and uninfected patients. So far, they have completed sequencing of 48 such samples and identified several disease-specific known and novel miRNAs. Validation and association studies are now in progress. At the end of this study, they are expecting to identify the dysregulated



A) Comparative expression pattern of the dysregulated genes in the three dengue groups. The heatmap shows the 63 common genes dysregulated in the DWS and DS groups when compared with the OFI group (Left panel). The colors red and green denote the high and low expression, respectively. (B-C) Expression pattern of neutrophil-associated genes *ELANE* and *MPO*. (B) Neutrophil elastase (NE) activity and MPO protein concentration in the plasma samples of the different dengue groups was measured by ELISA. (D) *NEAT1* expressions suppressed in dengue severe patients and becoming normal during convalescent phase (E).

miRNAs that could be useful as biomarker for dengue disease progression.

His team has started exploring the role of extracellular nano-vesicles, also called exosomes, during the infection. The exosomes can be isolated from many biological fluids including blood, cerebrospinal fluid, urine, and saliva. These exosomes contain molecular information about their cells of origin and play important roles in intercellular communication by acting as a carrier to deliver essential cell-specific information to target cells. Exosomes released from the infected cells contain several biologically active molecules (DNA, miRNA, LncRNAs, host



Platelet infection and platelet-leukocyte association in dengue patients. (A) A representative figure of platelets isolated from dengue patients stained with CD41a and anti-DENV-E antibody. (B) CD41a+ platelets were identified in CD45+ population, and the frequencies of indicated subset associated with CD41a+ was estimated relative to total CD45+ cells associated with platelets. N=9 and N=11 for healthy controls and dengue patients, respectively. Bar represents median value.

and viral proteins, viral RNA) and deliver the content to the distant cells. Several viruses utilize this machinery to evade immune response and subsequently help to spread the infection.

The objectives of the study are (1) to develop a protocol for identifying tissue origins of circulating exosomes, and (2) to compare and characterize exosomes content isolated from human blood, cerebrospinal fluid samples of healthy, mild, and severe patients. Information gained from these studies would help to develop carrier vesicles to deliver drugs to the specific tissues and organs like the brain for treatment of brain inflammation caused by the infection. It would also aid in development of disease-specific prognostic markers. (3) to understand the biological significance of exosomes released during infection and their impact on immune modulation and pathogenesis.

Dr. Guruprasad Medigeshi and his team are addressing **thrombocytopenia**, a characteristic feature during the acute phase of dengue infection associated with vascular leakage in severe dengue. Although dengue antigens have been observed in platelets, there is no strong evidence to suggest a direct infection of platelets by dengue virus as a contributing factor for thrombocytopenia.

Research Involving Human Participants
Population: Dengue NS1 positive children (4-14 years). **Comparison:** Healthy adult volunteers. **Objective:** Identification of correlates of disease severity.

Progress: The results show that dengue virus can enter platelets but replicate viral ribonucleic acid to a minimal extent and therefore, cannot produce infectious virus. Dengue antigen was undetectable in platelets isolated from dengue patients, however, they observed an increase in CD14+CD16+ monocyte-platelet complexes, suggesting a mechanism for platelet clearance.

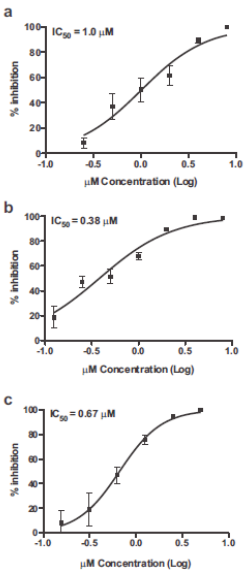
Dengue virus infection of bone marrow cells and the consequent suppression of bone marrow growth is one of the earliest reported clinical features of infection by this virus. Recent reports have further suggested that among bone marrow cells isolated from naturally infected humans, viral antigen is highly enriched in the cells of megakaryocytic lineage. Since these cells eventually differentiate to produce platelets or thrombocytes, it has been suggested **that infection of cells of megakaryocytic lineage hampers platelet production and thereby contributes to dengue-associated thrombocytopenia**. In the absence of a readily available animal model for dengue infection, **Dr. Sankar Bhattacharyya's** team is trying to get insight into megakaryopoiesis *in vitro* using cell lines, which would be later validated using primary hematopoietic stem cells. Towards this they have:

- Standardized an *in vitro* model of megakaryopoiesis using a cell line representing Megakaryocyte-Erythrocyte Progenitors (MEP), which can be pharmacologically induced to differentiate into megakaryocytes
- Developed the metrics for quantification of this differentiation process for comparison between uninfected and virus-infected states
- Characterized the infection cycle of dengue virus in both undifferentiated MEP and megakaryocytes which have been pharmacologically differentiated from these cells with respect to viral RNA replication and release of infectious virus particle

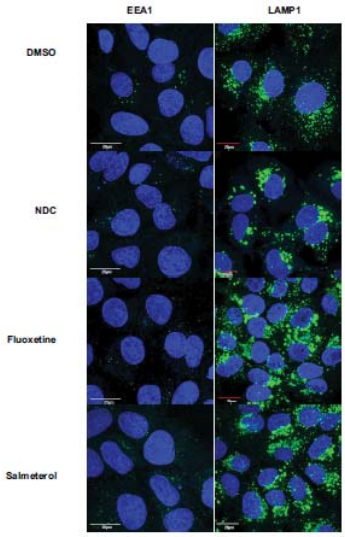
The future plan of his group is to elucidate how the differentiation process during megakaryopoiesis provides a suitable niche for virus replication, if dengue virus replication imposes any hindrance to megakaryopoiesis and mode of platelets activation upon dengue infection.

ANTIVIRALS FOR DENGUE

Dr. Guruprasad Medigeshi's team has made further progress in the **drug repurposing** strategy by characterizing the mechanism of action of dengue inhibitors that they had identified in a high-throughput screen. The three dengue inhibitors (a) N-Desmethylclozapine (b) fluoxetine hydrochloride and (c) salmeterol xinafoate inhibited dengue infection with an IC_{50} in the low micromolar range. All the three inhibitors interfered with the endo-lysosomal pathway and blocked dengue infection in cell culture. These three inhibitors that were



Determination of IC_{50} of dengue virus inhibitors. Huh-7 cells were infected with DENV-2 at an MOI of 3 and treated with 2-fold dilutions of inhibitors starting from a concentration of 8 µM. Viral titers in the supernatants were estimated by plaque assays at 24 h p.i. (a) N-Desmethylclozapine; (b) fluoxetine hydrochloride; (c) salmeterol xinafoate. Error bars represent means with standard errors of the means. IC50s of the respective drugs are indicated.



Effect of inhibitors on endolysosomal markers. Huh-7 cells were treated with DMSO or 4 µM N-desmethylclozapine (NDC), fluoxetine hydrochloride, and salmeterol xinafoate for 4 h; fixed; and stained with early endosome antigen 1 (EEA1) and lysosomal-associated membrane protein 1 (LAMP1) primary antibodies followed by secondary antibodies conjugated with Alexa 488 (green). Nuclei are stained with DAPI (blue).

identified are FDA-approved drugs. If the efficacy of these drugs on dengue infection in animal models is demonstrated, this will be furthered into clinical trials in humans.

Zinc is an acute-phase reactant whose plasma levels decrease during infections, however, the molecular mechanism behind modulation of zinc homeostasis in viral infections has not been elucidated. Dr. Guruprasad Medigeshi's group has shown that infection of intestinal epithelial cell line (Caco-2) with human rotavirus leads to an increase in the labile zinc levels measured using zinc-binding fluorophore, Fluozin-3, in epithelial cells. Supplementation of culture medium with exogenous zinc leads to an inhibition of infection. These results suggest that enhanced intracellular zinc concentration has an antiviral effect in host cells and, therefore, an increase in labile zinc concentrations may be a component of host antiviral response. Further experiments are underway to identify the pathways affected due to modulation in zinc homeostasis in viral infections.

COLLABORATORS

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JAPANESE ENCEPHALITIS

Japanese Encephalitis (JEV) is the main cause of viral encephalitis in many countries of Asia with an estimated 68,000 clinical cases every year. Permanent neurologic or psychiatric sequelae can occur in 30%–50% of those with encephalitis. 24 countries in the WHO South-East Asia and Western Pacific regions have endemic JEV transmission, exposing more than 3 billion people to the risk of infection.

Dr. Manjula Kalia's team focuses on:

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

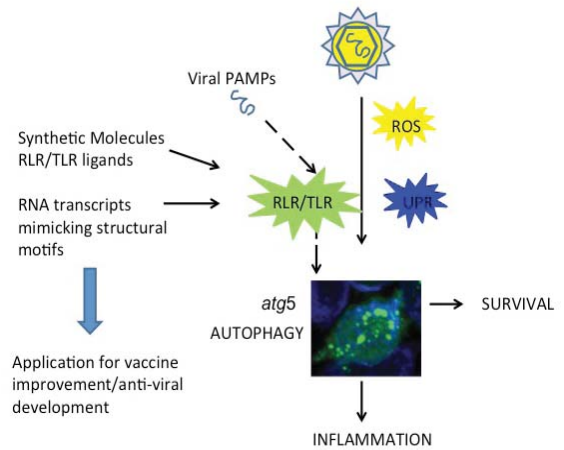
Viral infections lead to an upregulation of the cellular autophagy pathway through stress conditions created in cells. Oxidative stress is caused by production of reactive oxygen species (ROS), while accumulation of viral proteins leads to activation of ER stress and unfolded protein response (UPR). Autophagy influences viral pathogenesis directly by exerting an effect on cell survival and inflammation. Her research focuses on understanding how Pathogen Associated Molecular Patterns (PAMPs) can modulate innate immune responses through the sensors of infections-RIG-I-Like Receptors (RLRs) and Toll-Like Receptors (TLRs) via autophagy.

Her group has successfully completed a siRNA-based membrane trafficking screen of 144 genes in human neuronal and epithelial cell lines. They have identified 6 potential druggable targets that can block JEV replication. These are currently being validated and will further be tested in animal models.

The group has advanced research on understanding how the **host cellular autophagy pathway intersects with viral replication.** They have shown that the cellular autophagy pathway is modulated by stress responses in the cell- oxidative stress and ER stress. They are studying how autophagy influences the host immune response and the potential of modulating this pathway in enhancement of immune response and improvement of vaccine efficacy.

The research leads are being tested in animal models of disease and *in vitro* in primary human cells. Based on results obtained with animal experimentation, translatable clinical potential of these therapies will be tested.

An overview of Japanese Encephalitis Virus (JEV) interaction with the cellular autophagy pathway and its implications



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VIRAL HEPATITIS

Hepatitis E virus (HEV) causes acute hepatitis in many parts of the world including Asia, Africa and Latin America. Though self-limiting in normal individuals, it results in ~30% mortality in infected pregnant women. It has also been reported to cause acute and chronic hepatitis in organ transplant patients.

Dr. Milan Surjit's laboratory has been investigating multiple aspects of hepatitis E virus biology such as (a) development of a mouse model that mimics HEV infection in humans and use of this model to characterize the molecular mechanisms of HEV pathogenesis, (b) understanding the host-pathogen interactions involved in HEV pathogenesis, (c) understanding the mechanism of viral translation, replication and release, (d) identification of novel anti-HEV compounds that can be used as therapeutic drugs, and (e) development of a recombinant vaccine against HEV. The ultimate goal of the laboratory is to generate sufficient knowledge/resources for in-depth molecular understanding of the lifecycle of hepatitis E virus and development of efficient prophylactic and therapeutic products against the pathogen using the above knowledge/resources.

They have generated a **comprehensive network of protein-protein interactions (PPIs) between hepatitis E virus-encoded factors and its human host**. Based on the information obtained from the PPI network, they have demonstrated the essential role of several host translation regulatory factors in HEV translation/replication. The network has enabled them to establish the role of eIF2AK4/GCN2 as a host restriction factor against HEV.

In the near future, they plan to continue investigating the molecular details of HEV life cycle and develop novel anti-virals and a recombinant vaccine against HEV.

COLLABORATORS

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HEPATITIS-HYDROPERICARDIUM SYNDROME (HHS) IN POULTRY

Members of Fowl Adenovirus serotype 4 (FAdV4) are the causative agents of Hepatitis-Hydropericardium Syndrome (HHS) in poultry. Inactivated preparations of pathogenic FAdV4-infected liver homogenates are available commercially in the market as prophylactics for the control of the disease. However, their protective efficacy is only about 60-70% even in the Specific Pathogen-Free (SPF) chicken.

Live, naturally attenuated virus is an ideal candidate for the development of an effective vaccine against HHS. **Dr. Mohan B. Appaiahgari's** group recently isolated a novel FAdV serotype 4 from an apparently healthy poultry bird, sequenced and characterized its genome. They found that the virus had several novel features like (1) the virus codes for ORF19A that is phylogenetically related to that of FAdV serotype 10, (2) the region involving the ORF19 coding sequence in their isolate is derived through a major recombination event with that of FAdV10, and (3) the viral genome has undergone recombination events with the non-pathogenic strains within the genomic regions that code for proteins implicated in virus pathogenicity. Together with its sample source from an apparently healthy bird supports its novelty as well as its non-pathogenic nature. Based on the above data, they propose to develop a live, attenuated candidate vaccine and test its protective efficacy in poultry birds.

Currently, they are performing experiments to test the pathogenic potential of the isolate. For this, different doses of the purified virus starting from the highest possible dose are being tested for their ability to induce disease. These experiments are also aimed at investigating the immunogenic potential of different doses of the isolate. The above experiments are being done in the target species i.e. the poultry birds. Currently, all the experiments are being done in SPF chicken. However, upon successful demonstration of the immunogenic/protectogenic potential of the FAdV serotype 4 isolate in SPF chicks, they

would then carry out similar set of studies in birds housed in commercial poultry farms. Therefore, the present study would be a proof-of-concept study for future studies aimed at developing a live, attenuated vaccine against HHS.

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HIV/AIDS

The HIV Vaccine Translational Research (HVTR) Laboratory carries out early translational research and development under the joint partnership program between the THSTI and the International AIDS Vaccine Initiative (IAVI). It follows the principle of a center of excellence with unique strength towards accelerating the efforts for HIV vaccine development through partnering with other laboratories and clinical research centers both globally and locally. The overall goals of the THSTI-IAVI HIV Vaccine Design Program are:

- Rapid screening, identification, design and early development of HIV-1 envelope protein (Env) immunogens based on circulating strains of HIV-1 in India, that potentially would elicit broadly neutralizing antibodies following immunization.
- Isolation and characterization of broadly neutralizing antibodies (bnAbs) from donors of Indian origin.

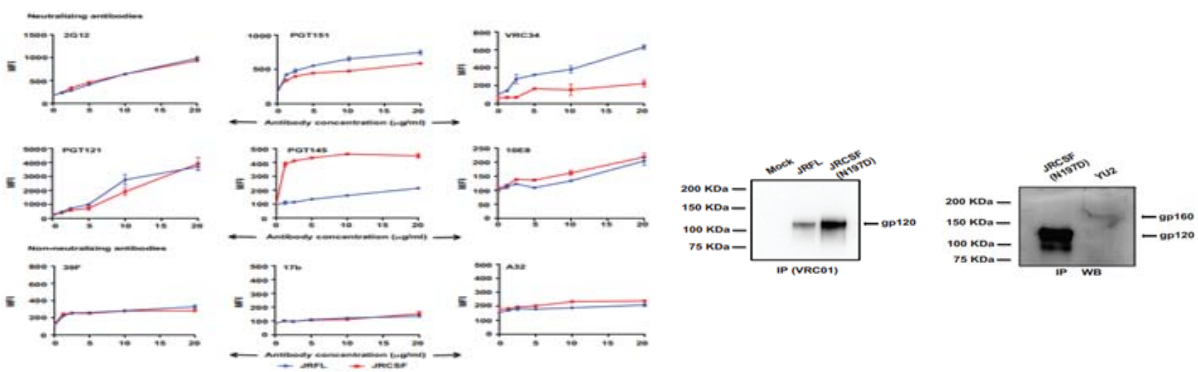
EFFORTS IN HIV-1 IMMUNOGEN DESIGN

Investigators:
Drs. Bimal K. Chakrabarti, Supratik Das, Shubbir Ahmed, Tripti Shrivastava, Sweety Samal, Rajesh Kumar, Vivek Kumar, Manish Bansal, Sandeep Goswami, Naresh Kumar, Jayanta Bhattacharya

Area of Research:
HIV-1 immunogen design

HIV-1 envelope (Env)-based vaccine immunogen design. A vaccine against HIV-1 is expected to be the most efficient way to control new infections and eradicate the disease. The only surface exposed antigen on the HIV viral surface is the envelope (Env) protein, gp140. The focus of this research is to develop Env-based vaccine against HIV-1. The team uses various approaches to screen, design and characterization of viral Envs for their appropriateness as potential vaccine candidates.

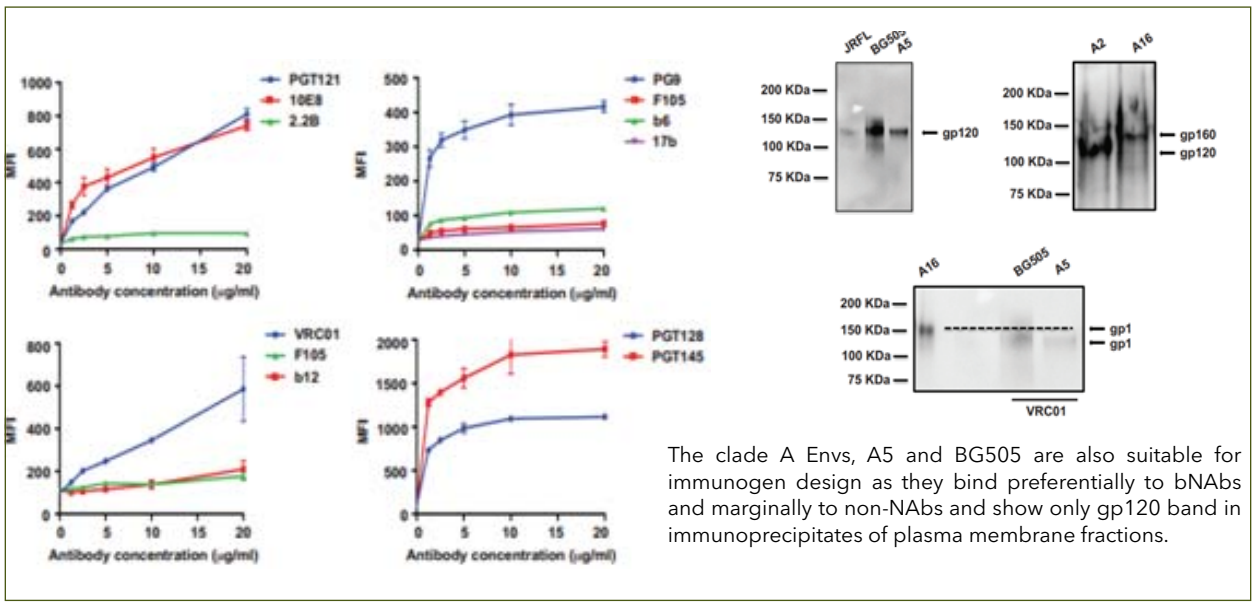
Identification and characterization of HIV-1 Envs belonging to subtypes A, B and C suitable for inclusion in the design of multi-clade immunogens



Naturally occurring, efficiently cleaved HIV-1 envelopes are ideal candidates for designing immunogens for a vaccine. The critical properties of such Envs are their ablity to bind broadly neutralizing antibodies (bNAbs) only and not non-neutralizing antibodies (non-NAbs), and show only gp120 band in immunoprecipitates (IP) of plasma membrane (PM) fractions. Here we show that the clade B Env, JRCSF is efficiently cleaved on cell surface as it binds specifically to bNAbs and poorly to non-NAbs and displays only gp120 band in PM-IP.

Lead Investigators: Dr. Supratik Das

HIV-1 diversity is a key impediment in developing an effective vaccine. Efficiently cleaved, membrane-bound HIV-1 envelopes with desirable antigenic properties are relatively rare but the closest mimics of native, functional Envs and are therefore suitable for immunogen design. Prior to this study, only one clade B Env, JRFL, was known which is efficiently cleaved in its membrane-bound form and shows preferable antigenic properties. By screening and examining a number of HIV-1 Envs belonging to clade A, B and C (which make up 75% of globally circulating strains) for their degree of binding to neutralizing and non-neutralizing antibodies in membrane-bound form, this team has identified three Envs: A5 (clade A), JRCSF (clade B), and 4-2.J41 (Indian clade C), which were found to bind majorly to the neutralizing antibodies and very minimally to few non-neutralizing antibodies in their membrane-bound form. These Envs have been extensively characterized for antigenic and biochemical properties and the plan is to evaluate their immunogenic potential as DNA vaccine candidates along with protein boost in small animal models.

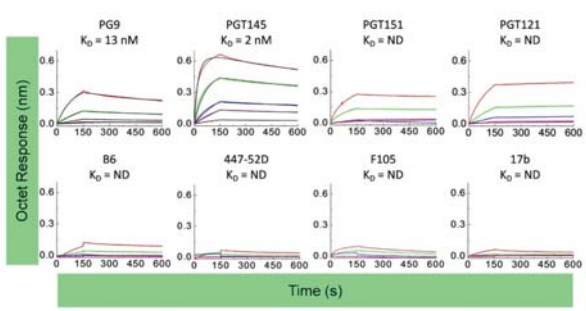


The clade A Envs, A5 and BG505 are also suitable for immunogen design as they bind preferentially to bNAbs and marginally to non-NAbs and show only gp120 band in immunoprecipitates of plasma membrane fractions.

Structure-guided design and stabilization of soluble HIV-1 clade C Env of Indian origin as means of rational immunogen design

Lead Investigator: Dr. Shubbir Ahmed

Designing an effective HIV-1 envelope glycoprotein (Env) immunogen for elicitation of broadly neutralizing antibodies (bNAbs) is a challenging task due to high sequence diversity, heavy glycosylation and inherent meta-stability of Env. The current rational approach in the field of HIV Env-based immunogen design is to make a stable version of the Env trimer, which mimics the native trimeric Env present on the viral surface. The team has attempted to stabilize a naturally occurring efficiently cleaved clade C Env, namely 4-2.J41, isolated from an Indian patient by swapping domain from BG505, a stable clade A Env. Using various biochemical and biophysical means they have confirmed that this engineered Env is cleaved, trimeric and retains native-like



Antigenic profile of successfully designed soluble, native-like, trimeric Env 4-2.J41 by biolayer light interferometry (BLI). Upper panel represents binding curves obtained with bNAbs, namely PG9, PGT145, PGT151, and PGT121. Lower panel represents binding curves with non-NAbs, namely b6, 447-52D, F105, and 17b.

quaternary conformation exposing mostly broadly neutralizing epitopes.

Their designed 4-2.J41 Env adds to the increasing pool of potential immunogens for HIV-1 vaccine, particularly for clade C, which is the most prevalent in India and many other countries. Besides, the approach used to stabilize 4-2.J41 Env may be used successfully with Envs from other HIV-1 strains as well. Additionally, a soluble native trimeric form of an efficiently cleaved membrane-bound Env, 4-2.J41, may be beneficial for immunization studies using various prime-boost strategies.

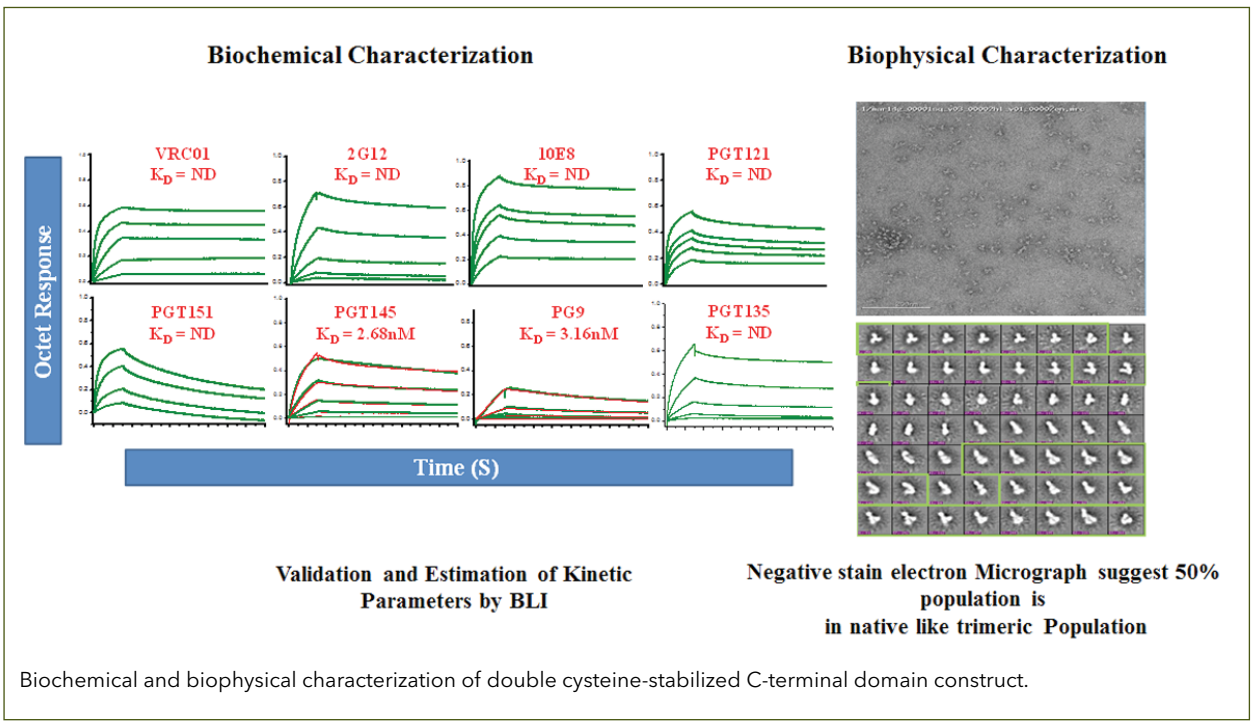
Understanding the structural-functional relationship of HIV-1 clade C Env as a rational approach towards successful immunogen design

Lead Investigator: Dr. Tripti Shrivastava

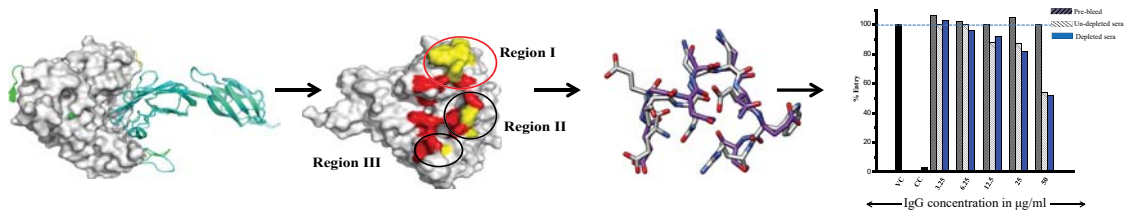
This project builds essentially on the following three specific aims: (1) identification and characterization of non-immunogenic surface protein of viral pathogens as a candidate for functional vaccine target, (2) characterization and evaluation of soluble immunogen and co-validation of functional aspect, and (3) structural insights into HIV Env and elucidation of their interaction with neutralizing antibodies.

Rational approach for HIV-1 Env protein-based immunogen designing: Towards stabilizing the soluble form of a major circulating clade C Env: native trimeric, efficiently cleaved membrane-bound 4-2.J41, a novel approach was developed. C-terminal stabilization-based approach has enabled in developing a vaccine candidate that contains Membrane Proximal External Region (MPER), which includes epitopes for broadly neutralizing antibodies (bNAbs). Details of this immunogenic region was missing in soluble form of trimeric Envs designed previously. Designed immunogen was further stabilized with the introduction of double cysteine residues at the bridging sheet region to limit the interaction with co-receptor antibodies. Antigenic profiles, biochemical, biophysical characterization, and electron microscopic studies have confirmed native-like trimeric structure of the Env.

- **Identification and characterization of a non-immunogenic surface protein of viral pathogens as a candidate for functional vaccine target:** This project is an ongoing research work as an attempt for proof of principle where the aim is to target regions of surface protein which are as per function not been characterized as immunogenic. Stretches of amino acid sequences around CD4-binding site were identified, which were accessible on the surface, as targets for scaffold-epitope



Biochemical and biophysical characterization of double cysteine-stabilized C-terminal domain construct.



Identification and characterization of non-immunogenic surface protein of viral pathogens as a candidate for functional vaccine target.

targeted immunogen development. As an attempt to block or hinder the access of CD4 to Env protein, scaffold-epitope was developed, cloned, overexpressed, purified and used for protein prime/protein boost. This was done in collaboration with Prof. M.S. Madhusudhan, Indian Institute of Science Education and Research, Pune. Experimental findings indicates that polyclonal sera have the potency to inhibit autologous virus entry to some extent, hence strongly validating the concept of designing scaffold-epitope for viral pathogens. The researchers have tested the immunogenicity of scaffold-epitope immunogen through protein prime/protein boost immunization regime on rabbits. The previous immunization studies done in rabbits with targeted peptide, suggested a need for binding antibodies. In protein prime/protein boost approach used here, immunization was done with Scaffold A followed by Scaffold B boosting, as an attempt to reduce immunogenic response against the scaffold backbone. Immunized sera further tested for inhibition of viral entry in TZM-bl cell-based assay platform showed a significant reduction in the viral entry of autologous virus.

- **Characterization and evaluation of a soluble immunogen and co-validation of functional aspect:** Genetic diversity and structural flexibility of HIV env have encountered numerous challenges for the development of soluble immunogen. Their attempts to stabilize newly identified 4-2.J41 to soluble form following strategies reported earlier including SOSIP.664 have not been successful. Therefore, the researchers have used a fusion protein-based approach to stabilize a trimer which mimics and displays an antigenic signature similar to Env protein when expressed on cell surface. In their study, antigenicity assays of 4-2.J41-gp140-fd proteins demonstrated that most bnAbs, including quaternary conformation-specific antibodies PG9, PG16 and PGT145 recognizes by foldon stabilized trimer with nano-molar affinity. DNA primer-fold on the stabilized protein boost immunization regime used, not only limited V3-directed response, but also hinted towards conformation-directed antibody response.

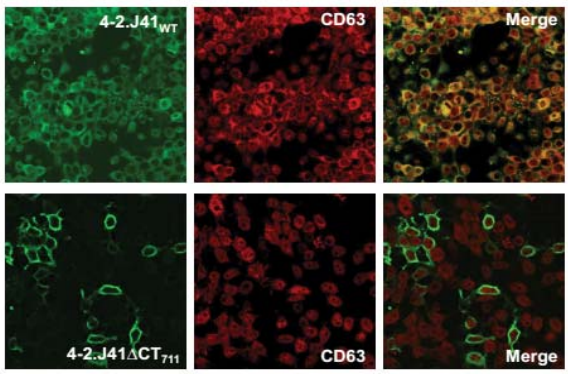
- **Structural insights into HIV Env protein and elucidation of its interaction with antibodies:** The objective of the current study is to reveal the high-resolution details of Indian clade C Env protein targeting different stabilized soluble variants. This study is targeting an iterative process and a platform for structure-based vaccine designing. The study outcome would leverage on the latest innovation approaches and platform technologies used globally in HIV vaccine research and would address key gaps in translational approaches for the design of HIV-1 Env-based immunogens.

Dissecting the crucial domains of HIV-1 virus Envelope (Env) proteins to facilitate in designing of both membrane-bound and soluble Env immunogens

Lead Investigator: Dr. Sweety Samal

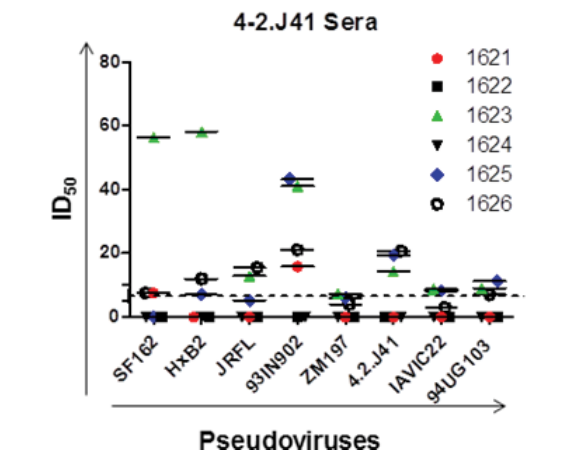
The major objectives are (1) understanding the role of conserved and variable domains of HIV-1 Env protein on its structural integrity and antigenicity, protein expression and conformation at virion level, and (2) identification of novel interactions between cellular proteins and HIV-1 proteins that

would enable designing of unique antiviral drugs and novel immunogens. The present work on HIV-1 Env cytoplasmic tail has given a new insight on variability of intracellular trafficking between inter- and intra-clades Env antigens inside the cell, thus regulating antigen conformation and antigenicity. This is a new finding that will broaden the vision on designing HIV-1 Env-based immunogens both in membrane-bound and soluble forms.



Co-localization of wildtype and del-CT Env with late endosome marker CD63.

Additionally, they evaluated the immunogenicity of Indian clade C efficiently cleaved Env 4-2. J41 in rabbits with DNA prime/foldon protein boost approach. Although a very modest neutralizing antibody response was observed, it was inadequate. Currently, work is in progress to modify the Env protein for its better stability and presentation as close mimics of trimeric conformation in soluble form.

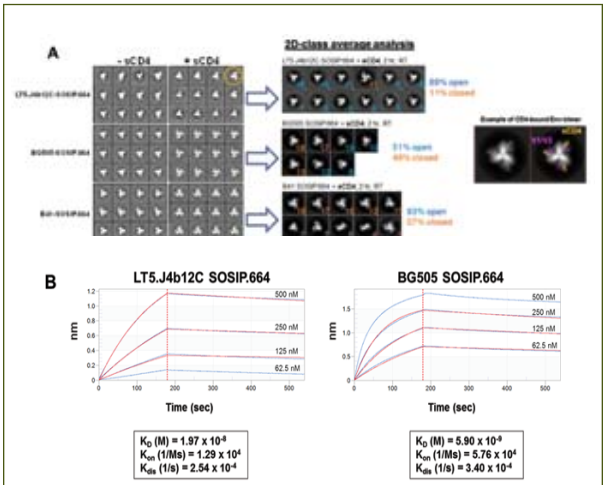


Neutralization titers (ID_{50}) of serum antibodies obtained from different rabbits immunized with 4-2.J41 Env immunogen against autologous and heterologous viruses. Color code indicates different rabbit groups.

Characterization of a stable HIV-1 B/C recombinant soluble trimeric Env that is highly resistant to CD4-induced conformational changes

Lead Investigator: Dr. Rajesh Kumar

The engagement of the HIV-1 gp120 glycoprotein with CD4 triggers conformational changes in gp120 that allow its binding to coreceptors, and is necessary for virus entry to establish of infection. Identification of native like HIV-1 Env immunogens representing distinct clades have been proposed to improve immunogenicity. In the present study, the basis of resistance of an HIV-1 B/C recombinant Env (LT5.J4b12C) to non-neutralizing antibodies targeting CD4-induced (CD4i) epitopes in presence of sCD4 was examined. By native polyacrylamide gel shift assay and negative stain electron microscopy, it was found that the prefusion conformational state of LT5.J4b12C-SOSIP was largely unaffected in presence of excess sCD4 with most Env trimers appearing to be in a ligand-free state. The resistance to CD4-induced conformational changes was further found to be associated with a lower affinity for CD4. Finally, the LT5.J4b12C SOSIP Env was found to preferentially bind to broadly neutralizing antibodies (bnAbs) with distinct specificities.



Biophysical characterization of LT5.J4b12C SOSIP.664. (A) 2D negative-stain EM class averages of various SOSIP.664 trimers, ligand free or in complex with a 6-fold molar excess of sCD4 (2 hour incubation at room temperature). Percentage of particles belonging to a specific class (open and closed conformations) are shown. Example, CD4-bound class with false coloring (bottom) for reference. (B) Biolayer interferometry (BLI Octet Red) kinetics analysis of SOSIP trimer binding to sCD4. Fitted curves (1:1 binding model) are shown in red.

Taken together, the researchers have identified a novel HIV-1 B/C recombinant native like trimeric Env that is highly resistant to CD4-induced conformational changes in soluble form, but still displays epitopes targeted by a diverse array of broadly-neutralizing antibodies. These features make this newly identified B/C recombinant trimeric Env a useful addition to the pool of other recently identified native like HIV-1 Env trimers suitable for use as an antigenic bait for broadly-neutralizing antibodies isolation, structural studies and potential immunogens. This unique Env antigen would be used for isolation of broadly-neutralizing antibodies from Indian donors and for assessment of its immunogenicity in small animal models.

Way ahead

While dissection of mechanisms of improving immunogen design are in progress, some of the promising Env trimeric antigens are being taken forward for assessing their immunogenicity in small animal models.

