DEPARTMENT OF BIOSCIENCES AND BIOENGINERING

List of Research Topics for Spring Semester 2019-2020

Sr. No.	Name of Guide/ Co-guide	Title/s of research project	Special academic prerequisites
BT			
BT-1	Shamik Sen	Role of glycocalyx in cancer progression & cancer invasion	FA Only
BT-2	Shamik Sen	Regulation of embryonic stem cell differentiation by MMPs	FA Only
BT-3	S.K. Ghosh	Studying epigenetic determinant and parasexual cycle in human fugal pathogen, *Candida albicans*.	None
BT-4	Ashutosh Kumar	Probing structure and recognition dynamics of proteins from SCF complex ubiquitin ligase	Should have Physics and Mathematics at B. Sc. level
BT-5	Ashutosh Kumar	Deciphering the molecular and pathological basis of aggregation of hIAPP in Type 2 Diabetes mellitus (T2DM)	Should have Physics and Mathematics at B. Sc. level
BT-6	Ranjith P.	Physics of chromatin organization in a cell nucleus	Students with M Sc Physics/Mathematics or B Tech/BE in core engineering subjects like Computer Science, Electrical Engg, Mechanical, Aero etc. Students should be willing to do computational study
BT-7	Dulal Panda Co-guide: Rohit Srivastava	Effects of T-cell activation on microtubule assembly and stability: Implications in cancer chemotherapy	CSIR-UGC-DBT, INSPIRE fellowship
BT-8	Dulal Panda	Targeting the cell division machinery of Mycobacterium smegmatis for discovering anti-tubercular drugs	CSIR-UGC-DBT, INSPIRE fellowship
BT-9	P.S. Phale Co-guide- P.V. Balaji	Understanding evolution o 1-Naphthol Hydroxylase at the molecular level	None
BT-10	Kiran Kondabagil	Exploring the environmental viromes	None
BT-11	Kiran Kondabagil Coguide- Prasenjit Bhaumik	Exploring DNA repair mechanisms in large viruses	None
BT-12	Anirban Banerjee	Extent of damage in the pathogen containing vacuole and cellular response	None
BT-13	Sanjeeva Srivastava Co-guide: Dr. Sudhir Nair, Professor and Surgeon, Head and Neck Surgery, Tata Memorial Centre, Mumbai	A proteogenomic characterization of oral cancer in Indian population	General biology background OK

BME			
BME 1	Ashutosh Kumar	Development of NMR based novel approach for assessment of the Higher Order Structure of Biopharmaceutical Products	Should have Physics and Mathematics at B. Sc. level
BME 2	Ambarish Kunwar	Computational study of interactions of various potential anti-cancer drugs with cancer drug-resistant tubulin istopyes	None
BME 3	Ambarish Kunwar	Computational study of cargo transport by a team of molecular motor proteins	None
BME 4	Ambarish Kunwar	Computational study of isotype specific interaction of motor proteins with microtubules	None

Prof. Rohit Srivastava
Head

BT

BT 1- Role of glycocalyx in cancer progression & cancer invasion (SSen)

The pericellular coat of polysaccharides and glycoproteins attached to the plasma membrane, i.e. glycocalyx, is present in most eukaryotic cells. The physical properties of the glycocalyx (such as their length, stiffness, and grafting density) are controlled by the expression profile of glycoproteins (such as mucins) and the extent of glycosylation of their side-chains. Interestingly, recent studies have shown that physical properties of the glycocalyx undergo drastic alterations across multiple types of cancer cells. However, how these properties influence different aspects of cancer remains inadequately understood.

The aim of this project will be to establish a connection between glycocalyx alterations and cancer progression, cancer invasion/tumor heterogeneity.

The student will combine cell and molecular biology tools with extensive microscopy and single cell biophysics to probe this question.

BT 2- Regulation of embryonic stem cell differentiation by MMPs (SSen)

The stem cell niche corresponds to the specialized microenvironment required by both adult and embryonic stem cells for their survival, self-renewal and differentiation. However, how the same niche regulates both self-renewal and differentiation is an intriguing question.

Matrix metalloproteinases (MMPs) are matrix degrading enzymes that regulate cell function not only by altering extracellular matrix (ECM) composition and organization, but also by releasing cytokines and growth factors tethered to the ECM.

This proposal will seek to probe the role of soluble and matrix anchored MMPs in regulating fate of mouse embryonic stem cells.

The aim of this thesis will be to address these questions by combining cell and molecular biology tools with extensive microscopy and single cell biophysics.

