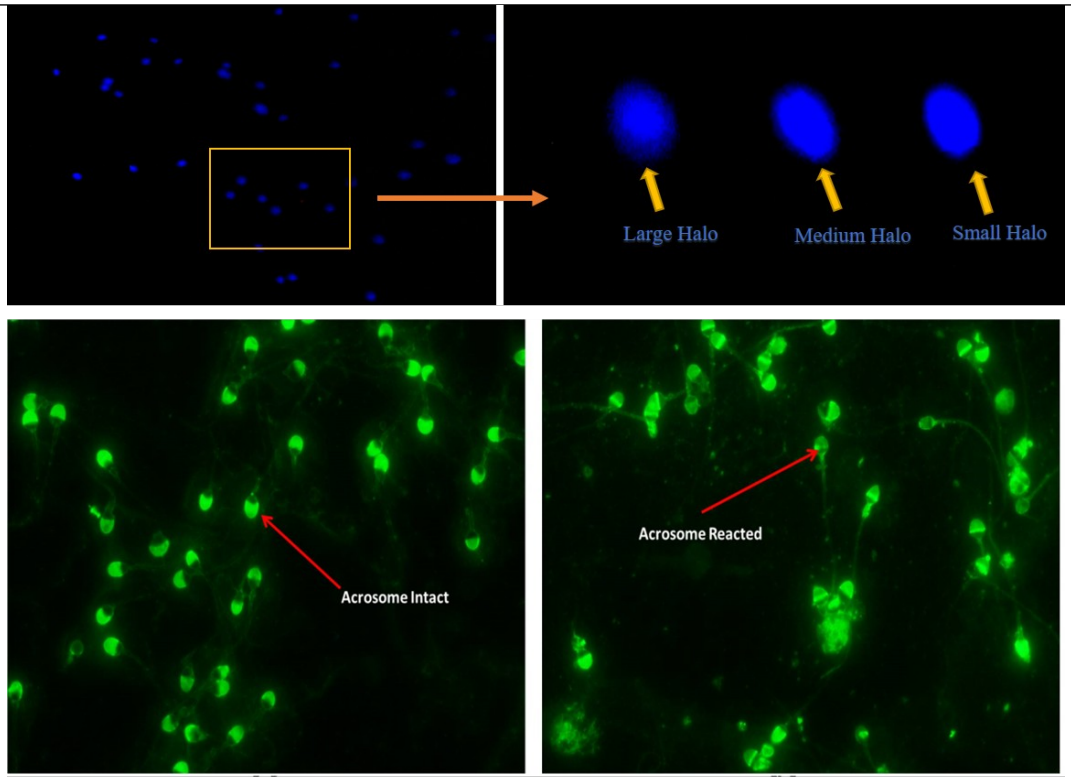
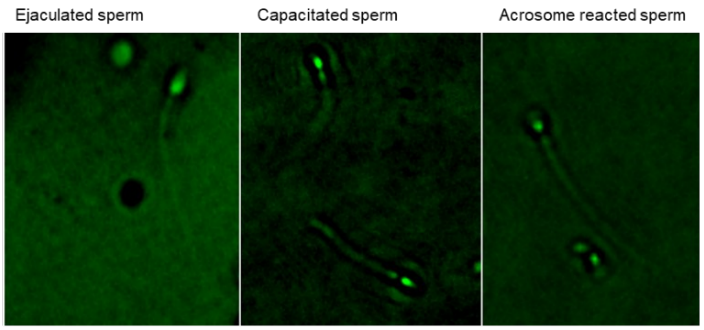
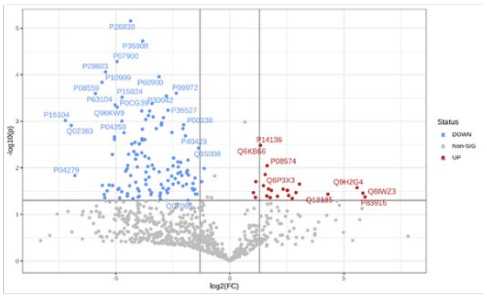
RESEARCH

Prof. Punit Kaur	
Research	My research specialization includes Bioinformatics, Structural Biology, X-ray Crystallography, and Rational Structure Based Drug Design. My research currently focuses on clinically relevant gram-negative bacteria where I have pursued a multidisciplinary approach to understand the antibacterial resistance mechanisms. Experimental and computational methodology including genomic, proteomic and structural analysis have been adopted to understand the mechanisms responsible for antibiotic resistance as well as develop strategies to counter determinants of drug resistance and drug resistant pathogens. I am also extensively working towards determination of molecular interactions of antibiotic resistance proteins and identification of novel antimicrobial scaffolds to bypass antibiotic resistance by exploiting the structural knowledge about the various protein targets for the design of new antibiotics. The various Mur ligase pathway proteins have been characterized and identified as novel drug targets. The biochemically isolated proteins are being processed to design newer molecules as anti-typhoidal compounds. The bacterial protein, DNA Gyrase has been explored as a novel target site for development of antimicrobials. My research also involves whole genome sequencing as a tool for drug development and to elucidate novel resistance genes and resistance mechanisms in clinical isolates of bacterial pathogens. My contributions in the structural biology and drug design projects include structure determinations of various proteins using the tools of X-ray Crystallography (i) Dimeric form of peptidoglycan recognition protein involved in innate cell immunity of action and complexes with various ligands to establish its role as antibacterial agent (ii) lactoperoxidase from various sources and its complexes with different ligands and ions to establish its mechanism of action (iii) a new family of mammary gland proteins - signaling glycoproteins from different (iv) first dimeric disintegrin, a strong integrin antagonist, for design of synthetic anti-coogulant agents (v) ribose inactivating proteins which are involved in plant defence from different plants (vi) several phospholipase A2s from diverse sources, their native as well as co-complexed structures with natural and designed inhibitors and design of potent inhibitors as strong drug candidates against arthritis and inflammation These extensive structural studies have led to a number of lead molecules which were designed against diseases such as inflammation, cancer and microbial infections. In addition to these macromolecular structures, I have contributed to the development of design rules using alpha, beta dehydro-residues for designing specific conformations of peptides. Research interests in bioinformatics include identification of novel targets for drug development, protein homology modeling, molecular docking and virtual screening and detection of lead molecules, identifying the structural basis of diseases due to point mutations and development of databases related to proteins/genes implicated in disorders/cancers.