EFFORTS IN ISOLATION OF BROADLY-NEUTRALIZING ANTIBODIES FROM ELITE NEUTRALIZERS OF INDIAN ORIGIN

Investigators:
Drs. Jayanta Bhattacharya, Huma Qureshi, Suprit Deshpande, Rajesh Kumar, Shubbir Ahmed, Sangeeta Kumari Sinha, Vivek Kumar, Ankush Rana

Area of Research:
Isolation and characterization of broadly-neutralizing antibodies from HIV-1 clade C infected elite neutralizers

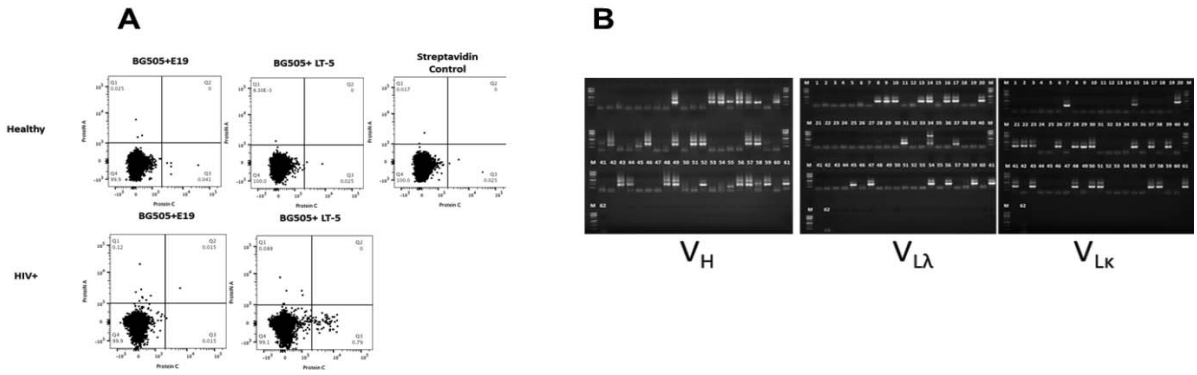
Isolation of mAbs that are able to cross-neutralize a diverse range of HIV-1 subtype C isolates would constitute reagents of clinical importance. Potent neutralizing mAbs with considerable breadth have the potential to be developed as a therapy for infected individuals as well as provide pre-exposure prophylaxis to individuals at high risk of HIV infection. Such mAbs therefore are attractive products that can be further engineered for other uses (e.g., vector-based immunoprophylaxis and as a potential microbicide). Monoclonal antibodies obtained from HIV-1 subtype C infection would be useful to understand the development of protective immune responses in individuals in India. Such information would also be crucial in rational immunogen design capable of eliciting cross-HIV-1 subtype C neutralizing antibodies.

Isolation and cloning of functional variable heavy and light IgG chains from single memory B cells (monoclonal) obtained from human peripheral blood mononuclear cells (PBMCs)

Lead Investigators: Drs. Huma Qureshi, Suprit Deshpande, Rajesh Kumar

Towards standardization and optimization of the isolation of broadly neutralizing antibodies from the HIV-1 Indian Subtype C infected donors, the team initiated single cell sorting of memory B cells from healthy donors. To perform single cell sorting of memory B cells, they isolated peripheral blood mononuclear cells (PBMCs) from healthy donors and stained these PBMCs with a panel of multicolor antibodies *viz.*, Live /Dead Aqua stain, CD8 PerCP, CD3 PerCP, CD19 BV421, IgM FITC, IgD FITC, IgG APC Cy 7, CD14 PerCP, CD16 PerCP. Thereafter, these stained PBMCs were gated on FACS Aria III using the gating strategy shown in the figure A. Following gating, they dumped the unwanted cell populations (T cells/NK cells/ Monocytes/ Naïve B cells) and sorted single memory B cells (CD19+IgG+) in 96 well plates containing pre-RT lysis buffer. RT-PCR was done on sorted single memory B cells (CD19+IgG+) using random hexamers and prepared cDNA. Variable heavy and light chains gene fragments from the cDNA were further amplified using two rounds of nested PCR. These amplified variable heavy and light chain (lambda/kappa chains) gene fragments were subsequently cloned into respective mammalian expression vectors; Igγ, Igλ, Igκ.

The recombinant IgG clones were expressed using 293T or 293F cells. Additionally, antigen-



(A) Single cell sorting of memory B cells from healthy and HIV-infected Indian donors. CD19 + CD27+/IgG+/IgGM-/IgD- B cells were first selected by staining with appropriate antibodies to selected markers and subsequently single cells sorted (FACS Aria III) in 96-well plates. (B) Amplification of variable heavy and light (kappa and lambda) IgG chains. Total RNA from lysed single B cells were used as template to amplify IgG variable heavy (VH) and light lambda (VLλ) and kappa (VLκ) chains by RT-PCR.

specific sorting of single memory B cells from HIV-1+ donor PBMCs was standardized using native like HIV-1 Env trimers. With further technical help from scientists at the International AIDS Vaccine Initiative-Neutralizing Antibody Consortium, Scripps Research Institute, La Jolla, California, USA, efforts have been initiated for isolation of broadly neutralizing antibodies from one elite neutralizer of Indian origin whose serum antibodies showed considerable neutralization breadth in the previous reporting period.

Broadly neutralizing plasma antibodies obtained from an Indian donor with specificity to novel epitopes in V2 region of viral Env preferentially neutralize HIV-1 clade C strains

Lead Investigators: Drs. Suprit Deshpande, Rajesh Kumar

The specificity of the serum antibody obtained from an HIV-1 clade C infected Indian donor (IAVI Protocol G Donor-G37009) had been characterized and was found to demonstrate considerable neutralization breadth (neutralized 70% of the panel virus tested with median ID50 value of 255). Interestingly, the serum antibody was found to preferentially neutralize HIV-1 clade C Envs. Virus neutralization using chimeric Envs prepared between heterologous Indian clade C Envs (16055-2.3 and PG80v1.eJ19) indicated that plasma antibodies have major specificity to V1V2 region. Significant loss of neutralization breadth of the plasma antibodies was found to be associated with depletion with monomeric gp120. Furthermore, competitive inhibition by different peptide sequences indicated that the neutralization breadth of the plasma antibodies was associated with linear epitopes in V2 region not reported earlier. bnAbs preferentially targeting novel epitopes in HIV-1 subtype C would advance the understanding in rational immunogen design.

Future plan

Work is in progress towards isolating functional bnAbs from elite neutralizers of Indian origin by single memory B cell cloning.

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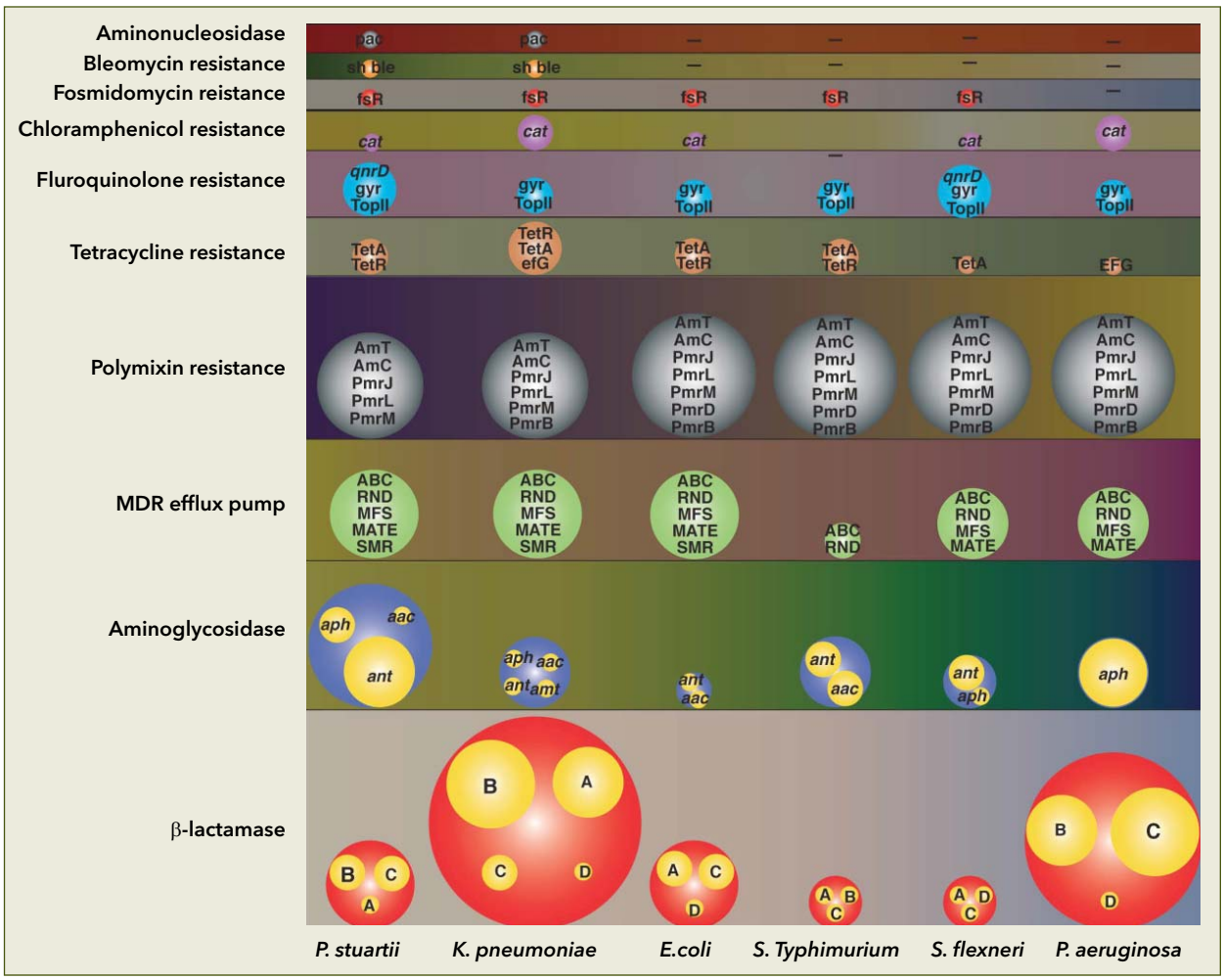
ANTIMICROBIAL RESISTANCE OF BACTERIAL PATHOGENS

Dr. Bhabatosh Das's team is investigating the molecular identity of antimicrobial resistance traits in enteric pathogens of public health importance such as *Vibrio cholerae, Shigella spp., Salmonella enterica* serotype *Typhi, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in developing countries. The research interest is mainly oriented in understanding the acquisition and dissemination mechanisms of antimicrobial resistance traits in enteric pathogens and development of a strategy to resensitize the multidrug resistant enteric pathogens.

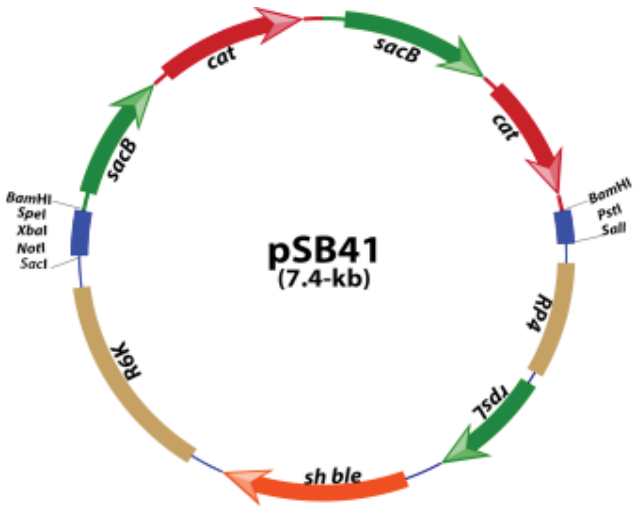
The findings in the analysis of complete genome of seven Extremely Drug Resistant (XDR) enteric pathogens (*Enteropathogenic Escherichia coli* (EPEC), *Shigella flexneri, Klebsiella pneumoniae, Salmonella enterica* serotype Typhimurium, *Providencia stuartii* and *Pseudomonas aeruginosa*) revealed hundreds of genes involved in virulence,



Antimicrobials resistance encoding genes in the XDR isolates. Bubble sizes correspond to the number of genes detected in the genome of isolates. Subclasses of the resistance function for each category are also mentioned inside the bubble. The picture was drawn to the scale. A, C and D denote serine--lactamase, whereas B denotes metallo-β-lactamase. *aph = Aminoglycoside phosphotransferase, aac = aminoglycoside acetyltransferase, ant = aminoglycoside nucleotidyltransferase, amt = aminoglycoside resistance methyltransferase, ABC = ATP-binding cassette transporter, RND = Resistance nodulation division, MFS = Major facilitator superfamily, MATE = Multidrug and toxic efflux, SMR = Small multidrug resistance, pmrJLM = Proteus mirabilis polymyxin B resistance encoding operon, pmrBD = Polymixin B resistance genes, TetA = Tetracycline resistance protein A, TetR = Tetracycline resistance regulatory protein R, EFG = Elongation factor G, qnrD = Quinolone resistance, gyr = Gyrase, topII = Type II topoisomerase, cat = chloramphenicol acetyltransferase, fsr = Fosmidomycin resistance protein, sh ble = Bleomycin resistance gene, pac = Puromycin N-acetyl-transferase.*

toxin production, disease development and antibiotic resistance in bacterial pathogens responsible for diarrhoeal diseases.

The genomes of all the sequenced XDR isolates harbor several mobile genetic elements such as plasmids, transposons, bacteriophages, integrative conjugative elements, integrons and genomic islands. The genome of each XDR isolate carried multiple resistance genes against β-lactam and aminoglycoside antibiotics, besides possessing multiple MDR efflux pumps. Except some of the MDR efflux pumps, all the resistance genes are physically linked with mobile genetic elements. These elements, therefore, appear to be responsible for disseminating drug resistance among bacteria through horizontal gene transfer. The findings would be useful to understand the genetics of resistance traits, evolution of pathogens and in deciding specific drug regimen against enteric infections.



Genetic map of conditionally replicating reporter plasmid pSB41-The backbone of the vector was derived from an integrative expression vector pBD61. The functional sacB-cat alleles were introduced into the BamHI site of pBD61. The XerC-XerD binding site (XBS) of pBD61 was replaced by the streptomycin sensitivity encoding rpsL gene.

Dr. Das and his group has developed a novel genetic tool to study the dynamics of mobile genetic elements encoding antibiotic resistance functions in the genome of enteric pathogens. The findings would be useful to identify compounds that may have the potential to re-sensitize XDR and MDR pathogens against routinely used antibiotics.

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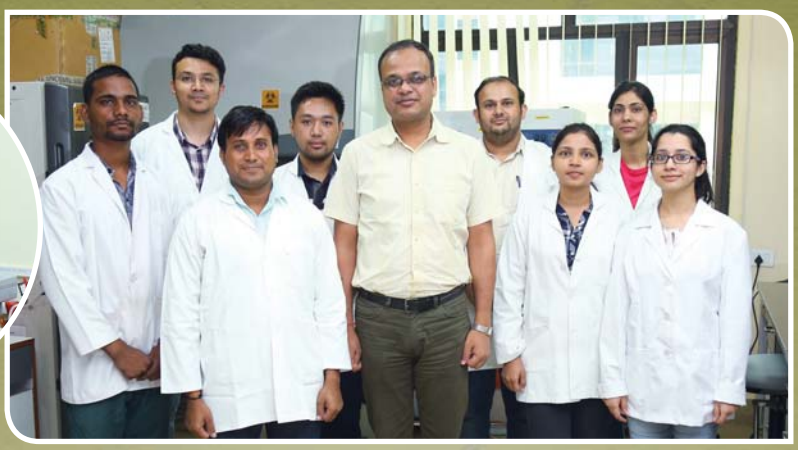

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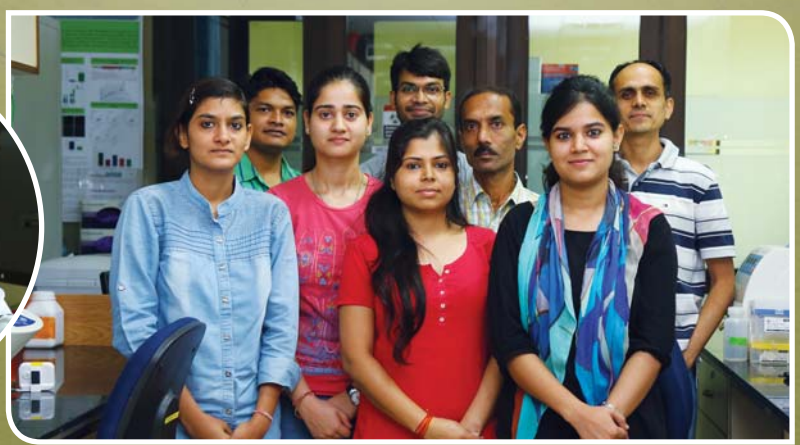

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DIAGNOSTICS FOR INFECTIOUS DISEASES

TROPICAL FEVERS

Acute Febrile Illness (AFI) is common in the tropics and sub-tropics, and can be caused by very diverse pathogens. The availability of a reliable Point-of Care Test (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. Infectious diseases that causes major burden of AFI in tropics and subtropics include malaria, dengue, chikungunya, typhoid/paratyphoid, scrub typhus, leptospirosis etc.

Despite the strong need, commercially available POCTs (singleplex) for these infections are of poor quality. Only some of the POCTs for malaria (only *Plasmodium falciparum*) fulfill WHO ASSURED criteria. Even for malaria, better POCTs are required for *P. falciparum* (low density infections, HRP2 negative strains and elimination settings) and non-Pf malaria especially *P. vivax* (routine diagnosis). Because of the issues in available singleplex tests, there is a strong need to develop high quality POCTs for tropical infections. It should be noted that despite the need, no multiplex POCT, which can be used in resource-limited settings for the detection of multiple etiologies of tropical fevers, is available in the market. A two-step approach is required-first, to develop high performance singleplex POCTs for individual infections that can reach the market in relatively less time, and second, to develop multiplex POCTs using the same diagnostic reagents. The successful development and implementation of singleplex and multiplex POCTs for AFI will not only help health care providers in choosing appropriate treatment option for the patient but will also help in controlling the problem of antimicrobial resistance through judicious use of antimicrobials.

Dr. Gaurav Batra's team is working on the development of Point of Care Tests (POCTs) for different tropical febrile illnesses. To fulfill the objectives of this goal they have developed:

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

Using antibody phage library (2 libraries from University of Turku), 75 unique synthetic recombinant antibodies against dengue NS1 antigen have been developed (with a wide specificity profile e.g. serotypes-specific, pan-dengue, pan-flavi NS1 etc.). Several promising antibodies suitable for the assay have been converted from singe-chain variable-fragment (scFv) to antigen-binding fragment (Fab) format because of the higher stability of FAb compared to ScFv. Work is underway to convert additional ScFvs to FAbs. The team has also developed a prototype well-based assay using these antibodies, both for the pan NS1 detection and for the detection of NS1 in serotype-specific manner. Once the well-based assay is completely optimized, lateral flow assay (LFA) based on gold as well as fluorescent nanoparticles will be developed.

Generation of ultrasensitive rapid diagnostic assay for malaria

A prototype ultrasensitive rapid lateral flow assay utilizing fluorescent nanoparticles for the detection of Pf-HRP2 antigen has been developed by Dr. Gaurav Batra's team. It has an ability to detect less than 5 parasites/µl (depending on the HRP2 type and strain). The stability and batch-to-batch consistency analyses are underway.

Antibody detection assay for scrub typhus

The group has selected suitable antigen for the development of assay for the detection of *Orientia tsutsugamushi* infection. Recombinant antigens derived from 2 strains of O. *tsutsugamushi* have been produced. Work is underway to produce recombinant antigens from 3 other

strains to cover the diversity. The cocktail of produced recombinant antigens will be used for development of ELISA and lateral flow assay for the detection of antibodies against *O. tsutsugamushi*.

Research Involving Human Participants

Population: Children with appropriate clinical and laboratory confirmation for the six febrile illness causing pathogens.

Comparison: Internal comparison with those with alternate diagnosis for other than the six pathogens.

Objective: To develop a panel of clinical specimens and to test the sensitivity and specifi city of the point of care tests for AFI.

Progress: Ethics committee approvals and staff hiring are in progress.

BLOOD BORNE PATHOGENS

Dr. Gaurav Batra's team is working on development of high sensitivity multiplex point-of-care assay systems for detection of blood-borne infections. The performance of commercially available rapid POCTs for HIV, HCV and HBV is inferior compared to central laboratory tests. Moreover, there is no commercially available POCT for the detection of HCV core antigen, which is a very important marker. Further, there is no commercially available multiplexed POCT for simultaneous detection of antigen and antibody markers for HIV, HBV and HCV. There is, however, one POCT available which detects anti-HIV, anti-HCV and anti-HBV antibodies, but not the antigens. A high performance multiplexed POCT for HIV, HBV and HCV, covering both the antigen and antibody markers, can be of enormous value and can be used in the following health settings:

- Emergency settings (emergency surgeries, emergency deliveries, emergency blood transfusion)
- Blood banks (donated blood screening)
- Sexually Transmitted Infection (STI) clinics
- Antenatal screening
- Population screening

LFA format is the most widely used point-of-care test format because it is easy to use, rapid, affordable and scalable. Nevertheless, traditional LFAs often suffer from many problems, which include poor assay sensitivity, subjectivity in reading the test results and limited multiplexing possibilities. Keeping this in mind, the researchers are working on a concept where the strengths of traditional LF format are taken. They replaced the colloidal gold (used for signal generation in traditional LFA) with upconverting phosphor nanoparticles (UCNPs) as tracer, with optimized flow properties. UCNPs are very stable and provide very high signal amplification which can be easily quantified. The background is very low (no auto-fluorescence from membrane or whole blood), resulting in very high signal-to-background ratios.

In the last one year, they have been able to generate required antigens for detection of anti-HIV antibodies and anti-HCV antibodies and also monoclonal antibodies for the detection of HIV-p24 antigen and HBsAg. These regents would be used for assay development. Work on generation of monoclonal antibodies against HCV core is undergoing.

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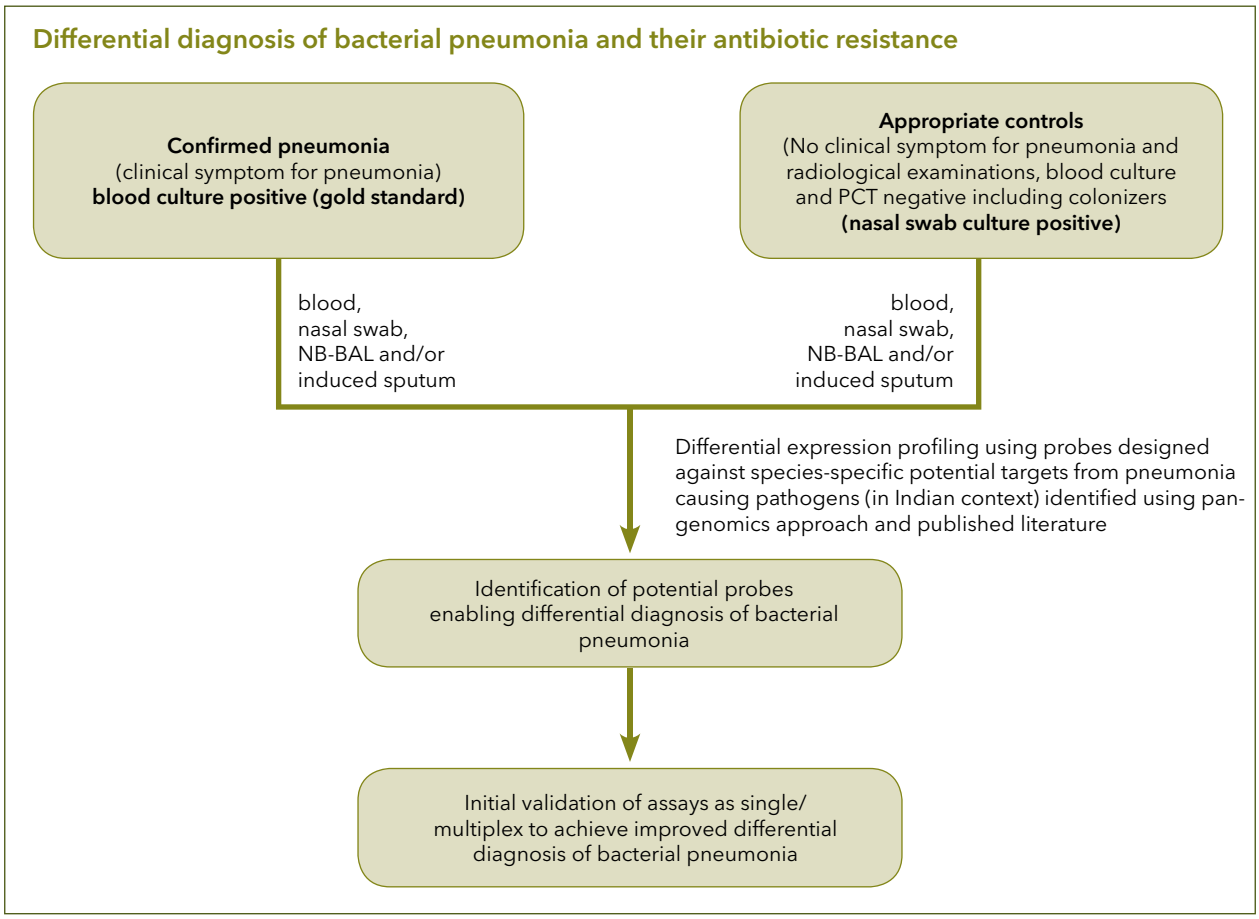
DIAGNOSIS OF PNEUMONIA

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. It 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 episode per child per year.

Pneumonia is clinically diagnosed based on cough, difficulty in breathing, rapid respiratory rate, chest in-drawing and/or decreased level of consciousness/danger signs. However, these



clinical criteria over-diagnose bacterial pneumonia and cannot differentiate between various etiologies of pneumonia. Even the chest radiography does not discriminate between bacterial and viral pneumonia conclusively.

Dr. Susmita Chaudhury and **Dr. Niraj Kumar's** team are working on a clinical research plan illustrated above. They have obtained Ethics Committee approvals for the proposal.

COLLABORATORS

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Gurugram Civil Hospital, Gurugram

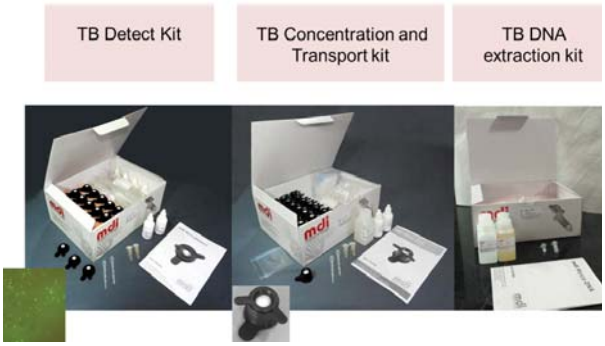
TB DIAGNOSTICS

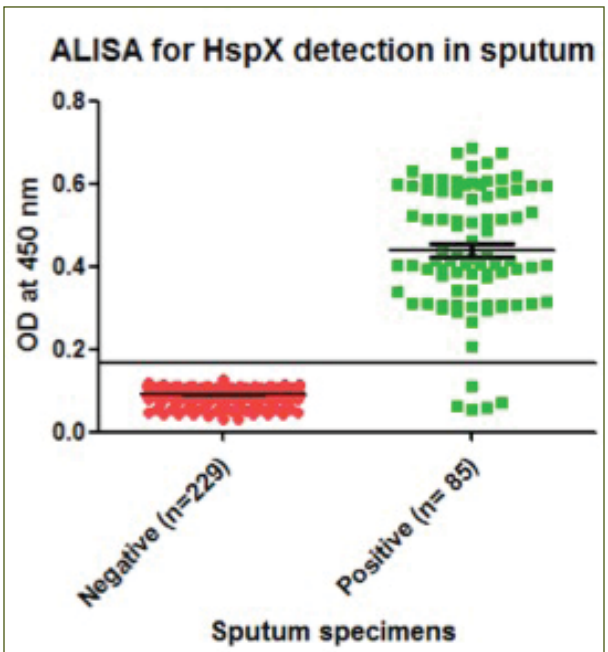
India has more than a million 'missing' TB cases every year that are not notified and remain either undiagnosed/unaccountable and inadequately diagnosed and treated in the private sector. In addition, drug-resistant TB is a major threat for TB control. India holds the dubious distinction of harboring 23% of the global TB burden: 2.2% of new TB cases and 20% of previously treated cases having MDR-TB.

Diagnosis of Pulmonary TB

Dr. Sagarika Haldar's team has developed **'TB Detect' and 'TB Concentration and Transport kit'** to replace centrifugation by filtration during sample processing. They combine sputum concentration, liquefaction and disinfection (biosafety) with *in situ* LED fluorescence microscopy (TB Detect) and molecular drug susceptibility testing TB Concentration and Transport kit. The TB Concentration and Transport kit also provides a mechanism for sputum sample transport in a filter device to an Intermediate or a National Reference Laboratory (IRL/NRL) for drug resistance testing. The TB DNA Extraction kit is for use at the IRL/NRL for isolating TB DNA from transported filter device for DNA sequencing or line probe assays for diagnosing MDR-TB/XDR-TB. These three kits have been prepared and validated via a SBIRI-funded collaborative project with Advanced Microdevices Pvt. Ltd. (industry partner), All India

Institute of Medical Sciences, National Institute of Tuberculosis and Respiratory Diseases and TB Hospital, Ambala. ~1500 sputum samples have been evaluated using the developed kits.





Detection of HspX in sputum samples showing ~95% sensitivity and 100% specificity for pulmonary TB diagnosis.

A multi-centric validation of TB-Detect, TB Concentration and Transport and TB DNA extraction kits is being initiated soon through Indian Council of Medical Research. This would be carried out at 6 sites across the country and would provide evidence for amalgamating these kits into the routine TB programme.

Dr. Tarun Sharma's team has developed **high affinity DNA aptamers** against TB-specific biomarker HspX and optimized the star aptamer candidate through post-systematic evolution of ligands by exponential enrichment (SELEX) truncation and mutations to develop a highly sensitive aptamer for the detection of pulmonary TB (PTB) in sputum samples. They have tested this aptamer in 314 sputum samples. This Aptamer Linked Immunosorbent Assay (ALISA) demonstrated ~95% sensitivity and 100% specificity for PTB. The team believes that this aptamer has a great potential to be used as a diagnostic tool for PTB.

COLLABORATORS

Developer Team
Industry: Advanced Microdevices Pvt. Ltd (mdi), Ambala
Academic: Dr. Jaya S. Tyagi, Dr. H.K. Prasad, Dr. Chanchal Kumar, Dr. Priya Kalra, and Mr. Abhijeet Dhimant, All India Institute of Medical Sciences, New Delhi
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Multi-centric validation sites clinical collaborator's-
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Dr. U.D. Gupta, National JALMA Institute for Leprosy and other Mycobacterial Diseases
Dr. Sanghamitra Pati and Dr. Dasarathi Das, Regional Medical Research Centre

Diagnosis of Extrapulmonary TB

Extrapulmonary TB (EPTB) accounted for 15% of the total new TB cases reported in 2015. Microbiological diagnosis using acid-fast bacilli (AFB) smear and culture is considered to be the gold standard, however, low bacterial load in various EPTB specimens limits their utility in early diagnosis. The inadequate gold standard increases the possibility of a false negative result. Hence, the diagnosis is dependent on a combination of microbiological, biochemical, cytological, histopathological and radiological findings (which constitute a composite reference standard) to accurately diagnose EPTB.

Dr. Sagarika Haldar's team is building a biobank of various EPTB samples including pleural TB, abdominal TB, TB meningitis, pericardial TB, hepatic TB, lymph node TB etc. All samples are being collected with paired serum and urine samples. In addition to antigen detection directly from the clinical sample, the possibility of doing antigen detection using alternate samples such

as serum/urine and also from exosomes derived from serum/urine samples is also being explored in this study.

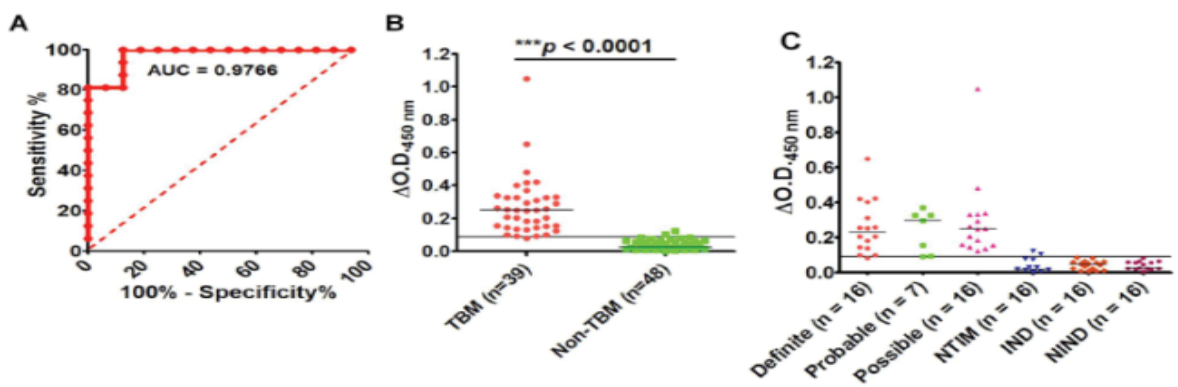
Initial study on exosome-based diagnostics: Continuing with the aim of employing serum sample (rather than sample from site) as surrogate sample for EPTB diagnosis, they assessed the utility of *Mtb* antigen (HspX) in serum and serum-derived exosomes (S-exosomes) of suspected EPTB patients (n=91) and compared the findings with the WHO-endorsed Xpert assay. These serum samples were derived from pleural and abdominal TB patients. Antigen detection in serum was the assay of choice for pleural TB with 63% sensitivity, whereas, for abdominal TB, antigen detection in S-exosomes performed better than serum ALISA (60% vs 20% sensitivity). Antigen detection was found to be superior to the Xpert assay (14% sensitivity). The researchers concluded that serum and/or S-exosomes derived *Mtb* antigens can serve as potential biomarkers for EPTB diagnosis. Currently, other TB markers viz. ESAT-6, CFP-10, MPT64, GlcB and MPT51 are being assessed in these samples.

Studies on Pleural TB: They have compiled a systematic review article assessing varied criteria used for pleural TB classification and the challenges afflicting pleural fluid-based DNA diagnostic tests, namely, PCR and Xpert MTB/RIF. In the 58 studies (PCR-n=33, Xpert-n=25) analyzed, reference standards were found to be heterogeneous and existing DNA-based tests (PCR/Xpert) pooled sensitivity values (range:0-100%) were inadequate. However, consistent high specificity of the Xpert test (range: 90-100%) indicated its utility as a "rule-in" test. The analysis concluded that rapid and accurate tests are warranted for pleural TB diagnosis.

Utility of nucleic acid and antigen-based detection tests for rapid diagnosis of pleural TB diagnosis on pleural fluid specimens (n=64). Her team has evaluated the performance of molecular tests by real-time PCR (qPCR) and Xpert MTB/RIF assay, and antigen detection by ELISA (antibody based) and ALISA (aptamer based) in pleural fluid specimens. In-house qPCR assay was carried out by targeting the *devR* gene. The detection of HspX antigen was done by ELISA and ALISA. Antigen detection by ELISA and Xpert assay had a poor sensitivity of ~18% with ~90% specificity. qPCR and antigen detection by ALISA methods yielded better sensitivity (45%) and specificity (97%). By combining qPCR and ALISA the sensitivity increased substantially to 64% with a slight decrease in specificity (90%). Even though sensitivity estimates were not optimal, they were better than the currently endorsed Xpert test. Currently, they are evaluating other TB markers viz. ESAT-6, CFP-10, MPT64, GlcB and MPT51 in these samples. Efforts are also ongoing to improve on the diagnostic accuracy of the molecular and antigen detection tests.

Dr. Tarun Sharma's group has developed a panel of aptamers and demonstrated their clinical utility for the detection of TBM (TB-Meningitis) in clinical

Aptamer-based detection of EPTB



(A) ROC curve was constructed using ΔOD450nm values of ALISA obtained with CSF from Definite (true positive) and NTIM group (true negative). The area under the curve is 0.976. (B) H63 SL-2 M6 aptamer-based ALISA. CSF samples were obtained from TBM patients (n=39) and non-TBM patients (n=48). ***p< 0.0001, statistically significant discrimination between TBM and control group. (C) H63 SL-2 M6 aptamer-based ALISA for various TBM groups (Definite, Probable and possible) and Non-TBM groups (NTIM, IND and NIND).

specimens (patient cerebrospinal fluid samples) using ALISA.