BT-3- Studying epigenetic determinant and parasexual cycle in human fugal pathogen, Candida albicans (SKG)

The yeast Candida albicans is the most important human pathogenic fungus and serves as a model organism for studying fungal virulence. The success of Candida as a pathogen depends on its ability to undergo phenotypic variation. Circumstantial evidence suggests that the phenotypic variation is regulated by epigenetic mechanisms. Therefore, characterization of the epigenetic proteins and elucidation of their functions are important steps towards developing therapeutic strategies against this pathogen. This study will use cell biological, genetic and biochemical tools to decipher the functions of these proteins in Candida. Importantly, in absence of meiosis, for generation of variation, C. albicans, relies on an event called parasexual cycle. The project will also characterize and examine the parasexual cycle in the context of requirement of the chromatin proteins

BT-4: Probing structure and recognition dynamics of proteins from SCF complex ubiquitin ligase (AK)

Ubiquitin-dependent proteolysis machinery regulates protein abundance and in turn serves as a central regulatory function in many biological processes. The SCF (Skp1-Cullin-F-box protein) complex ubiquitinates a broad range of proteins involved in cell cycle progression, signal transduction and transcription. In SCF complex, Skp1 is an adaptor protein, which directly interacts with F-box proteins and cullin-1. This complete assembly is responsible for targeting proteins for the ubiquitin-mediated degradation. Different SCF complexes vary in their F-box proteins, which are specific for the ubiquitination of their substrate proteins. Therefore, understating of structural basis of recognition of F-box and functionality of different proteins is crucial for delineating their role in the cell cycle regulation. In this project, we will explicate structure, dynamics and protein-protein interactions of skp1, F-Box proteins using various biophysical and biochemical approaches. Such information will be crucial for designing specific drug for a particular type of cancer.

BT-5: Deciphering the molecular and pathological basis of aggregation of hIAPP for rational drug design against Type 2 Diabetes mellitus (T2DM) (AK)

Diabetes is a chronic disorder that occurs either due to the inability of pancreas to produce enough insulin or the ineffectiveness of the body to use insulin that it produces. Lately, diabetes has transpired as major disease affecting all ages - children, adolescents, younger adults, and elderly individuals. Of the three major forms, type 2 Diabetes Mellitus (T2DM) is one of the most prevalent endocrine disorders and is associated with peripheral insulin resistance. The presence of fibrillar amyloid protein deposits of human islet amyloid polypeptide (hIAPP) in the pancreatic islets -cells is thought to be related to the death of insulin producing -cells in T2DM. Recent experimental evidences support the hypothesis that pre-fibrillar and small oligomeric states of hIAPP are the primary toxic species, which trigger pathological processes that lead to T2DM and its associated complications. It is believed that these oligomeric states interact differently with cell membranes, cause structural perturbations; induce inflammation, endoplasmic reticulum stress and mitochondrial damage in cells; thereby causing -cell cytotoxicity,. Therefore, detailed biophysical and cellular studies are required to understand the mode of interaction between different oligomeric/fibrillar states with membrane and their associated toxicity. In this project, we will structurally characterize different toxic species of hIAPP using various biophysical techniques. Further, using in-silico and in-vitro studies, we aim to design inhibitors of hIAPP aggregation and cytotoxicity to gain deeper insights into the mechanistic pathway.

BT- 6: Physics of chromatin organization in a cell nucleus (RP)

Nucleus of a cell is a puzzling self-organized system that is capable of “making decisions” based on signal that it receives. In this work we will examine this problem using ideas from physics and engineering.

BT-7: Effects of T-cell activation on microtubule assembly and stability: Implications in cancer chemotherapy (DP)

BT-8: Targeting the cell division machinery of Mycobacterium smegmatis for discovering anti-tubercular drugs (DP)

BT 9: Understanding evolution o 1-Naphthol Hydroxylase at the molecular level (PP)

BT 10: Exploring the environmental viromes (KK)