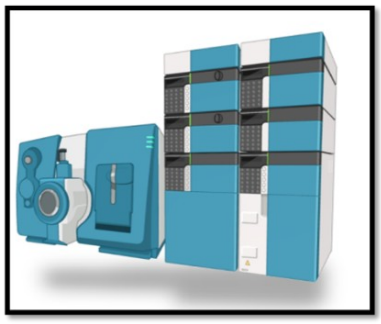
Prof. Savita Yadav	
Research	Prof. Savita Yadav's lab is engaged in reproductive biology and gynaecological cancer research at the interface of Biophysics and Biochemistry with an objective to communicate these findings for the advancement in research and translate these findings for diagnostic and therapeutic purposes. The major thrust area of her research is purification, identification and characterisation of proteins of different biological fluids, which are essential for complete understanding of reproductive physiology. Routinely engaged in the identification of novel proteins which can serve as candidate biomarkers of idiopathic infertility, her lab has pioneered in the identification of heparin binding and Concanavalin A binding proteins of human seminal plasma, and low abundant proteins of amniotic fluid. Broadly, her lab is working towards identification of markers of infertility in seminal plasma and sperm, markers of idiopathic recurrent pregnancy loss in sperm, markers for early detection of ovarian and cervical cancers in saliva. In addition, her lab is credited with purification of several proteins of clinical relevance, viz. HE-4, HSA, PSA, lactoferrin, and protein complexes – ZAG-PIP and HSA-PIP from native sources, i.e. seminal plasma, characterised them biochemically and functionally. Some of the recent research findings of prof. Yadav's lab include – 1. Proteomic changes in human spermatozoa during in vitro capacitation and acrosome reaction (Andrology, 2022): This study generated dynamic information about proteomic alterations in spermatozoa during capacitation and acrosome reaction. Compared to ejaculated spermatozoa, 44 and 141 proteins were found differentially expressed in capacitated and acrosome reacted spermatozoa, respectively. As expected, a large number of proteins were found downregulated, including clusterin, pyruvate dehydrogenase E1 component, semenogelin-1 and 2, heat shock protein 90, beta-microseminoprotein and keratin. 2. Identification of sperm proteins contributing to idiopathic recurrent pregnancy loss. (Reprod. Biol. 2021): Sperm proteins were identified by LC-MS/MS, and performed stringent statistical analysis for the selection of candidate biomarkers of iRPL. Seven proteins, viz. lactotransferrin, ATP synthase subunit beta mitochondrial, fatty acid synthase, anterior gradient protein 2 homolog, hemoglobin subunit beta, short-chain specific acyl-CoA dehydrogenase mitochondrial, cytoplasmic dynein 1 heavy chain, and 14-3-3 protein sigma were selected as plausible markers of iRPL. This study concluded an association between oxidative stress and iRPL. 3. MMRN1 expression in ovarian cancer (Mol. Biol. Reports, 2020): MMRN1 expression is associated with EOC progression and it has a potential to serve as biomarker of early-stage EOC detection. 4. Identification of differentially expressed proteins to evaluate fertility status in leukemia survivors. (Reprod. Biol., 2019): Differential proteome profiling was performed by 2D-differential in-gel electrophoresis, protein spots were identified by mass spectrometry and selective differentially expressed proteins (DEPs) were validated by western blotting and ELISA method. Out of eight DEPs identified, five proteins (isocitrate dehydrogenase 1,

	semenogelin 1, lactoferrin, prolactin-inducible protein, and human serum albumin) were upregulated and three (pepsinogen, prostate specific antigen and prostatic acid phosphatase) were downregulated. Expression profiles of these proteins are suggestive of reduction in semen quality in ALL survivors 5. Salivary protein signatures for early detection of ovarian cancer. (Int. J. Biol. Macromol., 2017): Differentially expressed SPS were identified by fluorescence-based 2D-DIGE coupled with MALDI/TOF-MS. The expression levels of three differential proteins (Lipocalin-2, indoleamine-2, 3-dioxygenase1 (IDO1) and S100A8) were validated using western blotting and ELISA. Immunohistochemistry and qRT-PCR were performed in an independent cohort of ovarian tumor tissues. 6. Proteomics markers of asthenozoospermia. (Mol. Cell. Proteomics, 2016): This study identified altered expression of proteins associated with axoneme activation and focal adhesion assembly, glycolysis, gluconeogenesis, cellular response to stress and nucleosome assembly.
Research Images	 Image: Assessment of sperm DNA Fragmentation (upper panel); Evaluation of acrosome reaction (lower panel)

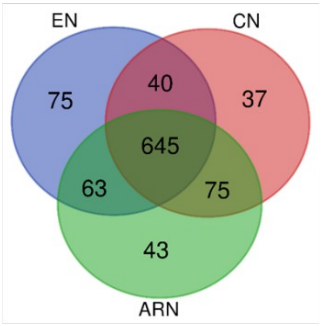


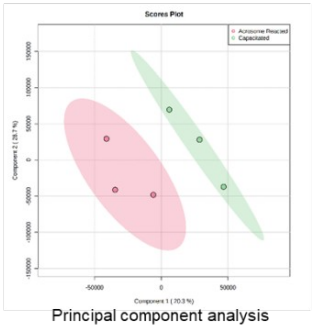


DEPs identified by Volcano plot



LC-MS/MS





Principal component analysis

Image 2: Sperm proteomics. EN=Ejaculated spermatozoa; CN: Capacitated spermatozoa; ARN: Acrosome reacted spermatozoa

Lab Members

Dr. Anil Kumar Tomar
Scientist- D

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Research Associate

Dr. Sunil Kumar Saini
Senior Research Associate

Abhinav Saini
SRF, Ph.D. student

Ayushi Thapliyal
SRF, Ph.D. student

Nivedita Vats
JRF, Ph.D. student

Swati Ranjan
M.Sc. student

Prof. Sharmistha Dey	
Research	The area of research of Dr. Sharmistha Dey is on proteins and peptides of biological significance can be grouped under three broad headings: bio-markers of cancer, bio-markers of ageing and age-related diseases; and plant proteins with therapeutic utility. In the field of ageing research, she has reported the role of some serum protein molecules which can emerge as markers of age associated pathologies namely “frailty”, Alzheimer’s disease and other dementias; and Parkinson’s disease; diagnostic. In the field of cancer research she has published on prognostic biomarkers of oral cancer and breast cancer. She has isolated proteins from ubiquitous plants such as Aloe vera, Bengal gram, ginger and garlic and have reported their therapeutic properties. She is working on therapeutic properties of Ayurvedic plants in in-vitro models of neurodegenerative disorders of ageing. She has established circulating sirtuin group of proteins as an important molecule in ageing biology in phenotypic prototypes such as “frailty”, Alzheimer’s disease and Parkinson’s diseases. Her research on pro-inflammatory proteins: cyclooxygenase and lipoxygenase in breast cancer patients and p38 Map Kinase in head and neck squamous cell carcinoma, as prognostic markers have been well appreciated. She has used surface plasmon resonance technology in most of my research and is considered as an expert in this technology in the country. Her group is actively involved in design and synthesis of peptides with property to modulate the activities of the proteins, which can be of value in drug development in future in cancer and neurodegenerative diseases. She has designed synthesized peptides which are effective against multi-drug resistant microbes. In order to achieve the desired result, she developed successful collaboration with clinicians and scientists within and outside the organization. All her work has been published in international journals. Some of the work has been awarded in national level in different research forum. All her research work has been funded from extramural as well as intramural research grants. She has over 145 publications on various aspects of my research work in reputed and high impact journals.

Lab Members	 **Dr. Sharmistha Dey Lab Members**  Dr. Masroor Anwar Scientist D

Dr. Rashmita Pradhan
Women Scientist

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Ph.D.

Abhinay Kumar Singh
Ph.D.

Sakshi Kumari
Ph.D.

Renu Prajapati
Ph.D.

Abhilasha Nayal
SRF

	 Mohd Suhail Ashar JRF  Priyajit Kaur M.Sc.
Alumni	1. Abhay Kumar Singh, Assistant Professor, Radiation oncology, Washington University in Saint Louis, Email: abhaysingh@wustl.edu 2. Dr. Rishi Somvanshi, Research Associate, University of British Columbia, Vancouver, Canada, Email: rishi.somvanshi@ubc.ca 3. Dr. Rahul Kumar, Assistant Professor, Gitam University, Visakhapatnam, Andhra Pradesh, Email: rkumar2@gitam.edu 4. Dr Kamal, Email: gill.kamal11@gmail.com 5. Dr. Suresh Kumar, Post Doc, University of St. Louis, Email: drsureshk85@gmail.com 6. Dr. Kusum Singh, Email: kusum19@gmail.com 7. Dr. Shashank Shekhar, Post Doc, UT Southwestern Medical Centre, Email: shashank.shekhar@utsouthwestern.edu 8. Dr. Nitish Rai, Assistant Professor, Deptt of Biotechnology, Mohanlal Sukhadia University (MLSU), Udaipur, Rajasthan, Email: nits6691@gmail.com 9. Dr. Vishal Sahu, Post Doc, MD Anderson, USA, Email: vishal.sahu2007@gmail.com 10. Dr. Vertica Agnihotri, Post Doc, John's Hopkins University, USA, Email: vertica.agnihotri13@gmail.com 11. Dr. Amrendra Pratap Singh, Post Doc, Stony Brook University, USA, Email: amrendra.bt@gmail.com 12. Dr. Vijay Goel, Associate Professor, Jawaharlal Nehru University, Email:

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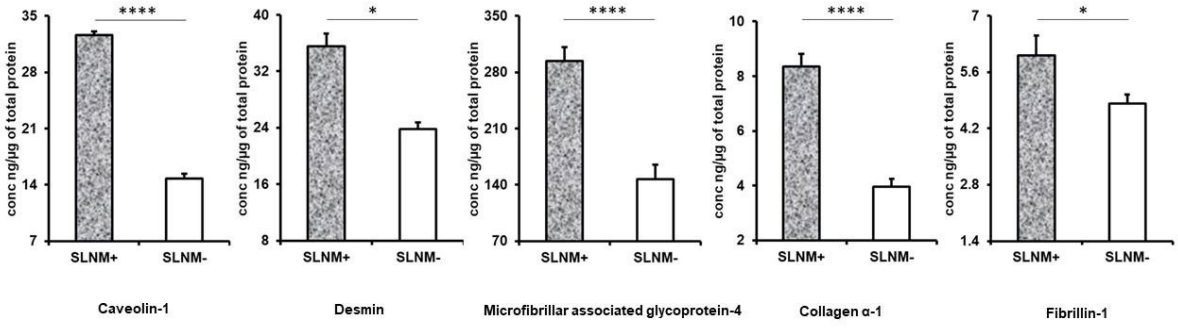
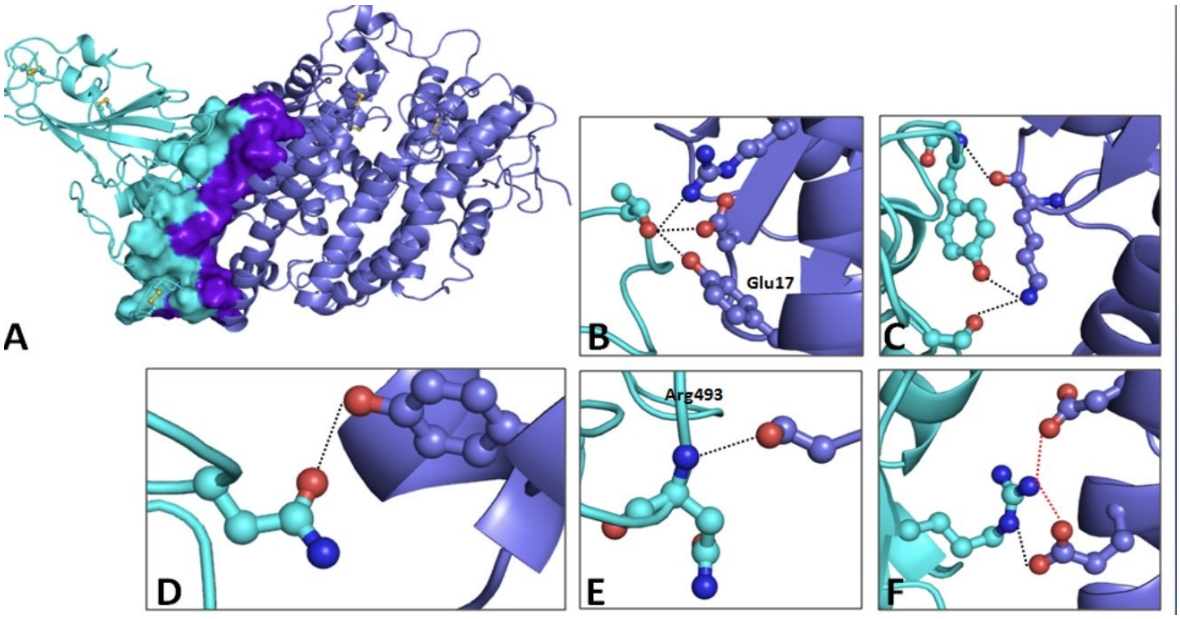
Prof. Hariprasad G.	
Research	**Proteomics of sentinel lymph nodes for identification of Extracellular matrix proteins to flag metastasis in early breast cancer:** Patients with early breast cancer are affected by metastasis to axillary lymph nodes. Metastasis to these nodes is crucial for staging and quality of surgery. Sentinel Lymph Node Biopsy that is currently used to assess lymph node metastasis is not effective. This necessitates identification of biomarkers that can flag metastasis. Early-stage breast cancer patients were recruited. Surgical resection of breast was followed by identification of sentinel lymph nodes. Fresh frozen section biopsy was used to assign metastatic and non-metastatic sentinel lymph nodes. Discovery phase included iTRAQ proteomics coupled with mass spectrometric analysis to identify differentially expressed proteins. Data are available via ProteomeXchange with identifier PXD027668. Validation was done by bioinformatic analysis and ELISA. There were 2398 unique protein groups and 109 differentially expressed proteins comparing metastatic and non-metastatic lymph nodes. Forty nine proteins were up-regulated, and sixty proteins that were down regulated in metastatic group. Bioinformatic analysis showed ECM-receptor interaction pathways to be implicated in lymph node metastasis. ELISA confirmed up-regulation of ECM proteins in metastatic lymph nodes. ECM proteins have requisite parameters to be developed as a diagnostic tool to assess status of sentinel lymph nodes to guide surgical intervention in early breast cancer.  **Structural modeling of Omicron spike protein and its complex with human ACE-2 receptor: Molecular basis for high transmissibility of the virus** Omicron is a new variant of SARS-CoV-2, which is currently infecting people around the world. Spike glycoprotein, an important molecule in pathogenesis of infection has been modeled and the interaction of its Receptor Binding Domain with human ACE-2 receptor has been analysed by simulation studies. Structural analysis of Omicron spike glycoprotein shows the 30 mutations to be distributed over all domains of the trimeric protein, wherein the mutant residues are seen to be participating in higher number of intra-molecular interactions including two salt bridges emanating from mutant residues thereby stabilizing their conformation, as compared to wild type. Complex of Receptor Binding Domain (RBD) with human ACE-2 receptor shows four mutations at interacting interface comprising of two ionic interactions, eight hydrogen bonds and seven Van der Waals interactions. The number and quality of these interactions along with other binding biophysical parameters suggests more potency of RBD