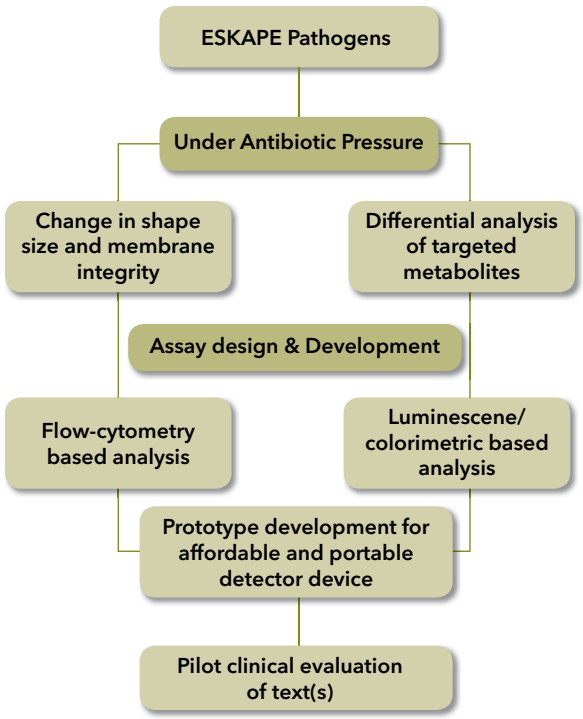
ANTIMICROBIAL RESISTANCE DETECTION IN BACTERIAL PATHOGENS

In India, >67% of prescriptions use antibiotics unnecessarily due to lack of diagnostic information of the pathogens and their drug susceptibility patterns. Over-the-counter access to antibiotics further accelerates prevalence of all classes of resistant pathogens in community levels. Rapid emergence and spread of Antimicrobial Resistance (AMR) has become a serious global health threat that is undermining our ability to effectively manage microbial infections. Although, culture-based susceptibility test is still the 'gold standard', several culture-independent molecular techniques are now available to detect pathogens with their resistance traits. However, implications of these molecular diagnostics in public health setups are still insufficient due to low-availability, high turn-around time, resource requirement and ultimately high cost. Furthermore, molecular diagnostic readouts of genetic resistance traits might not corroborate with phenotypic susceptibility. A rapid phenotypic susceptibility test holds immense promise to evolve as a future gold-standard diagnostics for AMR. This test would help clinicians to take guided decisions and avoid inappropriate use of antimicrobials.

Dr. Susmita Chaudhury and **Dr. Niraj Kumar** are working on a research plan to develop rapid assays to detect antimicrobial sensitivity/resistance in bacterial pathogens.

They aim to develop rapid protocols for evaluating changes in phenotypic parameter (like change(s) in shape, size, membrane integrity and metabolite generation in the bacterial cells) following antibiotic treatment in ESKAPE group of pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species), as these are the pathogens that contribute to major portion of AMR in India. They would test different tracer molecules comprising of chemicals, fluorescent molecules, luminescent molecules, metal nanoparticles etc., for developing these protocols into rapid diagnostic Aspartate Aminotransferase

Detection of antimicrobial resistance in ESKAPE pathogens



Test (AST). Time to result would be a critical parameter to be considered for developing such a test.

Initially, the protocols would be developed with a single organism from ESKAPE group with different groups of antimicrobials for standardization. They propose to use standard flow-cytometer and size-analyzer to evaluate change(s) in cell shape and size and membrane integrity. For metabolite analysis, they would use existing ligands and detection molecules compatible with fluorimeter or luminometer for readout. Designer reagents enabling improved detection would also be developed in parallel.

Preliminary studies from their group had shown significant differences in shape, size, membrane integrity and phosphate production between resistant and sensitive non-pathogenic laboratory strains of *E. coli* with different classes of antibiotics (cell wall, transcription and translation inhibitors), using flow-cytometry/luminometer-based methods. They were able to detect and differentiate sensitive and resistant phenotypes in ≤1 hour by using clinically relevant load of bacteria in laboratory samples (≤1000 bacterial cells/mL). The findings were also confirmed using Zeta-Sizer

(spectrophotometry based size analysis tool). This knowledge would be important for developing a rapid AST test for blood-borne infections.

COLLABORATORS

Indian Institute of Technology, Delhi
National Institute of Biomedical Genomics, Kolkata
Christian Medical College, Vellore
Maulana Azad Medical College, Delhi

DRUG SUSCEPTIBILITY TESTING FOR TUBERCULOSIS

Dr. Sagarika Haldar and her collaborators are working towards the establishment of a central molecular platform for TB drug susceptibility testing. This involves the (1) development of an unique and efficient DNA isolation technology which would be compatible with pulmonary, extrapulmonary and pediatric TB samples, (2) interrogation of all known mutations associated with all the drugs used for treatment of TB, and (3) making the platform adaptable for detecting emerging mutations. The project has potential public health impact as the platform will also be linked to providing the result to the patient within 1-2 days to start anti tubercular therapy as soon as possible to avoid further spread of resistance.

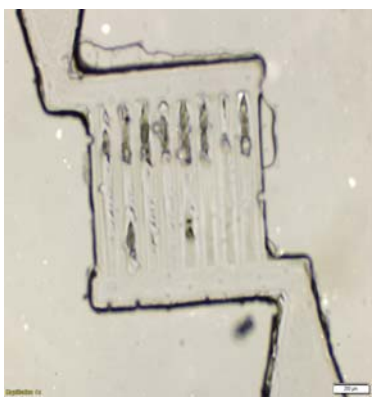
Towards this, the team has developed a novel DNA isolation methodology for isolating inhibitor-free DNA from pulmonary TB samples. This unique lysis solution permeabilizes *Mycobacteria* to provide high quality DNA for further molecular testing. A plasmid DNA library database of all existing mutations responsible for drug resistant TB has been prepared for ~100 SNPs. High Resolution Melt curve analysis (HRM) method for real time PCR has been developed and evaluated for rifampicin and isoniazid target mutations. Further efforts are ongoing to evaluate other drugs including pyrazinamide, ethambutol, streptomycin, fluoroquinolones etc. This method would be developed into a low cost, high-throughput population-based screening method for various forms of drug resistant TB. Once developed, it would also be evaluated for amalgamation with their already developed filter kits (for sample concentration, transport and DNA isolation) and then utilized in this high throughput platform.

MICROFLUIDIC DEVICES FOR ISOLATION AND EVALUATION OF DRUG RESISTANCE OF SINGLE BACTERIUM

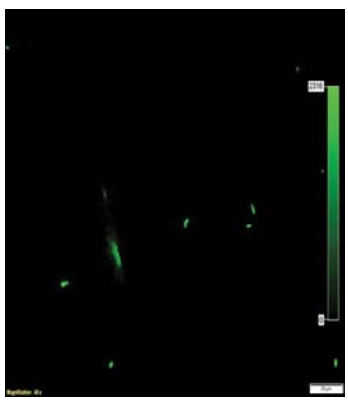
Dr. Jonathan Pillai and Dr. Krishnamohan Atmakuri have envisioned a microfluidic platform to isolate a single copy of the bacterium from a clonal population, maintain viability, and probe the bacteria with various stressors, including antibiotic drugs. Over the last year, they have evaluated four different device designs. Prototype devices have been fabricated from molds created using photolithographic techniques and subsequently replicated in an elastomeric material. Preliminary testing allowed them to isolate single copy of a bacterium and maintain viability for up to 30 minutes in the device. Ongoing work is focused on improving efficiency of isolation and testing the isolated cells to various antibiotics *in situ*.

Microfluidic devices for AMR detection in single bacterium

a) Complete microfluidic device



b) Microscopic image of a single chip of a multiplexed device



c) Fluorescence image of FITC-stained *E.coli* flowing through channels

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RESEARCH ON NON-COMMUNICABLE DISEASES

AUTOIMMUNE DISORDERS

METABOLIC DISORDERS

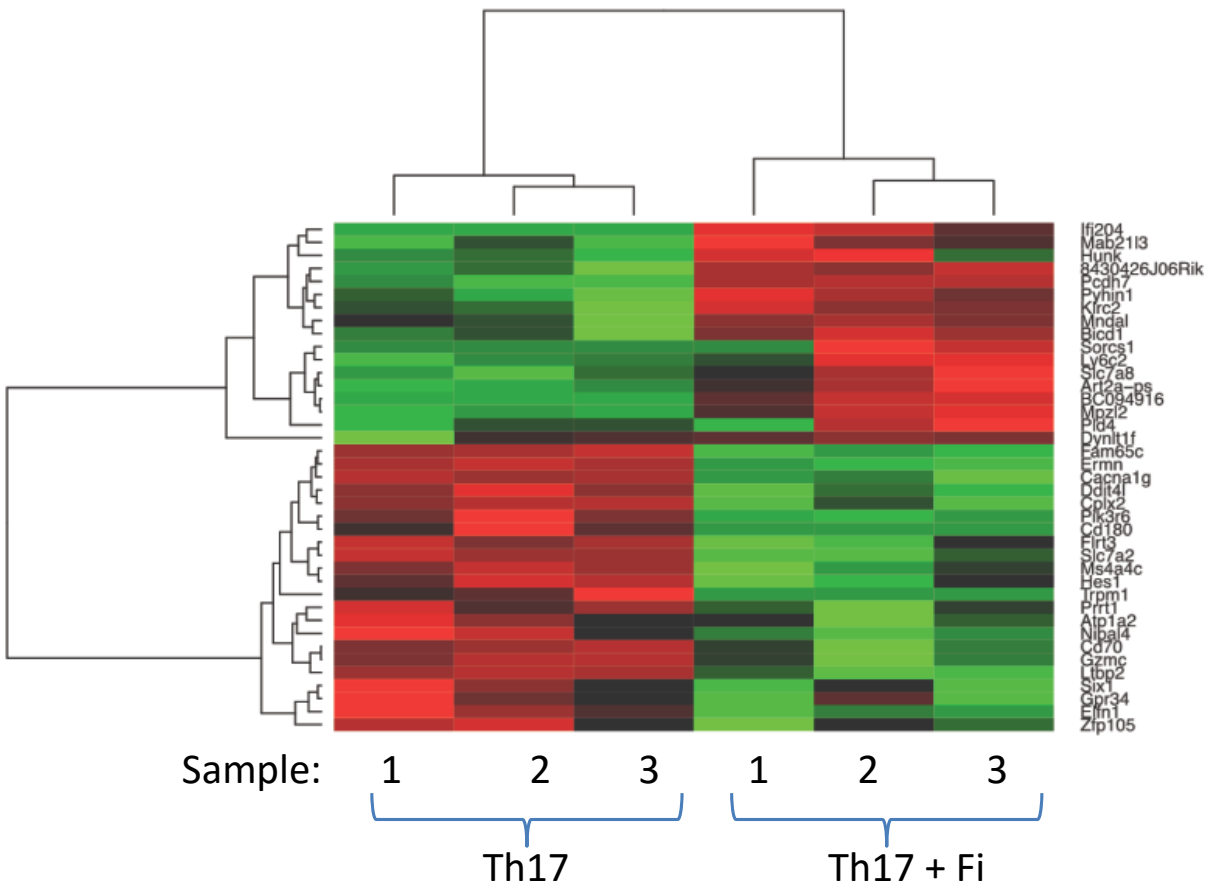
CARDIOVASCULAR COMPLICATIONS

AUTOIMMUNE DISORDERS

Inflammatory Bowel Disease (IBD), comprised of Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder of the gastrointestinal tract. It is estimated that the risk attributable to genetic predisposition alone is less than 25%, highlighting the importance of identifying environmental factors associated with IBD susceptibility. In addition, understanding the interrelationship between genetic markers and environmental factors, also known as gene-environment interaction, can provide insights into the etiopathogenesis of IBD.

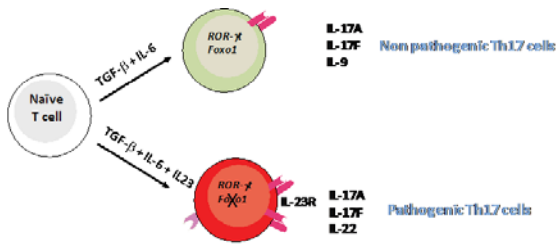
Dr. Amit Awasthi's laboratory works on understanding the molecular pathways defining the generation of effector and regulatory T cells in various inflammatory disease conditions. The primary focus is to understand the functions of Th9 and Th17 cells in inflammatory bowel disease and asthma. Th9 and Th17 are helper T cells, thought to play a role in development of autoimmune disorders.

It is suggested in the literature that Th17 cells can be divided into two types: pathogenic and non-pathogenic. Naïve T cells can be induced in the presence of TGF-β1 plus IL-6 to become Th17 cells. These cells produce signature cytokines of Th17 cells like IL-17A, IL-17F, IL-21 and IL-22. In addition, these Th17 cells also produce copious amounts of IL-9 as well. It is reported that Th17 cells that are generated with TGF-β1 plus IL-6 do



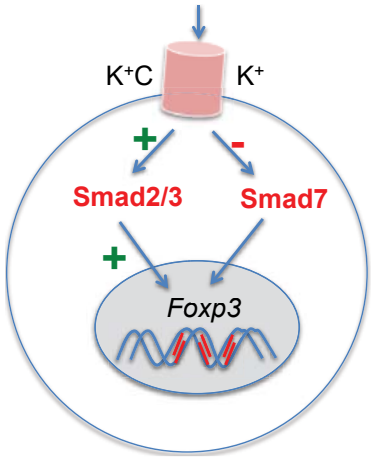
RNASeq analysis of Th17 cells in the presence Foxo1 inhibition. Naïve CD4+ T cells were sorted and differentiated into Th17 with and with out Foxo1 inhibitor (Fi) for 72 hrs, RNA was extracted and RNASeq was performed and analyzed.

not induce inflammatory disease such as colitis in mouse model, therefor they are termed as non-pathogenic Th17 cells. Interestingly, upon exposure with IL-23, these Th17 cells convert into pathogenic cells, and induce tissue inflammation in colitis. It is important to understand the factors that switch non-pathogenic Th17 cells into pathogenic ones. His group found that IL-23 inhibits the expression and functions of Foxo1, which represses Ror-γt and other Th17 cell-associated genes. In addition, Foxo1 acts as a switch, which determines the balance between IL-9 and IL-17 induction in Th17 cells. Inhibition of Foxo1 inhibited the allergic inflammation in experimental model of asthma.



Schematic representation of Foxo1 as a switch: modulating the induction of pathogenic or non-pathogenic Th17 cell. IL-23 inhibits IL-9 via inhibiting Foxo1 functions in Th17 cell.

His group also works on the molecular mechanisms underlying induction of T cell tolerance by extracellular potassium in IBD patients. Inflammatory T cells, Th1 and Th17, are critical for inducing tissue inflammation in IBD. Th1 associated factors, IFN-γ and T-bet, are crucial for development of inflammation in the gut during colitis, as IFN-γ and T-bet-deficient animals are resistant to colitis. Similarly, Th17 cell-associated factors, IL-23R and IL-17, are also critical for the pathogenesis of IBD. Most of the available therapies including steroid therapy, for IBD, target T cells functions. Dietary components may have immune-modifying functions and may have a potential to be used in decreasing inflammation in IBD. His lab has identified an inverse correlation between risk of IBD with excretory potassium and how extracellular potassium can lead to the development of T cell tolerance via inducing the generation of Foxp3$^+$ Treg cells. Extracellular potassium modulates Smad2/3 and Smad7 pathways which leads to Foxp3 induction in T cells.



Potassium induces the Foxp3$^+$ T cells. Extracellular potassium enhances TGF-β1 signaling by inducing Smad2/3 activation and decreasing Smad7 activation.

Treg induction with potassium

The lab has determined as to how retinoic acid enhances or suppresses human CD4+ T cells differentiation into Th1 and Th17 cells, as these are the two major effector T cells playing a dominant role in inducing tissue inflammation in IBD. Retinoic acid suppresses Th9 cells while enhancing Th17 differentiation. Retinoic acid-treated dendritic cells induce T cell tolerance due to inhibition of HLADR, CD80 and CD86 expression.

The future direction is to study the role of serum concentrations of vitamin A in IBD patients and their correlation with inflammation, T cell differentiation and disease pathogenesis.

Research Involving Human Participants

Population: Indian patients with clinical IBD.

Comparison: Control group without clinical IBD.

Objective: To study interplay between regulatory and functional T cells.

COLLABORATORS

Dr. Vijay K. Kuchroo, Harvard Medical School, Boston, Massachusetts, USA
Dr. Vijay Yajnik, Harvard Medical School, Boston, Massachusetts, USA
Prof. Vineet Ahuja, All India Institute of Medical Sciences, New Delhi
Dr. Balram Ghosh, CSIR-Institute of Genomics and Integrative Biology, New Delhi

The prevalence of IBD in the rural areas of Leh is extremely low. The diversity and basic functional attributes of gut microbiome of healthy Indians is not well understood. Thus, understanding the microbial ecology in the gastrointestinal tract of patients suffering from inflammatory bowel disease and severe ulcerative colitis by adopting targeted and shotgun metagenomic approaches is of interest to **Dr. Bhabatosh Das**.

People living in the low altitude rural and urban sites comprised 29 villages and 27 urban wards in Ballabgarh block in Faridabad district of Haryana state, which is 40 kilometers from Delhi. This low altitude urban group has distinct food habits compared to people living in the high altitude Leh, district of Ladakh, the highest plateau of the Indian state of Jammu and Kashmir with a height of 3,500 m. The gut microbial diversity in these Indian communities: rural and urban (n=49 each) residing in low altitude areas in Ballabhgarh and rural high altitude areas of Leh (n=35), revealed that the gut of Indian population is dominated by *Firmicutes* followed by *Bacteroidetes*, *Actinobacteria* and *Proteobacteria*. Although, 54 core bacterial genera were detected across the three populations, the gut bacterial community compositions displayed distinct signatures and observed to be influenced by the geographical location and dietary intake of the individuals.

The gut microbiomes of Indians living in Leh were observed to be significantly more homogenous, having a high representation of *Bacteroidetes* and minimal abundance of *Proteobacteria*. In contrast, the gut microbiomes of individuals living in Ballabhgarh areas harbored higher numbers of *Firmicutes* and *Proteobacteria* enriched with microbial xenobiotic degradation pathways. The rural communities from low altitude Ballabhgarh areas have a unique microbiome characterized not only by a higher diversity, but also a higher degree of homogeneity. The team observed that an accurate representation of gut microbial ecology is critically dependent on the DNA extraction methodology.

Research Involving Human Participants

Population: Rural and urban individuals residing in low altitude areas in Ballabhgarh.

Comparison: Low IBD group, rural high altitude areas of Leh, Ladakh in North India.

Objective: To define the microbial signatures for the IBD group.

COLLABORATORS

Prof. Kiyoshi Takeda, Osaka University, Japan
Prof. Vineet Ahuja, All India Institute of Medical Sciences, New Delhi

METABOLIC DISORDERS

According to the World Health Organization, the prevalence of diabetes is growing, particularly in low- and middle-income countries. India had 69.2 million people living with diabetes (8.7%) as per the 2015 data. Of these, it remained undiagnosed in more than 36 million people.

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin, a hormone that regulates blood sugar, gives us the energy that we need to live. If sugar cannot get into the cells to be burned as energy, it builds up to harmful levels in the blood.

Over time, high blood sugar can seriously compromise the functioning of every major organ system in the body, causing heart attacks, strokes, nerve damage, kidney failure, blindness, impotence and infections that can lead to amputations.

The human microbial ecology approach from **Dr. Bhabatosh Das's** lab studies the gut microbiome signatures in Indian and Danish study participants associated with pre-diabetes and T2D (Type 2 Diabetes). They aim to develop **novel biomarkers for early diagnosis of people at high risk of progression to overt T2D.**

They are performing metagenomic analysis to identify phenotype-specific gut microbiome profiles at microbial taxa and functional levels from total 900 individuals: 150 glucose tolerant individuals, 150 persons with pre-diabetes and 150 T2D patients from India and Denmark, respectively. Characterization of both common and ethnic-specific gut microbiome patterns is underway to examine how they associate with the glucose tolerance state, insulin sensitivity, insulin secretion, inflammation markers, blood metabolomics, circulating microbial non-coding RNA and blood group markers. In future, attempts will also be taken to develop and validate microbiome markers that discriminate between individuals having various degrees of glucose tolerance.

Research Involving Human Participants

Population: Type 2 diabetic Indian and Danish participants.

Comparison: Pre-diabetic and healthy, Indian and Danish participants.

Objective: To identify gut microbiome signatures in Indian and Danish study participants associated with pre-diabetes and T2D, thereby enabling development of novel biomarkers for early diagnosis of people at high risk of progression to overt T2D.

Type 2 diabetes is a metabolic disease primarily caused by obesity-linked insulin resistance. Both obesity and diabetes are characterized by a state of chronic low-grade inflammation with abnormal expression and production of multiple inflammatory mediators such as tumor necrosis factor and interleukins. In addition to well-established risk factors for type 2 diabetes including genetic predisposition, poor physical

COLLABORATORS

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Dr. V. Mohan, Madras Diabetes Research Foundation, Chennai, Tamil Nadu
Dr. Philip Abraham, P.D. Hinduja Hospital, Mumbai
Prof. Oluf Pedersen, University of Copenhagen, Denmark
Dr. Santanu Chattopadhyay, Rajiv Gandhi Centre for Biotechnology, Kerala

activity, and obesity, an altered configuration of the microbial community in our gut 'the microbiota' has been linked to the increasing prevalence of type 2 diabetes. The gut microbiota includes members from all three domains of life (Bacteria, Archaea, and Eukarya) as well as viruses, but is dominated by anaerobic bacteria. The gut microbiota protects against pathogens and helps maturate and constantly facilitates the functions of immune system. It also plays a role in regulation of intestinal hormone secretion and gastrointestinal nerve activity. Members of the gut microbiota synthesize vitamin K and several B-vitamins including folate and vitamin B12. They also produce short chain fatty acids (SCFA) by fermentation of otherwise non-digestible carbohydrates.

Dr. Prabhanshu Tripathi, a Ramalingaswamy Fellow at THSTI, is of the opinion that very little information has so far been provided in any of the published studies on diet, malnutrition, artificial sweeteners and medication.

Earlier studies in humans as well as in mice reported that obesity and impaired glucose metabolism are associated with an altered ratio between the two major phyla in the human gut, *Firmicutes* and *Bacteriodetes*. It has been hypothesized that the microbiome may function by influencing fatty acid or carbohydrate metabolism, concentration of gut hormones, inflammatory pathway signaling, intestinal permeability, induction of proinflammatory states, and/or influencing the function of metabolically active liver and adipose tissues. His interest lies in the dissection of relationship between the host and the microbiome. If the microbiome can be shown to play a direct and important role in the predisposition for and development of diseases such as diabetes and obesity, it may also provide potential targets for prevention and treatment. While some of the discrepancies between studies can be explained by ethnic or dietary differences, other factors such as intake of medications are most likely to influence the bacterial composition and functional potentials.

Metformin, the first-line drug of choice for the treatment of type 2 diabetes, increases the levels of *Akkamansia* species in high fat fed mice in parallel to its beneficial effects on glucose metabolism. Supplying mice with *A. muciniphila* orally has been reported to improve glucose tolerance and metabolic dysfunctions such as metabolic endotoxemia and adipose tissue inflammation. These promising results not only suggest novel glucose-lowering mechanisms of metformin, but also provide future potential targets for altering glucose regulation by means of bacteriotherapy.

The negative impact of consuming sugar-sweetened beverages on weight and other health outcomes has been increasingly recognized. Hence, many people have started using artificial sweeteners like aspartame, sucralose, and saccharin as a way to reduce the risk of these consequences. However, evidences suggests that these artificial sweeteners may also increase risk of excessive weight gain, metabolic syndrome and type 2 diabetes. The aim of his present project is to determine the importance of intestinal microbiota in regulation of glucose metabolism and their consequences.

His lab studies the effect of artificial or non-caloric sweeteners on Caco 2 cells (human epithelial colorectal adenocarcinoma cells), aimed at finding the direct impact of these compounds on gut epithelium. Monolayers of these cells were treated with different concentrations of commonly used Food and Drug Administration (FDA), USA-approved artificial sweeteners (aspartame, saccharin, acesulfame) for different time points. It was found that some of these artificial sweeteners reduced trans-epithelial resistance and produced leaky guts that increased access of gut bacteria to inner layers of the epithelial lining, having detrimental effects.

Significant changes were found in different proteins like glucose transporters and PYY (also known as peptide tyrosine tyrosine or pancreatic peptide YY) at protein as well as mRNA levels in artificial sweetener-treated cells. Animal experiments are underway to find the effect of these artificial sweeteners on gut microbiome and disease severity in type 2 diabetes model. The goal is to study the effect of diets (high fat or high fiber), artificial sweeteners and medications influencing the gut microbiota, thereby, resulting in pathogenic conditions with emphasis on type 2 diabetes so that possible therapies could be established.

Future studies would focus on the identification of gut microbial components of therapeutic potential

that can be further evaluated in preclinical studies for further translation.

Dr. Yashwant Kumar works on **mass spectrometer and data analysis tool to develop diagnostic platform** for diabetes. His team uses high resolution mass spectrometer-based metabolomics data of diabetes conditions in humans to find novel biomarkers and develop new approaches that can predict future conditions (diabetes/non diabetes) on the basis of present metabolic profile. A new method for better annotation of metabolite using tandem mass spectrometer (MSn) is being developed along with **Dr. Samrat Chatterjee**.

Four thousand human sera from non-diabetic, pre-diabetic and diabetic conditions were analyzed to identify novel biomarkers for diabetes. Principal component analysis of part of the data has shown **significant separation between diseased and non-diseased conditions.** This also suggests that there is change in metabolite expression after the disease. Using multivariate data analysis approaches, a potential biomarker has been identified and further machine learning algorithms have helped in predicting future conditions of subjects by their metabolomics data. They have annotated identified feature by in-house metabolite MS and MSMS library of highly pure 800 purchased standards. Using high resolution mass spectrometer, in general, can detect thousands of features with MS and MSMS information but identification of metabolite with confidence is still a big challenge because of similarity in fragmentation pattern of isomers. Towards this, they are developing a novel approach for metabolite annotation using machine learning. The team has completed data acquisition and preliminary analysis. The progress would continue to identify and confirm the potential biomarkers using multivariate data analysis and machine learning on complete data set. Work from this study would be patented and published after completion of analysis. In future, global metabolomics along with highly sophisticated machine learning approaches can help in developing diagnostic tool for diabetes and other diseases.

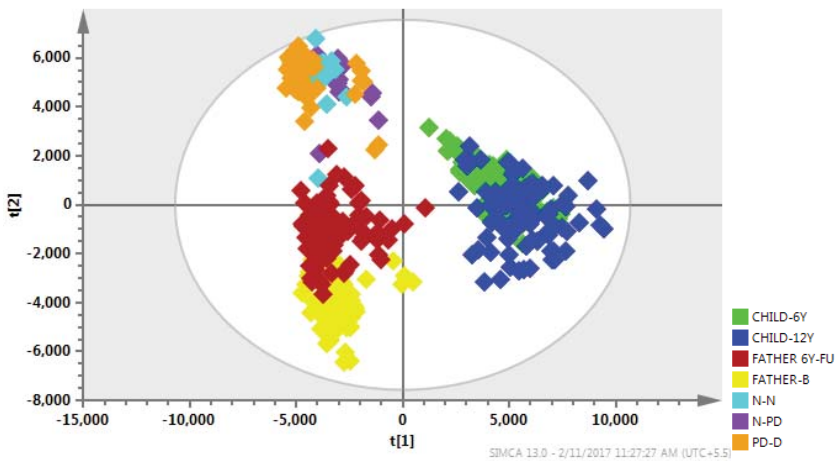

Figure represents principal component analysis of 537 samples from all three experimental conditions (N-N=50 samples, N-PD=50 samples, PD-D=37 samples, Father-B=100 samples, Father-6Y-FU= 100 samples, child 6Y= 100 samples, child 12Y= 100 samples). N-N= normal condition, N-PD= normal to prediabetic condition, PD-D= prediabetic to diabetic condition, Father-B= initial time point of diabetic father sample, Father 6Y-FU, six year followed up sample of father, Child 6Y=child sample of same father at 6Y age, Child 12Y=child sample at 12 year age. Child samples have been used for the prediction of probability of being diabetic in future. Diabetic father metabolome at initial time point and after six years of follow up shows different patterns of metabolome. Similarly, clustering of nondiabetic and prediabetic is visible from principal component analysis.

COLLABORATORS

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CARDIOVASCULAR COMPLICATIONS

Diabetes is a complex and multisystem disease that causes complications in different organs. There are several clinical evidences where data shows that inspite of proper diabetic medication, diabetic patients are prone to cardiovascular complications like hypertension, coronary artery disease, thrombosis, stroke and peripheral artery disease. It is difficult to diagnose early complications of diabetes. There are no ideal biomarkers to identify the progression of the disease or predict cardiovascular complications, especially in Indian patients.

The progression of **cardiovascular complications in diabetes** is the focus of **Dr. Sanjay Banerjee's** lab. Several factors like nutritional deficiency, high blood glucose levels and presence of lipopolysaccharide in blood can influence the progression of the disease. Inflammation, epigenetic changes and oxidative stress are key pathogenic events that make the heart vulnerable to failure and less contractile. His group works to identify a set of inflammatory and metabolic markers that distinguish diabetes from that with different cardiovascular complications i.e., hypertension, coronary artery disease and diabetic cardiomyopathy. They also work on simulating the human phenotype in animal models. The dysfunction of heart is being correlated with energy metabolism and mitochondrial dysfunction in the organ.

Their study indicates that **few inflammatory cytokines, metabolic hormones and metabolites might be significantly associated with an increased risk of cardiovascular complication in type 2 diabetes patients**. The group is making a multi-marker score comprising all important metabolites that would significantly improve risk prediction beyond established diabetes risk factors like body mass index, fasting glucose, and insulin resistance. This is being done using samples from patients in collaboration with Mediciti Hospital, Hyderabad and Safdarjung Hospital, New Delhi. Blood samples from patients with different kinds of cardio-metabolic phenotypes (coronary artery disease, hypertension, diabetes, heart failure etc.) are being analyzed to understand the disease in terms of insulin resistance, microbial infection, vitamin D deficiency and pro-inflammatory markers. The plan also includes involving non-alcoholic fatty liver disease patients to look for the role of hepatic fat deposition on insulin resistance.

The team has followed six vitamin D metabolites from diabetic patients with or without cardiovascular complications. Their data has shown that Vitamin D metabolites like 25(OH)D can predict Type 2 Diabetes Mellitus (T2DM), while 1,25(OH)2D can predict coronary artery disease in T2DM (Adela et al., Scientific reports, 2016). They are also trying to understand the role of vitamin D and its signaling pathway in animals. The study plan is to look at the effect of vitamin D receptor (VDR) agonist in high fructose-high fat fed rat models, by administering VDR agonist in rats after developing the disease and study its role to reverse cardiac phenotype and insulin resistance. In addition, the finding that increased Growth Differentiation Factor (GDF-15), a stress responsive cytokine, levels associated with increased angiotensin II levels among diabetic patients with hypertension (Adela et al., Personalised Medicine, 2016), will be explored further in animal models and clinical research setups.

Dr. Banerjee studies the effect of nutritional agents in cardio-metabolic disorders. Previous data from his group has revealed the therapeutic efficacy of two important nutritional agents: garlic and resveratrol, in reduction of cardiac hypertrophy and cardiac complication in diabetes, respectively. The group is exploring the molecular mechanisms of these two agents in hearts and other organs. Both garlic and resveratrol activate sirtuins leading to reduced inflammation and oxidative stress in a diabetic heart. An important stable active sulfur metabolite in blood has been reported in rats after oral administration of raw garlic. This molecule has been tested by administering its four different doses in rats to monitor preclinical toxicity and its

kinetics *in-vivo*. If this molecule shows less toxicity and good efficacy in animal models, It would be tested in human participants to find its role in patients with cardiovascular complications.

Research Involving Human Participants

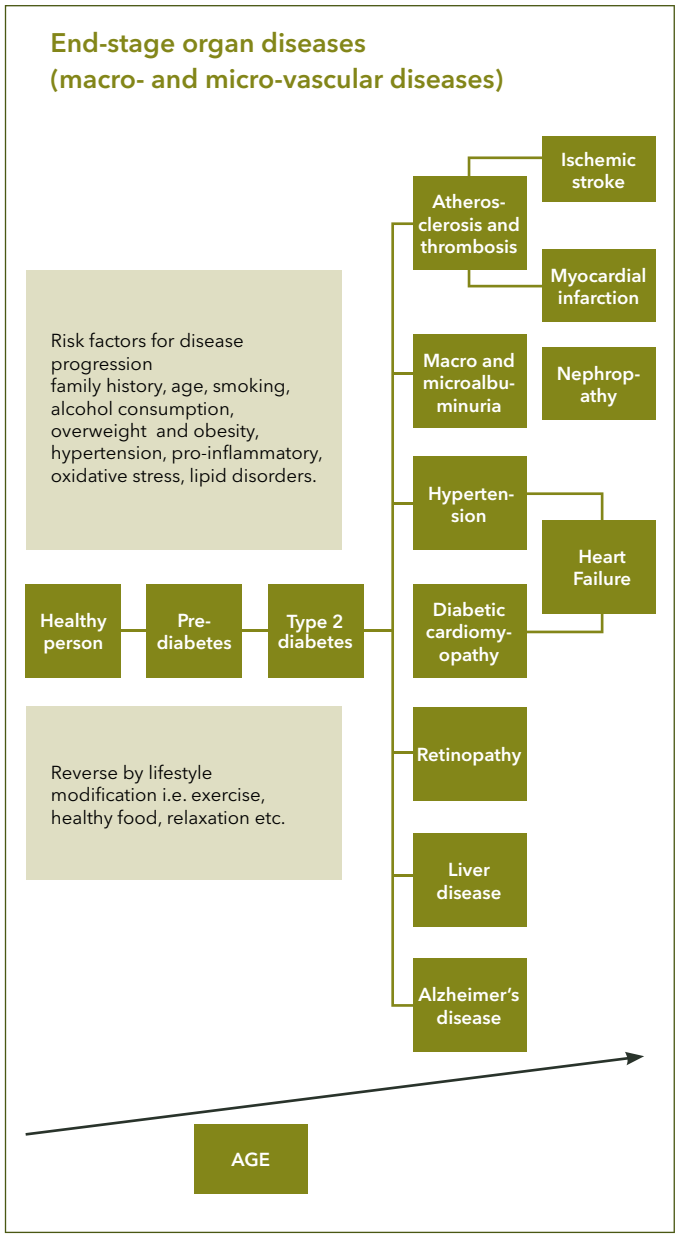
Population: Diabetic patients with and without cardiovascular complications.

Groups: Normal, diabetic, diabetic with hypertension, diabetic with coronary artery disease, coronary artery disease.

Comparison: Diabetes vs control, coronary artery disease vs control, diabetes vs diabetes with hypertension, diabetes vs diabetes with coronary artery disease, coronary artery disease vs diabetes with coronary artery disease.

Objective: Inflammatory cytokines, metabolites, metabolic hormones markers to predict cardiovascular risk in diabetes.

Dr. Sameena Khan's team is currently focused on decrypting the fine balance between ubiquitination and deubiquitination processes, and probing how this fine-tuning regulates apoptosis. The team aims to **identify E3 ubiquitin ligases and deubiquitinating (DUB) enzymes that regulate apoptosis of cardiomyocytes**. They are interested to see the pattern of ubiquitinated proteins in the cardiomyocytes and link it with the E3 ubiquitin ligases and DUB enzymes. Their present work focuses on the biochemical, biophysical and cellular investigations of E3 ligase and DUB components of the vast ubiquitin-proteasome machinery. The aim is to integrate the structure and cell biology data that is expected to yield novel targets for drug development against the cardiovascular disease.



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TOOLS AND TECHNOLOGIES FOR DRUG, VACCINE AND DIAGNOSTIC RESEARCH

BIO DESIGNS FOR
DRUG AND VACCINE DELIVERY

TOOLS TO DECIPHER AND
MODULATE BIOLOGICAL NETWORKS
AND DRUG TARGETS

BIOPROCESS IMPROVEMENT

BIODESIGNS FOR DRUG AND VACCINE DELIVERY

Biodesign is the integration of design with biological systems, often to achieve better ecological performance.

- William Myers

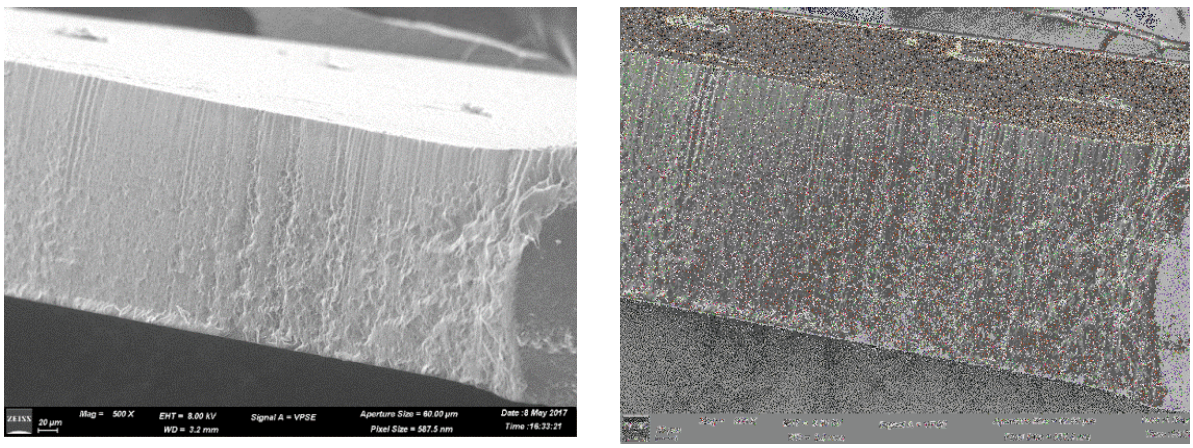
The Implants, Devices and Drug Delivery Systems laboratory of **Dr. Jonathan Pillai** works on pharmaco-engineering of nanomedicines and drug delivery systems for infectious diseases.

