ट्रांसलेशनल स्वास्थ्य विज्ञान एवं प्रौद्योगिकी संस्थान
TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE
(An Autonomous Institute of the Department of Biotechnology, Govt. of India)
NCR-Biotech Science Cluster, 3rd Milestone, Faridabad-Gurgaon Expressway, Post Box No.- 04, Faridabad-121001

Admission Notice No. THS/RN/16/2016

Result of the interview held for THSTI-JNU PhD program 2016 at THSTI, NCR Biotech Science Cluster, 3rd Milestone, Faridabad-Gurgaon Expressway, P.O. Box No. 04, Faridabad - 121001 on 23rd & 24th June 2016.

Candidates recommended for admission (in alphabetical order)

Sl. No.	Name	Reference ID
1.	ALEKSHA PANWAR	16916
2.	AMIT SHARMA	16898
3.	BINDU	16983
4.	DEEPA NAIR	16859
5.	FARHA MEHDI	16873
6.	NEERA PARMAR	17012
7.	PARMESHWAR BAJIRAO KATARE	16973
8.	PRIYANKA	16935
9.	PRIYANSHU SRIVASTAVA	16844
10.	RAHUL AHUJA	16968
11.	RAJDEEP DALAL	16874
12.	RAMACHANDRAN T	17009
13.	RANJAN KUMAR	16957
14.	RAVI PRAKASH SHALIWAL	16978
15.	RITU ARORA	16917
16.	RIYA SARKAR	16852
17.	SANPREET SINGH	16932
18.	SARLA YADAV	16899

19.	SHIV KUMAR	16987
20.	TANNU PRIYA GOSAIN	16991

The above candidates may interact with potential supervisors. Please download the Rank Preference form given on next page. Please go through the instructions given therein carefully before submitting the rank preference form by 04:00 pm of 28th June, 2016.

THSTI JNU PhD program-2016
Rank preferences of Potential Supervisors by Doctoral Candidates

S.No	Name	E-mail ID	Phone No.	Rank Order
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13.	Dr. Uma Chandra Mouli Natchu	unatchu@thsti.res.in	0129-2876356	
14.	Dr. Milan Surjit	milan@thsti.res.in	0129-3087318/0129-2876317	

INSTRUCTIONS

1. Assign a rank from **1-14** for each supervisor. It is advisable for the student to interact and rank all supervisors.
2. The assignment of Supervisor is based on matching according to the preferences given by the students and faculty. Students are advised to interact with supervisors through personal meetings/email/ Skype as may be the case at a mutually convenient time and location.
3. The forms ***must*** reach Mr. J N Mishra by email to jnmishra@thsti.res.in by ***4.00 pm of 28th June, 2016. No delays will be accepted. Non-receipt of the form will be considered as a decision to not accept the admission at THSTI.***
4. The final student–faculty match list will be displayed on THSTI website and communicated to the candidates on 29th June 2016 via e-mail.
5. Research interests of potential supervisors are also attached below.
6. Please address doubts in this matter before submitting forms to Mr. J.N. Mishra, Administrative Officer at 0129-2876441/442/440.

Date ____________________

Name of the candidate____

Signature of the Candidate______________________________________

PROJECTS FOR DOCTORAL STUDENTS

Project : Carbon metabolism in Mycobacterium tuberculosis and its implications on mycobacterial persistence

Principle Investigator : Dr. Amit Kumar Pandey

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

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

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

Genetic essentiality study of *Mycobacterium tuberculosis* under various growth and stress conditions
Advancement in new cost-effective high throughput sequencing techniques has led to the identification of complete genome of various pathogens. The volume of the data generated, failed in its objective of further understanding of microbial pathogenicity. Genetic essentiality study of a pathogen is one such technique where in a gene is functionally characterized and associated with a phenotype. In this laboratory the process of standardizing protocol to study genetic essentiality of Mtb under various growth and stress condition is in progress. To achieve the goal, the use of mariner based mycobacteriophage system for generating high-density transposon mutant library is planned. The library will passage through different growth and stress conditions and the genetic essentiality would be determined by comparing input and output libraries. Since it is demonstrated that cholesterol is required only during the late stages of Mtb infection, the hypothesis, that a genetic essentiality screen for the gene required for bacterial growth in cholesterol would be more relevant physiologically, if done under hypoxic conditions, is proposed. A better understanding on

cholesterol metabolism at the molecular level under physiologically relevant conditions would definitely help in designing of effective therapeutic solutions for TB.

