Procedure for selection of Thesis Mentors

NII PhD Program 2018

Selection of thesis mentors by students will be exclusively based on mutual interest and mutual consent.

July 9th: (9.30 AM): Student enrolment/joining, hostel allotment - Seminar Room I.

July 10th (9:30 AM - 6:00 PM): Presentations by Faculty members - Seminar Room I.

July 11th (9:30 AM - 1 PM): Presentations by Faculty members - Seminar Room I.

July 11th (2 PM - 6 PM) to **July 13th** (1 PM): Visit by students to various laboratories for discussion on potential projects. Each student will be given a form on which he / she must obtain the Guide's signature (with official seal), indicating acceptance.

Research programs of faculty members who are taking students this year are briefly described below. Dr. Arnab Mukhopadhyay's laboratory has **two** vacancies.

1. **Dr. Agam P. Singh**: Malaria liver stage parasites are excellent target for both vaccine and drug discovery. Broadly we work on Malaria Liver-stage Biology, Vaccine and Drug discovery, Protein-Protein interaction, Host-Parasite interaction, Creation and characterization of Parasite Knockout. A multi disciplinary approach is used to achieve the above goals

2. **Dr. Apurba Kumar Sau**: The laboratory has been working mainly on two topics; i) Interferon-gamma induced large GTPases and their role in the regulation of GTP hydrolysis. The study has also been extended to understand how GTP hydrolysis in these proteins is associated with the biological functions such as antiviral activity etc. ii) Structure-function studies of the enzymes that are involved in the polyamine biosynthesis pathways in Helicobacter pylori, a known gastric pathogen. The study has also been focused in designing and evaluating inhibitors against enzymes that are vital for pathogenesis. We therefore use various approaches such as protein engineering, biochemical, cell cultures etc. to elucidate these.

3. **Dr. Aneesh Kumar A.G**.: Cellular protein synthesis is tightly regulated based on developmental and environmental cues. But little is known about the role of the metabolic status of cells in the regulation of translation and how it affects the fate of the cells. Transfer RNAs (tRNA) are the adapter molecules that enable accurate, template-dependent protein synthesis and the decoding function of tRNAs are regulated by post-transcriptional modifications with chemical moieties, which are sourced from a range of metabolites. The theme of our laboratory focuses on the role of tRNA modifications in linking metabolic status of the cells to translation regulation during immune activation.

   Translation regulation in immune cells.

   An objective of this program is to understand the role of tRNA modifications in the regulation of translation in immune cells upon activation and differentiation. We aim to understand the effect of cellular metabolic changes on tRNA modifications and their role in altering translation programs and fate determination of immune cells.

Translation regulation by viral proteins: Several clades of viruses including retroviruses have a codon usage pattern entirely different from the host codon usage. We aim to identify how viruses like HIV overcome the negative impact of the suboptimal codon usage to achieve high levels of expression of its proteins. We also aim to identify the mechanism by which the HIV restriction factor SLFN11 counteracts the tRNA pool modulation by HIV.

Translation regulation in Mycobacterium tuberculosis. The objective of this study is to understand how mycobacterial translation is affected by various stress that the pathogen is subjected to in the host as well as to identify the effect of the pathogen in the host translation. In particular, we focus on the role of tRNAs in both host and bacterial translation.

4. **Dr. Bichitra K. Biswal**: *Mycobacterium tuberculosis (Mtb)*, the organism that causes tuberculosis (TB) in humans, starved of histidine (His) fails to grow/multiply. Primarily in the context of designing new anti-TB compounds, a major project, deciphering the structural and biochemical aspects of enzymes of His biosynthesis pathway, is being pursued. Such studies enable to unravel the molecular mechanisms underlying their action and design enzyme specific inhibitors through a structure-based approach. In another project, we focus on understanding how *Mtb* membrane associated proteases modulate host factors.