The lab is designing **biodegradable polymeric implants for sustained delivery of anti-tuberculosis drugs**. The tissue-like properties, ease of synthesis, biocompatibility, hydrophilicity and biodegradable properties make synthetic hydrogels very useful as drug delivery carriers. Moreover, the porosity of the hydrogels can be controlled by controlling the degree of cross-linking of the gel matrix, thereby regulating the drug loading efficiency and subsequent drug release in a rate-dependent manner. The group has exploited these biomaterials for designing controlled release implants for TB drugs, where the complex drug regimen is one of the main reasons for patient non-compliance.

They have fabricated polyethylene glycol-based hydrogel implants using a photo-crosslinking method. They checked the impact of variations in material compositions and changes in monomer cross-linking parameters affect the drug-loading capacity of the implant. Further, the surface and cross-sectional morphology of implants has been studied using scanning electron microscopy. A preliminary 30 days *in vivo* study of subcutaneous implantation was also done in a rabbit model. The implants showed excellent biocompatibility with no obvious inflammatory reactions and good integration with the surrounding tissue.

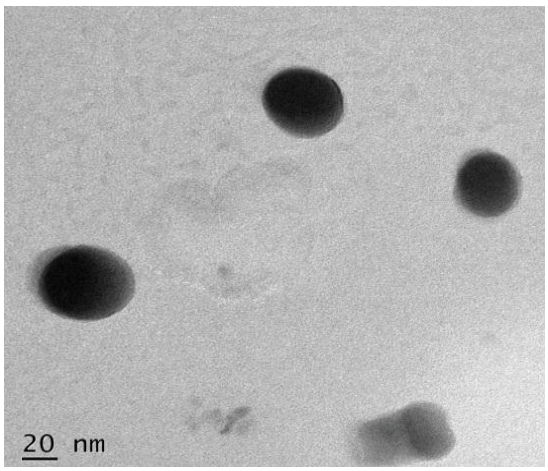
LIPID DRUG CONJUGATES (LDCs) OF HYDROPHILIC DRUGS TARGETING BOTH PULMONARY AND EXTRA-PULMONARY TUBERCULOSIS

It is well known that while hydrophilic drugs are easily soluble in aqueous media, they have significant difficulty in crossing hydrophobic membranes, including those of the gut and bacterial cell walls. A literature search revealed that among first line TB drugs, isoniazid (INH) is particularly problematic because of permeability issues, and suffers from extremely low bioavailability in serum. To compensate for this, large and frequent dosing is required, resulting in side effects and patient non-compliance. Dr. Jonathan Pillai's team has successfully synthesized and thoroughly characterized a novel lipid-drug



Surface structure of the hydrogel implant observed by SEM.

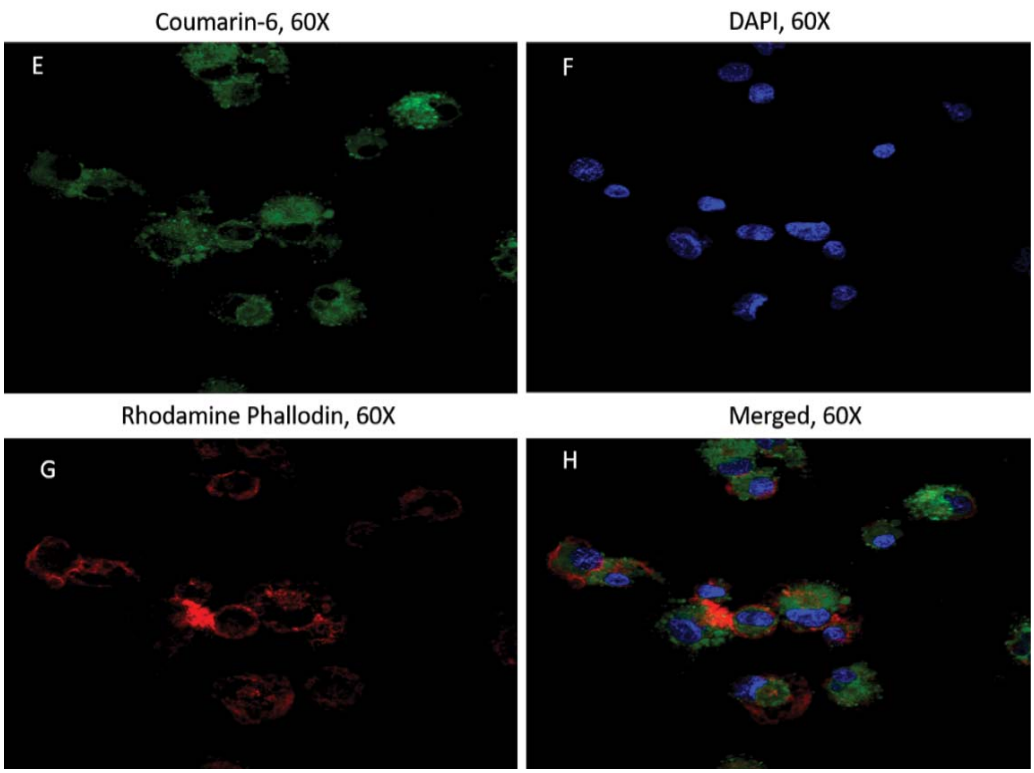
conjugate of INH with a biocompatible lipid chain. They have further synthesized nanoparticles from the novel LDC. Significant work has been done to establish the *in vitro* performance and *in situ* localization of the particles inside the human differentiated macrophages (THP-1 cell line).



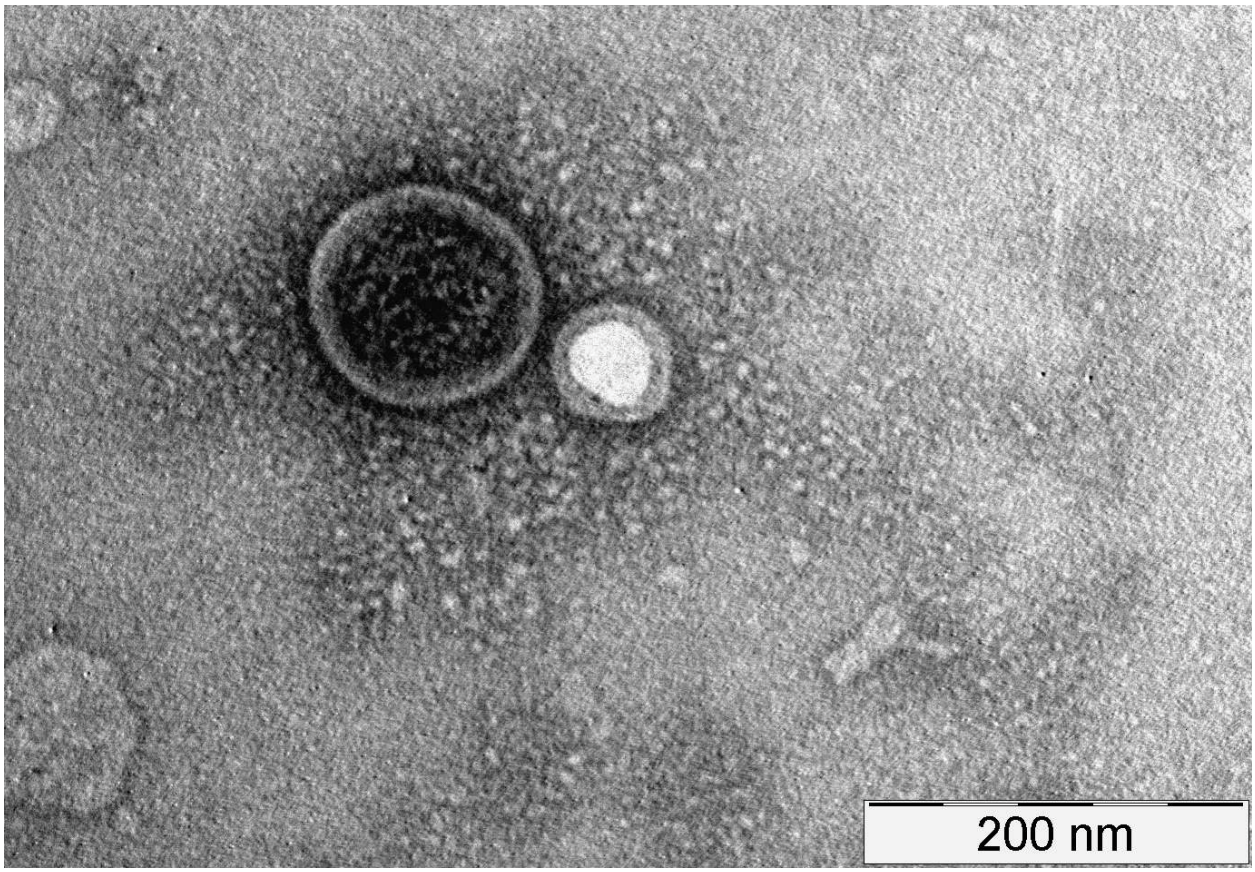
TEM images of LDC-NPs.

LIPID NANOPARTICULATE FORMULATIONS (LNFs) FOR ENHANCED PROTECTION IN GASTRIC pH ENVIRONMENT

The group has successfully synthesized and thoroughly characterized solid-lipid nanoparticle (SLN) and nanostructured lipid carrier (NLC) formulations combining two anti-TB drugs. As reported earlier, a novel Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC) method has already been developed and validated as per International Council for Harmonisation (ICH) regulatory guidelines. *In vitro* physico-chemical parameters such as total drug content, drug encapsulation efficiency, morphology (atomic force microscopy, scanning electron microscopy, transmission electron microscopy, particle size analysis (dynamic light scattering), zeta potential, thermogravimetry (differential scanning calorimetry-thermal gravimetric analysis), crystallinity (X-ray powder diffraction), drug-excipient compatibility (Fourier transform infrared spectroscopy), pH-dependent stability, and *in vitro* drug release



Confocal images (E-H) denoting coumarin-6 labelled NLCs uptake by macrophages. Green fluorescence indicates coumarin 6-labelled NLCs (E), nuclear staining (F), red fluorescence depicts actin staining by Rhodamine Phallodin (G). Merged image (H) reflects the internalization of NLCs.



Enriched OMVs isolated from *Mycobacterium smegmatis* loaded with a first-line drug against TB

profile were characterized in detail. During the last year, substantial progress has been made in establishment of the mechanism of intracellular uptake and quantification of drug release kinetics *in vitro*, through both fluorescence and confocal microscopy. Work is in progress to establish the *in vivo* biodistribution profile and pharmacokinetics of these novel anti-TB drug delivery systems in a rodent model. Successful demonstration of the therapeutic potential *in vivo* would pave the way for future translation to clinical use.

The biocompatibility and the biodistribution of drug release from two of these novel systems, viz, implants and LNFs are being tested in animals. These studies are important in establishing the safety profile of these systems in preparation for translation into the clinic.

The intra-institutional collaboration between **Dr. Jonathan Pillai and Dr. Krishnamohan Atmakuri** aims to use the **bacterial Outer Membrane Vesicles (OMVs) as novel vehicles for targeted anti-microbial drug delivery.** OMVs derived from non-pathogenic species of *Mycobacteria* can be engineered to serve as useful vehicles to enhance permeability and bioavailability of extremely lipophilic and poorly soluble drugs. To test the hypothesis, OMVs were previously isolated and characterized from non-pathogenic *Mycobacterium smegmatis* (*M. smeg*.) successfully. Over the past year, they have successfully incorporated detectable quantities of a first-line TB drug into the *M. smeg*. OMVs. Characterization of drug-loading capacity and evaluation of their therapeutic potential against

COLLABORATORS

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2. Dr. C.V. Srikanth, Regional Centre for Biotechnology

pathogenic laboratory strains are currently under progress.

Human Adenovirus-based vectors have been extensively tested in pre-clinical and clinical settings for their ability to efficiently deliver the transgene and induce transgene-specific therapeutic/prophylactic responses. While they demonstrated superior potential to do so in pre-clinical and early clinical trials, subsequent testing in advanced phase trials demonstrated certain safety and efficacy issues attributable to their strong antigenicity and to their undesired interactions with the human host system. In this direction, several groups across the world are working towards identification of suitable adenovirus serotypes isolated from different non-human species for the development of delivery vectors that can be used in humans. Majority of the animal adenoviruses, while being capable of infecting a wide range of human cell types with different receptor specificities without causing a clinical disease, are not known to have seroprevalence in human sera.

As part of the efforts to identify suitable adenoviral candidates for further development, **Dr. Mohan B. Appaiahgari's** team has now chosen three isolates, one each isolated from fowl, bovine and porcine species. For the fowl adenovirus isolate, in order to demonstrate its suitability for vector development, previously they have established the complete genome sequence, established its novelty, and demonstrated complete absence of anti-FAdV neutralizing immunity in human serum samples collected from unexposed population. With respect to the two other animal adenovirus isolates, they have recently generated enough preliminary data to demonstrate their novelty and suitability for development as candidate delivery vectors. Of note, they have found that the bovine isolate is a bovine adenovirus serotype 8 virus, which until date has not been attempted for vector development. With regard to suitability for vector development, they have found complete absence of its seroprevalence in human sera irrespective of their exposure state, and that this isolate is capable of infecting almost all the human cell types tested *in vitro*. The third isolate from an apparently healthy pig has shown similarity with the human adenovirus type 5, but only in the hexon gene region. Despite this, they observed that the human sera, which has very high levels of neutralizing immunity against HAdV5, has only low levels of such immunity against this isolate.

Similarly, to generate more experimental evidence for the suitability of animal adenovirus-based vectors over human adenovirus type 5-based vectors and also to investigate the differences, if any, in efficacies between different animal adenovirus-based vectors, they collaborated with Dr. Gerald Both in Australia to construct a recombinant ovine adenovirus 7 expressing the envelope protein derived from Japanese encephalitis virus. Through *in vitro* experiments, the ability of the ovine adenovirus recombinant to synthesize comparable levels of the recombinant protein with the human adenovirus recombinant carrying the same transgene cassette has been demonstrated. The goal of this study is to establish the vaccine potential of a model immunogen delivered by an animal adenovirus-based recombinant compared to that delivered by the HAdV5-based recombinant. With the availability of small animal experimental facility on campus, they are currently carrying out comparative immunogenicity studies in mouse models.

COLLABORATORS

Dr. Sudhanshu Vrati, Regional Centre for Biotechnology

Dr. Gerald Both, CSIRO Molecular and Health Technologies, New South Wales, Australia

Biotech Equity Partners Pty Ltd, New South Wales, Australia

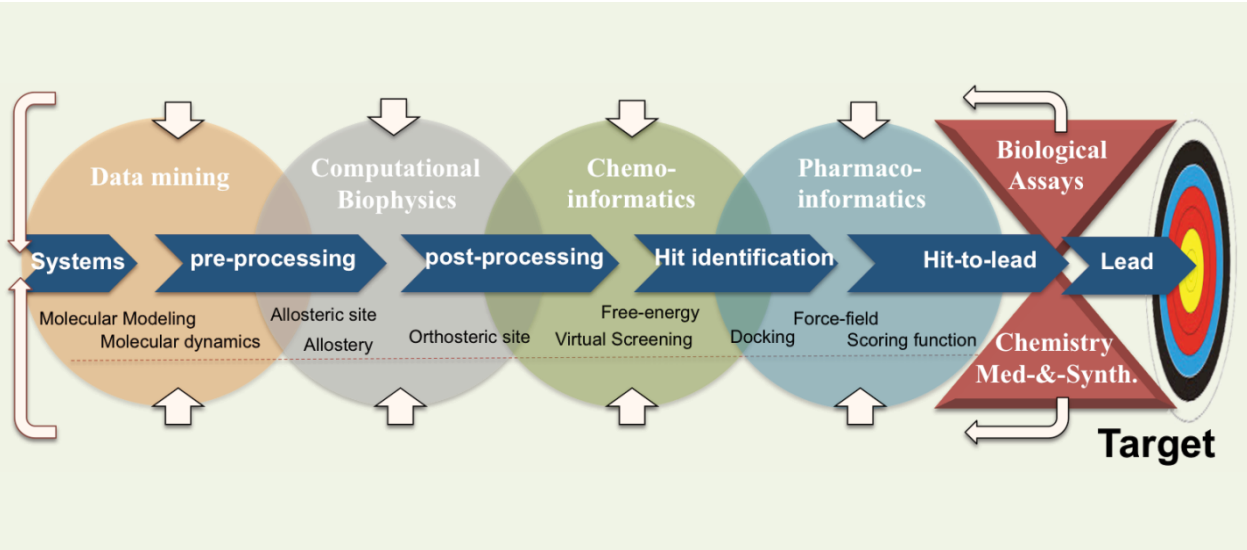
TOOLS TO DECIPHER AND MODULATE BIOLOGICAL NETWORKS AND DRUG TARGETS

The Structural Bioinformatics team of **Dr. Shailendra Asthana** is dedicated to understand proteins, their dynamics and, their biophysical and biochemical properties at molecular level, with the objective to accelerate **(1) designing small molecules against different targets, (2) structure-based vaccine designing, and (3) antibody designing.** Protein-protein interactions (PPIs) are involved in almost all physiological process and diseases. The changes in proteins (perturbation, structural-change, mutation etc.) are generally responsible for diseased states. Since most of the a protein's biological functions depends on its association with other proteins (interactors: function-dependent), therefore, it is essential to explore protein-protein interactions and how they modulate biological functions at atomic level resolution.

Dr. Dinesh Mahajan and his team contribute to drug discovery research at THSTI in medicinal chemistry. The focus spans around identification of hits for newly identified targets, optimization of hits to identify a lead with drug like properties, and further optimization of lead to identify a candidate for Investigational New Drug (IND) studies followed by process optimization of the lead candidates. The medicinal chemistry team contributes to target identification by providing chemical tools/ligands for study, elucidation or validation of novel targets or biochemical pathways.

Dr. Shilpa Jamwal and her team contribute to the drug discovery programmes at THSTI by conducting primary screening of chemical libraries on cell-based systems with an aim to identify novel chemical entities and develop highly sensitive assay systems. The screening modules adopted can facilitate either target-based or phenotype-based drug discovery. Following the pipeline, the unit also plays a role in validating and optimizing the lead molecules. Coupled with screening, they also develop biological disease models of translational significance, analogously developing sensitive and robust readout assays relevant to the systems.

Dr. Sameena Khan's team combines high-throughput RNAi screens with the techniques of cell and molecular biology. The group incorporates capabilities for recombinant cloning, expression, and purification of proteins. Biophysical characterization of purified proteins and protein- ligand interactions are achieved through techniques such as Surface Plasmon Resonance. Finally, their strong expertise in structural biology facilitates X-ray crystal structure elucidation of protein, protein-ligand, and protein-protein complexes.



CONTRIBUTIONS

mTOR-independent targets for autophagy: Lead Candidate Identification: HIV, Cardiac Hypertrophy, NASH

Area: HIV 1 (Dr. Shailendra Asthana, Dr. Dinesh Mahajan, Dr. Shilpa Jamwal, Dr. Kanury Rao).

Present stage of Development

A lead candidate with IC50 around 50nm to 500nm, when screened against CEM-GFP cells infected with HIV-1 based on ELISA readout, is in the pipeline. This is a collaborative project within DDRC which has identified a series of molecules as potent autophagy inducers. A subset of these molecules (autophagy inducers) also has dual activity in the form of being potent integrase inhibitors. Most of the required *in vitro* screening and limited pharmacokinetic evaluation in mouse have been completed. Some of the leads have shown strong potential against HIV infection. Being dual actors (autophagy inducers/integrase inhibitors), these molecules show strong activity against resistant form of HIV strains. This project is also recently funded by DBT under BIRAC scheme for complete pre-clinical development till efficacy studies in Monkey model. Two provisional patent applications have been filed to protect the chemical structure class. Currently, detailed pharmacokinetic analysis is in progress for identified drug leads which will be followed by off target screening and toxicity studies in animal models.

Area: Cardiac Hypertrophy (Dr. Sameena Khan, Dr. Dinesh Mahajan, Dr. Shailendra Asthana, Dr. Shilpa Jamwal, Dr. Kanury Rao).

Present stage of Development

Perturbed autophagy in cardiomyocytes has been causally linked to cardiac hypertrophy and heart failure: therapeutic strategies exploiting this aspect have not yet been adopted. The present interest was due to the fact that, DDRC had already identified a panel of novel heterocycles that were potent at inducing autophagy in a wide range of cell types. Initial studies identified a lead compound that inhibited both stress-induced apoptosis and hypertrophy in human and rat primary cardiomyocytes. Subsequent to this, they performed proof-of-concept experiments in rat model for cardiac hypertrophy. They found that treatment of diseased rats with lead compound yielded significant therapeutic benefits in terms of suppression of cardiac hypertrophy, improvement in cardiac function, and prevention of cardiomyocyte death. In a preliminary pharmacokinetic analysis, their lead had displayed a reasonable oral exposure in both mice and rats. With this initial understanding, they want to develop the lead compound by optimizing it further towards an Investigational New Drug (IND) candidate, with potential therapeutic value against cardiovascular complications.

Area: Non-alcoholic steatohepatitis (NASH) (Dr. Shilpa Jamwal, Dr. Dinesh Mahajan, Dr. Sameena Khan, Dr. Shailendra Asthana and Dr. Kanury Rao).

Present stage of Development

This translational programme aims to develop a first-in-class therapeutic approach and a new chemical lead molecule, generated at THSTI, which displays potent activity for treating NASH. Cell model for hepatosteatosis was developed and lead molecules were screened for reducing lipotoxicity in human hepatocytes. This extensive exercise lead to identification of a list of molecules with demonstrated potency in nM range. Importantly, the lead molecule(s), possesses the potential of stimulating cellular autophagy, and improving global cell health parameters in corroboration. The potential of these lead molecules befits the unmet medical need for NASH therapy.

Area: Sepsis (Dr. Shailendra Asthana).

Present stage of Development

Based on the novel hits from the interface of iNOS-NOSIP interaction, some meaningful peptides were designed at nanomolar level- binding potency. Furthermore, the identified peptide-binding site at iNOS, were screened through virtual screening approach (~5.4 million physical compounds). Finally, 12 compounds were selected based on their computational binding affinity and were picked for experimental evaluation.

Area: Osteoporosis (Dr. Shailendra Asthana).

Present stage of Development

Experimental binding affinities of peptides derived from IL3 and binding at IL3R were calculated for the IL3R-IL3 interface and/or IL3 sites.

Area: Dengue (Dr. Shailendra Asthana, Dr. Sankar Bhattacharyya).

Present stage of Development

Identification of anti-viral small molecules against NS2-3, NS5 and STAT2 in dengue. Three different series of compounds were designed and synthesized. The *in vitro* experiments are in process.

Area: Congenital Heart Disease (Dr. Shailendra Asthana, Dr. Sanjay Banerjee).

Present stage of Development

A pathogenic mutation identified by a collaborator in samples of patients with congenital heart disease was analyzed *in silico* to define the importance of the mutation in pathogenicity. From the multi-step analysis, it was proposed that mutation at a specific amino acid in NKX2.5 hindered its interaction with neighboring proteins, specially GATA4, and its destabilization lead to the loss of a series of polar interactions. GATA-4 and Nkx-2.5 co-activated Nkx-2 DNA binding targets, essential for regulating early cardiac gene expression. The loss of polar interactions unzipped the association between NKX-2.5 and GATA4, and as a consequence, the association of NKX-2.5 and GATA4 was disturbed significantly, which might lead to pathogenicity.

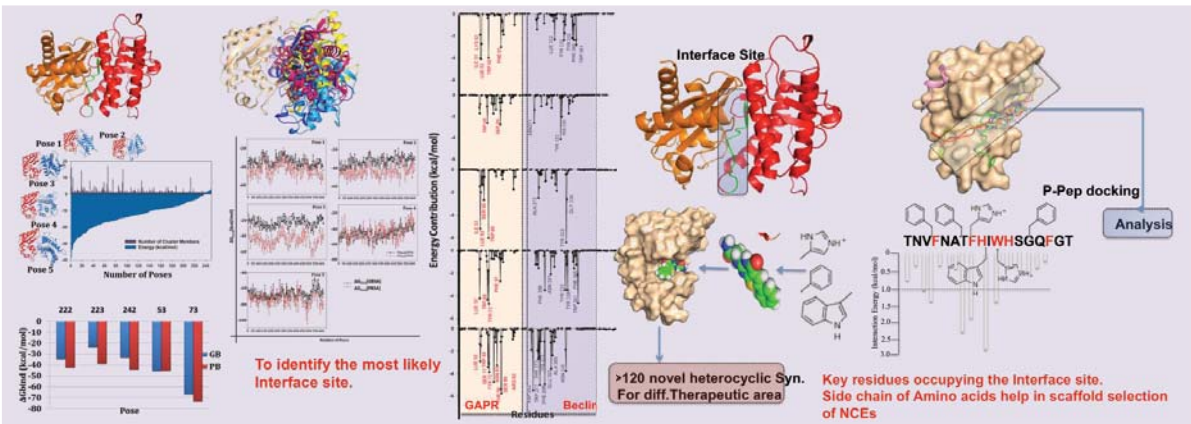
Area: Drug targets for *Mtb* (Dr. Dinesh Mahajan, in collaboration with Dr. Ramandeep Singh).

Present stage of Development

This is being pursued in active collaboration with Dr. Ramandeep Singh's laboratory and is focused around new drug targets as well as drug lead development. This is an early stage project, where the joint efforts of both the laboratories have resulted in identification of new chemical hits capable of inhibiting growth and replication of *Mtb in vitro*. The team is looking forward to work and develop these initial hits to lead molecules by establishing Structure Activity Relationship and ADMET profiling. The plan is to generate substantial preliminary data to file an extramural grant for pre-clinical development of identified hits in near future.

New synthetic process development for approved drugs/APIs and molecules of commercial importance

Under this project, the chemistry lab is focused on filling the gap between cost-efficient and environment friendly synthetic processes for molecules of commercial interest. This is of great national interest as, historically, this space has been dominated the Chinese. Almost all



Scheme: (Left Panel) Molecular docking studies between GAPR and Beclin: the quantitative details and selection of best pose criteria to identify the most likely interface sites among 10,000 differently generated conformations of GAPR-Beclin complexes. **(Right Panel) Peptidomimetics (key residues to small molecules)**: Identification of key residues from the identified peptides and their chemical conversation through peptidomemtic approaches. More than 120 different small molecules were identified for different therapeutic areas. GAPR (Golgi-Associated plant Pathogenesis Related protein) is a negative regulator of autophagy. The identified peptide from GAPR, blocks beclin (a positive regulator of autophagy) from binding of Nef and GAPR-1 and promotes autophagy induction.

key raw material and molecules of commercial interest are being imported from China by all Indian manufacturing industries. The chemistry lab is pursuing a low profile program for new process and reagent development. Under this program, they have developed few proprietary synthetic methodologies (provisional patent filed) for chemical transformation in a cost-effective manner. They are in progress of demonstrating the utility of these synthetic methodologies for cleaner synthesis of existing approved drugs, new active pharmaceutical ingredients and other molecules of commercial importance.

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Dr. Amit Kumar Yadav's group works on **mass spectrometry-based tools and techniques for large scale proteomics and post-translational modification** (PTM) analyses, and quantitation through development of computational tools and algorithms.

CONTRIBUTIONS

Investigators team: Dr. Amit Kumar Yadav, Dr. Kanury Rao, Suruchi Aggarwal, Dr. Shilpa Jamwal, Dr. Ajay Kumar, Puneet Kumar Kadimi.

High-resolution shotgun mass spectrometry data is used to search for post-translational modifications (PTMs) and their subsequent quantitation. PTMs play a crucial role in mediating biological functions through protein-protein interactions, structural binding, aiding enzyme activity, subcellular localization and this crosstalk drives disease development and progression. The group works on developing statistical tools, algorithms, software pipelines, and next generation visualization for high throughput analyses and interpretation of shotgun proteomics data. PTMs are the hidden players in regulation of cellular pathways with a swift activity and turnover. Their specific functional occurrence, stoichiometry and crosstalk with other PTMs can yield a treasure-trove of potential drug targets. Integrated together with structural insights and mathematical modeling, discovery and fine-tuning of biological regulatory nodes are possible.

ModST-copyrighted

ModST (Modification Search Tool) (pronounced as modest) is a tool to search post-translational modifications (PTMs) in mass spectrometry data in an automated unrestrictive manner using the MODa search algorithm. It can search for hundreds of modifications without any user provided information for variable modifications. Due to data level parallelization implemented in the pipeline, it is a fast, portable and easy-to-use solution of identifying and analyzing PTMs in MS/MS data.

QuantWiz-IQ-copyrighted

QuantWiz-IQ is a tool for reporter based MS/MS quantitation using iTRAQ or TMT tags from shotgun proteomics experiments. It allows analysis of multiplexed quantitation data in proteomics, supporting upto 10 samples in one shot of mass spectrometry run. It supports MGF and HUPO-PSI mzML standard format as input. It supports quantitation of reporter tags with iTRAQ 4-plex or 8-plex. It also supports TMT 2/6/10-plex quantitation.

Hyperplexing technology (SILAC+iTRAQ) with BONCAT to study secretome of THP-1 cells was filed as a patent. Along with the analysis tool developed (HyperQuant, copyrighted), it allows for 18plex quantitation from a single mass spec run.

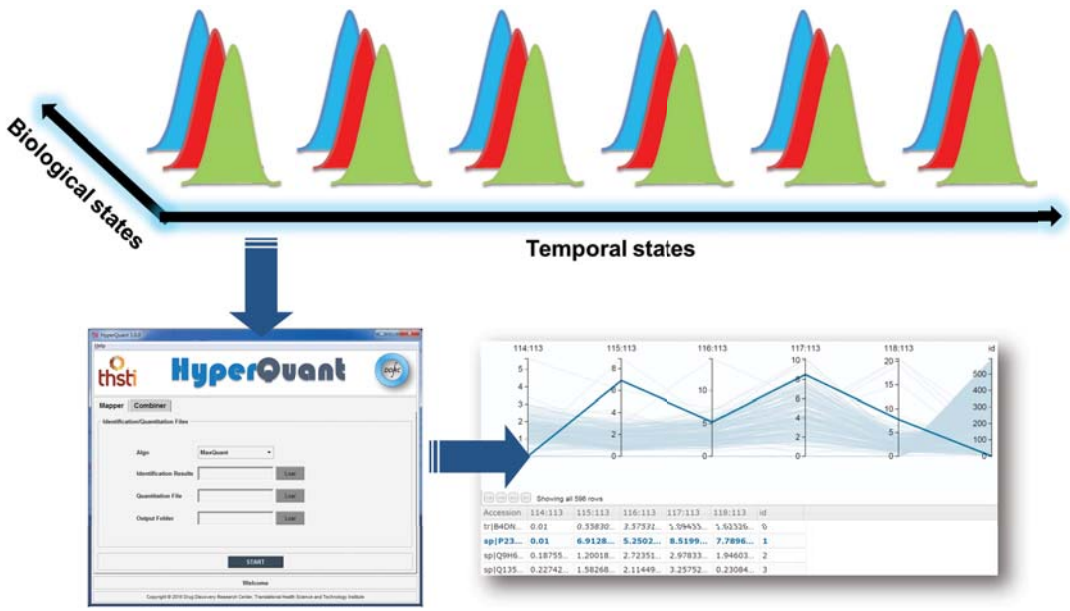
Application of the technology

An expansion of the quantitative coding capacity of quantitative proteomics using the method patented above enables the study of immune response of THP-1 cells upon infection with different strains of *Mtb*. Newly translated and

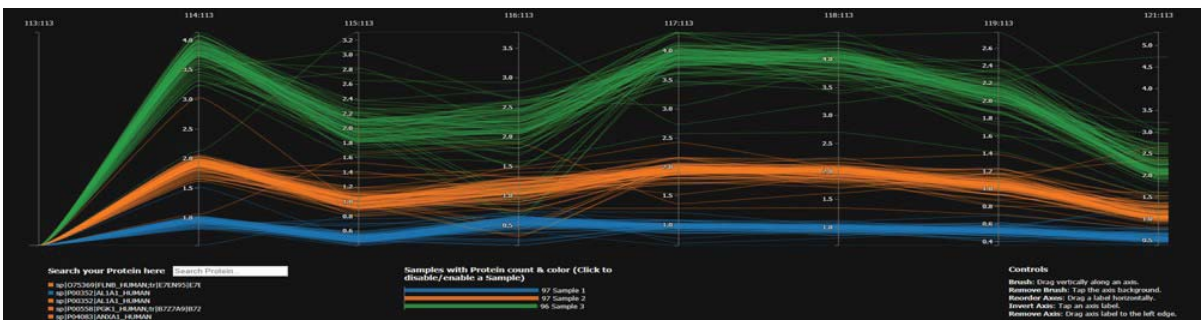
secreted proteins play a crucial role in establishing the infection or thwarting the pathogen depending on whether the species is virulent or avirulent. Analyzing the temporal dynamics of such newly translated proteins which are secreted after infection holds cues to understanding the mechanisms involved, and developing host-directed therapies for controlling the disease.

Proteome Explorer (copyrighted) for interactive visualization analysis of mass spectrometry shotgun proteomics data has been developed. Proteome-Explorer is a browser-based interactive application for exploratory analysis of MS/MS proteomics data. Single protein features like post-translational modifications, secondary structure, functional domains, binding sites and variants are displayed in separate tracks. For integrated data exploration, peptide spectrum matches are displayed in a spectrum viewer.

Mathematical and computational approaches for studying the underlying processes processes is the focus of **Dr. Samrat Chatterjee's** team. Using clustering algorithm, graph theory, and flux balance analysis his group studies high-



Hyperplexing patent and HyperQuant tool allow 18-plex multiplexing



Interactive visualization tools for quantitative proteomics data

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throughput data as well as small scale differential equation models to analyze any given biological process.

CONTRIBUTIONS

Area: Role of calcium oscillation in different tissues, currently focusing upon diabetic cardiomyocytes.

Approach: The team uses small-scale mathematical model build on ordinary differential equations (ODEs) and delay differential equations (DDEs) to understand the significance of calcium oscillation on normal cardiac functioning. Mathematical and computational tools are used to analyze those models using literature data and identify factors that could possibly be responsible for disrupting the calcium oscillation. Finally, through numerical simulation they have proposed possible therapeutic strategies to restore normal calcium oscillation, whose validity is checked by data in literature and/or through biological experimentation.

Area: Metabolic disorder, with focus on diabetes-disease progression algorithm.

Approach: The team is using temporal microarray data and the data available in open access databases, to capture disease progression in diabetes. The data is highly complex with 29,000 genes and their expression values for 10 different time points. The team has developed bi-clustering tools to identify important genes and important time points, and then connect the time specific discrete networks to form a continuous dynamical network capturing the disease progression. They theorize that the disruption of this network might block the information flow needed for disease progression.

The team has successfully developed an artificial intelligence algorithm that analyzes serum metabolome profile of an individual, and predicts the likelihood that s/he will succumb to T2DM in the future. This algorithm uses machine learning for training, and takes high-resolution mass spectrometric profile of serum metabolites of humans as inputs, to predict their T2DM susceptibility with high accuracy. To develop the algorithm, the team profiled the serum of human subjects at the time when they were healthy, and analyzed the metabolite composition against the fasting blood glucose levels that were measured 6 years later. The data was processed to give the intensity/concentration of each metabolite in each 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, alongwith 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, in the best possible way. 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.

Area: Host-pathogen interactions in the presence of *Mtb*.

Approach: To investigate how *Mtb* infection influences proteins specially associated with metabolic network of the host macrophage, time-dependent modulations in macrophage metabolism were examined, after infection with mycobacterial strains that varied in both genotype and phenotype. For the analysis recon network, a biochemical reaction network build with metabolites and proteins was used. The proteomics and metabolomics data were overlaid on the recon network to make context (strain and post-infection time)-specific networks giving the metabolic flux state in the experimental conditions. These context specific networks, made for each condition, were used in finding the critical reactions/genes whose deletion resulted in reverting/rewiring the disease state flux to normal state flux. These critical reactions/genes, also called choke points, could be potential drug targets. These are under experimental validation with collaborators.

Area: Effect of random perturbation in cell signaling leading to diseases like cancer.