Principle Investigator : Gaurav Batra

Research Interests

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

Goal of my lab is to develop diagnostic solutions, which are reliable in local conditions, affordable and practical. Major focus of our work is on the development of high quality diagnostic assays for acute febrile illnesses e.g. dengue, malaria, typhoid and scrub typhus and leptospirosis. My lab is also working the development of development of a multiplex point-of-care test for the blood borne infections (HIV, HCV and HBV). This project is funded by the Wellcome Trust, UK. To generate high quality diagnostic intermediates, my lab is using and constantly improving the following technology platforms:

- Yeast *Pichia pastoris* based expression toolbox for the production of recombinant antibodies and antigens. Host cell engineering to improve the secretion of antibodies and other complex proteins.
- Phage display
  - Genome fragment libraries (for immune epitope mapping and biomarker discovery)
  - Random peptide libraries (for immune epitope mapping and biomarker discovery)
  - Synthetic antibody libraries (for the generation of human framework monoclonal antibodies and biomarker discovery). Library access through University of Turku, Finland.
- Immunoassay development
  - Different formats (well based, lateral flow and all-in-one dry chemistry)
  - Different detection technologies (HRP/AP, Gold, TRF (Eu,TB chelate and nanopart.) and novel upconverting phosphors.

Most of the work in my lab is being done in collaboration with academic and industrial partners from India and Finland like ICGEB, New Delhi, University of Turku, Finland, University of Helsinki, Finland, Kaivogen Oy, Finland, Designinnova, India.

Major contribution

I was involved in the development of diagnostic intermediates and assays for the detection of anti-dengue virus IgG, IgM antibodies and NS1 antigen. This "know-how" was transferred to a diagnostic company, which resulted in a very successful commercial product for detection of dengue NS1 antigen & differential detection of IgM & IgG antibodies in Human Serum/ Plasma.

Projects that may be offered to the student

The project will be decided basis the student's attitude and aptitude. Projects could be around the following topics:

- *Pichia pastoris* host cell engineering for the enhanced secretion of recombinant antibodies.
- Development of novel upconverting phosphors based whole blood point of care assay for HCV
- Development of Ultrasensitive point of care assay for the detection of malaria parasite at very low parasite density

- Development of all-in-one dry chemistry based immunoassay for different targets including dengue and malaria.

Project : Understanding the interaction between viral infections and zinc homeostasis

Principle Investigator : Dr. Guruprasad Medigeshi

Background and objective: Zinc is an essential micronutrient which is involved in regulating the functions of about 10% of the human proteome. One of the most important functions of zinc is in maintaining the permeability barrier of epithelial and endothelial cells and therefore, infections that affect zinc homeostasis are likely to affect the functions of barrier forming cells. The objective of this project is to use viruses as a model for studying the functions of epithelial and endothelial barriers in the context of zinc homeostasis. The effect of virus infection on zinc homeostasis, the viral and host factors involved in mediating this effect and strategies to prevent disruption of barriers are some of the research areas that are of interest to the lab. The project will involve interaction with clinicians and will provide opportunity to study viral infections in a physiologically relevant context.

Project : Role of cellular autophagy in modulating dengue virus replication and innate immune response

Principle Investigator : Manjula Kalia

Our lab works on host-pathogen interactions of *Flaviviruses* (Japanese encephalitis virus, Dengue virus) with a focus on membrane trafficking, autophagy and development of innate immune response.