Metagenomics, which is the direct study of genetic material recovered from environmental samples, is the only tool available for assessing the bacterial and viral diversity and abundance. Advances in computational tools for the analysis of metagenomic sequence data are helping us in assessing the health and microbial risks of the environment. It is also helping in understanding the dynamics and drivers of antimicrobial resistance (AMR) genes dissemination in the environment; diversity of genes and their biochemical capabilities in an environment; indicators of pollutants etc. This project primarily involves deep sequencing of the total DNA from selected environmental samples to thoroughly characterize the bacterial and viral ecology, AMR gene diversity, and the metabolic capability of the metagenome using various computational pipelines. Candidate is expected to be familiar with or capable of learning various computational tools available for metagenomics sequence analysis. Biology background is not a must for this project. A recent publication from the lab in this regard is: Genomic and metagenomic signatures of giant viruses are ubiquitous in water samples from sewage, inland lake, waste water treatment plant, and municipal water supply in Mumbai, India. Chatterjee A, Sicheritz-Pontén T, Yadav R, Kondabagil K. Sci Rep. 2019 Mar 6;9(1):3690. doi: 10.1038/s41598-019-40171-y)

BT 11: Exploring DNA repair mechanisms in large viruses (KK)

Many of the recently discovered giant viruses carry huge genomes and code for an array of enzymes involved in DNA repair. Recently we characterized one such enzyme from Mimivirus (Mimivirus encodes a multifunctional primase with DNA/RNA polymerase, terminal transferase and translesion synthesis activities. Gupta A*, Lad SB*, Ghodke PP, Pradeepkumar PI, Kondabagil K. Nucleic Acids Res. 2019 Jul 26;47(13):6932-6945. Published as a cover page article). In addition to this enzyme, mimivirus encodes enzymes of the complete base-excision repair (BER) pathway. This project involves thorough biochemical and structural characterization (X-ray crystallography) of BER pathway and other repair enzymes from giant viruses.

BT 12: Extent of damage in the pathogen containing vacuole and cellular response (AB)

Following endocytosis in eukaryotic cells, pathogenic bacteria due to expression of pore forming toxins or various secretion systems puncture holes in the endosomal membranes. This leads to myriad of events, ranging from recruitment of autophagy adaptors targeting endosomes towards autophagic degradation, maintenance of vacuole to propel bacterial multiplication inside endosomes, cytosolic escape and cell to cell spread of the pathogen etc. However, these different outcomes depend primarily on the extent of damage on the endosomal membrane as well as on initiation of specific signaling cascades. It is therefore easy to rationalize that cellular response depends on the extent of damage. In this project, we aim to explore the different host-cell signaling mechanisms resulting in various host cellular response involving recruitment of various machineries, such as autophagic machinery, ubiquitination machinery etc. and connect it to the extent of damage in the endosomes caused by differential expression of a bacterial pore forming toxin.

Bt 13: A proteogenomic characterization of oral cancer in Indian population (SS)

Research in cancer has been significantly aided by the advancements in next generation sequencing, mass spectrometry and proteogenomics technologies. With the recent advent of the Cancer Moonshot Project and India being part of the International Cancer Proteogenome Consortium (ICPC), the critical role that proteogenomics can play in improving cancer patient treatment is increasingly being recognized. However, proteogenomic analysis of high throughput studies requires skilful integration of genomics and proteomics technologies along with computational expertise to handle large amounts of derived data for meaningful interpretation and insightful clinical correlation. To this end, the main purpose of this project on Oral Cancer Proteogenomics will be to utilize advanced genomic and proteomic expression platforms, address specific questions in the area of oral cancer, and from high-quality data generated from Indian human bio specimens, identify potentially actionable therapeutic molecular targets.

BME Topic 1: Development of NMR based novel approach for assessment of the Higher Order Structure of Biopharmaceutical Products (AK)

Project Summary: Monoclonal antibodies (mAbs) represent an important and rapidly growing class of biotherapeutics. Correct folding of a mAb is critical for drug efficacy, while misfolding can impact safety by eliciting unwanted immune or other off-target responses. Therefore, higher order structure (HOS) of complex biological therapeutics such as monoclonal antibodies is considered a critical quality attribute (CQA), alterations of which jeopardizes the safety and might lead to loss in efficacy of the drug product. Similar to the concept of generic drugs, innovator biologics are also re-produced upon patent cliffs and marketed as “biosimilars”. This project will aim to develop, evaluate and address the feasibility of exiting and novel 2D NMR fingerprinting method for structural mapping of an intact mAb at natural isotopic abundance. We will further study the binding interaction of the product with receptor protein by using NMR method and endeavor to develop a novel approach for conducting in-formulation assessment of lyophilized biopharmaceutical drug product using Solid-State NMR. In order to demonstrate the comparative

study of biosimilars with the reference product we will utilize statistical methods such as Linear Correlation Analysis and Principal Component Analysis (PCA).