Approach: The aim of the present study is to derive a mathematical formula to identify sensitive and robust nodes in large scale disease-specific networks under stochastic perturbation. The formula is derived using SDE models on different motif structures. The use of motif structures in defining noise-signal relation can be useful to

filter signal from noise in signaling pathways. A knowledge of the sensitivity nature of nodes can then be explored further in screening potential candidates for drug targets. The work started with a three-node feed forward loop to see how motif structure defines I/O relation under random perturbation. Extending this observation, further the idea was to formulate mathematical formulae to rank motifs and hence node base on their sensitivity to the perturbations. They found that motif structure not only plays an important role but could be used to rank nodes (proteins) based on their sensitivity. The study is being done with all possible motif structures covering any large network.

Dr. Renu Goel's team works on proteomics and metabalomics operations to carry out time-course analysis for determining the time points at which individual tissues/organs (liver, pancreas, skeletal muscle, visceral adipose, heart) first show the perturbations related to proteome. This approach will increase the knowledge of dysregulated pathways associated with progression of T2D, which will be useful in providing potentially new therapeutic strategies targeting these dysregulated pathways.

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CRISPR-CAS9 FOR GENOME EDITING

Dr. Ajay Kumar's group is actively working on designing in-house pool of Cas9 stable cell lines which can be used to tag genes of interest with a fluorescent marker. Tracking the endogenous expression of genes with help of fluorophores is a smarter way to study the effect of a potential drug target within a live cell. The approach would involve knocking-in a fluorescent marker (turbo GFP or mNeonGreen) within the genomic sequence of the target gene using CRISPR technology.

In line with these efforts the group has successfully generated Cas9 stable HEK293T cell line. Cas9 expression in the targeted cells was validated by western blot method over a range of protein concentrations using a Cas9 specific monoclonal antibody. CRISPR primers were designed targeting ABL1 gene to explore its role in different types of cancers, as well as targeting GLUT2 and SGLT1 genes for their role in pathophysiology of metabolic disorders like diabetes. The group is currently standardizing reaction conditions to validate knock-out of genes of choice in Cas9 expressing HEK293T cells. In parallel, they have also designed vectors that include a fluorescent marker which will eventually be used to tag the gene of interest. They plan to improvise their skills to manipulate genome using CRISPR-Cas9 technology in animal systems and use those models for screening potential drug targets.

The group is open for active collaborations with all research groups at THSTI.

Dr. Nisheeth Agarwal, who had successfully demonstrated the use of CRISPR-Cas9 technology in *Mycobacteria*, is working to improvise this technique further for large scale use in *Mtb* gene manipulation to assist ongoing TB drug discovery programs in India. His lab has provided strains/plasmids towards employment of the technology for gene manipulation to the following list of investigators:

Dr. Claudia Jessen-Trefzer, University of Freiburg, Germany (provided recombinant *M. smegmatis* for CRISPRi-based conditional knockdown of putative essential genes)

Dr. Florian Maurer, University of Hamburg, Germany (provided recombinant CRISPRi plasmids for creating knockdown strains of *M. abscessus*)

Dr. Jaroslaw Dziadek, Institute of Medical Biology of Polish Academy of Sciences, Poland (provided recombinant CRISPRi plasmids for creating knockdown strains of *Mtb*)

Dr. Astrid Lewin, Robert Koch Institute, Berlin, Germany (provided CRISPRi plasmids for creating knockdown strains of *Mycobacteria*)

Dr. Jarmila Hnilicova, Institute of Microbiology Academy of Sciences of the Czech Republic, Czech Republic (provided CRISPRi plasmids for

creating knockdown strains of *Mycobacteria*)

Dr. Jeremy Johnson, Butler University, USA (Provided recombinant CRISPRi plasmids for creating knockdown strains of *M. smegmatis*)

Dr. Jaya Tyagi, All Indian Institute of Medical Sciences, New Delhi (provided recombinant CRISPRi plasmids for creating knockdown strains of *Mtb*)

Dr. Jean-Louis Herrmann, UMR1173 INSERM-Versailles St Quentin University, France (provided CRISPRi plasmids for creating knockdown strains of *Mycobacteria*)

Dr. Sebabrata Mahapatra, Colorado State University, Ohio, USA (provided recombinant CRISPRi plasmids for creating knockdown strains of *Mtb*)

Dr. Priti Saxena, South-Asian University, Delhi, India (provided recombinant CRISPRi plasmids for creating knockdown strains of *M. marinum*)

Dr. Yogendra Singh, Delhi University, India (provided recombinant *Mtb* strains for CRISPRi-based conditional knockdown of putative essential genes)

Dr. Seetha Balasingham, Oslo University Hospital, Oslo, Norway (provided recombinant CRISPRi plasmids for creating knockdown strains of *Mtb*)

Dr. Gobardhan Das, Jawaharlal Nehru University, Delhi, India (provided recombinant *Mtb* strains for CRISPRi-based conditional knockdown of putative essential genes)

Dr. Alka Rao, Institute of Microbial Technology, Chandigarh, India (provided recombinant *Mtb* strains for CRISPRi-based conditional knockdown of putative essential genes)

Dr. Andre Kipnis, Instituto de Patologia Tropical e Saude Publica, Goias, CEP: 74605-050, Brazil (Provided CRISPRi plasmids for creating knockdown strains of *Mycobacteria*)

BIOPROCESS IMPROVEMENT

IMPROVING YIELD OF RECOMBINANT PROTEIN PRODUCTS FROM MAMMALIAN CELL-BASED INDUSTRIAL BIOPROCESS

High-quality mammalian recombinant proteins are extensively used in research, *in vivo* diagnostics as well as in therapy and are among the highest revenue-generating products in biopharmaceutical industry. Since global demand is increasing over time, world-wide sales of recombinant proteins has crossed $100 billion (projected to be nearly $150 billion by 2020), and the market is still growing at a CAGR of 8%. However, the cost of these products remains high due to complex and challenging industrial scale production process. This process includes expression of gene of interest in the host cell line, identification of rare best producer clones, production process optimization, large-scale cultivation and process monitoring, harvesting and product purification. Optimal performance at nearly every step in the process is pre-requisite for optimal yield.

Currently, mammalian cells specifically Chinese Hamster Ovary (CHO), Vero and murine myeloma/hybridoma are the most commonly used host cell lines for industrial production of high-quality recombinant proteins. Efforts are being made to improve the performance of mammalian cell-based production process, and by today, it is possible to achieve a yield of >10g/L. However, further improvements in the production capabilities of bioactive recombinant proteins are of eminent importance to meet the global demand at affordable cost.

Dr. Susmita Chaudhury and Dr. Niraj Kumar's team is working on:

(1) **Improving production capability of cells in culture** (cell-specific productivity, cell density and culture longevity)

Using OMICS tools, they investigate various bioprocess designs (such as culture temperature-shift, nutrient-shift and chemical regulation) that arrest cell growth, minimize cell death, nutrient consumption, and waste accumulation in culture and ultimately improve cell-specific productivity and yield. They are also working to identify factors that destabilize foreign mRNA in host cells. Inhibition of these factors using genetic approaches may stabilize these foreign mRNAs and improve their availability for translation contributing to improved product production.

(2) **Minimizing product degradation and heterogeneity**

Till now, limited efforts have been made to investigate secretome of bioprocess-relevant mammalian cells. The secretome generally refers to the collection of proteins that are secreted and/or released from the cell during different phases of culture (lag, log, stationary and decline/death). It may contain numerous substances: (1) proteolytic enzymes which may degrade products, (2) host cell proteins whose knowledge could play important role in developing strategies for efficient product purification from culture media, and (3) peptides/proteins that regulate cell-to-cell and cell-to-extracellular matrix interactions and affect cell growth and productivity. So, in-depth knowledge of proteins/peptides present in conditioned media alongwith the product holds great potential to enable designing of improved strategies for minimizing product degradation and product purification and enhanced overall yield.

They observe an enrichment of specific proteolytic enzymes in microvesicles produced from CHO cells during late-log and stationary phase of production culture (complete specification of Indian patent is filed). Removal of these microvesicles results in a significant reduction of product degradation. They are currently working towards developing a product prototype for filtration-based on-line removal of microvesicles from production culture and minimizing proteolytic enzyme-induced product degradation.

The product would also enable to collect these microvesicles in sterile conditions for

bioprocess, medical, research use or other related purposes.

(3) **Improving product purification process**

Currently available methods were developed and designed 2-3 decades ago to deal with cultures achieving <1g/L yield. However, a significant improvement has been made in the area of cellular protein production to achieve upto 10g/L. The purification strategies also need to be improvised to deal with high yield production culture. They aim to develop processes and products that could help in product purification process. Work is already ongoing for online removal of host cell generated cellular debris as well as microvesicles from the production culture. This may help to improve culture longevity and yield from such bioprocesses.

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RESEARCH ON MATERNAL AND CHILD HEALTH

ADVERSE BIRTH OUTCOMES

DEVELOPMENT OF EARLY LIFE IMMUNE SYSTEM

PEDIATRIC B-CELL LEUKEMIA

EVIDENCE GENERATION THROUGH INTERVENTIONS

SOCIAL INNOVATION IMMERSION

India's 12th five year plan aims to reduce Infant Mortality Rate (IMR) to 25 per 1,000 live births and Maternal Mortality Ratio (MMR) to 100 per 1,00,000 live births by 2017. THSTI has embarked on major clinical research programs of Maternal and Child Health (MCH) in alignment with the nation's goal. The research programs are multi-institutional, and multi-disciplinary and they address adverse birth outcomes, clinical severe infections, characterization of immune system in neonates and infants, and pediatric leukemia. In addition, THSTI has been a part of the clinical trials of interventions for Rotavirus Gastroenteritis in children and Social Innovation Immersion Programme for Maternal and Child Health.

ADVERSE BIRTH OUTCOMES

PRE-TERM BIRTH

Program Co-ordinator: Dr. Shinjini Bhatnagar

Institutional Collaborators: Regional Centre for Biotechnology, National Institute of Biomedical Genomics, Civil Hospital Gurugram, Safdarjung Hospital, Maulana Azad Medical College, All India Institute of Medical Sciences.

Low maternal and child mortality rates are two key indicators of good health of a society. In India, infant mortality rate is 40 per 1000 live births; one-third of these deaths occur in the first month of life. Babies born preterm are the most vulnerable. Among the 27 million babies born annually, 3.6 million babies are born preterm. Over 3,00,000 of these preterm babies die soon after birth, mostly due to compromised or under-developed physiological processes.

India, with its highest number of preterm birth (PTB) and the highest number of preterm deaths worldwide, contributes 25% of the overall global preterm related deaths. Many of these deaths are preventable. Neonatal infections are a risk factor for death in at least 50% of the preterm babies. Even those preterm babies who are able to survive beyond the neonatal period are at high risk for developing serious ailments throughout their lives including poor physical growth, hearing and vision disabilities, cognitive defects, cerebral palsy, chronic lung disease and other chronic diseases like hypertension and diabetes. This overall disability and need for special care imposes a huge burden on families, community and the government. Predisposition to preterm birth has clinical (acute and chronic medical conditions), environmental (physical stress, exposure to alcohol, indoor and outdoor pollution, etc.) and biological (genetic, psychosomatic, etc.) causes that interact in complex ways. A clear understanding of these factors will allow prediction of preterm births, and ways to prevent these births.

Dr. Shinjini Bhatnagar

Population: Pregnant women enrolled at before 20 completed weeks of gestation (POG) followed till delivery

Comparison: Healthy Birth outcomes

Objective: (i) to do an appropriate risk stratification of pregnant women who may deliver preterm by measuring modifiable clinical and epidemiological factors, maternal genes, proteins, and vaginal microbes, and (ii) to accurately categorize the PTB phenotype

Public health implications

- Prediction algorithms (using clinical and biological markers) will be improved on an ongoing basis using inferences from this research.
- Simple, non-invasive ultrasound-based image processing tools and methods for assessing health of the fetus *in utero*, and growth will be developed. There is limited data on longitudinal fetal growth in the country. The data on the gestational weight gain across pregnancy will be used for creating Indian references and inform policy.
- Newer methods of assessing gestational age at birth will be developed and validated.

- Dietary patterns of the participants across pregnancy will be assessed to determine their effects on poor pregnancy outcomes including maternal metabolic conditions; this research would add to the developing evidence-based guidelines for nutritional counseling in pregnancy.

Progress

A hospital-based cohort of pregnant women has been initiated at a district hospital in Gurugram (GCH), Haryana, for following a cohort of pregnant women from before 20 completed weeks of gestation (POG) until delivery to collect information on clinical and epidemiological parameters, bio specimens such as blood, saliva, high vaginal swab at different POG (< 20 weeks, 18-22 weeks, 26-28 weeks, delivery) and cord blood at delivery. These bio-specimens are being analyzed by global "o_m_i_c_s_" approaches including genomics, epigenomics, proteomics and for microbiomic alterations. Serial ultrasound imaging is done at similar time points to document accurate "dating" of pregnancy, congenital anomalies and fetal growth.

In order to further enhance innovation and application potential of this large ongoing pregnancy cohort, platforms have been created that will have (1) electronic clinical record repository, (2) imaging bank of ultrasound images, (3) biospecimen repository, and (4) omics data bank with a long term vision that this will result in a valuable national and global resource.

A total of 11,279 (5,200 last one year) women attending the antenatal clinic at GCH were screened out of which 4,201 (2,092 previous year) women were found to have pregnancy with <20 weeks period of gestation (POG) based on the ultrasound evaluation of the gestational age. More than two-third i.e. 2,980 (1,462 last one year) were confirmed to have an uterine pregnancy of <20 weeks POG on ultrasound (USG) evaluation and were enrolled in the pregnancy cohort. More than a third of women were enrolled in <11 weeks and almost 60% were enrolled before 14 weeks. All enrolled women were being followed at regular intervals as per the protocol. All obstetric and other medical parameters were recorded at each visit during different stages of pregnancy. **The study has documented outcomes in 1587 (87.0%) participants and currently has documented 229 (15.2%) preterm births (POG < 37 weeks) out of 1503 live births. The large numbers 202 (13.4%) of these preterm babies were born between 32 and up to 37 weeks of gestation. Notably, the rate of prematurity is substantially higher in India than what is generally believed.** This is important and invaluable data. Conceptual frameworks around how infection, nutrition, environment and other domains may prime early labour and delivery are being developed. In a very preliminary univariate analysis, an association between environmental pollution and prematurity has been seen. This is being evaluated further.

A biorepository of 3,13,521 bio-specimens inclusive of maternal serum, saliva, feces, high vaginal swabs, urine, cord blood, paternal saliva is being maintained with an added collection of placenta (10,721 till now). Currently, there are at least 472 complete longitudinal collections of the total enrolled participants who provided bio-specimens at all scheduled time points across pregnancy and at the end of pregnancy. The repository is being maintained with appropriate data management and Quality Control and Quality Assurance measures. The online data management process is available for real time tracking of each bio specimen using a unique identification code (UIC) for each participant. The clinical information and the biospecimen details are linked through the UIC. The database has been developed on c.sharp.net as front-end and SQL server as the back-end. The server management SOP with backup plans is in place. The ultrasound images in the repository has a collection of 1,68,716 images of longitudinal data collected on morphology, biometry, blood flow of uterus, fetus, and placenta.

MOLECULAR CHARACTERIZATION STUDIES FOR ADVERSE PREGNANCY OUTCOMES

Placental Influences

Candidate Gene Approach

Investigator Team: Dr. Pallavi Kshetrapal and Dr. Shinjini Bhatnagar.

Collaborator: Dr. Sunita Sharma, Gurugram Civil Hospital, Gurugram-Site Investigator.

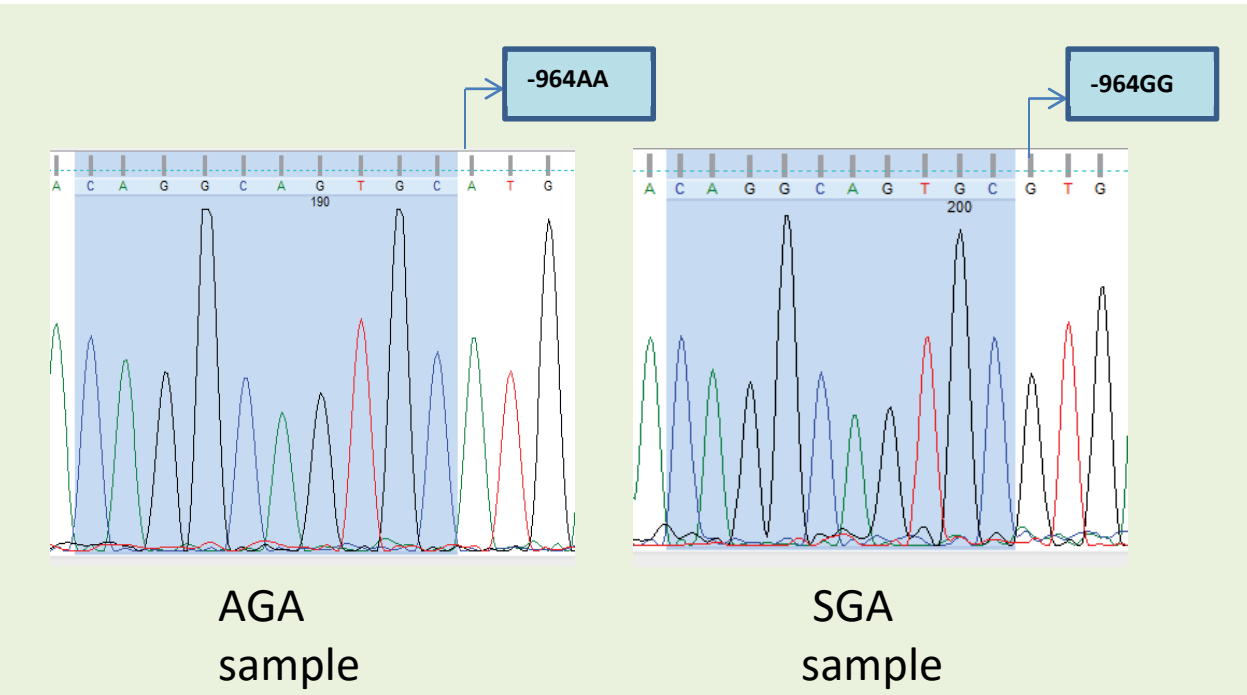
HLA-G (Human Leukocyte Antigen–G), a non-classical major Histocompatibility Complex class I molecule, is expressed in the extra-villous trophoblast lining on the maternal-fetal side of the placenta. It plays an important role in prevention of fetal cell cytolysis by regulating the uterine natural killer 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. There is a growing body of evidence suggesting that pregnancy complications such as preeclampsia, recurrent pregnancy loss (RPL), fetal growth restriction (FGR), and premature birth could be associated with aberrant immunologic interactions at the fetal-maternal interface. These aberrant immunological interactions have several causes, one of them being the differences in the HLA–G expression. Despite evidence for HLA-G playing an important role during pregnancy, the precise relationship between genetic variation in HLA-G and the pregnancy outcome, i.e. birth of SGA/AGA neonates remains unresolved.

Population: Small for Gestational Age neonates.

Comparison: Appropriate for Gestational Age neonates.

Objective: to study the role of Human Leukocyte Antigen-G (HLA-G) in adverse birth outcomes

Progress: The cases (SGA) and controls (AGA) have been selected from two study populations, where the umbilical cord blood samples have been stored along with curated clinical data on the medical history of the participant mothers. The neonates have been categorized as SGA or AGA on the basis of Fenton Growth Charts 2013. Umbilical cord blood DNA is being isolated from all the selected samples, quantified, and PCR amplified. These samples are being purified and sent for Sanger sequencing. The sequences are aligned and compared using an online tool MUSCLE: MUltiple Sequence Comparison by Log Expectation. Shown below are the genetic screening results for one of the SNP sites compared between 22 AGA and 20 SGA samples.



Chromatogram showing the presence of A allele at -964 nucleotide position in AGA sample and G allele at the same position in SGA sample.

Out of 256 SNPs reported in this gene, most have been identified in the HLA-G 5' URR (upstream regulatory region) and are located within or near regulatory elements, suggesting that these SNPs could influence the proper binding of the regulatory transcriptional factors. -725C/G/T single nucleotide polymorphism (SNP) in the 5' URR of HLA-G has been significantly associated with fetal loss rate. It has also been demonstrated that the presence of G in position -725 significantly increases HLA-G transcription rate in JEG-3 cell line.

The association of HLA-G with the birth of SGA neonates will be studied by comparing the presence of SNPs in the neonate at the genomic level to the protein expression in the mothers giving birth to those neonates.

Agnostic approach

Investigator Team: Dr. Pallavi Kshetrapal and Dr. Shinjini Bhatnagar.

Collaborators: Dr. Ram Kumar Menon, The University of Texas Medical Branch at Galveston, USA.

Dr. Carlos Solomon, University of Queensland centre for Clinical Research, Australia.

The human placenta is a transient organ that provides nutrition and functions as an immune-tolerant zone for the fetus. It prepares the mother's body to help develop the fetus by sending out signals into the mother's circulation for favorable changes to occur in order to enhance growth and proper development of the allogenic fetus. There is limited data on longitudinal growth of the developing placenta, due to the unobtainability of the tissue. Use of surrogate markers of placental growth and function, such as multi-vesicular bodies in the maternal circulation will not only help understanding the function of the placenta, but also identify new markers of fetal well-being.

Population: Pregnant women enrolled at before 20 completed weeks of gestation (POG) followed till delivery.

Objective: Understanding placental exosome-specific proteome imbalance and signatures in the feto-placental development for prediction of abnormal pregnancy outcomes.

Progress: The team is working towards its objective through (1) metabolome, proteome and microRNA profiling on the placental-specific exosomes derived from longitudinally collected maternal sera/plasma, (2) tracking the concentration of the metabolites, proteins and transcripts to determine the differences and fluctuations in the levels between the mothers delivering term and preterm babies, and (3) analyzing the metabolite, protein and RNA 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. Isolation of placental exosomes from the plasma samples has been standardized and protein cargo as well as transcripts have been isolated from the same. The protein lystaes will be subjected to mass spectrometry analysis.

There is evidence to show that neonatal complications are influenced by gestational age more than by the birth weight. **Determination of the correct gestational age is crucial** to guide post-natal care and monitor long-term neuro-cognition. A critical challenge in the clinical settings is that antenatal ultrasounds are not easily available, and gestational age determined by last menstrual period (LMP) is not reliable because of poor recall by women. Additionally, use of scales on neonates for assessment of gestational age like the New Ballard Score and the Dubowitz Gestational Age Assessment require specific training of staff which is challenging in high burden and poor resource centres.

Investigator team: Dr. Pallavi Kshetrapal and Dr. Shinjini Bhatnagar.

Collaborators: Dr. Siddharth Ramji and Seema Kapoor.

Population: Neonates

Comparison: Gestational age prediction by ultrasound.

Objective: Prediction of neonatal gestational age by measuring the metabolites using tandem mass spectrometry and comparing it with ultrasound biometric evaluation as the gold standard, in low and middle income resource Indian setting.

Progress: As a part of the ongoing pregnancy cohort, the cord blood samples collected on Whatman cards and are being stored in the Bio-repository. In addition to the samples being collected and processed for the pregnancy cohort, additional samples of the neonate heel pricks are being collected on Whatman cards and stored as Dried Blood Spots (DBS). Once the sample size for this sub-study will be attained, the cord blood DBS and neonate heel prick DBS will be processed for lysate preparation and metabolite estimation using tandem mass spectrometry will be carried out..

The skeletal muscle tissue besides enabling movement, serves as a secretory organ exerting systemic and tissue-specific effects, and is in itself a target organ in the patho-physiology of other tissues. It will be interesting to investigate mechanisms regulating fetal and infant muscle mass as a consequence of maternal nutrient availability, the lack of which results in **fetal growth restriction**.

Investigator team: Dr. Suchitra Devi, Gopinath, Jayesh Kumar Sevak.

Collaborators: Dr. Shinijini Bhatnagar, THSTI, Dr. Aneeshkumar A.G., National Institute of Immunology.

Progress: Using an animal model, Dr. Gopinath has demonstrated that vitamin D signaling maintains proteostasis *in vivo* by inhibiting the expression of myostatin and promoting the mammalian target of rapamycin (mTOR) signaling pathway through its effectors, p70S6 kinase and its substrate ribosomal protein S6 (rpS6). Importantly, muscle groups that are metabolically different display heterogeneity in their response to vitamin D signaling. Although muscles lacking vitamin D signaling display no overt degenerative or necrotic changes, preliminary experiments suggest a block in autophagy and decline in sarcomeric integrity, suggesting that the synthesis of specific subsets of proteins might be affected, an aspect that the team aims to address by ribosomal profiling. To further elaborate the link between vitamin D signaling and muscle mass in fetal growth, they will assess myogenic populations derived from umbilical cord blood stem cells of first and second trimester vitamin D-deprived mothers from Northern India for their ability to execute the myogenic program. A corollary of this program is to address whether the mechanisms leading to lean muscle mass alterations in responses to vitamin D signaling overlap with those observed in other diet-induced myopathies and whether they are accompanied by compensatory changes in other tissues such as white adipose tissue, thereby altering body composition. Using a powerful cutting edge technology of ribosome profiling coupled to deep-sequencing to identify translational details downstream of vitamin D signaling, the team hopes to use these targets as candidates of muscle mass regulators in understanding the role of maternal vitamin D levels in promoting fetal growth index.

DEVELOPMENT OF EARLY LIFE IMMUNE SYSTEM

The team effort is aimed to understand the developmental and functional properties of the neonatal immune system, specifically looking at the differences between SGA and AGA infants. Understanding the functional properties of different cell lineages between the adult/neonate and AGA/SGA immune systems will be a potential advancement in the development of vaccines that can elicit better immune responses.

Investigator Team: Dr. Shailaja Sopory, Dr. Nitya Wadhwa, Dr. Pallavi Kshetrapal.

Collaborators: Dr. Pratima Mittal and Dr. Achla Batra, Department of Obstetrics and Gynaecology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi.
Dr. K.C. Aggarwal and Dr. Harish Chellani, Department of Pediatrics, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi.
Dr. Prasenjit Guchhait, Regional Center for Biotechnology, Faridabad.

Population: Small for Gestational Age Infants.

Comparison: Appropriate for Gestational Age infants.

Objective: Phenotypic and functional characterization of T cells, B cells and monocytes between adult and cord blood (SGA vs AGA) and follow up of these infants for a period of 6 weeks for infectious morbidities.

Progress: Over the past one year, the team has done immunophenotyping and followed up 90 AGA infants and 14 SGA infants. Cord blood mononuclear cells from AGA (n=50) and SGA (n=10) samples have been cryopreserved for functional studies.

Preliminary functional analysis for monocyte subsets has been carried out to compare adult and AGA cord blood. It has been observed that cord blood patrolling monocytes are not stimulated efficiently with LPS (Ligand for TLR4) and R848 (Ligand for TLR7/8), but there is some stimulation of classical monocytes from cord blood (as determined by an increase in intracellular TNFα and IL-1β). T cell stimulation assays using anti-CD3 and anti-CD28 as physiologic stimulants are being performed on cord blood and adult blood mononuclear cells, both at the level of the total CD4+ population or in the sorted naïve T cell population (CD4+, CD45RA+). A two-fold activation in the cord blood as against the adult counterpart has been observed using early and late activation markers (CD69+ and CD25+ respectively). Further experiments will be performed to investigate the role of signaling pathways in regulating these T cell effector function differences between the two groups, namely adult and cord T cell populations.

PEDIATRIC B – CELL ACUTE LYMPHOBLASTIC LEUKEMIAS

Childhood acute lymphoblastic leukemia (ALL) is an aggressive type of hematologic malignancy that results from malignant transformation of normal developing B cells. Recent reports about the involvement of Notch 3 and Hes5 in B-ALLs substantiate our objective to investigate for the Notch synergies in these disease conditions. The Notch signaling pathway plays crucial roles in proliferation, differentiation, survival and apoptosis in many developmental systems. Though it is now becoming clear that Notch signals are synergistically involved in many oncogenic events, the complete roster of genes capable of cooperating with Notch receptor activation to influence proliferation events, particularly in B-Alls is not yet known.

Notch has been implicated to have either an oncogenic or tumor suppressor effect in a context specific manner. The goal of this study is to evaluate the effects of Notch signaling (and synergies) in pediatric B-acute lymphoblastic leukemias. In case our study connects the Notch pathway to B-Alls, the effort is using this as a step towards finding novel leads for therapeutic interventions.

Investigator team: Dr. Pallavi Kshetrapal

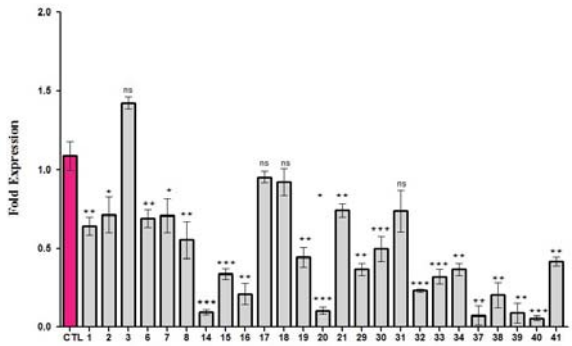
Collaborators: Dr. Rachna Seth, Additional Professor, Department of Pediatric Oncology, All India Institute of Medical Sciences-Site Investigator.

Population: Pediatric B-acute lymphoblastic leukemia peripheral blood and bone marrow.

Comparison: Age matched healthy controls.

Objective: To elucidate the possible role of Notch and its synergies in pediatric B-ALLs.

Progress: Peripheral blood and bone marrow samples from pediatric patients were used in expression analysis using quantitative Real-time PCR. Transcriptional profiling (qPCR) was carried out for samples of precursor B-ALLs and the age matched healthy donors (N=27, N=6). The qPCR data revealed a marked down-modulation of Notch 1 transcript in 70% of the cancer samples. A representative figure of collated data from the individual experiments is depicted below.



Mildly down-regulated /not regulated samples (between 0 and -4fold) – **Low**
Severely downregulated Notch-1(between -5 and -20 fold)-**Very Low**
Two discrete categories of Notch expression were observed. 15 out of 27 displayed mild downregulation (~4 fold) and the remaining 12 had moderate to severe down regulation (~ 5-20 fold) of Notch-1 expression relative to healthy controls.

Dr. Kshetrapal claims this is a novel finding as Notch 3 and Notch 4 have been associated with B cell acute lymphoblastic leukemia, but not Notch 1. The team is in the process of analyzing the same in a larger sample size. Futher, other candidate modifier genes (LMO2, HLF) in pediatric B-ALL samples are being analyzed by qPCR to understand the mechanism these genes adopt in the progression of the disease using invitro cell culture approaches.

EVIDENCE GENERATION FROM HUMAN PARTICIPANTS: INTERVENTIONAL STUDIES

CLINICAL SEVERE INFECTIONS

Zinc as an adjunct for the treatment of clinical severe infection in infants younger than 2 months

Almost half of the 6.3 million deaths in children under 5 years of age occur in the first month of life (the neonatal period) and about three quarters of these deaths are in the first week of life. More than 70% of the neonatal deaths occur in Africa and South East Asia. Severe infections like pneumonia and sepsis contribute to approximately one fourth of the deaths and are also a major cause of hospitalization in infants. In India more than a quarter of the annual 1 million neonatal deaths result from serious infections likes pneumonia, sepsis, and meningitis. While appropriate antibiotics are available in many hospitals in low and middle income countries, second-line antibiotics may be 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 outcomes and reduce case fatality.

In a recent randomized placebo-controlled trial conducted in 3 tertiary hospitals in New Delhi the investigators 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 thereby not a strong driver for policy change. Based on the promising results of the above-mentioned trial, a large, multicenter 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.

Investigator team: Dr. Nitya Wadhwa, Dr. Shinjini Bhatnagar (THSTI); Dr. Sudha Basnet (Tribhuvan University, Nepal), Dr. Tor Strand (University of Bergen, Norway)

Co-Investigators:

THSTI: Drs. Uma Chandra Mouli Natchu, Shailaja Sopory, Guruprasad Medigeshi

VMMC and SJH: Drs. Meenakshi Bhatt, Harsh Chellani, K.C. Aggarwal, Rani Gera, Ajay Kumar, Ratan Gupta, Sugandha Arya

MAMC and associated hospitals: Drs. NB Mathur, Siddharth Ramji, Sangeeta Yadav, Ajay Kumar, Vijay Gupta, Raghvendra Singh

CNBC: Drs. Anup Mohta, Mamta Jajoo, B Talukdar, B Rath, Manish Kumar, Karnika Saigal

KH: Drs. Anuradha Govil, Sunita Bhatia
University of Bergen: Dr. Halvor Sommerfel
Nepal: Drs. Laxman Shreshtha, Ganesh P Shah, Imran Ansari, Srijana Basnet, Ram H Chapagain, Binod M Shreshtha

Population: Infants with clinical severe infection as defined by WHO IMCI.

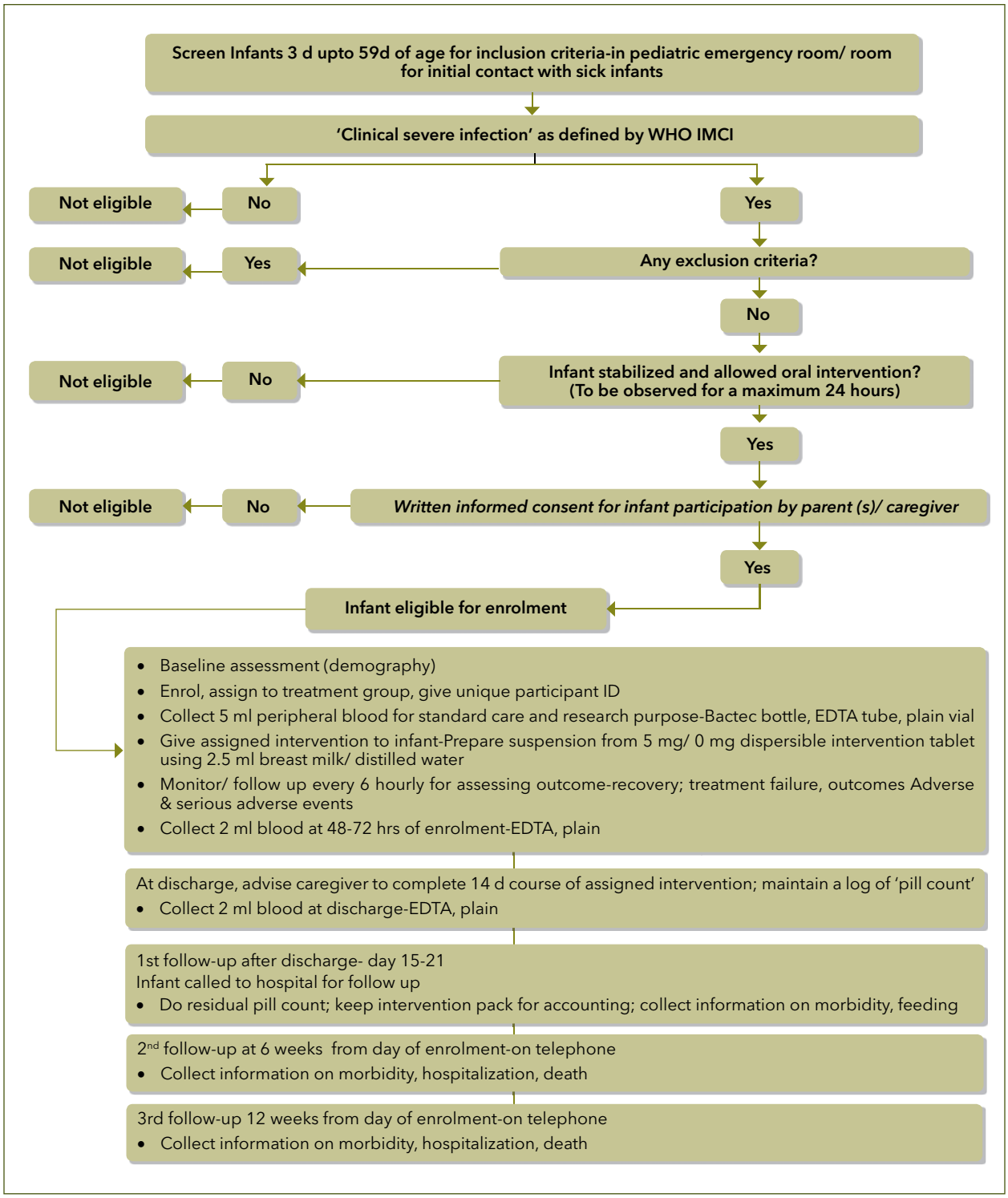
Comparison: Infants not receiving the intervention (placebo group).

Objective: To estimate the efficacy of 10 mg elemental zinc administered orally as an adjunct to standard antibiotic therapy to infants aged 3 days (48 hours and more) up to 2 months (59 days) hospitalized with 'clinical severe infection' against case fatality.