Dengue is the most prevalent arboviral disease world-wide and is spread by the mosquito *Aedes aegypti*. Infection with DENV leads to disease ranging from subclinical infection to the severe forms- dengue haemorrhagic fever and dengue shock syndrome. DENV infects 400 million people world-wide annually resulting in ~ 100 million cases of dengue fever and 21,000 deaths.

Autophagy, a lysosomal degradation pathway eliminates protein aggregates, damaged organelles and intracellular pathogens. Autophagy plays crucial roles in bacterial and viral infections either by directly degrading the pathogen in autophagosomes or by intersecting with the pathogen replication and by modulating the innate and adaptive immune response. Recent work from our laboratory on another *flavivirus*, JEV has shown that autophagy negatively regulates virus replication and suppresses virus induced cell-death. Virus replication occurs on membranes derived from ER-associated degradation (ERAD) pathway and are marked by nonlipidated LC3-I, a crucial autophagy protein.

The current PhD project aims to understand the role of autophagy in DENV replication, cell-death and modulation of innate immune response. The role of cellular autophagy pathway/ crucial autophagy proteins (ATG 5, ATG 7, ATG 16L, Beclin 1, LC3) on DENV replication and formation of infectious virions will be checked. The relevance of interactions between the host autophagy machinery and DENV on activation of innate immune sensors and its influence on secretion of type-I IFN will be characterized.

Project : 1. Exploring the role of micro RNAs in modulating Hepatitis E virus (HEV) replication
Project : 2. Investigation of the mechanism(s) controlling expression of ORF4 and elucidation of the role of ORF4 in the life cycle of genotype-1 HEV

Principle Investigator : Milan Surjit

Interested student may choose any one project from the following.

Project 1. Exploring the role of micro RNAs in modulating Hepatitis E virus (HEV) replication.
Micro RNAs have been shown to control the life cycle of many viruses. Among the RNA viruses causing hepatitis, Hepatitis C virus is controlled by a host micro RNA. This project aims at exploring the role of host micro RNAs in modulating HEV replication. A combination of biochemistry, molecular biology and imaging techniques will be employed to identify and characterize the role of host miRNA(s) in modulating the life cycle of genotype-1 and genotype-3 HEV.

Project 2. Investigation of the mechanism(s) controlling expression of ORF4 and elucidation of the role of ORF4 in the life cycle of genotype-1 HEV.
We have recently identified a new protein called ORF4, synthesized under conditions of endoplasmic reticulum stress by internal translation from an overlapping ORF located within ORF1 of genotype-1 HEV. ORF4 plays an essential role in viral replication [Nair et. al. Plos Pathogens, 2016, 12(4):e1005521]. We want to further explore the mechanism(s) controlling internal translation of ORF4. We will also focus at characterizing the properties of this protein (such as post-translational modifications, turn-over rate etc) so as to identify the conditions crucial for its functional activity. A combination of biochemistry, molecular biology and imaging tools already established in the laboratory (see the reference paper for details) will be employed to achieve the objectives.

Project : Understanding the protein translocation by Sec translocase in *Mycobacterium tuberculosis*

Principle Investigator : Dr. Nisheeth Agarwal

Membrane organization of a pathogen plays significant role in determining its virulence. The host-pathogen interaction is driven by the unique arrangement of several membrane proteins on the envelope of both the partners. The fate of these membrane proteins is in-turn governed by specialized transporters known as protein translocases. There are several proteins embedded in both the cell membrane and outer wall which regulate important biological processes crucial to mycobacterial virulence such as transport of materials across the membrane, interaction with host and subsequent elicitation of host immune response upon infection etc. These membrane proteins are specifically localized to envelop by a group of proteins known as pre-protein translocases. Protein export pathways play critical role in bacterial virulence. In *M. tuberculosis* three essential pathways are reported which regulate majority of protein export viz. the general secretion (Sec) pathway, the twin-arginine transport (TAT) pathway and the early secretory antigenic target 6 export (ESX) pathway. The Sec pathway involves multi-protein complexes such as SecYEG, SecDF and SecA for the transport of a protein containing lysine or arginine residue prior to the hydrophobic domain. Moreover, this pathway regulates the secretion of unfolded proteins e.g. lipoproteins as well as the insertion of proteins into the cell membrane. Most of the Sec proteins are predicted essential for bacterial growth and may or may not involve another small preprotein translocase, known as YidC. Recently we have characterized the role of YidC translocase in *M. tuberculosis* where we observed that this protein is involved in transportation of certain respiratory proteins to cell envelope and regulates the respiratory metabolism (1). There are few other studies which characterize the function of SecA component which assist protein transport by other Sec components. However, a thorough study investigating the role of crucial Sec proteins such as SecY and SecD is pending. Here we propose to disrupt the SecY and SecD proteins by CRISPRi