	domain to the receptor as compared to the wild type counterpart. Results of this study explain the high transmissibility of Omicron variant of SARS-CoV-2 that is currently observed across the world. 
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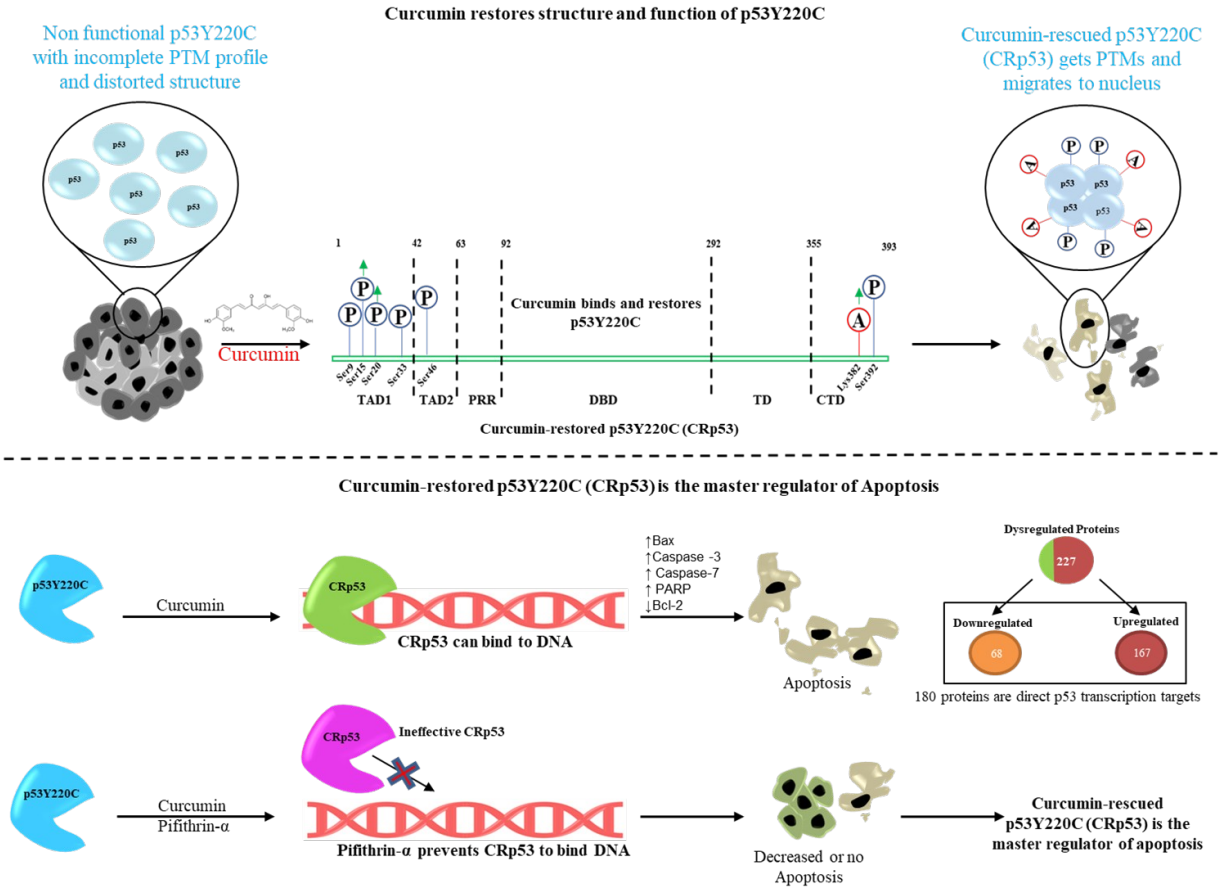
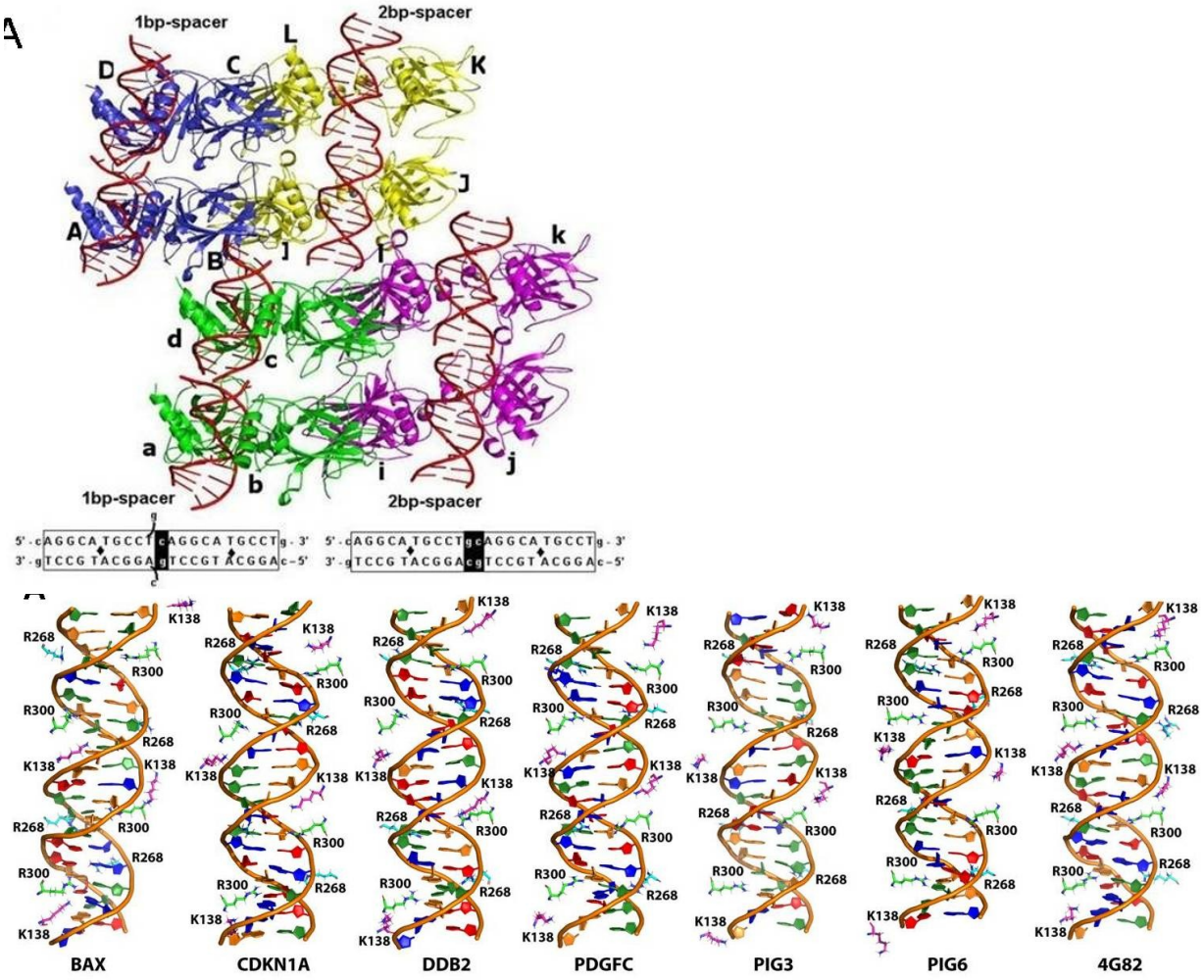
Dr. Ethayathulla Abdul Samath	
Research	In my research laboratory, we are interested in understanding the effect of missense mutations in p53 molecular structure and function, enabling us to answer specific questions about the loss of p53 function in cancer. Our lab focuses on structural mutants of p53, where the protein becomes non-functional due to loss of fold. We use biophysical, biochemical, computational, X-ray crystallography, and in vivo cell-based studies to identify small molecule chaperones from natural sources or by chemical design to reactivate mutant p53 to functional protein to prevent tumorigenesis. Restoring mutp53 function to its wild type by selectively targeting the structural crevice with small molecules is a pivotal strategy to promote apoptosis. Our lab is also focused identification of cellular pathways upregulated or downregulated upon p53 mutation by proteomics. Recently, we have shown that curcumin binds and rescues mutp53Y220C to an active wild-type conformation and restores its apoptotic transcription function in BxPC-3-pancreatic cancer cells. (Malhotra et al. 2021; 2022)  Our lab also works on the p53 family protein p73, a functional and structural homolog of p53. Although it was identified in 1997 and considered as an isoform to mimic p53 functions, recently it is identified as a master regulator of diverse processes like embryonic development, tissue homeostasis, and cancer. Overexpression of p73 can activate typical p53-responsive genes, and activation of p73 has been implicated in apoptotic cell death induced by aberrant

cell proliferation and some forms of DNA damage. The promiscuous nature of recognizing both cell fate and development genes and the underlying RE selectivity mechanism by p73 is not well understood. Recently, we solved the crystal structure of p73 DNA binding domain in complex with DNA promoter sequence and proposed a mechanism for recognizing promoter sequences (Koley et al. 2022)



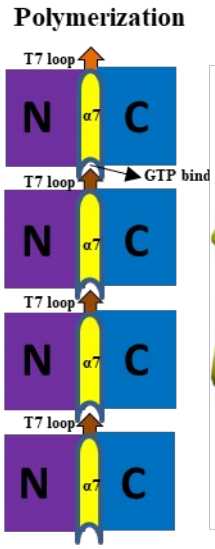
We also work on the identification of lead compounds for the development of antibacterial drugs against MDR pathogens. Our research drug targets are bacterial cell division proteins essential for bacterial cytokinesis.