Work Plan: The recruitments for this multicenter study are taking place in 7 hospitals, 4 in New Delhi, India (Vardhman Mahavir Medical College and Safdarjung Hospital, Maulana Azad Medical College & associated hospitals, Chacha Nehru Bal Chikitsalaya and Kasturba Hospital) and 3 in Kathmandu, Nepal. The participants are randomized to receive zinc or placebo in a 1:1 allocation ratio. The intervention (zinc or placebo dispersible tablets) is administered daily at 12 hrly intervals from the time of enrolment for 14 days. 4140 infants with clinical severe infection will

be enrolled, given intervention for 14 days and followed up till discharge and until 12 weeks from the day of enrolment.

Progress: In the last one year the team has formally collaborated with the 7 hospitals by signing 'clinical trial agreements' with them. 'Clinical research units' have been set up at the hospital sites. Ethics approvals for conduct of study have been obtained from 10 ethics committees (5 in India, 4 in Nepal and one in Bergen). The staff (28 study nurses, 18 technicians, 4 senior research officers, 1 clinical research coordinator, 1 project officer) has been recruited and has undergone a structured trained in clinical research and study specific activities. They are ensuring uniformity in standard case management across the hospital sites by developing and following detailed SOPs for each and every study activity. **The study was initiated in India in February 2017.**



ROTAVIRUS GASTROENTERITIS

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

Investigators: Dr. Temsunaro Rongsen-Chandola, Dr. Sudhanshu Vrati, Dr. Nidhi Goyal

Collaborators: CHRD-SAS and THSTI under PSPC; Department of Biotechnology, Govt. of India; PATH; Bharat Biotech International Limited

Project Details: Rotavirus infections are the leading cause of diarrhea-associated mortality in developing countries. Rotavirus infections are estimated to cause ~527,000 deaths annually, predominantly in developing countries. In India, by age 5, nearly every child will have an episode of rotavirus gastroenteritis. The Indian rotavirus vaccine based on a neonatal rotavirus strain 116E developed as a Public-Private Partnership (PPP), under the Indo- US Vaccine Action Program and coordinated by the Government of India (Department of Biotechnology) has recently completed a multicentre phase III clinical trial in India. The licensure has been obtained by Bharat Biotech International Limited in January 2014.

This study is a phase III, randomized, double blind, placebo-controlled trial to assess non-interference of ORV 116E to the childhood vaccines and clinical consistency in the immune responses to the three production lots of ORV 116E. The study was conducted in the urban neighborhoods of Govindpuri-Sangam Vihar-Tigri-Dakshinpuri and Tuglakabad in South Delhi, India.

Ethical clearances were obtained from THSTI-IEC and Western Institutional Review Board. The study was approved by the office of the Drugs Controller General (India) and was conducted as per the protocol, Schedule Y and Good Clinical Practices.

Prior to study initiation, the study clinic was set up. The clinic was manned by paediatricians and physicians, open 24x7, equipped to handle all emergencies and there are systems in place to escort subjects to the hospital, if required. All categories of staff were trained on the protocol, filling case report forms, standard operating procedures and good clinical practice.

Subjects were enrolled into the study at 6 weeks of age after obtaining consent under audio visual recording and subsequent screening at the study clinic. Subjects were given 3 doses of the ORV 116E/Placebo along with childhood vaccines at 6, 10 and 14 weeks of age. A baseline blood specimen of ~1.5 mL was collected from all subjects for rotavirus IgA assays. Around 6mL of post immune blood specimens was collected 28 days after the third dose of the Test Article/ Placebo for assessing immunogenicity to the childhood vaccines.

The study team made daily contacts for 14 days after each of the three doses till four weeks after the third dose to ascertain serious adverse events and signs and symptoms of intussusception. Additionally, after four weeks of the third dose, the subjects were contacted weekly till the age of one year for signs and symptoms of intussusception and events of death, if any.

If the SAE was diarrhea, stool specimens were collected and sent to Translational Health Science and Technology Institute for RV detection and typing. If a confirmed RV positive report was obtained, an aliquot of the stool specimen was sent to the Wellcome Laboratory, Christian Medical College, and Vellore for detection of diarrheagenic *E. coli and Shigella*. For assessing clinical lot consistency, blood specimens were collected 28 (±5) days after the third dose of ROTAVAC®/placebo. The serum anti-RV IgA assay was performed by the central laboratory at THSTI where clinical lot consistency was assessed by the GMTs of IgA antibody. All serious adverse events were reported to the regulatory authorities and THSTI-IEC within 24 hours of coming to know of the event.

The study was initiated in May 2014. Enrolment of 1356 subjects was completed in September 2014 and follow up in August 2015. Enrolled subjects have received three doses of the vaccine. **Data analysis was completed and the Clinical Study Report was submitted to the Project Management Committee on March 5, 2016.** The article has been published in Heliyon. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5435614/pdf/main.pdf.

Project Title: Phase III, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of live attenuated bovine-human rotavirus reassortant pentavalent vaccine (BRV-PV) against severe rotavirus gastroenteritis In healthy Indian infants.

Investigators: Dr. Nidhi Goyal, Dr. Sudhanshu Vrati, Dr. Vikash Kedia.

Collaborators: CHRD-SAS and THSTI under PSPC; Department of Biotechnology, Govt. of India; Serum Institute of India Limited; PATH Vaccine Solutions (PVS).

Project Details: According to the WHO-coordinated Global Rotavirus Surveillance Network, 37% of deaths are attributable to diarrhea and 5% of all deaths in children under 5 years. Five countries accounted for more than half of all deaths attributable to rotavirus infection; India alone accounted for 22% of deaths (98,621 deaths) in this study. Although commercial rotavirus vaccines are currently available and have been demonstrated to be safe and effective in low-income, high-burden populations, they are not affordable in developing countries. Serum Institute of India is developing a live attenuated bovine-human (UK) reassortant pentavalent rotavirus vaccine for oral vaccination against human rotavirus gastroenteritis in healthy infants. To establish proof of vaccine efficacy in the proposed efficacy trial, infants were enrolled in six sites in India representative of different demographic, climatic and socio-cultural factors. In Delhi, it is being conducted in the urban slums of South Delhi.

Prior to study initiation, the study clinic was set up. The clinic is manned by paediatricians and physicians, open 24x7, equipped to handle all emergencies and there are systems in place to escort subjects to the hospital, if required. All categories of staff were trained on the protocol, filling case report forms, standard operating procedures and good clinical practice. Ethics clearances were obtained from THSTI-IEC and Western Institutional Review Board. The study was approved by the office of the Drugs Controller General (India), ethics committees of each of the participating sites Government of India's Health Ministry Screening Committee and the State Governments.

Subjects were enrolled into the study at 6 weeks of age after obtaining informed consent under audio visual recording and subsequent screening by a physician at the study clinic. Subjects are given 3 doses of the BRV-PV/Placebo at 6, 10 and 14 weeks of age along with OPV and Pentavalent vaccine (containing DPT, HepB and HiB) primary doses and Measles, MMR and booster vaccines according to the national immunization schedule. Active surveillance for Gastroenteritis, Intussusception and other illnesses is done by weekly contacts with the participating infants starting from the time of the first vaccination until infants reach two years of age. Once an episode of gastroenteritis is identified, study personnel maintain close contact with the parent until the child's illness is resolved.

Diarrhea Diary Cards are being used by the parents during gastroenteritis episodes to record number and duration of looser than normal stools, axillary temperature, number and duration of vomiting episodes, any treatment given and duration of hospital stay, if any. Stool samples are collected from all subjects having gastroenteritis. All Serious Adverse Event are reported to the regulatory authorities, Ethics committee and Sponsors, as per the applicable guidelines, throughout the study period.

The study was initiated in August 2014 and completed enrolment of 2100 subject in April 2015. All subjects have received dose 1 of BRV-PV/Placebo; 1934 subjects received dose 2 and 1878 subjects received dose 3. Subjects were followed up till the age of two years. The last follow up of the youngest subject was on Q1, 2017. A subset of the participants has been enrolled in an "immunogenicity cohort" to assess immune response to the vaccine. Blood samples were obtained just before vaccination and 4 weeks (+/- 7 days) after the third vaccination in the infants in this cohort. The sera will be tested for anti-rotavirus IgA at the Wellcome Trust Research Laboratory in Vellore. In addition, the sera might be tested for poliovirus antibodies.

The follow up of all subjects was completed in February 2017.

The safety and efficacy results of the interim analysis done when the primary efficacy endpoint was reached in October 2015, were submitted to the DCGI **and the vaccine has been licensed for use in India.**

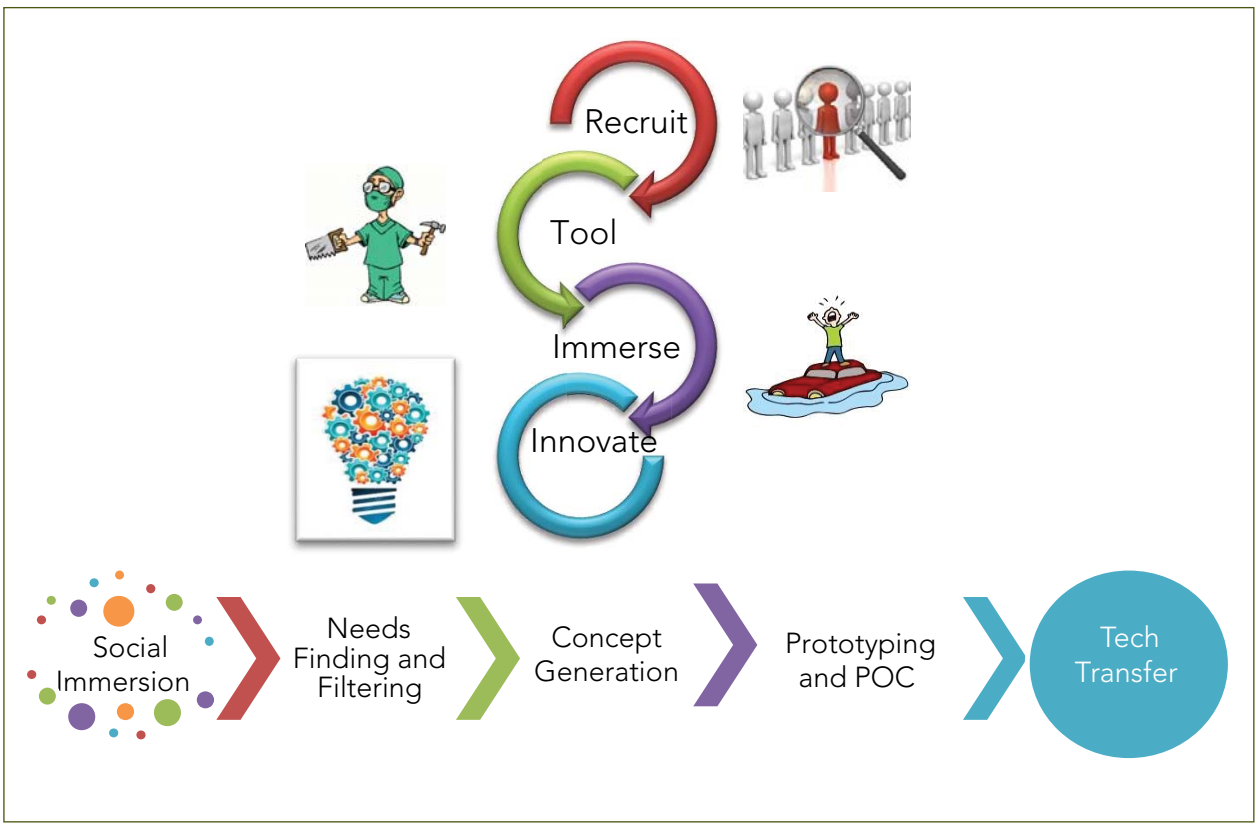
The manuscript has been submitted to Vaccine and is under review for publication.

SPARSH – Social innovation program for Products: Affordable and Relevant to Societal Health. Fellowship program for innovation in maternal and child health

This BIRAC funded grant was awarded in 2014 and began in 2015. Three recruited fellows were trained in human physiology, anatomy, health care systems and basic maternal and child health. They also underwent training in the fundamentals of biodesign processes. After a 6-8 month long immersion and needs assessment process, the fellows completed needs filtering with supervision from clinical mentors from All India Institute of Medical Sciences, Gurugram Hospital and Maulana Azad Medical College.

The top three identified needs were a low cost "disposable" incubator for newborns, a simple to use bone marrow biopsy needle (biopsy and aspiration in a single entry) and a bedside hand held device to detect hypocalcemia. In 2016, fellows worked on these three needs to develop multiple iterations of concepts. Subsequently, prototypes were developed for 2 designs of bone marrow biopsy needles, two versions of external structures for use as transport incubators and a very preliminary version of a strip for calcium estimation.

Sumit Sharma was able to refine his bone marrow biopsy prototype further and was able to make a real dimensions "working" prototype. Other designs and iterations were made in plastic by 3D printing (we acquired a 3D printer for prototype making later in the year). The bone marrow biopsy needle designs will be patented after some more refinements. They hope to convert this program into a THSTI supported program of innovation for the base of the pyramid and for primary and secondary level health care centres providing maternal and health care services.



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POLICY RESEARCH

SITUATION ANALYSIS

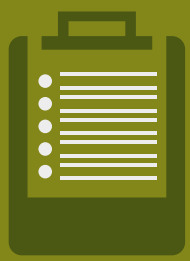
DIAGNOSTICS

VACCINES

MATERNAL AND CHILD HEALTH

NEGLECTED TROPICAL DISEASES

ONE HEALTH



A key goal of THSTI is an end-to-end approach to science and technology from discovery to policy in support of health care in India. As part of this endeavor the Policy Centre for Biomedical Research (PCBR) has been engaged in several activities relevant to landscaping the resources, activities and gaps that have the potential to affect the delivery of public health in India. Broadly, the activities of PCBR can be described as reviews or landscaping.

SITUATION ANALYSIS

DIAGNOSTICS

A review of diagnostics, particularly point of care diagnostics has been ongoing for the past few years. In the past year, the following have identified for further consideration:

Tuberculosis: The challenges of diagnostics in tuberculosis (TB) are well-known and are briefly described in the table below. Among these, the Loop Mediated Amplification (LAMP) test has been recently considered by WHO, but validation of the applicability and utility of this test at the Community Health/ Primary Health Centres in India is awaited.

Common TB Diagnostics in use	Challenges
Microscopic imaging (National Programme)	30-60% sensitivity
LED microscopy	Higher sensitivity but low penetration
Liquid Culture (BACTEC MGIT, BacT/ALERT 3D, Biomerieux)	Unsuitable as PoC due to costly equipment, not easily accessible
Serological tests	Not fit for purpose, banned
IGRAs (Quantiferon TB Gold in tube Test/ Gold test) and Tuberculin tests	WHO recommends should not be used in LMICs for suspected active TB. Used for latent TB
In house PCRs	Not reproducible
Hand held PCR (Molbio, Bengaluru)	Needs revision
GeneXpert; Cepheid, USA	Needs constant power supply for 2 hour, sophisticated equipment, expensive
Line Probe assay by Genotype MTBDR plus by Hain Life Science, Germany can detect both INH and Rifampicin resistance.	Endorsed by WHO, for sophisticated laboratories, needs high degree of QA. Not able to detect new resistance mechanisms.
Multicentric TB toolbox Trial (Lagrange)	Non-specificity
Loop Mediated isothermal amplification for TB (TB LAMP)	Recommended by WHO for the diagnosis of pulmonary tuberculosis, as a replacement for microscopy. Needs validation in India.

Visceral Leishmaniasis: Testing is challenging, although the rK29 is been employed in several testing and found to be useful. In collaboration with the Rajendra Memorial Research Institute of Medical Sciences, Patna, the PCBR is exploring new diagnostics for leishmaniasis.

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

VACCINES

In vaccines, the PCBR has considered the following,

Cholera Prevention and Control: The first Oral Cholera Vaccine (OCV) to be WHO prequalified is manufactured in India. It has good safety and immunogenicity profile and is being used in 29 countries globally to control endemic and epidemic cholera, but India does not have a strategy to use OCV yet despite repeated outbreaks reported from across the country.

A roadmap for cholera prevention and control in India is being developed. We have analysed the existing data on cholera from published and unpublished literature, data collected from hospitals and laboratories. We have also analysed the Integrated Disease Surveillance Program (IDSP) data for the last six years (2010-2015) along with the parameters of risk for cholera, including water, sanitation and hygiene preparedness as well as the vulnerability to natural disasters. Cost effectiveness of OCV, vaccine security and knowledge, attitude and practices about cholera are being studied.

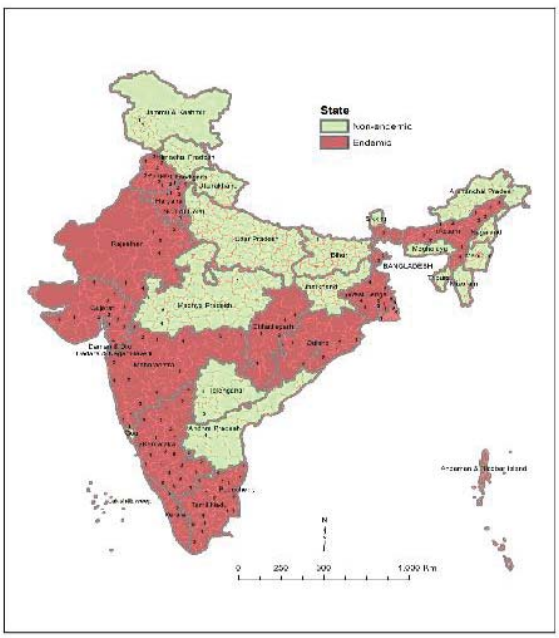
Trends and seasonal distribution of cholera cases and deaths (2010-2015) have been described. Within the cholera endemic and non-endemic states, we have identified "Hotspots of cholera" based on cases reported to IDSP.

The cost-effectiveness of oral cholera vaccination in various settings and under various implementation strategies using the VICE Calculator (Figure 2) showed that it is very cost effective to vaccinate the age group of 1-5 years as incidence is high (high-risk population group). In addition, it is easy to vaccinate 6-15 years as they are school going children. In contrast, OCV to adults is not cost-effective as case fatality rate is low and the incidence of cholera is low. In addition, mass vaccination of the entire population is not cost-effective, and vaccination should be considered only in areas with high disease burden. Results from icddrb on delivering the 2 doses of vaccine through the EPI (one dose from fixed booth and other handed over to the mother to be given after 15 days) are awaited to inform implementation strategies.

In order to develop an evidence base of cholera and oral vaccines, a journal supplement has been planned and is being compiled.

PI and Co PI: Prof. N.K Ganguly and Dr. Sanjukta Sen Gupta

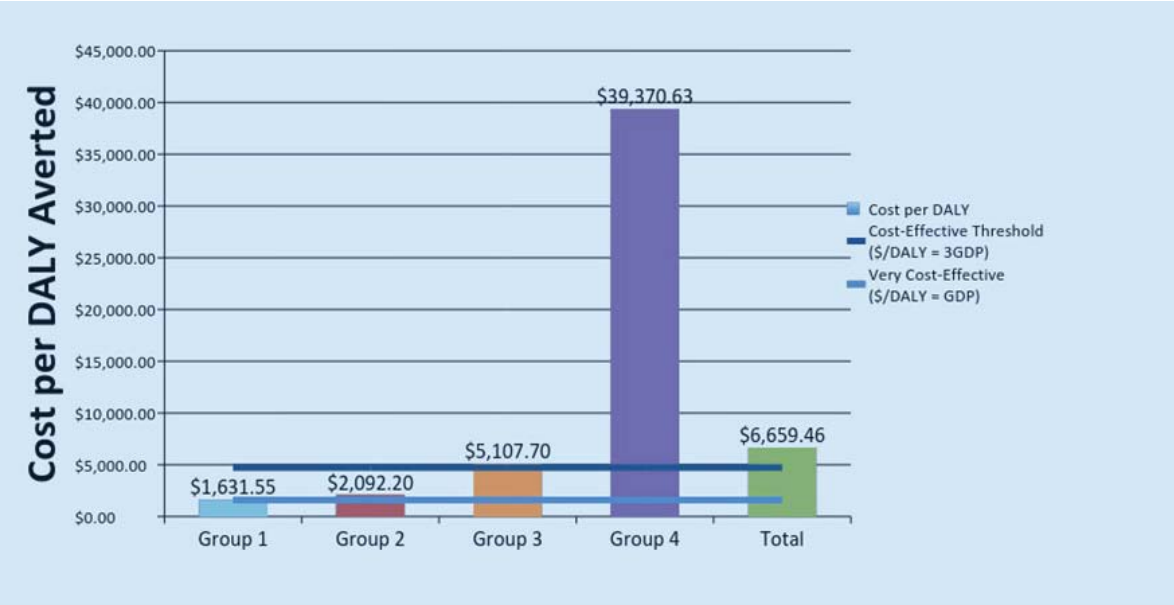
Figure 1: Cholera endemic and non-endemic states in India, bases on analysis of IDSP data from 2010-2015



- 12 states "endemic"
- 150/641 districts reported cholera
- A total of 27,615 cases in six years

(regions reporting cases in 3 or more years in 6 years)

Figure 2: Cost effectiveness of cholera



Base Scenario

Extramural grant

Title of the project: National Roadmap for Cholera prevention and Control

Funding Agency: Bill and Melinda Gates Foundation

Grant Amount : $ 107,307

Duration : 2015-2017

Publication: Sen Gupta S, Bharati K, Sur D, Khera A, Ganguly NK, Nair GB. Why is the oral cholera vaccine not considered an option for prevention of cholera in India? Analysis of possible reasons (2016) Indian J Med Res. 143: 75-81.

Pneumococcal Conjugate Vaccine: PCBR helped organize a multi-stakeholder International Symposium on Roadmap for PCV introduction in November 2015. Subsequently, an analysis of the current surveillance networks for pneumococcal pneumonia, their source of funding, geographical location, outcomes studied and their capacities to carry out impact evaluation of PCV introduction was presented as a poster at the 10th International Symposium on Pneumonia and Pneumococcal Disease (ISPPD) Glasgow, June 26-30, 2016.

PI from PCBR: Dr. Sanjukta Sen Gupta, Prof. N.K. Ganguly

Maternal immunization: There is considerable interest in the potential for reduction of maternal and infant morbidity due to respiratory infections by maternal immunization during pregnancy. The existing data on use of influenza vaccine in pregnant women was reviewed to conclude that the lack of sufficient data on influenza infection among pregnant women and newborns is one of the major barriers in creating the evidence-based policy for use of the vaccine among this 'high risk' group in India.

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

Typhoid: Typhoid fever caused by Salmonella typhi remains a serious systemic infection in the developing world. Though there are scattered clinical studies on the status of typhoid fever in India, countrywide data is lacking. With the availability of the new typhoid conjugate vaccine data on disease burden are important for policy decisions on vaccine introduction. A project titled 'Retrospective Review of Existing Data Surveillance for Enteric Fever in Asia Project (SEAP)' was undertaken by PCBR in 2016.

This project analyzed hospitalized enteric fever cases for 2014 and 2015 (2 years). The hospital based retrospective data was collected from 5 hospitals, namely, Medanta Medicity Hospital,

Figure 3: Map of India showing the study hospital sites

Gurugram; Apollo Hospital; Kolkata, Postgraduate Institute of Medical Sciences and Experimental Research, Chandigarh; Christian Medical College, Vellore and Kasturba Medical College & Hospital, Mangalore.

The objective of the project was to describe the clinical profile, severity and outcomes of laboratory-confirmed enteric fever cases, and characterize the antimicrobial sensitivity patterns of enteric fever isolates through the retrospective collection of laboratory- and hospital-based data from selected sites in India. The hospitals were from both private and public sectors.

Unexpectedly, it was observed that corporate hospitals with high socio-economic status patients also identify large numbers of enteric fevers. Age groups most affected were < 10 yrs and 15-30 yrs, and 23% of patients admitted for enteric fever showed various complications. Antimicrobial resistance to the routinely used antibiotics was observed in all the hospitals. Presently, ceftriaxone and azithromycin is being prescribed across the country, as fluoroquinolone resistance is high. The SEAP study, funded by the Coalitition Against Typhoid has been completed, data analysed and the manuscript is under preparation. The data generated will serve as a part of the evidence base for policy decisions on typhoid vaccine introduction in India.

MATERNAL AND CHILD HEALTH

The main objectives of this flagship program are:

- to identify successful technologies/solutions currently being implemented in different parts of the world as affordable, sustainable solutions for promoting maternal and child health.
- to identify bottlenecks for maternal and child health programmes.
- To recommend measures to implement successful technologies in India.

Role of mHealth and eHealth in the reduction of maternal and newborn morbidity and mortality in different regional countries have been studied and following outcomes are suggested:

- mHealth to reduce the delays that prevent timely access and utilization of needed services for mothers and newborns.
- Strategic integration of eHealth and mHealth at the most appropriate delivery points along the maternal newborn continuum of care to strengthen the health systems.
- Capacity of frontline health workers in the most remote populations, will be enhanced.

Contributors: Dr. Dipika Sur, Dr. N.K. Ganguly, Swati Verma and Nisha Arora

NEGLECTED TROPICAL DISEASES

PI and Co PI: Prof. N.K Ganguly and Dr. Gautam Kumar Saha

Leishmaniasis: All the endemic nations of South Asia have committed to push for elimination of the disease by 2020. WHO estimates that 900 000–1.3 million new cases and 20 000 to 30000 deaths occur annually due to leishmaniasis. Of the three forms of leishmaniasis, cutaneous, mucocutaneous and visceral leishmaniasis (VL),

VL causes the most severe disease affecting visceral organs and is also responsible for post-Kala-Azar dermal leishmaniasis (PKDL) syndrome in treated patients. The 2016 G-Finder Analysis showed funding is required to bring new products to market for NTDs There is an urgent need for a comprehensive policy for research towards VL elimination now that the number of cases have decreased (Figure 3) and the Indian Council for Medical Research is exploring expansion of its Vaishali model across all affected districts. In addition, based on prior experience of long delays, regulatory issues for drugs and vaccines need to be addressed. Hence, a collaboration with the Rajendra Prasad Medical Research Institute and with the Central Drugs Standards Control Organisation has been established to evaluate the feasibility of a vaccine for Kala Azar in India and endemic countries. An analysis of the regulatory processes to speed up parasitic vaccine development has been initiated. Landscape of the current R and D in parasitic vaccines with focus on VL vaccine candidates is being created, to assess feasibility of production in India and to create a roadmap for introduction of a vaccine against VL.

Contributed to G Finder Reports publication by Policy Cures

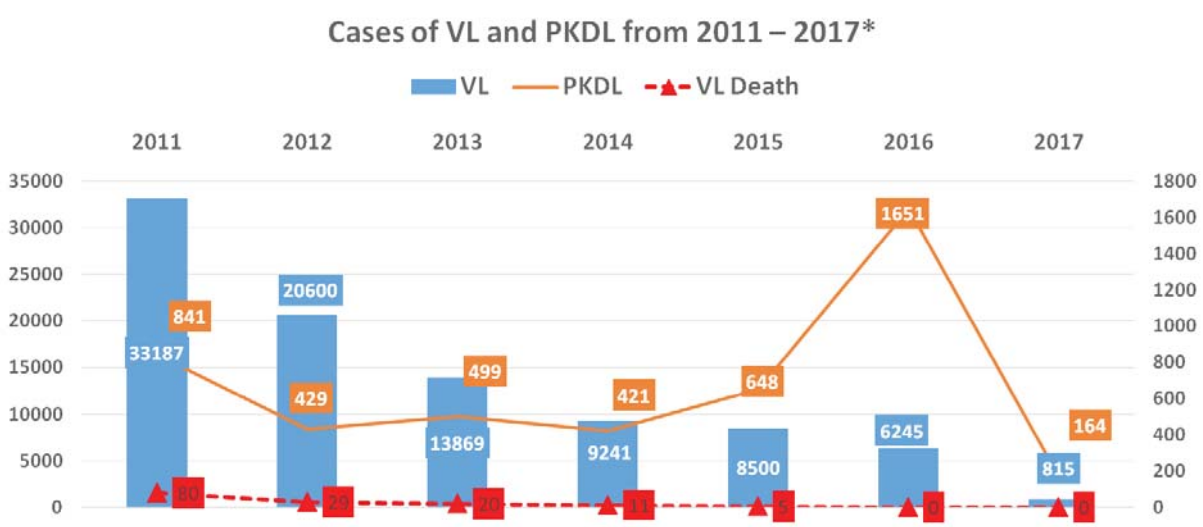
Publication: G-finder 2016. Neglected Disease R&D: A Pivotal Moment for Global Health.

Contributors: Dr. Gautam Kumar Saha

Lymphatic Filariasis: Lymphatic Filariasis is one of ten Neglected Tropical Diseases (NTDs) targeted for control, elimination or eradication in the WHO's 2012 NTD Roadmap and the 2012 London Declaration on NTDs. India launched the National Filaria Control Program (NFCP) in 1955 and is a signatory to the 1997 World Health Assembly (WHA) resolution for global elimination of LF by 2020. In 2004, the government of India launched the Mass Drug Administration (MDA) program. As of 2015, Transmission Assessment Surveys (TAS) has been completed and MDA stopped in 72 endemic districts in India. According to the National Vector Borne Disease Control Program (NVBDCP), 222 districts in India had achieved microfilaria rates of less than 1% qualifying them for TAS in 2016. However, despite achieving nearly 99% of geographical coverage and 78% program coverage by 2015, 33 districts were classified as 'hot spot' districts where microfilaria rates remain high. A renewed focus for LF under the National Health Policy 2017 provides the perfect opportunity to accelerate implementation.

In alignment with the government's proposed action plan for elimination of LF, in collaboration with ICMR and NVBDCP, PCBR will support the programme by develop a financing policy paper for the expansion of LF elimination activities.

Figure 4: Visceral leishmaniasis and post-kala-azar dermal leishmaniasis reported in India



Monograph : Overview of Leishmaniasis with special emphasis on kala azar in South Asia, Kwang Poo Chang, Bala K. Kolli and Collaborators (Gautam Kumar Saha and Prof. N.K. Ganguly)

In collaboration with Global Health Strategies (GHS), PCBR will elevate LF-related issues through appropriate media channels at the national and state level and disseminate success stories through case studies, newsletters and human interest stories.

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

Partnerships: GHS, ICMR, WHO, PATH, project Submitted to BMGF: Awaiting Fund

ONE HEALTH

The rise of zoonotic diseases in the recent past, with outbreaks of SARS, Ebola, and Zika raising the alarm, has underscored the importance of surveillance as well as the need for educating the community about effective combat of the future outbreaks. A framework needs to be built that can aid in promoting and implementing the concept of One-Health, thus paving way for achieving sustainable health and development goals The proposed framework for One-Health forums will bring together educationists and researchers from various fields of science. The forum will provide professionals working in animal and human health; environment and others related to social sciences, an avenue to find common goals, and further the concept of formulating sustainable growth programs. A pilot concept project is being created with partnership with One Health Global Think Tank for Sustainable Health and Well-Being – 2030 and in association with One Health Initiative and One Health Commission.

ACHIEVEMENTS

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

Dr. Gautam Kumar Saha selected as Member of One Health Global Think Tank for Sustainable Health & Well-Being – 2030 (Commonwealth secretariat).

Publication: Creating a platform that allows evidence gathering, deliberation and policy support for the concept of 'One-Health' (Article in Review SEEJPH).

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PUBLICATIONS, GRANTS, PATENTS AND AWARDS

PEER-REVIEWED PUBLICATIONS

EXTRAMURAL GRANTS

PATENTS

HONORS AND AWARDS

SEMINARS AND CONFERENCES

INVITED TALKS

BOOKS AND BOOK CHAPTERS PUBLISHED

DATASETS SUBMITTED

FACULTY ENTREPRENEURSHIP

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Ochieng J.B., Mintz E.D., O'Reilly C.E., Berkeley L.Y., Livio S, Tennant S.M., Sommerfelt H, Nataro J.P., Ziv-Baran T, Robins-Browne R.M., Mishcherkin V, Zhang J, Liu J, Houpt E.R., Kotloff K.L., Levine M.M. The burden of *Cryptosporidium* diarrheal disease among children < 24 months of age in moderate/high mortality regions of sub-Saharan Africa and South Asia, utilizing data from the global enteric multicenter study (GEMS). PLoS Negl Trop Dis 2016;10(5):e0004729.

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76. Ali M, You Y.A., Sur D, Kanungo S, Kim D.R., Deen J, Lopez A.L., Wierzba T.F., Bhattacharya S.K., Clemens J.D. Validity of the estimates of oral cholera vaccine effectiveness derived from the test-negative design. Vaccine 2016; 34(4):479-85.

77. Mahapatra T, Mahapatra S, Pal D, Saha J, Lopez A, Ali M, Banerjee B, Manna B, Sur D, Bhattacharya S, Kanungo S. Trials and tribulations of conducting interventional studies in urban slums of a developing country: Experiences from Kolkata, India. Hum Vaccin Immunother 2016; 12(1):182-6.