approach (2) in wild-type and YidC-depleted *M. tuberculosis* cells followed by their detailed characterization using genetic, proteomic and biochemical approaches.

Title: Functional characterization of GroE chaperone of *Mycobacterium tuberculosis*.

There are three GroE chaperones encoded by *M. tuberculosis* genome, GroEl1, GroEL2 and GroES. Interestingly, GroEL1 is found non-essential whereas GroEL2 is essential of *in vitro* growth of *M. tuberculosis*. It was shown that GroEL1 is involved in mycolic acid biosynthesis and biofilm formation, whereas the roles of GroEL2 and GroES are completely unknown in *M. tuberculosis*. In this study we propose to characterize the functions of GroEL1 and GroES chaperons by depleting their expression followed by comparative proteome analysis. We will also conduct various other biochemical and genetic experiments to identify their putative substrates which will help us better understand the underlying mechanism of protein folding in mycobacterial pathogens.

Suggested readings:

1. Thakur, P. et al. Sci. rep. **6,** 24998; doi:10.1038/srep24998 (2016)
2. Choudhary, E. et al. Nat. Commun. **6,** 6267; doi: 10.1038/ncomms7267 (2015)

Project : *Understanding mechanisms of persistence of M. tuberculosis and validation of new drug target pathways to combat tuberculosis.*

Principle Investigator: Dr. Ramandeep Singh

Tuberculosis kills annual 2 million people globally and an estimated one-third of world population is infected with latent tuberculosis, 10% of them have a risk for developing active TB disease. This situation has further aggravated due to HIV-TB nexus and emergence of various drug resistant strains of *M. tuberculosis*. Eradication of this dreaded disease requires understanding of the pathways that enables the bacteria to persist in the host and design of strategies aimed at targeting these non-replicating/latent bacteria residing in host tissues. The current focus of my research group is to identify metabolic pathways that enable *M. tuberculosis* to adapt to various conditions and to persist in the host. Another focus of the lab is to identify synthetic molecules that are active against non-replicative/persistent bacteria and to understand their mechanism of action.

Bacterial drug-tolerance is reported to result from lower metabolic requirements for processes that characterize actively growing cells such as transcription, translation, replication and cell wall synthesis. An attractive hypothesis for the origin of these persisters is that they arise from stochastic over expression of endogenous regulators of macromolecular synthesis in a subset of cells, toxin antitoxin modules or activation of stringent response pathways of *M. tuberculosis*. In our lab we have characterized enzymes involved in polyphosphate metabolism and showed that polyphosphate deficiency increases susceptibility of Mtb to various front line TB drugs (Singh et al., 2013; Singh et al., manuscript submitted). We have also biochemically characterized toxin-antitoxin systems of Mtb and observed that these TA systems are differentially regulated upon exposure to various stress conditions (Tiwari et al., 2015). In a recent paper published we show that these ribonucleases contribute cumulatively to the ability of Mtb to survive in oxidative, nutritional and in guinea pigs (Tiwari et al., 2015). Currently, experiments are in progress to identify the pathways regulated by these ribonucleases and polyphosphate in Mtb (manuscript under preparation). We have also biochemically characterized phosphoserine phosphatase enzyme and identified novel scaffolds that specifically inhibit SerB2 enzyme from Mtb (Arora et al., 2014). In the drug screening activities of the group, we have identified various scaffolds that inhibit Mtb growth *in vitro*. We have also raised revertants for few of these scaffolds and are currently performing Next-gen sequencing to identify SNPs in these revertant strains (Unpublished data). In collaboration with various medicinal chemists we have identified few chemical entities that are active against Mtb in low micromolar range (Kumar et al., 2014a, b, Bansal et al., 2014, Beena et al., 2012, Unpublished data). In addition to this we have also initiated few projects such as (i) Understanding the role of rTCA enzymes in physiology and pathogenesis of Mtb, (ii) Modulation of host sumoylation pathways upon Mtb infection, (iii) Understanding the role of Nucleoid associated proteins and GntR transcription factors in physiology and pathogenesis of Mtb. iv) Validation of