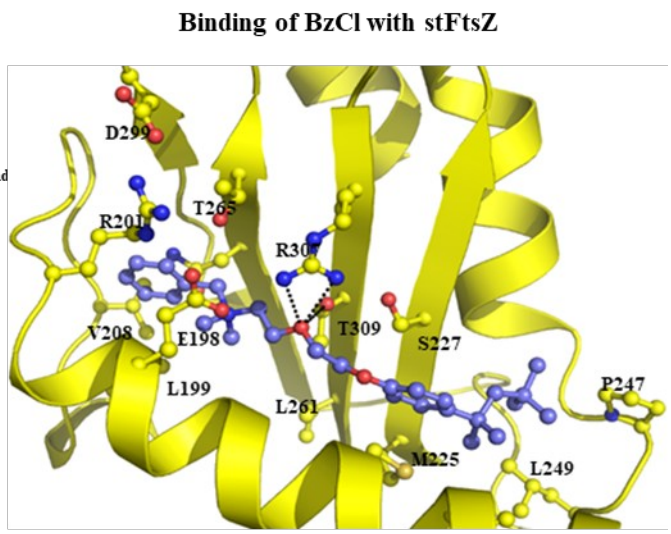
Recently by the computational-based drug repurposing of FDA-approved compounds, we have identified an inhibitor of bacterial cell division protein FtsZ from Salmonella Typhi.

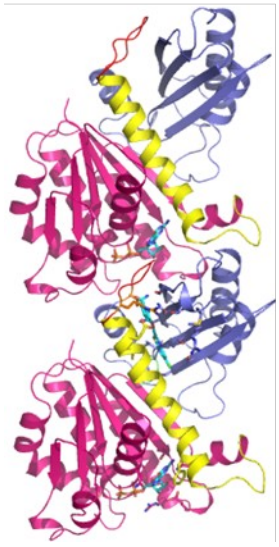
The drug BzCl targets stFtsZ at the hydrophobic cleft formed between the C-terminal domain and helix α7 with a binding energy of -8 kcal/mol. At 8 µM concentration it inhibits stFtsZ GTPase activity by 80% and prevents polymerization and the drug BzCl has excellent antibacterial activity against the bacterial culture of Salmonella Typhi, Staphylococcus aureus and Escherichia coli with the MIC values of 8 µg/mL, 1 µg/mL and 12 µg/mL, respectively. Based on our current study, the scaffold of BzCl can be used for the development of broad-spectrum antibacterial agents against drug-resistant pathogens(Naz et al. 2020; 2022).

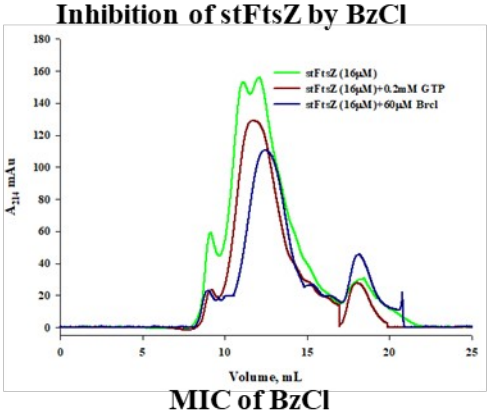
The knowledge generated from these studies has practical significance as a lead molecule to

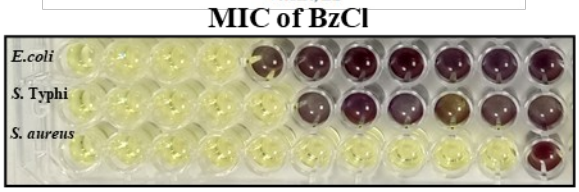
design more potent drugs against MDR pathogens for pharmacological intervention.