EXTRAMURAL GRANTS

DR. BHABATOSH DAS

Project: *Helicobacter pylori* infection and modulation of gastro-intestinal microbiome in the context of peptic ulcer and gastric cancer

Funding agency: Department of Science and Technology, Govt. of India

Duration of sanction: 2016-2019

Amount: INR 47,22,000

Collaborator: Dr. Santanu Chattopadhyay, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram

DR. SANJAY K. BANERJEE

Project: Identification of transcription factors perturbed at early stages of heart development during pregestational diabetes

Funding agency: Department of Biotechnology, Govt. of India

Duration of sanction: 2017-2019

Amount: INR 39,55,000

Project: *In vivo* hypocholesterolemic effect of bioconjugates of starch nanoparticles with gamma oryzanol and tocotrienols extracted from rice bran (Twining Project)

Funding agency: Department of Biotechnology, Govt. of India

Duration of sanction: 2016-2018

Amount: INR 79,60,000

Collaborator: Dr. CharuLata Mahanta, Tezpur University, Tezpur

DR. SUBHAM BANERJEE

Project: Prophylactic transdermal patch against neurotoxin poisoning in biological warfare situations

Funding agency: BIRAC-SRISTI GYTI Award, Department of Biotechnology, Govt. of India

Duration of sanction: 2017-2019

Amount: INR 15,00,000

Collaborators: Dr. A Ghosh, Dept. of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi

Dr. P Chattopadhyay, Defence Research Laboratory, Tezpur

Dr. S Karmakar, Bioeqivalence Study Centre, Jadavpur University, Kolkata

DR. SHAILENDRA ASTHANA

Project: Functional characterization of finger loop with/without inhibitors in HCV RNA-dependent RNA Polymerase: A microscopic picture through computational simulations and its application for new antiviral drug development

Funding agency: Science and Engineering Research Board, Department of Science and Technology, Govt. of India

Duration of sanction: 2016-2018

Amount: INR 33,00,000

Collaborators: Dr. Ranjith Kumar C. T., Indraprastha University, Delhi

Dr. K.V.S. Rao, THSTI, Faridabad

DR. SAMRAT CHATTERJEE

Project: Unravelling the architecture of biological networks to identify points of sensitivity under perturbation (Dr. K.V.S. Rao, Co-PI, THSTI, Faridabad)

Funding agency: Department of Biotechnology, Govt. of India

Duration of sanction: 2016-2019

Amount: INR 69,26,600

Collaborator: Prof. Joydev Chattopadhyay, Indian Statistical Institute, Kolkata

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

Funding agency: Council of Scientific and Industrial Research, Govt. of India

Duration of sanction: 2016-2019

Amount: INR 22,00,000

DR. SAMEENA KHAN

Project: Molecular dissection of the functioning of ubiquitin proteasome modules; Mulan and USP 18 and their implications in metabolic disorders

Funding agency: Indian National Science Academy, New Delhi

Duration of sanction: 2016-2019

Amount: INR 15,00,000

Project: Illuminating the structural aspect of Trim72 E3 ligase in metabolic syndrome

Funding agency: Science and Engineering Research Board, Department of Science and Technology, Govt. of India

Duration of sanction: 2017- 2020

Amount: INR 18,00,000

DR. TARUN SHARMA

Project: *Mycobacterium tuberculosis* antigen-detection based point-of-care test using aptamer technology for tuberculous meningitis (TB meningitis)

Funding agency: Biotechnology Ignition Grant, Biotechnology Industry Research Assistance Council

Duration of sanction: 2017-2018

Amount: INR 50,00,000

Collaborators: Prof. Jaya S. Tyagi, All India Institute of Medical Sciences, New Delhi

Dr. Neera Sharma, Dr. Ram Manohar Lohia Hospital, Delhi

Project: Aptamer-based tuberculosis diagnostics toolbox

Funding agency: Department of Biotechnology, Govt. of India

Duration of sanction: 2017-2019

Amount: INR 65,00,000

Collaborators: Prof. Jaya S. Tyagi, All India Institute of Medical Sciences, New Delhi

Dr. V.P. Myneedu, National Institute of Tuberculosis and Respiratory Diseases, New Delhi

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, Govt. of India

Duration of sanction: 2017-2020

Amount: INR 87,00,000

Collaborators: Dr. Sujata Mohanty, All India Institute of Medical Sciences, New Delhi

Dr. Anirban Basu, National Brain Research Centre, Manesar

DR. MANJULA KALIA

Project: Interactions between Japanese Encephalitis Virus and host autophagy pathway: Implications for pathogenesis

Funding agency: Science & Engineering Research Board, Department of Science and Technology, Govt. of India

Duration of sanction: 2016-2019

Amount: INR 68,00,000

Collaborator: Dr. Sudhanshu Vrati, Director, Regional Centre for Biotechnology, Faridabad

DR. GAURAV BATRA

Project: High sensitivity multiplex point-of-care assay systems for the detection of blood borne infections in emergency settings

Funding agency: The Wellcome Trust, United Kingdom

Duration of sanction: 2016-2019

Amount: INR 8,00,00,000

Collaborators: International Centre for Genetic Engineering and Biotechnology, New Delhi

University of Turku, Finland

Project: Multiplexed point of care assay for acute febrile illnesses

Funding agency: World Health Organization

Duration of sanction: 2017-2018 (20 months)

Amount: INR 6,00,00,000 (1st tranche)

Collaborators: International Centre for Genetic Engineering and Biotechnology, New Delhi

All India Institute of Medical Sciences, New Delhi

University of Turku, Finland

DR. SUSMITA CHAUDHURY AND DR. NIRAJ KUMAR

Project: Differential diagnosis of bacterial pneumonia and their antibiotic resistance

Funding agency: Indian Council of Medical Research, New Delhi

Duration of sanction: 2017-2019

Amount: INR 63,00,000

Collaborators: Dr. Varindar Singh, Kalawati Saran Children's Hospital, New Delhi

Dr. Rakesh Lodha, Dr. J.S. Tyagi, Dr. S.K. Kabra, All India Institute of Medical Sciences, New Delhi

Dr. Shinjini Bhatnagar, Dr. Nitya Wadhwa, THSTI, Faridabad

Dr. Radhesh Pathak, Gurugram Civil hospital, Gurugram

Dr. G.B. Nair, World Health Organization, South-East Asia Regional Office

DR. SAGARIKA HALDAR

Project: *Mycobacterium tuberculosis* antigen-detection based point-of-care test using aptamer technology for tuberculous meningitis (TB meningitis)

Funding agency: Biotechnology Industry Research Assistance Council under BIG scheme, Department of Biotechnology, Govt. of India

Duration of sanction: 2016-2019

Amount: INR 50,00,000

Collaborators: Dr. Tarun Sharma, THSTI, Faridabad

Dr. Jaya Tyagi, All India Institute of Medical Sciences, New Delhi

Advanced Microdevices Pvt. Ltd., Ambala

Dr. Neera Sharma, Dr. Lokesh Sharma and Dr. R S Taneja, Dr. Ram Manohar Lohia Hospital, New Delhi

Project: Aptamer-based tuberculosis diagnostics toolbox

Funding agency: Department of Biotechnology, Govt. of India

Duration of sanction: 2017-2020

Amount: INR 65,00,000

Collaborators: Dr. Tarun Sharma, THSTI, Faridabad

Dr. Jaya Tyagi, All India Institute of Medical Sciences, New Delhi

Dr. Neera Sharma, Dr. Lokesh Sharma and Dr. R.S. Taneja, Dr. Ram Manohar Lohia Hospital, New Delhi

Dr V. P. Myneedu, National Institute of Tuberculosis and Respiratory Diseases Hospital, Delhi

DR. RAMANDEEP SINGH

Project: Understanding the role of Rv1955-Rv1956 Toxin-Antitoxin (TA) locus of *Mycobacterium tuberculosis* in pathogen biology

Funding agency: Department of Biotechnology, Govt. of India

Duration of sanction: 2016-2019

Amount: INR 34,41,000

Collaborator: Dr. Amita Gupta, University of Delhi South Campus, New Delhi

Project: Dissecting the physiological role of Rv3423.1, a novel histone acetyl transferase in *Mycobacterium tuberculosis* H37Rv in bacteria as well in infected guinea pigs

Funding agency: Department of Science and Technology, Govt. of India

Duration of sanction: 2017-2019

Amount: INR 25,00,000

Collaborators: Dr. Ajay Kumar, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram

DR. SUCHITRA DEVI GOPINATH

Project: Role of Vitamin D signaling in regulating muscle mass of insects

Funding agency: Innovative Young Biotechnologist Award, Department of Biotechnology, Govt. of India

Duration of sanction: 2016-2019

Amount: INR 70,16,800

DR. PALLAVI KSHETRAPAL

Project: Profiling of placental physiologic signature during pregnancy in maternal liquid biopsies

Funding agency: Bill and Melinda Gates Foundation

Duration of sanction: 2016-2017

Amount: INR 31,93,824

Collaborators: Dr. Ram Kumar Menon, The University of Texas Medical Branch at Galveston, USA

Dr. Carlos Solomon, University of Queensland Centre for Clinical Research, Australia

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. Shinjini Bhatnagar, Dr. K.V.S. Rao, 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, Govt. of India

Duration of sanction: 2017-2019

Amount: INR 30,00,000

Collaborators: Dr. Shinjini Bhatnagar, Dr. K.V.S. Rao, THSTI, Faridabad

PATENTS

Title: Novel molecules and their HIV inhibitory activity

Application No.: 201711009180

Filing Date: 16 March 2017

Authors: Kanury Rao, Dinesh Mahajan, Shailendra Asthana, Shilpa Jamwal, Sameena Khan and Debashish Mitra

Title: Novel molecules and their HIV inhibitory activity

Application No.: 201711009179

Filing Date: 16 March 2017

Authors: Kanury Rao, Dinesh Mahajan, Shailendra Asthana, Shilpa Jamwal, Sameena Khan and Debashish Mitra

Title: Method of hyperplexing in mass spectrometry to elucidate temporal dynamics of proteome.

Application No.: 201611029904

Award Date: 1 September 2016

Authors: Ajay Kumar, Shilpa Jamwal, Suruchi Aggarwal, Kanury V.S. Rao and Amit Kumar Yadav

Title: Aptamers against *Mycobacterium* malate synthase and uses thereof

Application No.: 201611021901

Filing Date: 27 June 2016

Authors: Tarun K Sharma, Jaya S Tyagi, Abhijeet Dhiman, Chanchal Kumar and Ishara Datta

Title: Novel DNA aptamers against nucleoid-associated protein HupB of *Mycobacterium tuberculosis* and uses thereof

Application No.: 201711001246

Filing Date: 12 January 2017

Authors: Tarun K Sharma, Priya Kalra, H.K. Prasad and Jaya S. Tyagi

HONORS AND AWARDS

2016

Dr. Gagandeep Kang received the Infosys Prize in life sciences from the Infosys Science Foundation, India, for her pioneering contributions to understanding the natural history of rotavirus and other infectious diseases.

Dr. Bhabatosh Das received the 2016 Young Investigator Award (1st Prize) from Yakult India Microbiota and Probiotic Science Foundation, India.

Dr. Sameena Khan received the 2016 NASI Young Scientist Platinum Jubilee Award, The National Academy of Sciences, India.

Dr. Subham Banerjee received the award for Best Oral Presentation at the Nano Bio Interface, Jawaharlal Nehru University, New Delhi.

2017

Dr. Amit Awasthi received the G.P. Talwar Mid-Career Scientist Award by the Indian Immunology Society India.

Dr. Tarun Sharma received the DBT-Innovative Young Biotechnologist Award (IYBA).

Dr. Subham Banerjee received the Gandhian Young Technological Innovation Award at the Rashtrapati Bhawan, New Delhi.

Dr. Subham Banerjee received the Innovators Under 35 Award at the MIT-Technology Review & Mint, India.

MEMBERSHIP

Dr. Sameena Khan was selected for the Associateship of the Indian Academy of Sciences, IAScin 2016.

Dr. Amit Awasthi was elected as executive council member of Indian Immunology Society Member in 2017 and was nominated as member of Molecular Immunology Forum in 2017.

TRAVEL GRANTS

Dr. Amit Awasthi received the American Association of Immunologists (AAI) Early Career Faculty Travel Grant for attending AAI annual meeting at Seattle, Washington, 2016 and 2017 consecutively.

Dr. Amit Awasthi received the American Association of Immunologists (AAI) Travel Grant for attending the International Congress of Immunology 2016 held at Melbourne, Australia.

Drs. Supratik Das, Shubbir Ahmed, Tripti Shrivastava, Sweety Samal, Rajesh Kumar and Suprit Deshpande received full scholarship and travel grants to attend the HIV R4P meeting 2016 (a conference on HIV for Prevention) held at Chicago, USA.

Dr. Sagarika Haldar received The Global Health Travel Award for attending Keystone Symposium: A5, New Developments in Our Basic Understanding of Tuberculosis held at Vancouver, British Columbia, Canada, 2017.

SEMINARS AND CONFERENCES

1. Srivastava M, Singh M, Suri C, Rao K.V.S, and Asthana S. Molecular dynamics simulations reveal the mechanisms of allosteric inhibition of ubiquitin specific proteases 7. International Conference on Drug Design and Discovery, Jawaharlal Nehru University, 2017.

2. Suri C, Srivastava M, Singh M, Asthana S. Inducing autophagy using computational structural biology. International Conference on Drug Design and Discovery, Jawaharlal Nehru University, 2017.

3. Kumari A, Mittal L, Suri C, Rao K.V.S, Asthana S. Identification of fatty acids transport protein 5 blockers: A molecular modeling studies. International Conference on Drug Design and Discovery, Jawaharlal Nehru University, 2017.

4. Mittal L, Kumari A, Suri C, Rao K.V.S, Asthana S. Targeting template entrance site of RNA-dependent RNA polymerase for antiviral drug discovery in bovine viral diarrhea virus. International Conference on Drug Design and Discovery, Jawaharlal Nehru University, 2017.

5. Zucca P, Asthana S, Sanjust E, Vargiu A.V, Ruggerone P, Rescigno A. Hydroxycoumarins as inhibitors for mushroom tyrosinase: in vitro and in silico study. Vienna polyphenols, Vienna, Austria, 2017.

6. Srivastava M, Singh M, Suri C, Rao K.V.S, and Asthana S. A protein-protein interaction approach to unravel the mechanism of protein rescue and degradation. RSG-Germany Student Symposium on Computational Genomics, Institute of Molecular Biology, Mainz, Germany, 2016.

7. Suri C, Rao K.V.S, and Asthana S. Discovery of small molecule mTOR independent autophagy inducer-A computational approach. Biophysical Society, USA, 2016.

8. Kumari A, Mittal L, Suri C, Rao K.V.S, Asthana S. Molecular modelling studies of fatty acids transport proteins-inhibitory compounds. National Conference on Computational Biology, C-DAC Pune, 2016.

9. Mittal L, Kumari A, Suri C, Rao K.V.S, Asthana S. Mechanism of cavity formation in presence of lead molecule at template entrance tunnel in bovine viral diarrhea virus RNA-dependent RNA polymerase. National Conference on Computational Biology, C-DAC Pune, 2016.

10. Singh M, Srivastava M, Suri C, Rao K.V.S, Asthana S. Molecular modeling of the disordered regions of Sirt-1 to understand the atomistic protein-protein interaction mechanism. World Congress on Drug Discovery and Development, Indian Institute of Science, Bengaluru, 2016.

11. Srivastava M, Singh M, Asthana S. Insertions at catalytic site provide novel insights for lead discovery: A structure-based in-silico approach. International Conference on Ubiquitin and Ubiquitin-Like Modifications: Mechanisms and Implications for Human Diseases. National Centre for Biological Sciences, Bengaluru, 2016.

12. Shrivastava T, Samal S, Goswami S, Ahmed S, Ozorowski G, Ward A, Chakrabarti B.K. Novel approach for stabilizing soluble native trimeric HIV-1 clade C Env harboring MPER by linking partial cytoplasmic domain. Proceedings of the Conference of the HIV Research for Prevention, Chicago, USA, 2016.

13. Ahmed S, Shrivastava T, Kumar N, Ozorowski G, Ward A and Chakrabarti B.K. Stabilization of soluble an Indian clade C Env, 4-2.J41, in a native trimeric form. Proceedings of the Conference of the HIV Research for Prevention, Chicago, USA, 2016.

14. Samal S, Shrivastava T, Boliar S, Das S, Kumar N, Tyagi A.K, Bhattacharya J, Koff W.C. and Chakrabarti B.K. The conserved hydrophilic domain in cytoplasmic tail of Indian clade C HIV-1 Env plays a critical role in stabilization of native-like conformation. Proceedings of the Conference of the HIV Research for Prevention, Chicago, USA, 2016.

15. Das S, Boliar S, Mitra N, Samal S, Bansal M, Koff W, Chakrabarti B.K. V2 and C2 domain-dependent antigenic properties of efficiently cleaved HIV1 clade B Env, JRCSF that can be used as a platform for immunogen design. Proceedings of the Conference of the HIV Research for Prevention, Chicago, USA, 2016.

16. Deshpande S, Patil S, Kumar R, Hermanus T, Murugavel K.G, Srikrishnan A.K, Solomon S, Morris L, Bhattacharya J. V1 loop length limits neutralization of HIV-1 clade C primary viruses by broadly neutralizing antibodies targeting the V3 glycan. Proceedings of the Conference of the HIV Research for Prevention, Chicago, USA, 2016.

17. Kumar R, Patil S, Yadav V.K, Ozorowski G, Holden L.G, Ward A.B, Bhattacharya J. Antigenicity of a HIV-1 B/C recombinant trimeric envelope protein that retains its near native conformation in CD4-bound state. Proceedings of the Conference of the HIV Research for Prevention, Chicago, USA, 2016.

18. Deshpande S, Patil S, Kumar R, Shrivastava T, Srikrishnan A.K, Murugavel K.G, Chakrabarti B.K, Koff W.C, Bhattacharya J. Association of V3/C3 mutations with enhanced sensitivity of autologous HIV-1 clade C envelope to contemporaneous broadly cross neutralizing plasma. Proceedings of the Conference of the HIV Research for Prevention, Chicago, USA, 2016.

19. Arora S, Mathew B, Kumar S, Majood M, Bhatnagar S, Kumar N, Bhattacharya S, Chaudhuri S. Investigating the role of RIDD pathway in quantitative modulation of recombinant protein production by hybridoma cells. Bioprocessing India, Mohali, 2016.

20. Majood M, Mathew B, Kumar S, Arora S, Bhatnagar S, Bhattacharya S, Chaudhuri S, Kumar N. Understanding the role of cell growth regulators in regulating cell growth and recombinant protein production by mammalian cells. Bioprocessing India, Mohali, 2016.

21. Lavania S, Anthwal D, Bhalla M, Singh N, Haldar S, Tyagi J.S. Direct detection of rifampicin resistance from Ziehl-Neelson-stained slides by bio-safe sputum processing method. 71st National Conference of Tuberculosis and Chest Diseases, Chandigarh, 2016.

22. Tyagi S, Kumari P, Lavania S, Sharma N, Gadpayle A.K, Rath D, Sharma T, Dhiman A, Anthwal D, Tyagi J.S, Haldar S. Utility of qPCR, Gene Xpert and antigen detection tests for the diagnosis of pleural TB, 71st National Conference of Tuberculosis and Chest Diseases, Chandigarh, 2016.

23. Anthwal D, Gupta R.K, Bhalla M, Tyagi J.S, Haldar S. Direct detection of MDR-TB in sputum samples by high resolution melt curve analysis. 71st National Conference of Tuberculosis and Chest Diseases, Chandigarh, 2016.

24. Haldar S, Anthwal D, Gupta R.K, Bhalla M, Tyagi J.S. Rapid detection of multi-drug resistance in Mycobacterium tuberculosis from direct smear-negative sputum samples by high resolution melt curve analysis. 47th Union World Conference on Lung Health, Liverpool, UK, 2016.

25. Kumari P, Lavania S, Tyagi S, Sharma N, Gadpayle A, Kumar D, Dhiman A, Sharma T, Tyagi J.S, Haldar S. Evaluation of real-time polymerase chain reaction and antigen detection for the efficient diagnosis of pleural tuberculosis. Scientific program on THSTI Foundation Day, THSTI, Faridabad, 2016.

26. Anthwal D, Gupta R.K, Bhalla M, Tyagi J.S, Haldar S. Direct detection of MDR-TB in sputum samples by high resolution melt curve analysis. Scientific program on THSTI Foundation Day, THSTI, Faridabad, 2016.

INVITED TALKS

2016

Dr. Bhabatosh Das delivered a talk on "Microbiome of the Indian Population: Current Understanding and Future Challenge" at the 40th Annual Conference of Indian Association of Medical Microbiologists held at Postgraduate Institute of Medical Education and Research, Chandigarh.

Dr. Subham Banerjee delivered a talk at the Nano-Biointerface 2016 held at the Jawaharlal Nehru University, New Delhi.

Dr. Subham Banerjee delivered a talk at the International Conference on Advances in Nanomaterials and Nanotechnology (ICANN 2016) held at Jamia Millia Islamia, New Delhi.

Dr. Nisheeth Agarwal delivered a talk at the All India Institute of Medical Sciences, New Delhi and at the University of Delhi South Campus, New Delhi.

Dr. Jayanta Bhattacharya delivered a talk at the MSD-Wellcome Trust Hilleman Laboratories, Jamia Hamdard Campus, New Delhi.

Dr. Jayanta Bhattacharya delivered a talk on "Dissecting molecular specificities of broadly neutralizing antibodies elicited in natural infection to HIV-1" at the Symposium on Biology and Molecular Pathogenesis of Viruses held at the Indian Institute of Science, Bengaluru.

Dr. Jayanta Bhattacharya delivered a talk at the Science Workshop on Vaccine R and D opportunities conducted by the MSD-Wellcome Trust Hilleman Laboratories at the Hotel Leela Palace, New Delhi.

Dr. Jayanta Bhattacharya delivered a talk on "Protective antibodies to HIV-1 elicited in natural infection guide rational vaccine design" at the 85 SBC Meeting held at CSIR-Central Food Technological Research Institute, Mysore.

Dr. Sagarika Haldar delivered a talk on "Diagnosis of tubercular meningitis" at NATCON 2016, and at the 71st National Conference of Tuberculosis and Chest Diseases held at Chandigarh.

Dr. Ramandeep Singh delivered talks at the Science Setu Program at Acharya Narendra Dev College and Maitreyi College, New Delhi; TB conference held at Indian Institute of Science, Bengaluru and at the Association of Microbiologists of India, Jawaharlal Nehru University, New Delhi.

2017

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.

Dr. Bhabatosh Das delivered a talk on "Dysbioisis: How to measure it and its association with various diseases" at the Faculty Development Programme held at Kalinga Institute of Medical Sciences, Kalinga Institute of Industrial Technology, Bhubaneswar.

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

Dr. Bhabatosh Das delivered a talk on "Antimicrobial resistant enteric pathogens: Molecular insights

into resistance traits of isolates from India" at the National Institute of Science Education and Research, Odisha.

Dr. Bhabatosh Das delivered a talk on "Gut microbiome of the Indian population: Current understanding and future challenges" at the National Institute of Science Education and Research, Bhubaneswar.

Dr. Bhabatosh Das delivered a talk on "Multidrug Resistant Enteric Pathogens: Molecular Insights into Resistance Traits of Isolates from India, SUPERBUGS V/S SUPERDRUGS: The Looming Global Antibiotic Resistance Crisis" at the Amrita School of Biotechnology, Amritapuri, Kollam, Kerala.

Dr. Nisheeth Agarwal delivered a talk at Kalinga Institute of Industrial Technology, Bhubaneswar.

Dr. Jayanta Bhattacharya delivered a talk on "HIV Vaccine R and D-Connecting the Dots" at the National AIDS Research Institute, Pune.

Dr. Jayanta Bhattacharya delivered a talk on "Genetic and neutralization properties of HIV-1 obtained from an Indian elite neutralizer" at the 5th Molecular Virology Meeting held at the THSTI, Faridabad.

Dr. Jayanta Bhattacharya delivered a talk on "Broadly neutralizing antibodies in HIV-1 therapy and vaccine development" at the 7th IMAPAC World Vaccine Summit, Pune.

Dr. Jayanta Bhattacharya delivered a talk on "Genetic and Neutralization Properties of HIV-1 obtained from an Indian elite neutralizer" at the Molecular Biophysics Unit, Indian Institute of Science, Bengaluru.

Dr. Suchitra Gopinath delivered a talk at the Annual Myogenesis Meeting held at Tuscany, Italy.

BOOKS AND BOOK CHAPTERS PUBLISHED

Suruchi Aggarwal, Manu Kandpal, Shailendra Asthana, Amit Kumar Yadav. Perturbed Signaling and Role of Post-translational Modifications in Cancer Drug Resistance. Drug Resistance in Bacteria, Fungi, Malaria, and Cancer (Springer Nature) 2017.

Manu Kandpal, Suruchi Aggarwal, Shilpa Jamwal, Amit Kumar Yadav. Emergence of Drug Resistance in *Mycobacterium* and other Bacterial Pathogens: The Post-translational Modification Perspective. Drug Resistance in Bacteria, Fungi, Malaria, and Cancer (Springer Nature) 2017.

Dhirendra Kumar, Amit Kumar Yadav, Debasis Dash. Choosing an Optimal Database for Protein Identification from Tandem Mass Spectrometry Data in Proteome Bioinformatics. Methods in Molecular Biology series, 1549 (SpringerNature) 2017.

eBook (2017). Filamentous Bacteriophage in Bio/Nano/Technology, Bacterial Pathogenesis and Ecology. Edited by: Jasna Rakonjac, Bhabatosh Das, Ratmir Derda. Publisher: Frontiers Media SA. ISBN: 9782889450954.

DATASETS SUBMITTED

1. Nutan Gupta, Shweta Duggal, Noor Jailkhani, Samrat Chatterjee, Kanury V.S. Rao, Ajay Kumar. Dataset to delineate changes in association between Akt1 and its interacting partners as a function of active state of Akt1 protein. Data in Brief 2017; 13:187-191.
2. Shweta Duggal, Noor Jailkhani, Mukul K Midha, Kanury V.S. Rao, Ajay Kumar. Defining the Akt1 interactome data and delineating alterations in its composition as a function of cell cycle progression. Data in Brief 2017; 11:252-257.
3. Ajay Kumar, Shilpa Jamwal, Mukul K Midha, Baseerat Hamza, Suruchi Aggarwal, Amit K Yadav, Kanury V.S. Rao. Dataset generated using hyperplexing and click chemistry to monitor temporal dynamics of newly synthesized macrophage secretome post-infection by mycobacterial strains. Data in Brief 2016; 9: 349–354.

FACULTY ENTREPRENEURSHIP

APTABHARAT INNOVATION PVT. LTD

Dr. Tarun Sharma founded a company called 'AptaBharat Innovation Pvt. Ltd.' that has received a Biotechnology Ignition Grant to develop aptamer-based rapid diagnostic test for tuberculous meningitis.

RESEARCH INFRASTRUCTURE

SMALL ANIMAL FACILITY

CLINICAL DEVELOPMENT SERVICES AGENCY

EXTERNAL RELATIONS AND INSTITUTIONAL DEVELOPMENT OFFICE

SMALL ANIMAL FACILITY

The purpose of most biological investigations, even of the most chemical and molecular kinds, is to comprehend the living system well enough to intervene usefully, in favor of human and animal health. Thus, all investigations ultimately lead to the whole animal system. In fact, the more sophisticated, detailed and specific is the knowledge generated at the biochemical and molecular level, the more it raises the likelihood of leading to useful work, that can only be done on whole animal systems. Rodent models are extremely important for such pre-clinical research. Animal usage in scientific research is common and a necessity in an organization involved in pre-clinical research. As of today, there is no dependable, alternate testing method available which can replace the use of animals in scientific research. Once *in-vitro* screening results are obtained for any new molecule, *in-vivo* screening needs to be conducted to check its efficacy and safety before it can be progressed further for drug development. New drug discovery specifically involves *in-vitro* testing using cell culture, tissues etc., *in-vivo* testing such as efficacy studies in mice/rats and other animal models, preclinical safety evaluation studies in rodent and non-rodent species, and clinical testing in humans. Therefore, a small animal research facility is an integral requirement for any research laboratory conducting research in biomedical and biological sciences. The small animal facility at THSTI is aimed at providing support to all biological departments at THSTI and RCB to perform their different animal studies through the routine maintenance and supply/issuance of required laboratory animals.

INFRASTRUCTURE DEVELOPMENT

In 2008, the Department of Biotechnology initiated the process of creating two major research institutes viz. THSTI and RCB in NCR Biotech Science Cluster (BSC) at Faridabad. It was envisaged that a large number of scientists recruited in these institutes would require animal facility for conducting their animal-related research. Therefore, it was proposed to build a state-of-the-art Small Animal Facility (SAF) at Bhankri village, Faridabad to facilitate animal experimentation for the scientific community of this cluster. The main objectives of the facility are (1) to breed and maintain genetically defined inbred strains of mice and rat, (2) to provide sufficient space and infrastructure to the investigators for conducting animal research work, and (3) create a specialized animal biosafety containment facility for undertaking animal research on infectious diseases.

ACHIEVEMENTS

After obtaining due clearances from various government regulatory authorities, the actual construction work of SAF was started in July 2011 which got completed in year 2013. Thereafter, installation of heating, ventilation and air conditioning (HVAC) system was initiated. After installation, the system was tested for about 9 months to validate its performance in summer, rainy and winter seasons.

LAYOUT OF THE FACILITY

The total built-up area of the facility is 4939.69 square meters that comprises of ground plus 3 floors. The ground floor mainly serves as a support area to all the remaining floors. It consists of changing rooms, quarantine room, stores, offices, laboratory area, wash/autoclave area, clean processing and storage areas. There are defined routes for material, animal and human movements to prevent cross-contamination.

The remaining three floors are dedicated for animal housing and animal-related work. All these three floors are identical in design and have a floor area of 1230.38 square meter each. These floors have a central clean corridor and two dirty corridors for the movement of personnel and related animal supplies. Each floor can house approximately 20,000 to 25,000 mice or 10,000 to 17,500 rats at a given point of time. There is a dedicated procedure room to perform animal-related procedures, equipped with necessary equipment like *in vivo* imaging system, anesthesia system, euthanasia system, needle cutters etc. Environmental conditions being maintained in animal quarters include temperature of 19 to 26°C, relative humidity 30 to 70%, 14 hours light and 10 hours dark cycle, minimum 12 to 15 air changes per hour are maintained in the animal rooms with the provision of centralized air conditioning

system. The light intensity and sound level in the animal rooms are maintained at less than 400 lux and less than 85 decibels, respectively.

STATUTORY CLEARANCE

The partner institutes,THSTI and RCB, constituted their Institutional Ethics Committee (Animal Research) and requested Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) for approval of animal experimentation in the small animal facility. The facility was inspected and approved by CPCSEA for in-house breeding and experimentation on small laboratory animals.

CURRENT STATUS

The Small Animal Facility started functioning from September 2016 with a few mice brought for "trial run": testing their survival and behavior in this newly established facility. After satisfactory observations, some breeding pairs of two genetically defined strains of mice viz. C57BL/6 and BALB/c were obtained and the breeding program was initiated. Currently, the facility houses approximately 2,500 mice and 70 rats in its breeding and experimental colonies. 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 chances of contamination. Sterilized feed, water and bedding material are being used to maintain the animals in a healthy state. Appropriate SOPs are followed for animal handling, supplies and animal-related procedures. The animal facility records and detailed census records of the animals housed in the facility are being maintained in accordance with the CPCSEA guidelines. The facility has a full time veterinarian to provide veterinary care to animals. Animal caretakers are deputed to perform routine work in the facility on weekends and holidays as well. A quality control (QC) lab is being set up and necessary equipments and furniture have been procured and installed. The laboratory would be functional shortly.

Since several projects undertaken by the investigators of Biotech science cluster deal with research on infectious diseases like TB, HIV/AIDS, JE etc., a specialized animal biosafety containment facility is coming up as an integral part of this facility. This facility is nearing completion and will become operational in due course of time.

Future plans

Currently, only one floor (3rd floor) out of all three floors is being used for animal housing. Since the facility is now fully validated and is running smoothly, the investigators are in the process of procuring more genetically defined strains of mice, including immunocompromised ones. Necessary preparations will be made to house and expand the mice colonies as per research needs.

CLINICAL DEVELOPMENT SERVICES AGENCY (CDSA)

INTRODUCTION

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 eco-system for training and learning and work with public sector institutions, and small and medium enterprises (SME) to translate innovative technologies into medical products for public good.

Focus Areas

The main objectives of CDSA have been:

- As a training academy, CDSA aims to build capacity and capability in the area of clinical development and translational research. They conduct training programs for young clinical researchers, ethics committee members and other personnel in becoming an efficient clinical research professional.
- Monitor public health studies for compliance to Schedule Y regulations, CDSCO-GCP guidelines, Study Protocol and other requirements.
- Support Investigators and SMEs by providing Clinical Study Support Services like regulatory consultation, project management, medical monitoring, audit, data management and biostatistics.
- CDSA with 5 Centers of Excellence (CoEs) has formed a collegium of Centers of Clinical Research Excellence for collaboration in education, training and capacity building and collaboration in research, innovation, and clinical development support services. The institutions are: KEM Hospital, Pune; Society of Applied Sciences (SAS), New Delhi; Center for Chronic Disease Control (CCDC), New Delhi; JSS University, Mysore and CMC Vellore.

Clinical Research Focus

- Maternal & child health (pre term birth, respiratory distress syndrome, neonatal sepsis).
- Infectious and communicable diseases (tuberculosis and polio).
- Psychiatric illnesses.

Training

The training department works on a national mandate to enhance the capacity and capability of clinical development and translational research in India. It works coherently with the Indian drug regulators, Central Drugs Standard (CDSCO) and Indian Council of Medical Research (ICMR) in training biomedical researchers, clinicians, scientists, ethics committee members in the area of Good Clinical Practice (GCP), Good Clinical Laboratory Practice (GCLP), Good Laboratory Practice (GLP), and ethics in clinical research among various areas. Along with Biotechnology Industry Research Assistance Council (BIRAC), it reaches out to various industries SMEs, start-ups, research institutions, organisations in clarifying several doubts on regulatory issues with a strong platform called 'Meet the Regulators'. These are in various areas like new drugs, phytopharmaceuticals, medical devices, diagnostics, biologicals etc.

Clinical Development Services Agency team

Research Methodology, PGIMER, Chandigarh; October 19-20, 2016

Current Regulations on Medical Devices and in vitro Diagnostic Kits Venture Centre, Pune; September 29, 2016

Good Clinical Practice (GCP) Assam Medical College and Hospital, Dibrugarh; September 14-15, 2016

TRAININGS 2016-2017

Table 1: Trainings at CDSA: A Snapshot

	2009-12 (3 years)	2012-13	2013-14	2014-15	2015-16	2016-17	Total
Trainings	3	10	14	17	21	29	**94**
Faculty	11	112	146	175	233	236	**913**
Participants	41	436	894	1241	1906	1510	**6028**
Institutions Represented	10	117	222	428	536	391	**1704**
Cities	2	5	10	10	9	15	**36**

Table 2: Learning Opportunities created by CDSA (2016-17)

S. No.	Date	Program Name	Funding	City	No. of Faculty	No. of Participants	No. of Attendee Institutions
1	Mar 31, Jun 04, 2016	Manipal University - CDSA Bioethics Certificate Course	Collaborative Training Program with Manipal University	Online Program with Contact sessions at Manipal	20	49	17
2	Apr 27, 2016	Current Ethical & Regulatory Requirements for Clinical Trials (An Awareness Program)	TMC, Kolkata	Kolkata	5	22	2
3	Apr 28, 2016	Good Clinical Practice (An Awareness Program)	TMC, Kolkata	Kolkata	7	55	2

S. No.	Date	Program Name	Funding	City	No. of Faculty	No. of Participants	No. of Attendee Institutions
4	May 7-8, 2016	Research Methodology	CDSA	ANIIMS, Port Blair, A&N Islands	3	67	8
5	May 09, 2016	Good Clinical Practice	CDSA	ANIIMS, Port Blair, A&N Islands	6	60	9
6	May 10, 2016	Current Ethical & Regulatory Requirements for Clinical Trial/Research (An Awareness Program)	CDSA	ANIIMS, Port Blair, A&N Islands	6	70	9
7	May 17-19, 2016	National Workshop on Laboratory Quality Management System in Biotherapeutics	NIB, Noida	Noida	22	29	19
8	29-May-16	Requirements for Members of Ethics Committee	CHRD-SAS	New Delhi	3	14	1
9	26-Jul-16	Good Clinical Practice	CDSA & THSTI	Faridabad	9	76	14
10	Aug 10-11, 2016	Good Clinical Practice (GCP) & Good Participatory Practice (GPP)	IAVI	KIMS, Karad Maharashtra	9	30	2
11	29 Aug-02 Sep, 2016	Research Methodology	CDSA	ICGEB, New Delhi	12	34	22
12	14-15 Sep, 2016	Awareness Program on Good Clinical Practice (GCP) Requirements for Potential Clinical Research Professionals	DBT NER Grant	AMCH, Dibrugarh	8	68	2
13	19-20 Sep, 2016	Basics of Statistics and Fundamentals of SAS® in Clinical Research	AIIMS	AIIMS, New Delhi	1	28	1
14	27 Sep, 2016	Good Clinical Practice (Awareness Program)	IISER, Pune CSIR- NCL Venture Center Pune Prashanti Cancer Care Mission, Pune BIRAC	IISER, Pune	10	141	57
15	28 Sep, 2016	Current Regulatory Requirements for the Members of Institutional Ethics Committee Program (Awareness Program)	IISER, Pune CSIR- NCL Venture Center Pune Prashanti Cancer Care Mission, Pune BIRAC	IISER, Pune	6	137	43

S. No.	Date	Program Name	Funding	City	No. of Faculty	No. of Participants	No. of Attendee Institutions
16	29 Sep, 2016	Current Regulation on Medical Devices and in vi-tro Diagnostics (IVD) Kits	IISER, Pune CSIR- NCL Venture Center Pune Prashanti Cancer Care Mission, Pune BIRAC	IISER, Pune	8	87	36
17	19-20 Oct 2016	Research Methodology		PGIMER, Chandigarh	10	60	5
18	19-20 Oct 2016	Good Clinical Practice (Ba-sic Program)		PGIMER, Chandigarh	10	62	15
19	22-25 Nov 2016	Training Course on Basics of Good Laboratory Practice (GLP)	DBT-NER/ HRD/22/2015	Assam Medical College & Hospital, Dibrugarh	4	36	5
20	05-Dec-16	GCLP	1	CDSA, THSTI, Faridabad	1	27	2
21	06-Dec-16	GCP	CDSA	Delhi	2	23	1
22	20-22 Dec 2016	GCP & GCLP	CISMAC, Norway	Kathmandu, Nepal	6	29	9
23	04-05 Jan 2017	GCLP for RePORT	DBT	Chennai	4	38	6
24	24-Jan-17	AIIMS CDSA EC Training Workshop for IIT Delhi	IITD, AIIMS, CDSA	AIIMS, New Delhi	7	34	2
25	25-Jan-17	GCP	GMC Mewat	Mewat, Haryana	8	44	1
26	08-10 Jan 2017	National Workshop on Laboratory Quality Man-agement System in Diag-nostics	NIB, Noida	Noida	22	38	29
27	16-17 Feb 2017	Critical thinking & GCP	JSS Mysore	Mysore	10	40	3
28	15-Mar-17	BIRAC CDSA Regulatory Workshop in Biopharma	BIRAC	Venture Centre, Pune	8	38	22
29	30-Mar-17	BIRAC CDSA Regulatory Workshop in Medical Devices & IVD Kits	BIRAC	C-CAMP, Bengaluru	9	74	47
Total				**15**	**236**	**1510**	**391**

OUTREACH

We have mapped all the cities from where our participants come and a database of 5300+ professionals has been created at CDSA in order to reach out to all for any new events or upcoming training programs.

Figure 1: Cities where CDSA Programs had were held and to be held

Figure 2: Cities from where participants have come to attend CDSA Programs

CLINICAL STUDY SUPPORT SERVICES

CDSA collaborates with Government Agencies and Institutions, Academic Institutions, and Small and Medium Enterprises (SMEs) in coordinating and/or implementing their clinical studies. A broad range of services offered by CDSA include: regulatory consultation, project management, clinical monitoring, medical writing, safety monitoring, audit, data management and biostatistics.

Department of Clinical Portfolio Management

The department (CPM) has been established to undertake and implement cost effective clinical research services in product development for government, semi-government, government-funded academic and non-academic institutions, non-profit, and small and medium sized enterprises. The main objective of Clinical Portfolio Management department is to direct, supervise and coordinate a network of clinical studies in India.

Through active participation for policy and advocacy we engage in health programs to improve or protect health policies. For example, CDSA as per the directions from inter-ministerial committee for severe acute malnutrition (SAM) alliance program has convened national consultative meeting for projects implemented and completed under SAM program.

Based on the experience gained while working as independent monitoring agency we plan to establish operational guidelines, educational module and study management tools customized to the need of the research in public health domain. These will be a value addition for the public health research for benchmarking the quality standards and CDSA will be extending advisory support for these as requested by the stakeholders.