other amino acid metabolic enzymes as drug targets for Mtb. v) VapC toxins: Identification of their cellular targets and their role in drug tolerance and virulence of Mtb.

Projects on offer for new Ph.D. students.

1. Using proteomics and genomic approaches to identify metabolic pathways regulated by toxin-antitoxin systems and polyphosphate levels. Using RNA-seq approach to study cross- talk between these pathways.
2. Development of an assay system to identify inhibitors for essential transcription factors of Mtb.
3. We have developed various attenuated strains of Mtb, therefore, we would want to evaluate these strains for their protective efficacy in various animal models.
4. Screening of libraries to identify novel inhibitors for Mtb and identify their drug targets using reverse genetic approach.
5. Structure-activity relationship studies to improve the activity of already screened scaffolds (For Students with preferably M.Sc (H) Chemistry).

Project : Viral replication and modulation of innate immune response by viral proteins.

Principal Investigator: Dr. Ranjith Kumar

Although many different kinds of viruses are known to cause human disease, antiviral therapies are approved only for a handful. There is an urgent need to develop effective antivirals against emerging and reemerging viruses for which no vaccines or antiviral therapies are available.

My laboratory is interested in studying the replication mechanisms of RNA viruses such as hepatitis C virus (HCV) and hepatitis E virus(HEV), and understanding their interaction with the host. Our research is focused on characterization of virus replication complex that includes RNA dependent RNA polymerase (RdRp) and RdRp-associated host proteins with the goal of exploring them as potential antiviral drug targets. Our study extends to understanding the strategies used by viruses to evade host innate immunity responses with the aim of developing attenuated vaccines. Host proteins or pathways utilized by multiple viruses are attractive targets for the generation of broad-spectrum antivirals with an added advantage of higher genetic barrier to antiviral resistance.

Principle Investigator : Dr. Sanjay K Banerjee

Project details:

Research goal of Dr. Banerjee's laboratory is to investigate the molecular mechanisms of cardiovascular and metabolic disorders, and drug discovery through screening of small molecules. One of the objectives of my lab is to understand cardiovascular complication in diabetes and to reverse the disease progression by targeting key proteins. Regulation of protein by post-translational modifications (PTMs) is an important mechanism that modulates protein/enzyme activity. PTMs, in particular protein phosphorylation or acetylation, are increasingly being recognized as key regulators in many cellular processes, including mitochondrial energy metabolism. Metabolites data from tissues at different stages of disease progression will be correlated with PTM. We believe that direct regulation of proteins/enzymes by PTMs provides one of the fastest ways for cells to adjust to environmental cues and internal stimulus.

Previously we have shown SIRT-1, which deacetylates NFkB-p65 at lysine 310 and histone 3 (H3) at lysine 9 position, play important role disease pathogenesis. SIRT1 activation leads to decreased binding of NFkB-p65 to DNA and attenuated cardiac hypertrophy and oxidative stress through reduced transcription of NADPH oxidase subunits. We also confirmed that knockdown or inhibition

of SIRT1 in H9C2 cells increased acetylation of NFkB-p65 K310 and H3K9. Our data demonstrated that SIRT-1 activation attenuates cardiac oxidative stress and complications in diabetes. We would like to explore the role of SIRT1-SIRT3 axis to modulate cardiovascular complication in diabetes.