5. **Dr. Debasisa Mohanty:** ***Molecular modelling of biomolecular systems using knowledge-based approaches and all atom simulations***

   The main theme of the research projects is to develop novel computational approaches for prediction of the structures of proteins/nucleic acids and specificities of protein-ligand or protein-nucleic acid complexes. These prediction approaches for structure and substrate specificity are being used to analyze various genomes for identifying novel biosynthetic pathways, protein-protein interaction networks and regulatory networks.

   The specific objective of the various projects currently pursued in the laboratory are to investigate, whether the combination of knowledge-based and *ab initio* approaches can be used for (A) *in silico* identification of secondary metabolites by genome mining (B) deciphering substrate specificity of various peptide recognition modules (PRMs) like kinases, PTB, PDZ and SH2/SH3 domains and genome wide prediction of their interaction networks (C) structure based analysis of RNA-protein and DNA-protein interactions associated with gene regulation.

   The research projects available for new members joining the group would involve application of machine learning approaches to problems in the area of structural bioinformatics with potential applications for deciphering structural basis of disease associated mutations in protein-protein interaction (PPI) and regulatory network involving protein-DNA/RNA complexes. In view of the steady increase in availability of experimental data for training and remarkable improvements in deep learning algorithms, we plan to explore the use of deep multi layer neural networks for protein-peptide/protein-nucleic acid interaction predictions. Knowledge based computational methods will be developed for identification of TFs and scaffolding proteins binding to lncRNA We also plan to develop implicit solvent scoring functions for ranking protein-DNA and protein-RNA complexes. These projects would involve extensive analysis of biomolecular big data available in public domain from TCGA and other major international consortiums like ENCODE etc.

6. **Dr. Devinder Sehgal**: My laboratory employs a multidisciplinary approach to address questions in the area of microbial interface biology and associated host immune response to the human pathogen Streptococcus pneumoniae. We are interested in host-pathogen interaction, infection and immunity, and vaccine development. We are particularly interested in the molecular biology of B cells and developing a molecular understanding of how glycoconjugate vaccines work. We

combine immunological, molecular and proteomics approaches with *in vitro* and animal models for these studies.

7. **Dr. Madhulika Srivastava**: Epigenetic regulation of the eukaryotic genome

The knowledge gained in field of epigenetics has immensely enhanced our understanding of metazoan development and disease but has also raised several intriguing questions which are pertinent to understand the full scope of genetic-epigenetic framework that controls gene expression. Beyond the histone modifications that alter the chromatin structure at nucleosomal level, higher order chromatin organization influences interactions amongst cis-acting regulatory elements like enhancers, insulators, silencers. There is considerable paucity of understanding of the organization of chromatin at various levels that accomplishes spatial and temporal regulation of gene expression. Architectural Proteins like CTCF and cohesin and a few long non coding RNA (LncRNA) have emerged as crucial factors that orchestrate higher order chromatin organization. Future studies are likely to reveal more such factors and provide the necessary mechanistic details.

We are addressing some aspects underlying higher order chromatin organization using mouse TCRb locus as a model since at TCRb locus transcription as well as RAG mediated VDJ recombination is exquisitely regulated during development to generate a vast repertoire of TCRb chains present on the T cells and crucial for adaptive immunity.

CTCF has thousands of binding sites in mouse and human genomes but exhibist functional diversity. While some of these CTCF binding sites (CBS) act as enhancer blocking insulators, the others facilitate enhancer-promoter interactions. The molecular basis for the diverse functional outcomes of CTCF binding is not clearly known and is likely to be revealed by investigations of several parameters by which CTCF binding sites differ. We have generated mouse mutants carrying ectopic CTCF binding sites that have presented a very interesting phenotype (Shrimali et al 2012, Rawat et al 2017). We continue to explore various aspects of the CTCF mediated organization.