Clinical Data Management (CDM)

CDSA provides specialized Clinical Data Management services to, government and non-governmental innovators and 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.

Biostatistics

This division aims to provide bio-statistical support to various clinical projects. CDSA has Statistical Analysis System® (SAS) Version 9.4 as statistical analysis tool software and program required for effective analysis of the data.

Also, a dedicated IT-infrastructure (data servers, systems, access-controls, etc.) has been deployed to run the activities as per the standards of data security and safety. Currently it is helping ongoing projects for their statistical requirements.

Regulatory Affairs

CDSA provides regulatory advisory services for development and registration of new drugs, medical devices, diagnostics, phytopharmaceuticals and biopharmaceuticals/ biosimilar including vaccines to small and medium sized enterprises and public funded pre-clinical and clinical stage research projects.

ONGOING CLINICAL PROJECTS/ PROGRAMS

CDSA is providing clinical study support services to the following projects and programs listed in the table below.

Project Title (Funding Agency)	Principal Investigator/ Sites	CDSA Role
Inter-Institutional Program for Maternal, Neonatal and Infant Sciences: A translational approach to studying preterm birth (DBT)	Multi-Institutional Program – THSTI, RCB, NII, NIBMG, AIIMS & SJH (Site: General Hospital Gurugram)	• Study Start Up Support • Clinical monitoring • Quality Management • Lab Monitoring
A Phase IV, interventional, open label, multicenter, single arm clinical trial to assess the Safety, Tolerability & Immunogenicity of Bivalent Oral Polio Vaccine (bOPV) in healthy Indian infants (BIBCOL/ DBT)	8 sites across India	• Medical Writing • Regulatory advisory • Project management • Clinical monitoring • Data management • Statistical services
Evaluating the Efficacy and Safety of Indigenous Goat Lung Surfactant Extract (GLSE) in a pilot sample of preterm infants with Respiratory Distress Syndrome (Wellcome Trust)	Dr. Ramesh Agarwal, AIIMS (12 sites across India)	• Project Management • Clinical Monitoring • Data Management • Medical Monitoring
Inhibition of host-induced my co-bacterial efflux pumps as a novel strategy to counter drug tolerance and virulence of pulmonary tuberculosis (DBT)	Dr. Padma (NIRT) Clinical site: NITRD, Delhi	• Regulatory Advisory • Medical writing • Clinical Monitoring • Medical monitoring • Data management
Concurrent Monitoring of Laboratory component of Comprehensive National Nutrition Survey (CNNS) (MoHFW / UNICEF)	UNICEF, Delhi	• Field monitoring • Clinical laboratory monitoring
Zinc as an adjunct for the treatment of clinical severe infection in infants younger than 2 months (CISMAC, Norway)	Dr.Nitya Wadhwa, PBC, THSTI and Dr.Sudha Basnet, IOM Nepal	• Study start-up support • Quality Management • Clinical monitoring

Project Title (Funding Agency)	Principal Investigator/ Sites	CDSA Role
Investigation Of Rheumatic Atrial Fibrillation Using Vit K Antagonists, Rivaroxaban or Aspirin (PHRI)	Dr. G. Karthikeyan, AIIMS (15 sites across India)	• Study start-up support • Quality Management
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 • Quality Management • Clinical monitoring • Medical writing • Medical monitoring
Iron Supplement in Infant Phase 2 Clinical Trial (NIH)	Dr.Sanjiv Amin, Rochester University	• Co-applicant/Co-PI • Clinical operations • Medical monitoring

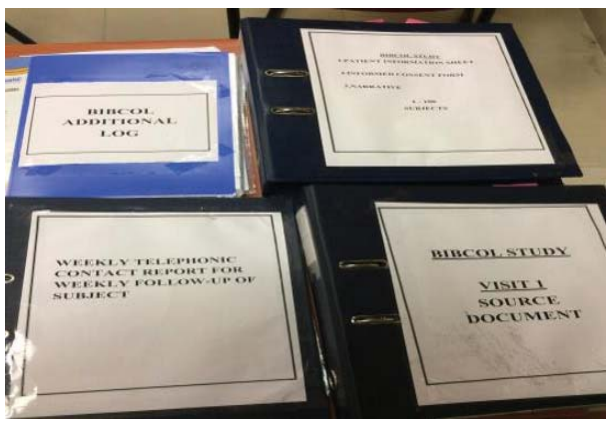
TRAININGS AND MEETINGS

Medical Department

CNNS Project Meeting
CDSA, THSTI, Faridabad; February 01, 2017

DSMB Meeting
AIIMS, New Delhi; December 08-09, 2016

Data Management



Subject data maintained at site

LIST OF COLLABORATORS

- UNICEF
- World Health Organization
- Wellcome Trust
- Bill and Melinda Gates Foundation
- National Institute of Health, USA
- Indian Council of Medical Research
- Centre for Intervention Science in Maternal and Child Health
- Population Health Research Institute, Canada
- All India Institute of Medical Sciences, New Delhi
- National Institute for Research in Tuberculosis
- Safdarjung Hospital, New Delhi
- Biotechnology Industry Research Assistance Council

EXTERNAL RELATIONS AND INSTITUTIONAL DEVELOPMENT OFFICE (ERID)

External Relations and Institutional Development (ERID) office continues its functions in the areas of grants support, regulatory compliance for ethics committees, communications and public relations. Ms. Vidhya Krishnamoorthy is responsible for the grants support and ethics secretariat functions of the ERID. At the time of this reporting, ERID welcomed Dr. Divya Khatter who will be in charge of internal communications among members of the THSTI research community as well as external outreach programs.

REGULATORY COMPLIANCES

THSTI has renewed the registration of its Institutional Ethics Committee (Human Research) with the licensing authority. The re-registration number **ECR/167/Inst/HR/2013/RR-16** is issued as per the provisions of Rule 122DD of the Drugs and Cosmetics Rule, 1945.

The small animal facility has been approved for breeding by CPCSEA with the registration number **1685/GO/REBi/S/2013/CPCSEA.** The registration and renewal is valid until10.03.2021.

Ms. Vidhya Krishnamoorthy Dr. Divya Khatter

ACADEMIA

Ph.D. PROGRAM

THSTI is a recognized R&D institute of the Jawaharlal Nehru University, New Delhi to offer doctoral programs in biomedical and clinical research. The broad domains of ongoing research at THSTI are:

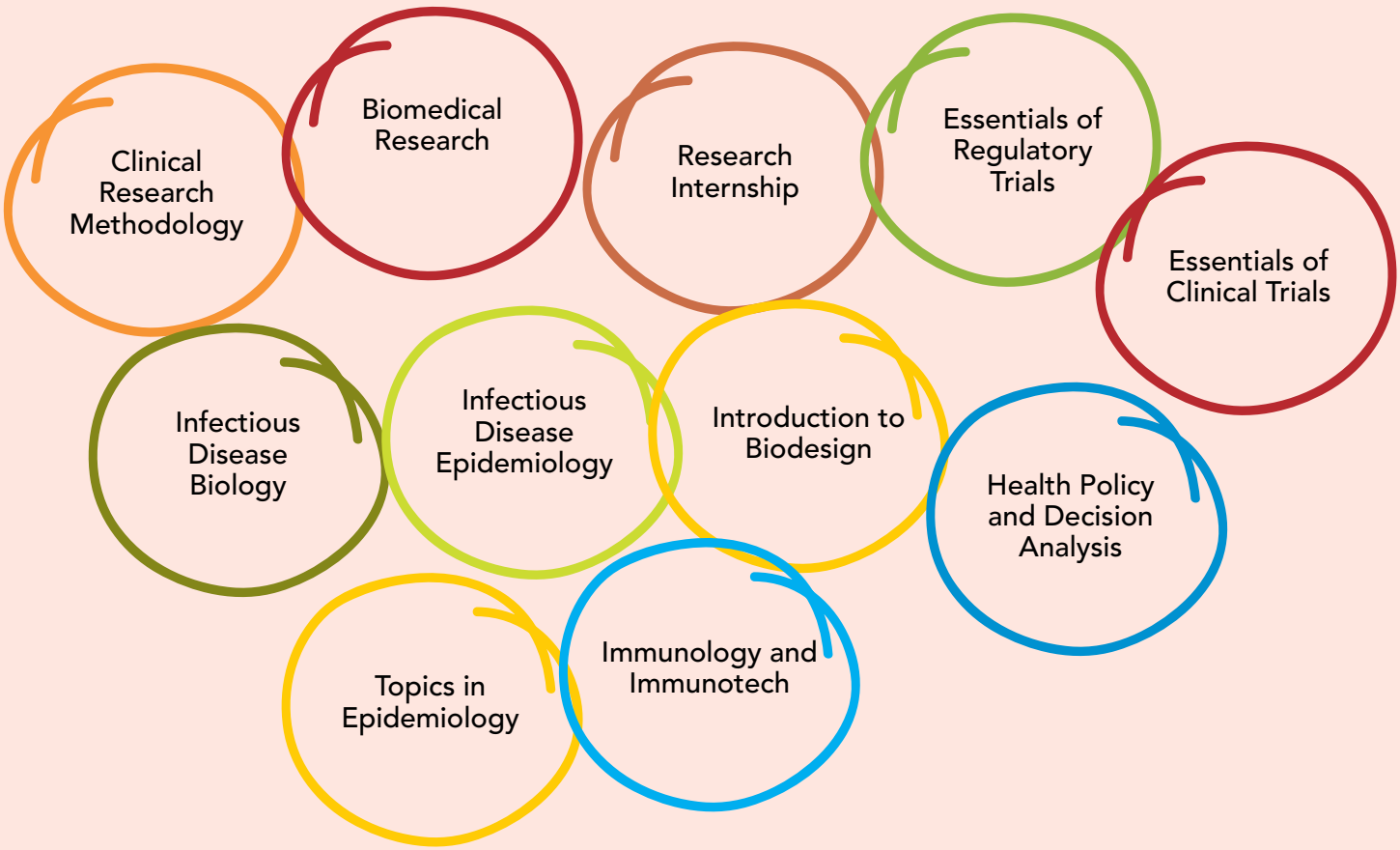
- Biology of infectious diseases such as dengue, Japanese encephalitis, Hepatitis E and tuberculosis, vaccine and anti-viral development
- Physiology of nutrition and developing immune system, immune responses in pregnancy and childhood
- Clinical research and epidemiology, with a focus on maternal and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

POST-DOCTORAL PROGRAM

THSTI offers post-doctoral training to young researchers through specific options for post-doctoral program at various niche centers of THSTI. The various post-doctoral options are:

- 'Vaccine Research Innovation (VRI) Award Scheme' at the Vaccine and Infectious Disease Research Centre
- 'Innovation Award' scheme in Biodesign at the Centre for Biodesign and Diagnostics
- 'Microbiome Innovation Award' scheme at the Centre for Human Microbial Ecology

COURSES OFFERED



- Indo-Finnish Post-doctoral fellowship in Diagnostics

EARLY CAREER MEDICAL RESEARCH AWARD (ECMRA)

The goal of ECMRA is to strengthen and expand the pool of physician-scientists in the country. THSTI has created this award to nurture outstanding young physicians who have a strong aptitude towards research and a desire to grow into independent principal investigators. The aim is to provide rigorous, high quality training for doing hypothesis-driven research to the ECMR awardees. The awardees are expected to generate new hypothesis-driven innovative research ideas and learn to drive a research process. At present, the award is implemented in the maternal and child health area.

Ph.D. STUDENTS THAT JOINED IN 2016-2017

Aleksha Panwar
Deepa Nair
Farha Mehdi
Neera Parmar
Neha Kaushik
Rajdeep Dalal
Ravi Prakash Shaliwal
Ritu Arora
Riya Sarkar
Sarla Yadav
Shiv Kumar
Tannu Priya Gosain

ACHIEVEMENTS

Poster Presentation Awards

Suruchi Aggarwal, 7th Annual THSTI Foundation Day, THSTI

Parmeshwar Katare, 14th Annual Meeting of International Society of Heart Research, New Delhi

Sakshi Talwar, 7th Annual THSTI Foundation Day, THSTI

Mitul Srivastava, International Conference on Drug Discovery, New Delhi

Oral Presentation Awards

Bharti Kumari, 7th Annual THSTI Foundation Day, THSTI

Mrityunjay Singh, World Congress on Drug Discovery and Development, Bengaluru

International Travel Grants

Bharti Kumari received grants from DBT-CTEP, DST-SERB and a bursary from G.P. Talwar Immunology Foundation to present her work at a Keystone Symposia, Austin U.S.A

Mitul Srivastava received a grant to present his work at the Institute of Molecular Biology, Mainz, Germany

ADMINISTRATION

THSTI ADMINISTRATION

The THSTI administration aims to provide unstinted support for the smooth functioning of the institute. The personnel in the administration comply with the Government of India Rules and related financial norms in their functioning. The THSTI Administration comprises of several functional sections, namely, General administration, Human Resource (HR) Management and Finance and Accounts, Stores and Purchase, Information Technology (IT), Engineering and Estate Management and Intellectual Property Management. Information on some of the important activities performed by various sections under THSTI administration is provided below.

THSTI GOVERNING BODY / THSTI FINANCE COMMITTEE / THSTI SOCIETY MEETINGS

On the governance front, THSTI conducted two meetings of the Finance Committee and Governing Body and one meeting of the Society and 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, Internal Complaints Committee dealing with sexual harassment complaints. The constitution of these committees are given in the later part of this report.

JOINT RCB-THSTI COMMITTEE

To facilitate making the campus operational, the existing two partners of the NCR Biotech Science Cluster, namely, THSTI and RCB jointly constituted a Committee of Operational Protocols to make recommendations regarding common requirements in the new campus. The continuous efforts of this committee resulted in finalizing good contractors for electromechanical services, house-keeping services, security services, horticultural services, catering services, environmental management services, transport services and signage.

RIGHT TO INFORMATION

On the communication front, it has been the endeavor of THSTI to maintain high degree of transparency with regard to the entire official processes through the website especially about recruitments and tenders. During the period 2016-17, THSTI received 29 applications under the RTI act. Among these applications, 14 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 37 recruitment notices for filling 303 positions. The rolling advertisement in the case of JRF/SRF/RA positions, which was introduced during the year 2013-14, to cater to the frequent requirements of the projects, was continued with new vacancies being advertised and filled up successfully every month. For all positions, the selection process included a skill test followed by the interview. As per DoPT guidelines in modified FCS, three faculty members were promoted from assistant professors to associate professors during this financial year.

FINANCE AND ACCOUNTS

Finance and Accounts section of the institute monitors and controls the expenditure against the above funds and also attends to the day-to-day financial matters, payments to contractors/ suppliers, payment of salaries to staff, payment of personal claims in respect of the employees of the institute 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, perishable and non-perishable chemicals and reagents, other consumables and services from overseas and local markets. THSTI has invested Rs. 18,81.66 Lakhs on consumables and Rs. 21,17.89 Lakhs on equipment and furniture during this financial year.

INFORMATION TECHNOLOGY

THSTI IT section takes care of the hardware, networking, website and software requirements of the institute. To enable smooth functioning of the section, IT has a dedicated IT policy and SOP concerning all major IT functions. During this financial year, it helped in the upgradation of M/s Reliance lease line to 34Mbps from the backup internet line. A dedicated 10Mbps line has been fixed for video-conferencing. The fiber connectivity has been successfully extended to the student hostels and MAC binding has been enabled for securing internet connections. IT has also installed CCTV cameras and access controls to monitor any unauthorized activities in the building.

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 understands the importance of intellectual property and it screens outcomes from projects on routine basis to identify the intellectual property vested in it. During this financial year, THSTI filed eleven patent applications including six in India, one in South Africa, one at WIPO and three in US. Seven of eleven patent applications filed are outcomes of collaborative research. Intellectual Property assets owned by THSTI are regularly advertised on its website to seek industry partners having capacity to commercialize the laboratory scale technologies.

EVENTS AT THSTI

THSTI observed all the important occasions as directed by the Govt. of India alongwith the Foundation day of THSTI. A brief on these activities is provided below.

Independence Day

THSTI celebrated 70th Independence Day with lots of activities like tree plantation, dance and drama, rangoli competition, poem recitation competition, fancy dress competition etc. THSTI faculty participated warmly in the events with their family members.

Hindi Saptah Samaroh

Hindi Week was celebrated from 9th September 2016 to 15th September 2016. As part of the celebrations, various competitions were organized in Hindi such as poem recital, essay competition, extempore speech and quiz. Dr. Rajendra Gautam, Professor, Delhi University was the chief guest for the valedictory session.

Vigilance Awareness Week

THSTI observed vigilance awareness week from 31st October 2016 to 5th November 2016. The week commenced with a pledge administered by Dr. G. R. Medigeshi, Chief Vigilance Officer. During the week, various competitions were organized on the topic of anti-corruption drive.

Foundation Day

The occasion was celebrated with enthusiasm on 15th July 2016 by the THSTI community along with officials from the Department of Biotechnology, collaborators and well-wishers.

Sports Competitions and Family Get-together Event

THSTI organized various sports competitions, fun activities and games on 4th March 2016, with enthusiastic participation from the THSTI community.

BALANCE SHEET

Amount (In Rs.)

LIABILITIES	Schedule	31.03.2017	31.03.2016
Corpus /Capital Fund	1	1,550,653,102	1,402,924,129
Reserves and Surplus	2	125,316,862	77,766,161
Earmarked/Endowment Funds	3	-	-
Secured Loans and Borrowings	4	-	-
Unsecured Loans and Borrowings	5	-	-
Deferred Credit Liabilities	6	-	-
Current Liabilities and Provisions	7	272,880,968	235,969,984
TOTAL		**1,948,850,932**	**1,716,660,274**
ASSETS			
Fixed Assets	8	1,534,101,018	1,311,202,875
Investment From Earmarked/Endowment Funds	9	-	-
Investment-Others	10	-	-
Current Assets, Loans, Advances etc.	11	414,749,914	405,457,399
Miscellaneous Expenditure (to the extent not written off or adjusted)		-	-
TOTAL		**1,948,850,932**	**1,716,660,274**
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

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

Sd/-
(M.V. SANTO)
Head Administration

Sd/-
(Dr. GAGANDEEP KANG)
Executive Director

Sd/-
(M.L. AGRAWAL)
Partner
M No.086469

Place: Faridabad
Date: 01/09/2017

INCOME AND EXPENDITURE

		Amount (in Rs.)	
INCOME	**Schedule**	**31.03.2017**	**31.03.2016**
Income from Sales/Services	12	3,391,229	128,656
Grants/Subsides	13	220,000,000	169,967,000
Fees/Subscriptions	14	69,500	241,768
Income from Investments	15	-	-
Income from Royalty, Publication etc.	16	-	-
Interest Earned	17	5,914,358	10,881,328
Other Income	18	2,943,876	2,694,875
Increase/(Decrease) in stock of Finished goods and works in progress	19	-	-
Deferred Income-Fixed Assets		87,383,256	68,028,866
TOTAL (A)		**319,702,219**	**251,942,493**
EXPENDITURE			
Establishment Expenses	20	58,675,196	77,617,344
Other Administrative Expenses etc.	21	126,093,066	126,444,445
Expenditure on Grants, Subsidies etc.	22	-	-
Interest	23	-	-
Depreciation (Net Total at the year-end-corresponding to Schedule 8)		87,383,256	68,028,866
Prior period Adjustment A/c (ANN-A)		-	-
TOTAL(B)		**272,151,518**	**272,090,655**
Balance being excess of Income Over Expenditure (A-B)		**47,550,701**	**(20,148,162)**
Transfer to special Reserve (Specify each)		-	-
Transfer to/from General Reserve		47,550,701	(20,148,162)
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

Sd/-
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(M.L. AGRAWAL)
Partner
M No.086469

Place: Faridabad
Date: 01/09/2017

CONSOLIDATED RECEIPTS AND PAYMENTS

	Amount (in Rs.)	
RECEIPTS	**31.03.2017**	**31.03.2016**
OPENING BALANCE		
Fellowship	(165,480)	235,931
Projects	334,640,661	211,862,939
THSTI	33,069,216	26,840,781
Grant-in Aid Received		
Fellowship	21,013,738	31,179,830
Projects	545,702,086	582,817,222
THSTI	300,000,000	289,967,000
Other Receipts -THSTI		
Application Fees	69,500	61,500
Earnest Money Deposit	7,960,012	482,466
Guest House Receipt	-	75,500
Income from Sales and Services	3,229,728	-
Income Tax Refund Received	762,577	-
Interest Received from Banks	5,864,795	10,881,328
Interest Received from Income Tax	49,563	-
Miscellaneous Receipts	-	750
Other Receipts	2,781,090	2,124,504
Overhead THSTI	-	85,000
Penalty Receipt	-	66,904
Receipt from short term training program	-	180,268
Recruitment Fee	35,100	59,400
Refund of Security Deposit	-	250,000
Rental/License fees/Usage charges	-	116,667
RTI Receipt	186	150
Sales of Scrap	161,500	128,656
Security / Hostel Deposit Received	683,526	1,386,121
Tender Fee	127,500	166,000
Accrued Interest Received	4,432,367	435,443
Decrease in advances	28,695,798	14,133,655
Govt. Dues Payable	557,722	3,318,797
Other Liabilities/Payable	7,091,381	4,652,051
TOTAL	**1,296,762,566**	**1,181,508,863**

	Amount (in Rs.)	
PAYMENTS **Particulars**	**31.03.2017**	**31.03.2016**
Fellowship	**34,347,071**	**31,581,241**
Projects	**588,535,737**	**460,039,500**
THSTI		
Work-in-Process-Building	40,000,000	80,000,000
Fixed Assets	28,730,390	24,573,948
Administrative Expenses	82,832,841	82,475,762
Manpower	54,459,034	59,160,860
Consumables	37,236,911	46,383,355
Advances, Receivables and Liabilities	34,133,521	29,749,800
Closing Cash & Bank Balance		
Fellowship	**(13,498,813)**	**(165,480)**
Projects	**291,807,008**	**334,640,661**
THSTI	**118,178,864**	**33,069,216**
TOTAL	**1,296,762,566**	**1,181,508,863**

As per our separate Report of even date attached
For Kumar Vijay Gupta & Co
Chartered Accountants

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

Sd/-
(M.V. SANTO)
Head Administration

Sd/-
(Dr. GAGANDEEP KANG)
Executive Director

Sd/-
(M.L. AGRAWAL)
Partner
M No.086469

Place: Faridabad
Date: 01/09/2017

AUDITORS' 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 2017 and the relative Income and Expenditure Account and Receipt and Payment Account for the period ended on that date, annexed thereto. 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 and Expenditure Account and Receipt and 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 and Expenditure account and Receipt and Payment Account dealt 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 31st March 2017; and

      ii. In the case of Receipt and 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

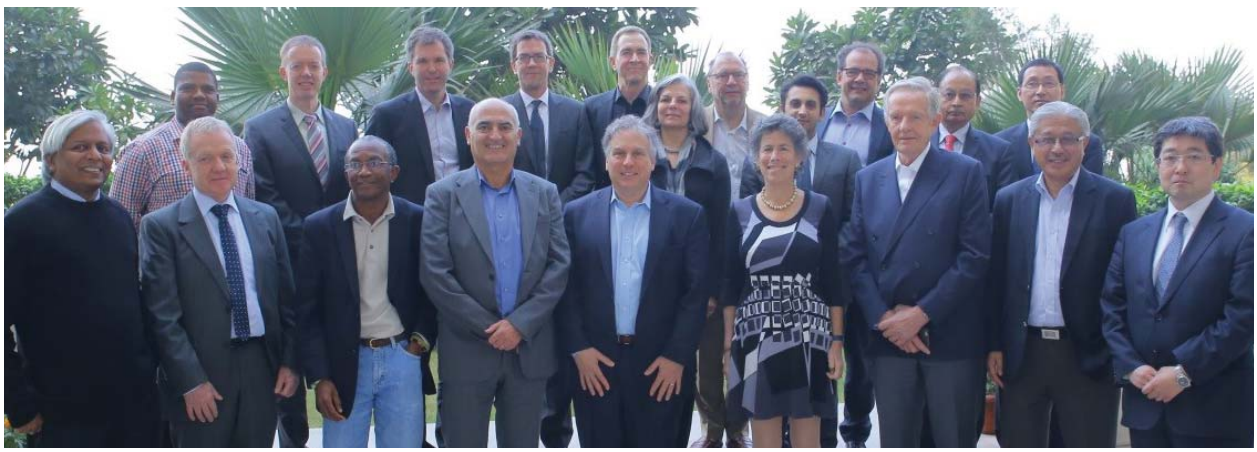
Sd/-
M.L. Agrawal
(Partner)
M.No. 086469

Place: Faridabad
Date: 01/09/2017

SCIENTIFIC EVENTS AT THSTI

BOARD MEETING OF GLOBAL COALITION FOR EPIDEMIC PREPAREDNESS INNOVATIONS (CEPI)

The CEPI focuses on the development of new vaccines for known and unknown pathogens and being a founder of the coalition, Department of Biotechnology, was hosted the second meeting of CEPI. THSTI organized a scientific meeting on the "Role of the India Vaccine Industry in Global Public Health" on 15th December, 2016 followed by the Second Meeting of the CEPI on 16th December, 2016. Hon'ble Cabinet Minister for Science and Technology and Earth Sciences, Government of India, Dr. Harsh Vardhan was the Chief Guest at the event. The event was attended by Dr. VijayRaghavan, Secretary, Department of Biotechnology, and Dr. Jeremy Farrar, Director, Wellcome Trust along with more than 30 participants from India and abroad.



5th MOLECULAR VIROLOGY MEETING

The 5th Molecular Virology meeting was held at THSTI on 11th and 12th February 2017. The meeting covered both basic and applied research and provided a platform to discuss latest developments in areas of host-virus interactions, immune responses and vaccine development, molecular biology, evolution and epidemiology of viruses and emerging therapeutics and diagnostics. The meeting brought together leading researchers working on different aspects of virology and included poster presentations by the students from various institutes.

AWARD OF Ph.D. DEGREES

Mr. Manish Sharma and Ms. Minu Nain, research scholars of Molecular Virology Lab (VIDRC), successfully defended their Ph.D. thesis and were awarded their degrees from Jamia Hamdard. They hold the proud distinction of being the first two Ph.D. scholars from THSTI.

SCIENCE SETU

As a part of the Science SETU program, THSTI faculty visited Acharya Narendra Dev College, New Delhi on 14th and 15th Feb 2017. The program had scientific lectures and interactive sessions. Further, they visited Maitreyi College, New Delhi on 18th October 2016 and on 24th and 25th January 2017 for interaction with students and teachers. Presentations and discussions covered topics from systems biology, conceptual understanding of the language of biology, vaccines and drugs for tuberculosis, biology of viruses, host-virus interactions and current and future prospects of virology.

GRAND CHALLENGES INDIA 2017 DELEGATE VISIT

A group of project investigators and experts in science, policy, academia, and social entrepreneurs visited Civil Hospital Gurugram (CHG), the primary clinical research site of three crucial grants funded to the Pediatric Biology Centre of THSTI under the All Children Thriving (ACT) initiative, on 25th March 2017. The visit was planned to observe the research activities at the site and to exchange views on similar programs across the world.

FINNISH AMBASSADOR VISITS THSTI

THSTI is one of the locations for the Indo-Finnish Diagnostic Research Centre (IFDRC) which is a collaboration between University of Turku, Finland and THSTI. It was set up to complement and enhance the research capabilities of its Indian and Finnish scientific networks from academia and industry in the area of diagnostics. Her Excellency Ms. Nina Vaskunlahti, Ambassador of Finland visited THSTI on 10th January, 2017 showing her interest in the projects going on at THSTI under this Indo-Finnish Co-operation.

US DELEGATES VISIT THSTI

Speakers from the 'International seminar on technology transfer as a tool to optimize IP and innovation' organized by National Development and Research Centre on 9th January 2017 visited THSTI on 10th January 2017 to explore collaboration opportunities.

THSTI COMMITTEES

S. No.	Committee	Members
1.	**THSTI Management Committee**	a. Prof. Gagandeep Kang b. Dr. Shinjini Bhatnagar c. Dr. Kanury V.S. Rao d. Dr. T. Ramamurthy **Chairperson-Executive Director**
2.	**Maintenance Committee**	a. Dr. Ramandeep Singh b. Dr. Bhabatosh Das c. Dr. U.C. Mouli d. Dr. Niraj Kumar e. Dr. Shailendra Asthana f. Mr. G.R. Agarwal g. Mr. Vishal Gupta h. Mr. Narender Sharma **Chairperson–Dr. Ramandeep Singh/Dr. Bhabatosh Das**
3.	**Purchase Committee**	a. Dr. Nisheeth Agarwal b. Dr. Sanjay Banerjee c. Dr. Amit Awasthi d. Dr. Shailaja Sopory e. Dr. Jonathan Pillai f. Mr. C.B. Yadav g. Mr. Mohd. Shahid **Chairperson-Dr. Nisheeth Agarwal/Dr. Sanjay Banerjee**
4.	**IT and Communication Committee**	a. Dr. Guruprasad Medigeshi b. Mr. M.V. Santo c. Dr. Samrat Chatterjee d. Dr. Amit Yadav e. Mr. G.R. Agarwal f. Ms. Taruna **Chairperson–Dr. Guruprasad Medigeshi/Mr. M.V. Santo**
5.	**Institutional Ethics Committee–Human Research**	a. Prof. Satinder Aneja b. Prof. Subir Kumar Maulik c. Dr. Ujjayini Ray d. Mr. Munawwar Naseem e. Ms. Jasmine Singh f. Ms. Vidhya Krishnamoorthy g. Mr. D Raghunandan h. Dr. Ashutosh Tiwari i. Dr. Suvasini Sharma j. Dr. Sarmila Mazumder k. Dr. Tarun Batra l. Prof. Rajiv Janardhanan m. Dr. Sivaram Mylavarapu **Co-ordinator-Ms. Vidhya Krishnamoorthy**

S. No.	Committee	Members
6.	**Institutional ethics committee–Animal Research**	a. Dr. Sudhanshu Vrati b. Shri M.T. Sambandam c. Dr. Harbans Lal d. Shri Ranvir Parashar e. Dr. Krishnamohan Atmakuri f. Dr. Niraj Kumar g. Dr. Amit Pandey h. Dr. Amit Awasthi
7.	**Biosafety Committee**	a. Dr. Sudhanshu Vrati b. Dr. Nisheeth Agarwal c. Dr. Susmita Chaudhuri d. Dr. Shailaja Sopory e. Dr. Vinay Kumar Nandicoori f. Dr. Uma Chandra Mouli Natchu g. Dr. Anirban Basu **Chairperson–Dr. Sudhanshu Vrati**
8.	**Institutional Committee for Stem Cell Research**	a. Prof. Narinder K. Mehra b. Prof. Nalin Mehta c. Dr. Sujata Mohanty d. Dr. Ujjayini Ray e. Mr. Munawwar Naseem f. Dr. Shailaja Sopory g. Ms. Vidhya Krishnamoorthy **Coordinator–Ms. Vidhya Krishnamoorthy**
9.	**Academic Committee**	a. Dr. Guruprasad R. Medigeshi b. Dr. T. Ramamurthy c. Dr. Krishnamohan Atmakuri d. Dr. Susmita Chaudhuri e. Dr. Nitya Wadhwa f. Dr. Samrat Chatterjee g. Mr. J.N. Mishra **Chairperson–Dr. Guruprasad R. Medigeshi**
10.	**RTI Act**	a. Dr. Krishnamohan Atmakuri–PIO b. Dr. Shinjini Bhatnagar–Appellate Authority c. Mr. M.V. Santo–Nodal Officer d. Executive Director–Public Authority e. Dr. Sudhanshu Vrati–Transparency officer
11.	**Internal Complaints Committee**	a. Dr. Shinjini Bhatnagar b. Dr. Shobha Broor (external member) c. Dr. Nita Bhandari (external member) d. Dr. Manjula Kalia e. Dr. Monika Bahl f. Mr. M.V. Santo **Chairperson–Dr. Shinjini Bhatnagar**

S. No.	Committee	Members
12.	**Student Welfare and Hostel Committee**	a. Dr. Amit Kumar Pandey (Hostel Warden) b. Dr. Nitya Wadhwa (Hostel Warden) c. Dr. Sankar Bhattacharyya d. Dr. Sucheta Kurundkar e. Mr. J.N. Mishra f. Two student representatives **Chairperson–Dr. Amit Pandey/Dr. Nitya Wadhwa**
13.	**Tender Opening Committee**	a. Mr. Deepak Baghele b. Mr. Manoj Kumar c. Mr. Eklavya Srivastava
14.	**Vigilance Officer**	a. 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

Dr. Kanury Venkata Subba Rao
THSTI, Faridabad

Visiting Professor of Eminence

Prof. N.K. Ganguly

Honorary International Visiting Faculty

Dr. Madhukar Pai, M.D., Ph.D.
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
Senior Scientist, National Institute of Immunology, New Delhi

Dr. Vineeta Bal
Senior Scientist, National Institute of Immunology, New Delhi

Prof. Anil K. Tyagi
Vice Chancellor, Indraprastha University, New Delhi

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

Prof. Sudhanshu Vrati
On Deputation to RCB as Executive Director
Regional Center for Biotechnology, Faridabad

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

SEMINARS AND MEETINGS

Date	Topic	Speaker
30-03-2017	Studies on host interactions and pathogenesis of emerging human viruses: Zika and Influenza in focus	Dr. Shashank Tripathi, Research Assistant Professor, Global Health and Emerging Pathogens Institute, Microbiology Department, Icahn School of Medicine at Mount Sinai, New York
24-03-2017	β-lactams and tuberculosis: new insights and new opportunities	Dr. Gyanu Lamichhane, Associate Professor, Division of Infectious Diseases, Johns Hopkins School of Medicine
23-03-2017	Drug resistant tuberculosis and development of new inhibitors	Dr. Pankaj Kumar, Helen Taussig Young Investigator, Johns Hopkins School of Medicine
27-02-2017	Precision Medicine (Immunohistochemistry (IHC), PTMScan and proteomics) and successful steps to get reproducible results by standard western blotting	Dr. Andy Zou, Cell Signaling Technology, USA
11-02-2017	5th Molecular Virology Meeting	N/A
23-01-2017	MST workshop at THSTI: An opportunity to measure binding affinities for your own samples	N/A
22-11-2016	Metagenomics: From algorithms to microbiome investigations	Dr. Tarini Shankar Ghosh, Computational and Systems Biology Lab, Genome Institute of Singapore
02-11-2016	Multigene families of *P. falciparum* are central to severe malaria in humans	Dr. Suchi Goel, Assistant Professor, Karolinska Institutet, Sweden
03-10-2016	Nanopore sequencing technologies' case studies from Genotypic in healthcare and agriculture	Dr. Deepti Saini, Principal Scientist, Genotypic Technology
11-08-2016	Hijacking host kinases to regulate the balance between mRNA and genomic RNA synthesis during influenza virus infection	Dr. Arindam Mondal, Department of Medical Microbiology and Immunology, University of Wisconsin, Madison
28-07-2016	Bridging the gap between research and commercialization in development of novel bacterial vaccines	Dr. Manoj Kumar, Director, R and D at the MSD-Wellcome Trust Hilleman Laboratories
28-04-2016	Health and hygiene (daily life cycle diseases)	Dr. Jitender Kumar, Director Nephrology and Kidney Transplant, Asian Institute of Medical Sciences, Faridabad
12-04-2016	Bio Layer Interferometry	Dr. Vishal Kamat, Scientist, HTS Biomolecular Center, Regeneron Pharmaceuticals
05-04-2016	Biology of human aging: the immune component	Dr. Anis Larbi, Singapore Immunology Network, Singapore

FACULTY SCIENTIST PRESENTATION SERIES

Date	Topic	Speaker
27-03-2017	*Shigella sonnei* colicin: Biology and genetic mechanism of colicin resistance	Dr. T. Ramamurthy
20-03-2017	Systematic computational approach to target protein-protein interaction site for drug discovery	Dr. Shailendra Asthana
17-02-2017	Deciphering *Mycobacterium tuberculosis* arsenal	Dr. Krishnamohan Atmakuri
10-02-2017	Structure, function and diversity of the healthy human gut microbiome	Dr. Bhabatosh Das
03-02-2017	HIV Vaccine: Need, challenges and probable solutions	Dr. Bimal Chakrabarti
27-01-2017	Disrupting proteomics-new tools of the trade	Dr. Amit K. Yadav
27-01-2017	Cohorts and cognitive Function	Prof. Gagandeep Kang
13-01-2017	Evidence to policy	Dr. Shinjini Bhatnagar
16-12-2016	Exploiting systems-based approaches for drug target discovery: The genesis and architecture of DDRC	Dr. Kanury Rao
23-12-2016	Translational approach to identify target for cardiomyopathy	Dr. Sanjay K Banerjee
09-12-2016	Dissecting biological complexity through mathematics	Dr. Samrat Chatterjee

ट्रांसलेशनल स्वास्थ्य विज्ञान
एवं प्रौद्योगिकी संस्थान

TRANSLATIONAL HEALTH SCIENCE
AND TECHNOLOGY INSTITUTE

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

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