References:

1. Khatua TN, Dinda AK, Putcha UK, Banerjee SK. Diallyl disulfide ameliorates isoproterenol induced cardiac hypertrophy activating mitochondrial biogenesis via eNOS-Nrf2-Tfam pathway in rats. ***BB Report***, 2016, 5:77–88
2. Bagul PK, Deepthi N, Sultana R, Banerjee SK. Resveratrol ameliorates cardiac oxidative stress in diabetes through deacetylation of NFkB-p65 and histone 3. ***Journal of Nutritional Biochemistry,*** 2015, **26**;11:1298–1307.
3. Adela R, Nethi SK, Bagul PK, Barui AK, Mattapally S, Kuncha M, Patra CR, Reddy PN, Banerjee SK**.** Hyperglycaemia enhances nitric oxide production in diabetes: a study from South Indian patients. ***PLOS ONE.*** 2015;10(4):e0125270.

Project : Inflammation and Linear growth in infants

Principle Investigator : Dr Shailaja Sopory

Stunting (low height for age) is a major cause of concern in Indian neonates with 45% of children below the age of 5 being stunted. In fact Indian children are shorter even when compared to children in some of the poorest countries in the world (Sub Saharan Africa). Stunted growth reflects a process of failure to reach linear growth potential as a result of suboptimal health, high inflammatory status and/or nutritional conditions.

The process of stunting can begin as early as in utero and as the child grows the chances of catch up growth decreases.

We are interested in understanding the underlying causes of stunting in Indian infants by looking at various parameters that include but are not limited to infections, inflammation, microbial load and hormonal imbalances. In this process find possible biomarkers that can detect early stunting so that preventive measures can be taken early in life to prevent further growth failure.

Principle Investigator: Dr. Shinjini Bhatnagar

A cohort of pregnant women has been established at the Gurgaon district hospital. The enrolled subjects are being followed from early pregnancy, before 20 completed weeks of gestation until delivery to capture their exposure to important environmental, clinical and biological factors and to assess associations of these factors with **preterm birth, fetal growth restriction and post natal growth linear growth in infancy**. The Phd student will be expected to develop research questions where classical epidemiology can be linked with molecular mechanisms for clinical benefits. Some of the **relevant domains** are (i) observational studies that would help in expanding on epidemiology of preterm birth/ fetal growth restriction/ post-natal growth linear growth, and identifying significant clinical, environmental and social determinants, (ii) association of infections/ inflammation with adverse pregnancy outcomes, linear growth, and immune functions in the first year of life, (iii) endocrine influences influencing fetal growth restriction, gestational age and linear growth, (iv) studies to identify effective diagnostics or preventive or therapeutic interventions, (iv) expanding knowledge in implementation science, and novel technology around diagnostics/interventions.

Project : Understanding the Japanese encephalitis virus attachment and receptor system

Thesis supervisor : Prof. Sudhanshu Vrati

Japanese encephalitis virus (JEV) is a major cause of human encephalitis and is responsible for considerable morbidity and mortality in India. The first step in JEV infection requires interaction between the virus envelope (E) protein and the cellular receptor/s present on the surface of the host cell. Precise molecular events involved in JEV entry into permissive cells are not well understood. Since the E protein mediates the primary attachment of the virus to its target cell, it determines, at least in part, the host cell tropism and pathogenesis of the virus. Thus, it is important to elucidate the functional role of JEV E protein in virus binding and interactions with cellular proteins. Using the yeast-two-hybrid system and other proteomics-based strategies, the proposed study aims to identify the host cell membrane protein/s that bind JEV E protein, and thus might be acting as the virus receptor. No specific drug treatment is presently available to treat JEV infection. The knowledge generated here could be useful to design novel molecules with potential to interfere with / abrogate JEV interaction with the receptor, thereby inhibiting the virus infection of the host cells.