Our group is also interested in understanding how enhancers function. Although identified nearly three decades ago, the mechanism underlying enhancer based activation of cognate promoters remains incompletely understood. Chromosome Conformation Capture assays (3C, 4C, HiC) have revealed chromatin looping between enhancers and their cognate promoter by currently unknown mechanisms. Our studies have previously investigated the enhancer-insulator-promoter interactions (Varma et al 2015) and molecular requirements for theses interactions are being investigated.

Our studies require an integration of molecular, biochemical, cellular and genetic approaches for investigations to understand the chromatin organization in context of nuclear functions. Beyond VDJ recombination, additional interests in the lab are in context of genomic imprinting, cellular differentiation and diseases caused due to epigenetic mis-regulation.

References :

Rawat P, Jalan M, Sadhu A, Kanaujia A, **Srivastava M** (2017) Chromatin Domain Organization of TCRb locus and its perturbation by ectopic CTCF binding. ***Molecular and Cellular Biology, 37, Issue 9, e00557-16***)

Varma G, Rawat P, Jalan M, Vinayak M, **Srivastava M** (2015), Influence of a CTCF dependent insulator on multiple aspects of enhancer mediated chromatin organization (***Molecular and Cellular Biology, 35, 3504-3516***)

8. **Dr. Nimesh Gupta**: Our research group aims to understand the biology and function of follicular T helper (Tfh) cells in long-term protective immunity. Tfh cells are the unique subset of CD4 helper T cells specialized in providing help to B-cells. Therefore, Tfh cells are limiting for the magnitude and quality of protective antibody responses. By employing cutting-edge human immunology techniques, we are investigating the multifaceted biology of Tfh cells in

controlled human vaccination or acute flavivirus infections.The global aim is to identify and harness the positive attributes of Tfh cells for rational design of next generation vaccines.

9. **Dr. Arnab Mukhopadhyay**: **Understanding the molecular basis of aging and mechanisms of longevity assurance**

Aging is a phenomenon that afflicts most living organisms. It is often associated with debilitating diseases like diabetes, cancer and neurodegenerative disorders. In order to prolong healthy life span, we first need to find themolecular causesof aging and decipher the mechanisms of longevity assurance.In our lab, we use the model system *Caenorhabditis elegans* to understand the fundamental biology behind the process of aging using a mix of molecular geneticsand genomics. We are currently focusing on nutrient signalling pathways (like insulin signalling, mTOR signalling) as energy homeostasis plays a critical role in controlling life span. The following are aspects that we are currently investigating. As we know now, there is much conceptual as well as mechanistic overlaps between these individual lines of research.

Molecular mechanisms of Dietary Restriction (DR)

DR is the only non-genetic intervention that is known to extend longevity in most organisms. It has been shown to delay aging and multiple age-related pathologies across the animal kingdom, including non-human primates as well as humans. We are using *C. elegans* as well as mice models to understand how DR works.

Organelle-specific stress response and aging

Aging is caused by deterioration in the protein quality assurance pathways in the cell. Endoplasmic reticulum (ER) is a major site of protein quality control and the ER functions qualitatively deteriorates with age. We are trying to understand why ER quality assurance declines with age, the role of nutrients in this process and how DR can resurrect the ER function during aging.

Mechanisms of food-choice-dependent life span regulation

The quality of food has profound effect on longevity. How does specific food interact with our genes? There are a few examples of these "diet-gene" pairing and we have discovered a new one. We are trying to understand how this pairing works in terms of cellular signalling and inter-tissue signalling.

Role of novel kinases that interact with the insulin signalling pathway

The insulin signalling is one of the most well-characterized pathway that modulates aging and development across species. We are interested in finding and characterizing new kinases that interact with the insulin signalling pathway.In this quest, we have identified a cyclin-dependent kinase that modulates this pathway to control development of the germ cells. We are trying to decipher the molecular mechanism of this interaction.