Lab Members

Dr. Saurabh Sharma
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Alankrita Singh
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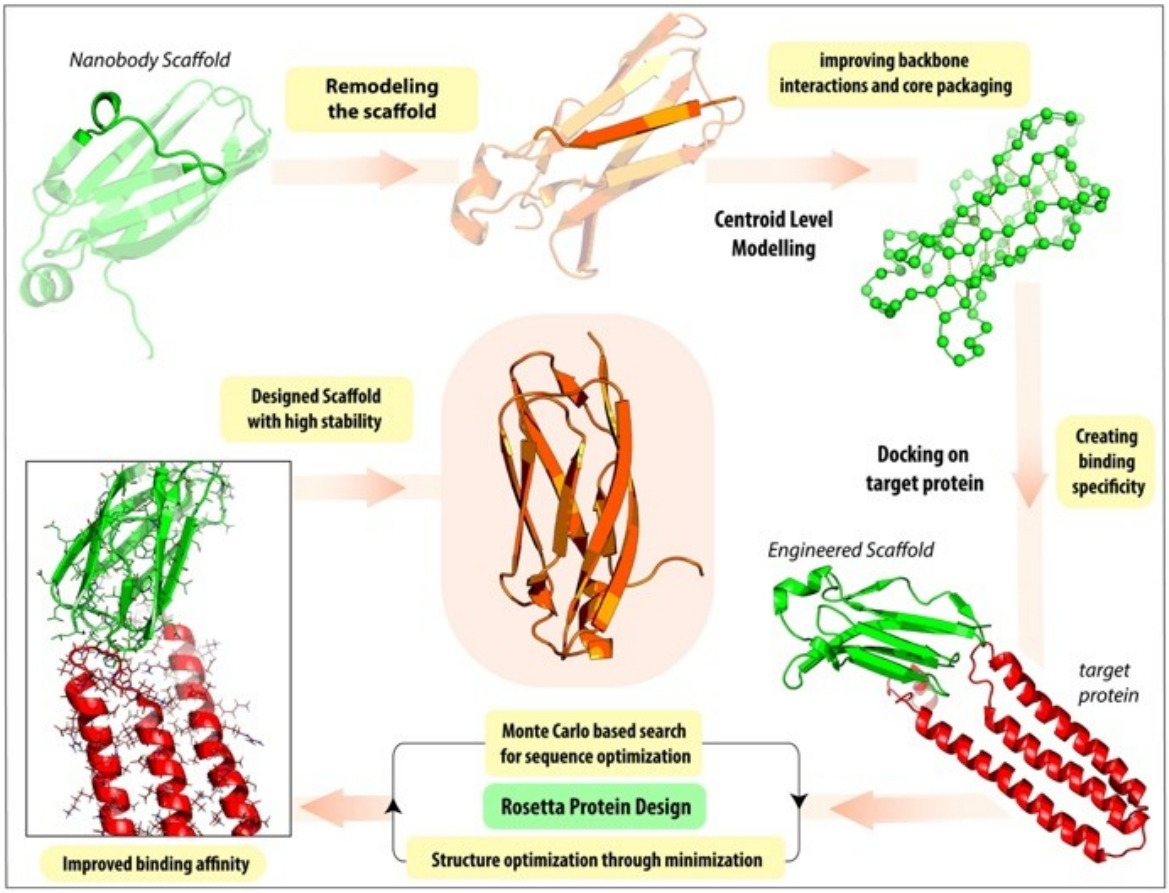
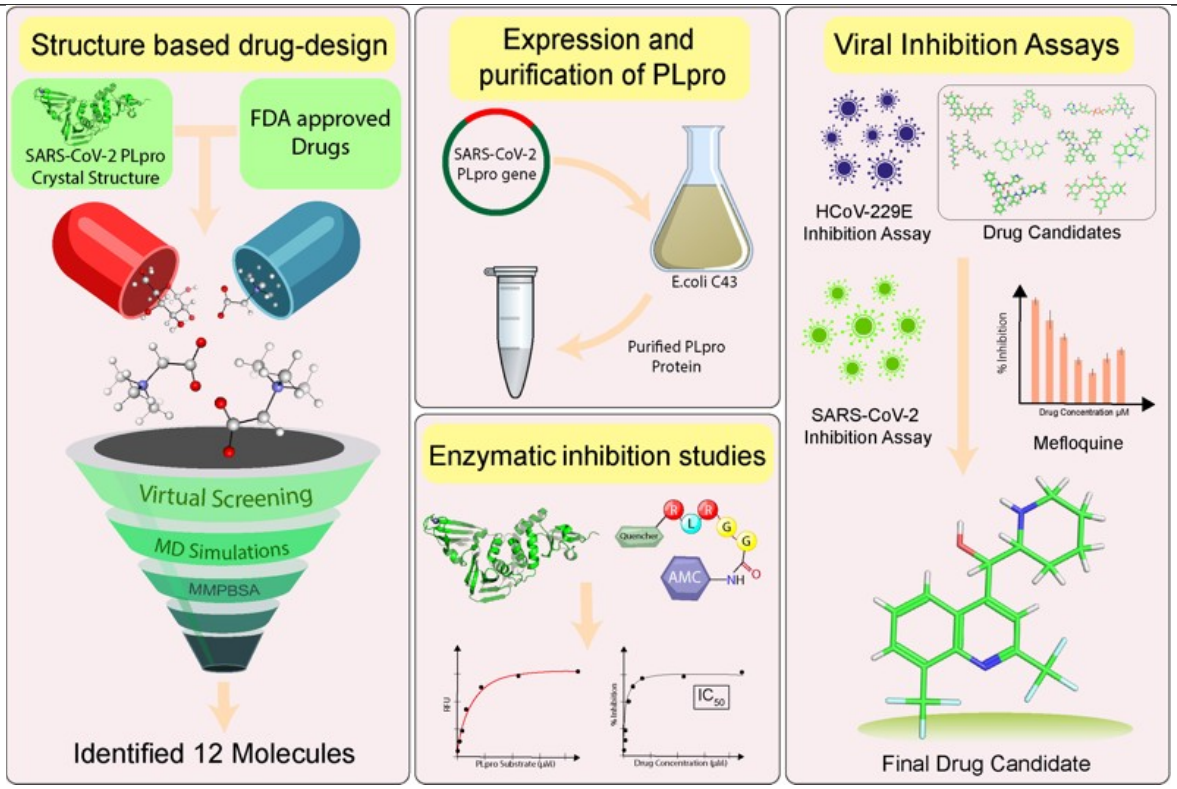
Dr Krishna Kishore Inampudi	
Research	1. **Lung Cancer (NSCLC) therapeutics:** Our main focus is designing the inhibitor molecules against Epidermal Growth Factor Receptor (EGFR), a major drug target validated for treating several cancers, including NSCLC. Although tyrosine kinase inhibitors (TKIs) hold a crucial place in the treatment regime for EGFR-positive NSCLC, the potential of protein therapeutics has not been harnessed since no monoclonal antibody is currently FDA-approved for the treatment of NSCLCs. The foibles of antibodies can be overcome with nanobody scaffolds like fibronectin (^{10}Fn3). The small size and stability of fibronectin propound it as a candidate for anticancer therapeutics. Our current research focuses on developing fibronectin-based molecules to treat NSCLC by integrating protein engineering with structural biology. We employ computational protein design to engineer fibronectin specific to the extracellular domain of EGFR along with mRNA display to obtain high-affinity binders, followed by their in vitro and in vivo validation. In parallel, we are actively designing and synthesizing the TKI for drug-resistant EGFR kinases to increase overall survival. In this journey, we have confirmed good hits by in vitro assays and cell-based studies. Evaluation and validation of these molecules are in progress. Further, we have also been involved in identifying Aptmer inhibitors against EGFR by SELEX and Cell-based methods.  2. **Multi-omics and Biomarkers:** Understanding the disease mechanism is critical for identifying biomarkers and establishing potential drug targets. We are interested in

	NSCLC, Oral Squamous Cell Carcinoma (OSCC), and Coronary Artery Disease (CAD) to find molecular alterations using a multi-omics approach. Blood has traditionally been used for the discovery of biomarkers in these diseases. For this purpose, we are studying the exosomal miRNA, proteome profiling, and whole blood metabolomics of disease patients in comparison to age & gender-matched healthy individuals in the Indian population. Integration of multi-omics approaches like miRNomics, proteomics and metabolomics will provide a panoramic view of the disease and allow the identification of potential biomarkers. This will help screen the NSCLC, OSCC and CAD for better patient care management. 3. **Understanding the catalytic mechanism of the peptidyl-tRNA hydrolase and designing the small molecule inhibitors for M. tuberculosis:** The bacterial translation system is a target for several major classes of antibiotics, including molecules that block translation rescue factors. Peptidyl-tRNA hydrolase (PtH) is a critical rescue factor in the translation mechanism and established drug target against bacterial pathogens. My group is trying to understand the PtH catalytic mechanism with stable peptidyl-tRNA analogues using X-ray crystallography, NMR and computational modelling. Using this information, we have identified a few small molecule inhibitors and their validation studies are in progress. The long-term goal is to find a potential inhibitor against PtH to combat drug-resistant tuberculosis. 4. **Identification of small molecule drugs against viral non-structural proteins:** Identifying the potential small molecule inhibitors against the conserved non-structural proteins is crucial since the mutations in the structural proteins make the available vaccines feeble. My lab employs computer-aided drug design (CADD) methodologies to identify potential inhibitors and validate them against viral proteases and RNA-dependent RNA polymerase (RdRp). Specifically, our long-term goal is to develop broad-spectrum antivirals that are equally potent against all the known pan-coronavirus and Dengue pan-serotypes. Recently, our lab has identified mefloquine (FDA-approved) as a promising inhibitor of papain-like protease (PLpro) from SARS-CoV2.