Principle Investigator : Dr. Uma Chandra Mouli Natchu

The student would broadly be working in the area described:

Nutrition is known to influence the immune system in many ways. We are attempting to understand the influences of micronutrient deficiencies and supplementation on immune responses of infants and children from birth; Specifically, immune responses that influence the outcomes of immunization and infections. The students will work on micronutrients, clinical factors that influence immune responses in human studies (potentially also modes of deficiency that can be used to understand mechanisms of interactions between nutrition and immunity.

Principle Investigator : Dr. Amit Awasthi

Research Activity in Dr. Awasthi's Lab

Auto-reactive T cells induced tissue inflammation in both Multiple Sclerosis (MS) and Inflammatory Bowl Disease (IBD). Recently discovered Th17 and Th9 cells play a major role in inducing tissue inflammation. Major focus of my work is to define the transcriptional landscape of effector Th17, Th9 cells and Type1 regulatory T cells (Tr1). To understand the pathogenic functions of pathogenic Th17 cells, I have developed IL-23R reporter/KO mouse models to track Th17 cells in various target organs during inflammation. I have found that TGF-β3, instead of TGF-β1, is essential for the development of pathogenic Th17 cells, and interestingly the expression of TGF-β3 is dependent of IL-23 exposure. I have generated TGF-β3-YFP and TGF-β3-DTR mice to delineate the role of TGF-β3 in the development of pathogenic Th17 cells.

We have also identified the Th9 cells, which is mainly involved in lung inflammation in Asthma and anti-tumor immune response. On the same line, we have identified a novel transcription factors for the development of Th9 cells, which are crucial effector T cells for inducing tissue inflammation in allergic inflammation in asthma. Given a importance of Th9 cells in anti-tumor immunity, we will be performing the metabolomics profile of Th9 cells and would like to identify novel metabolite that can regulate the generation and function of Th9 cells during tumor response.

In second project, we will understand the transcriptional regulation of Tr1 cells and they are associated controlling autoimmune response in IBD.

Funding agencies:
DBT-Wellcome Trust
Glue-grant, DBT India

Selected Publication:

Korn T, Reddy J, Gao W, Bettelli E, **Awasthi A**, Petersen TR, Backstrom BT, Sobel RA, Wucherpfenning KW, Strom
TB, Oukka M, Kuchroo VK. Myelin-specific regulatory T cells accumulate in the central nervous system, but fail to
suppress pathogenic effector T cells at the peak of autoimmune inflammation. **Nature Medicine 2007; 13: 423-31.**
Korn T, Bettelli E, Gao W, **Awasthi A**, Jäger A, Strom TB, Oukka M, Kuchroo VK. IL-21 initiates an alternate
pathway to induce proinflammatory Th17 cells. **Nature 2007; 448: 484-7. Cited 705 times.**

Awasthi A, Carrier Y, Peron JP, Bettelli E, Kamanaka M, Flavell RA, Kuchroo VK, Oukka M, Weiner HL. A dominant function for interleukin 27 in generating interleukin 10–producing anti-inflammatory T cells. **Nature Immunology 2007; 12:1380-9.**

Awasthi A*, Dardalhon V*, Kwon H, Galileos G, Gao W, Strom TB, Oukka M, Kuchroo VK. IL-4 inhibits TGF-binduced-
Foxp3+T cells and generates a Foxp3- IL-10/IL-9 T cell population. **Nature Immunology 2008; 9:1347-55**

Lee Y*, **Awasthi A***, Yosef N, Quintana F, Xiao S, Kunder S, Regev A, Sobel R, Kuchroo VK. Induction and
molecular signature of pathogenic TH17 cells. **Nature Immunology 2012; 13:991-9** [**Shared first and Co-senior author**].

Yosef N, Shalek AK, Gaublomme J, Jin H, Lee Y, **Awasthi A,** Wu C, Karwacz K, Park H, Kuchroo VK, Regev A. Reconstruction of the dynamic regulatory network that controls Th17 cell differentiation by systematic perturbation in primary cells. **Nature 2013, 25;496:461-8.**