P38 MAP kinase pathway and its role in nutrient signalling

The p38 MAPK pathway plays critical role in oxidative stress response as well as in innate immunity. However, its role in nutrient sensing is not well-characterized. We are in the process of understanding its role in terms of DR, food-type-dependent life span as well as in organelle-specific stress response. We are trying to find how p38 is activated by lipid signalling and how it controls its downstream genes through conserved transcription factors, in a tissue-specific manner.

RNA regulatory processes that control aging and their modulation by DR

We and others have shown that RNA regulatory process like alternative splicing and non-sense-mediated decay play important role in aging. We continue to ask whether other RNA regulatory processes like alternate polyadenylation or alternate last exon usage have role in aging. We are using Next generation sequencing to study these processes.

Pharmaceutical agents to treat age-related diseases

We are trying to reposition FDA-approved drugs to treat complications arising from type II diabetes, an age-related disease. We have shown that Rifampicin reduces glycation, a non-enzymatic reaction that modifies proteins, nucleic acids and lipids, leading to loss of their native function. We are trying to develop variants of this drug that can be used in combination with existing treatment modalities, to prevent accumulation of glycated proteins. Parallelly, we are trying to design pharmaceutical interventions that can mimic DR and its beneficial effects.

The interests of our lab are diverse but interlinked with multiple students (having their independent projects) contributing to each project (see below). We are also excited to ask new questions beyond these areas of research and interested in applying inter-disciplinary approaches to get insight.

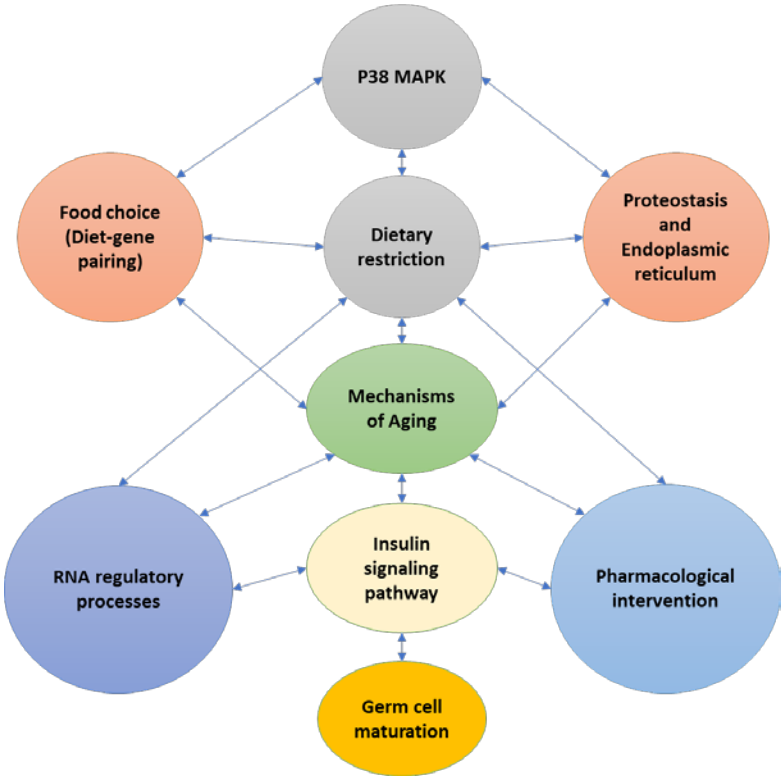

Figure 1. Interconnections between the different ongoing projects in the lab

10. **Dr. RP Roy**: We work at the chemistry-biology interface developing novel chemo-enzymatic strategies for creating synergy between recombinant and chemical approaches of protein engineering enabling unprecedented construction of well-defined macromolecular protein assemblages, cyclic and branched proteins linked through normal peptide bond as well as unusual isopeptide linkages. We are currently using sortase enzymes of gram-positive bacteria as a

tool in this endeavor. Contemporaneously, we are also engineering sortase enzymes endowed with enhanced catalytic activity, stability and altered specificity to expand the sortase toolkit".