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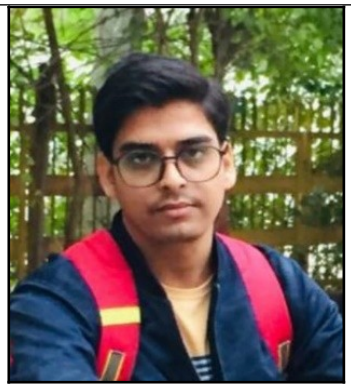
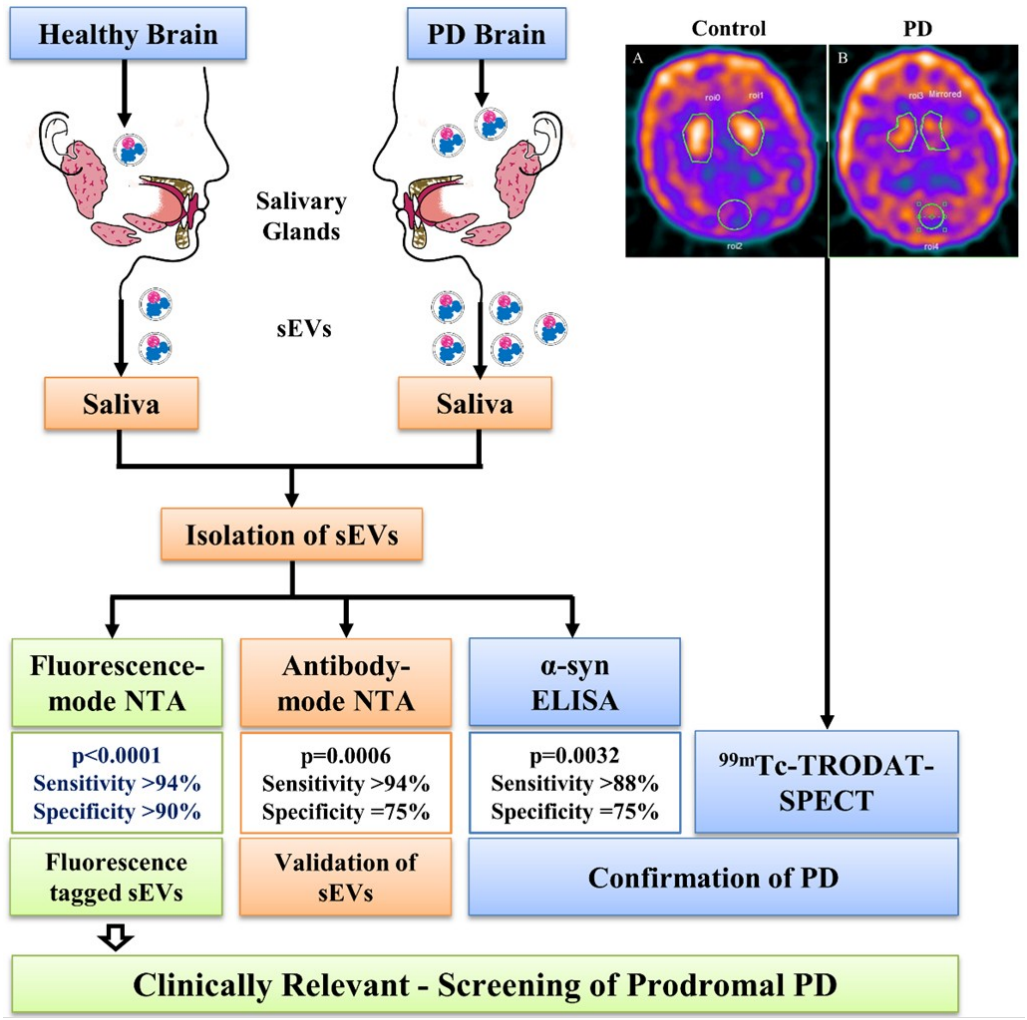
	 Kamal Ph.D. Student kamalbaswal13@gmail.com  Dr. Vishal Yadav M.D. Student imdrvishal@gmail.com  Saras H Tiwari Project Staff sarastiwari12@gmail.com
Alumni	Dr. Asad Reza (M.D. Biophysics) Ms. Prachi Jain (M.Sc. Biophysics) Ms. Irene Elsa Abraham (M.Sc. Project Trainee) Mr. Akbar Mutasa (M.Sc. Project Trainee)

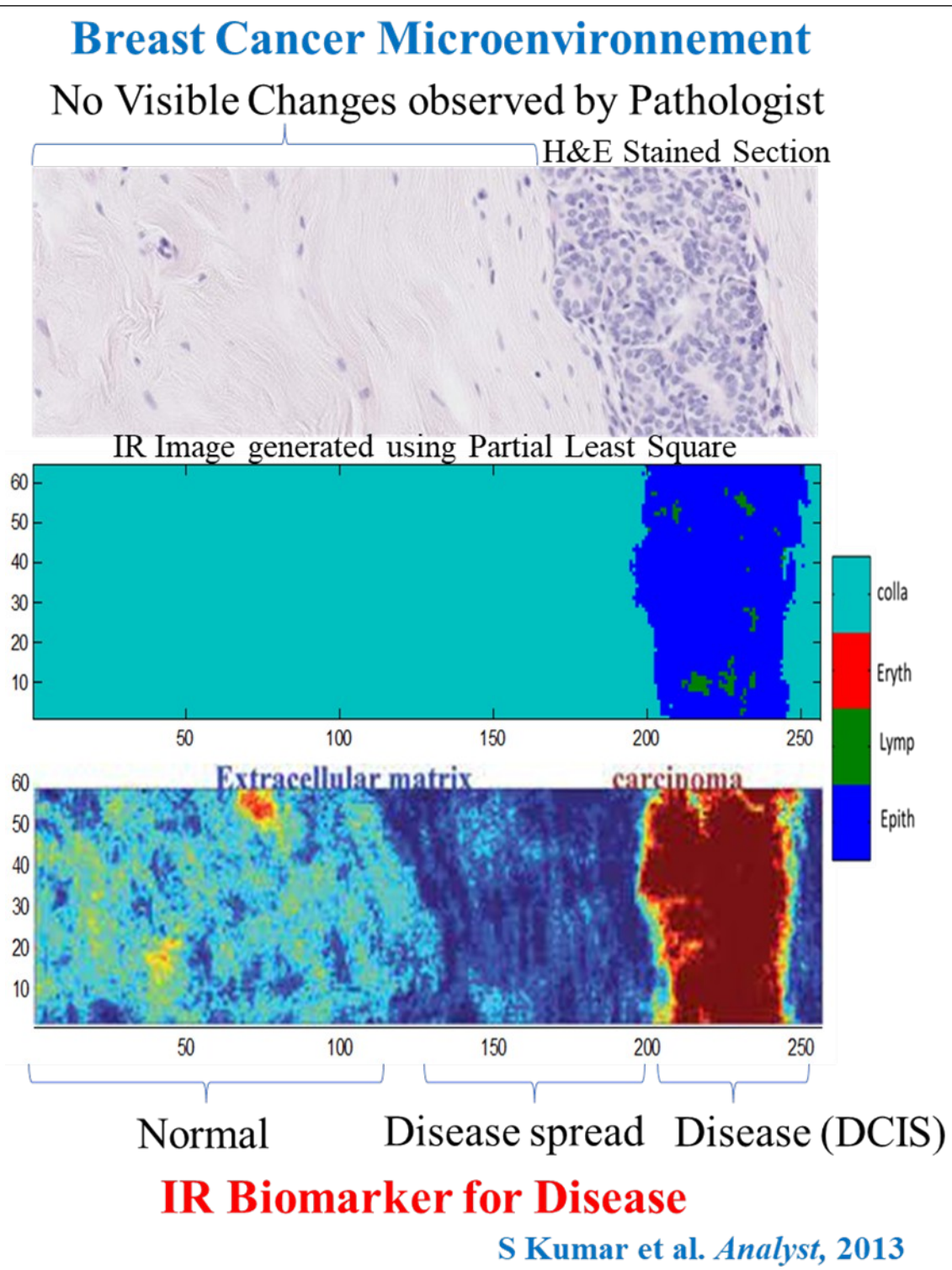
	Ms. Nishika Sabharwal (M.Sc. Project Trainee) Mr. Jeebak Deoghuria (M.Sc. Project Trainee)

Dr. Saroj Kumar	
Research	Dr Saroj has taken part in successfully developing the three methods for infrared spectroscopy and a method for exosome isolation (see patents). He is also an adjunct faculty at the Lulea University of Technology, Sweden under MedTech4Health. At AIIMS, he has established the infrared-based bio-imaging laboratory for bio-diagnosis. He also initiated to develop the exosome-based diagnostic and therapeutic modalities for neurodegenerative (Parkinson's and Alzheimer's) and cancer diseases. His laboratory becomes a leading place for exosome-based research. His current research projects include (for details: **www.skumarlab.com**): 1. **New ways to develop an early screening methodology and to evaluate the drug response in Parkinson's and Alzheimer's diseases:** Parkinson's (PD) and Alzheimer's (AD) diseases are chronic progressive neurodegenerative diseases. To date, there is no effective treatment to arrest disease progression hence these diseases have a huge burden on the health care system. In recent years, the role of exosomes in the pathogenesis of various types of cancers as well as neurodegenerative diseases is studied. We aim to isolate (see patents), characterize and validate the exosomes from the patient samples and develop a non-invasive method to correlate the exosome level with disease severity. This target is to be a potential cost-effective novel biomarker for diagnostic approaches. Also, we are focusing on the identification and validation of novel biomarker targets using target-free multi-omics approaches. We are also taking part in the development of novel probes and drugs/compounds for improving diagnosis as well as therapeutics in AD (see patents).