BME 2: Computational study of interactions of various potential anti-cancer drugs with cancer drug-resistant tubulin istopyes (AKun)

Microtubules are essential for cell division and are important target for various anti-cancer drugs. Microtubules are polymers of tubulin monomers whose sizes are few nanometers. Disruption of microtubule dynamics induced by anticancer drugs leads to cell growth arrest and hence leading to cell death.

There are many drugs which display toxicity towards multidrug resistant cells and destroys non-dividing cells. A complete understanding of interaction of such drugs with tubulin is essential to develop better analogues in future for effective cancer treatment.

The goal of proposed research is to develop a molecular level understanding of interactions of these drugs with tubulin using Molecular Docking and Molecular Dynamics (MD) Simulation while working very closely with experimentalists.

Reference:

1. Bajarang Vasant Kumbhar, Vishwambhar Bhandare, Dulal Panda and Ambarish Kunwar, Delineating the Interaction of Combretastatin A-4 with αβ tubulin Isotypes present in Drug Resistant Human Lung Carcinoma using a Molecular Modeling Approach, Journal of Biomolecular Structure and Dynamics (2019) DOI: 10.1080/07391102.2019.1577174

2. Bajarang Vasant Kumbhar, Dulal Panda and Ambarish Kunwar, Interaction of microtubule depolymerizing agent indanocine with different human αβ tubulin isotypes, PLoS ONE 13(3): e0194934 (2018)

3. Bajarang Vasant Kumbhar, Anubhaw Borogaon, Dulal Panda and Ambarish Kunwar, Exploring the Origin of Differential Binding Affinities of Human Tubulin Isotypes αβII, αβIII and αβIV for DAMA-colchicine using Homology Modelling, Molecular Docking and Molecular Dynamics Simulation, PLoS ONE 11(5): e0156048 (2016)

BME 3: Computational study of cargo positioning by a team of molecular motor proteins (AKun)

Eukaryotic cells employ motor proteins for transporting organelles and vesicles from one location to another in a regulated and directed manner. These molecular motor proteins are mechano-chemical enzymes that often work collectively as a team while transporting cargos. Cytoplasmic dynein and kinesin are two important motor proteins that are involved in bidirectional cargo transport. Biophysical properties of single motor proteins such as velocity changes as temperature and force experienced by motors changes. Goal of this project is to understand how cargos are positioned to different parts of the cells by the motor proteins which are involved in bidirectional transport mediated by cytoplasmic dynein and kinesin motors.

Reference:

1. Weili Hong, Anjneya Takshak, Olaolu Osunbayo, Ambarish Kunwar and Michael Vershinin, The Effect of Temperature on Microtubule-Based Transport by Cytoplasmic Dynein and Kinesin-1 Motors, Biophysical Journal, Vol. 111, 1287 (2016)

2. Anjneya Takshak and Ambarish Kunwar, Importance of anisotropy in detachment rates for force production and cargo transport by a team of motor proteins, Protein Science, Vol. 25, 1075 (2016)

3. Roop Mallik, Arpan Kumar Rai, Pradeep Barak, Ashim Rai and Ambarish Kunwar, Teamwork in Microtubule Motors, Trends in Cell Biology,Vol. 23, 575 (2013)

BME 4: Computational study of isotype specific interaction of motor proteins with microtubules (AKun)

Collective transport and force generation by a team of motor proteins is important for many vital cellular processes including cell division. It is know that microtubules are essential for cell division and therefore they are important targets for many anti-cancer drugs. Overexpression of different tubulin isotypes are associated with drug resistance which arises from inability of various drugs to bind to tubulin. Cancer cells have abnormal mitotic behaviour. Recent experimental observations suggest that functional properties of motor proteins also change in such cancer cells where overexpression of different tubulin isotypes are observed. However, a molecular level understanding of how the interaction of different motor proteins involved in mitosis changes in presence of different isotypes is still lacking. A molecular level understanding of these interaction would help to design new therapeutic approaches targeting both motor proteins and microtubules, novel formulations to enhance the efficacy of existing anti-cancer drugs and expand their therapeutic spectrum. A combinations of computational approaches combining Molecular Modelling, Molecular docking and Molecular dynamics (MD) simulations will be used in this project to understand motor-microtubule interaction.

Reference:

Mitra Shojania Feizabadi, Babu Reddy J N, Omid Vadpey, Yonggun Jun, Dail Chapman, Steven Rosenfeld and Steven P. Gross“Microtubule C-Terminal Tails Can Change Characteristics of Motor Force Production” Traffic (2015)