11. **Dr. Pushkar Sharma**: It is well known that extracellular signals control biological responses in most eukaryotic cells by regulating specific intracellular signaling and trafficking cascades. We are interested in signalling and trafficking events in two diverse cell types: 1) Apicomplexan parasites like *Plasmodium falciparum* and *Toxoplasma gondii* and 2) mammalian neurons. A multidisciplinary approach that combines modern OMICS approaches with reverse genetics, cell biology and biochemical studies is employed to dissect signalling pathways in these organisms, which will shed light on novel mechanisms involved in their development.

12. **Dr. Rajesh S. Gokhale**: Focus of our laboratory is to elucidate complex Interplay between metabolic reprogramming and immunity in the context of Tuberculosis and the autoimmune skin disorder Vitiligo.

13. **Dr. S. Gopalan Sampathkumar**: Our Laboratory of Chemical Glycobiology (CGB) is broadly focused on the investigations of glycosylation pathways and their functional relevance in immunity, auto-immune diseases, CNS disorders, and cancer. The currently active projects are: (A) Design, synthesis, and development of carbohydrate-based small molecules to engineer, intercept, and inhibit protein and lipid glycosylation, (B) Glycoproteomics based characterization of CD antigens, (C) Development of multi-functional nanomaterial systems for engineering of glycoconjugates in vivo, and (D) Design, synthesis, and development of glycopeptidomimetics derived inhibitors for matrix metalloproteases against cancer metastasis.

14. **Dr. Sandeep Saxena**: DNA replication is a vital process of life and must be completed precisely during each cell cycle. When mammalian cell experiences DNA damage, it activates checkpoint mechanisms to stall the progression of the cell cycle and DNA replication. Our laboratory is interested in understanding the mechanisms by which microRNA and checkpoint proteins stall the cell cycle, preventing genomic instability and cancer.

15. **Dr. Sangeeta Bhaskar**: Combined Chemo-Immunotherapeutic Strategies to Combat Cancer

    &

    Vaccine Development for Tuberculosis and Understanding the Mechanisms of protection

16. **Dr. Sanjeev Das:** The focus of the laboratory is to explore the regulatory milieu of tumor suppressor proteins. The lab also has an active interest in understanding tumor cell metabolism. We employ diverse approaches including mass spectrometry, live-animal imaging, microarrays etc. to examine the role of different regulatory networks and metabolic processes in tumorigenesis. Since neoplastic transformation entails the rewiring of diverse cellular processes, our studies investigate the regulatory and metabolic perturbations intrinsic to tumorigenesis.

17. **Dr.Monica Sundd:** Leishmania, fatty acid biosynthesis pathway, protein structure, protein-protein interactions, enzyme structure and function

18. **Dr. Sarika Gupta**: My group is a multi-disciplinary group adapting an integrated approach in drug discovery that combines medicinal chemistry, basic biology and biochemistry principles for efficient drug design process. Interests of the group lie in identifying underlying principles in a disease pathogenesis to discover new targets, designing molecular intervention strategies and confirming the biological/therapeutic activities of the designed compounds. The small molecule regulators contribute to both drug development and understanding biological systems in human body.
    Currently my lab is working on these diseases: Parkinson's disease (PD), Alzheimer's disease (AD), Prion disease and transthyretin-related amyloidosis to address these issues. We also work on to

understand the mechanisms and factors that modulate the activity, structure and expression of glutamate transporters and endoplasmic reticulum associated proteins in neurological diseases.

19. **Dr.Soumen Basak**: Crosstalk-dependent tuning of immune signaling and potential therapeutic appeals.

Tuning immune signaling through pathway-crosstalk

While insufficient inflammatory immune response causes immune-deficiencies, unabated inflammation has been linked to a plethora of human ailments, including cancers. Microbial substances or cytokines activate the canonical NF-kappaB signaling pathway, which triggers inflammatory gene-expressions. In addition, tissue-microenvironmental cues activate a set of seemingly distinct immune-differentiating pathways, including the noncanonical NF-kappaB pathway, in immune cells. In a series of studies, Dr. Basak's group at the National Institute of Immunology, India, has illuminated crosstalk between these concomitantly activated cell-signaling pathways and established the significance of pathway crosstalk in human health and disease.

Combining experimental analyses and computational modeling studies, they show that noncanonical NF-kappaB signaling amplifies the inflammatory response to gut pathogens elicited by the canonical pathway. They identify how pathway-crosstalk differently modulates innate and adaptive immune compartments. Finally, their work reveals that aberrant pathway-crosstalk impart resilience in myeloma cells to apoptosis-inducing agents.The NF-kappaB system is involved in a vast number of biological processes; therapeutic targeting of NF-kappaB signaling leads to unacceptable side effects. The proposed crosstalk mechanisms may provide for specific therapeutic targets in inflammatory and autoimmune disease as well as in cancers in the future.

20. **Dr.Sagar Sengupta**: *Title: Determining the signalling and repair pathways that are altered in human cancer*

Theme of Research:

The broad aim of the research program has been to study the signaling pathways which have undergone alterations during the process of cancer development. Tumor suppressors are a group of extremely specialized proteins whose mutations lead to the development of cancer. In other words they are the caretakers and gatekeepers of our body. We are focused on the mechanisms of tumour suppressor functions. For example we ask how the tumoursupporessors are activated in response to DNA damage and thereby recruited to the sites of the lesions, the mechanism of their turnover, whether and how the regulation takes place via the post-transcriptional, post-translational, epigenetic mechanisms and how these proteins counteract the functions of the oncoproteins, which are known to drive neoplastic transformation, immortalization and tumorigenesis. Finally effort in the group is also focused in determining how the tumour suppressors, either directly or indirectly, help to maintain the fidelity of the genome by regulating the different repair processes, in conjunction with other tumour suppressors or with other process-specific proteins of the different repair pathways. The focus is not only on the nuclear genome maintenance – but also on the lesser-worked mitochondrial genome, specifically on the role of mitochondrial replication in the genome maintenance process.

Our primary interest lies in an unique group of proteins called RecQ helicase family. We chose this family of helicases as three of its members, *BLM, WRN* and *RECQL4*, when mutated lead to cancer predisposition syndromes called Bloom syndrome (BS), Werner Syndrome (WS) and Rothmund-Thomson syndrome (RTS) respectively. Hence these proteins (BLM, WRN and RECQL4) can be classified as caretaker tumour suppressors. Work in the laboratory is focused on the functions of BLM and RECQL4 helicases. BLM is a nuclear helicase – which has been shown to affect multiple steps in DNA damage response and DNA repair pathways. On the other hand, the lab was the first group to show that RECQL4 is a mitochondrial helicase, which play a role in the maintenance of the mitochondrial replication. The research in the near future will focus on trying to understand the mechanisms of signal transduction during genome integrity using a combination of biochemical

assays, cell culture based models involving immortalized cells obtained from patients, imaging techniques, mice models and patient tumour samples.

21. **Dr. Vinay K. Nandicoori**: **Deciphering kinase-mediated signaling networks in *Mycobacterium tuberculosis (Mtb)***

In order to effectively treat tuberculosis, it is imperative to find newer targets, which are important for the *in-vivo* bacterial survival and persistence. Phosphorylation based signaling cascades modulated by Eukaryotic like Serine/Threonine Protein Kinases and phosphatase in *Mtb,* transduce extracellular stimuli to a cellular response ensuing pathogen's growth, persistence and pathogenesis. There are 11 eukaryotic-like STPKs in *Mtb*, and we have worked towards analyzing the functional roles of the phosphorylation events mediated by these kinases. Investigating the signaling events in the pathogen contributes significantly towards understanding the biological events that are coupled to the manifestation of the disease.