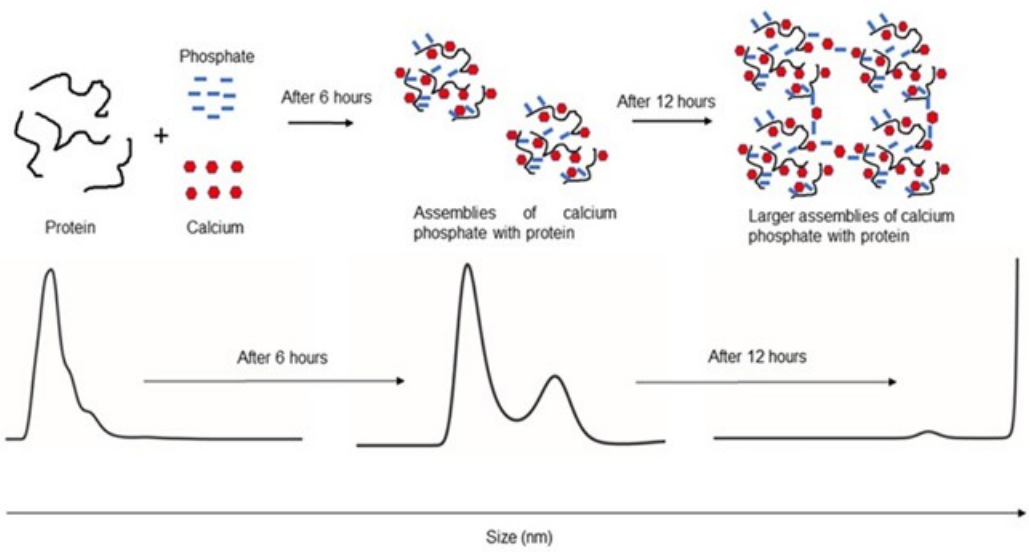


Rastogi S et al., 2022 (under publication)

2. **Understanding Breast Cancer Microenvironment and Utilizing FTIR imaging to improve bio-diagnosis:** Breast cancer is a major global health issue. Despite extensive research and different tools that have been developed to assist clinicians in selecting patients who should receive adjuvant therapy, it remains a challenge. We are developing method to improve diagnosis where no reagent and special sample preparation is required for FTIR imaging to make this technique very economical. Accompanying this method, exploiting the role of fibroblast in breast cancer microenvironment is important in understanding the pathogenesis of the disease. This technique gives information on chemical changes that started with the initiation of disease; hence helps the clinician for early detection and increased the rate of survival. The long-term purpose is to develop the infrared biomarker-based methodology for other cancer and neurodegenerative disease.



3. **Understanding the tooth biomineralization:** Our present work describes an efficient method for isolation and purification of protein extracts from four types of human teeth i.e., molar, premolar, canine, and incisor. Detailed structural characterization of these protein extracts was done through various biophysical techniques which showed for the first time that a major fraction of the proteins present is unstructured in nature. We have also shown these protein extracts have elevated the mineralization of calcium phosphate, compared to

	controls. This means these protein extracts are potent enough to be used as "effective mineralization agents". Our current biophysical study provides novel insights into the structural characterization of proteins of human teeth, in understanding tooth biomineralization. This is the first of its kind of study in the area of medical life sciences. **Our proposed mechanism for teeth biomineralization**  Source: Sharma, V. et al. Characterization of protein extracts from different types of human teeth and insight in biomineralization. Scientific Reports 9, 9314, doi:10.1038/s41598-019-44268-2 (2019).
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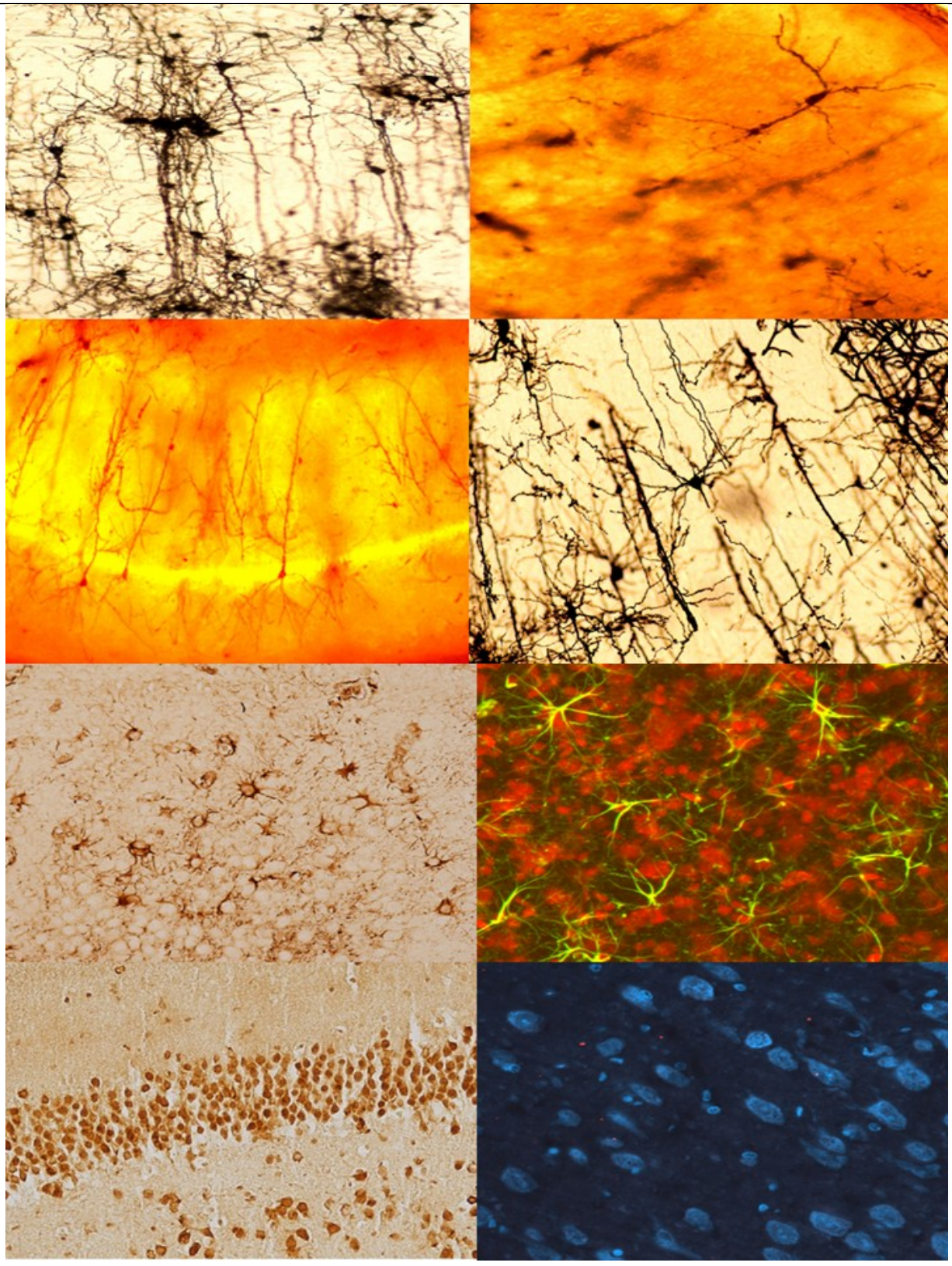
Dr Jyotirmoy Banerjee	
Research	We are primarily involved in studying the function of ion channels involved in synaptic transmission. We are investigating the abnormal synaptic transmission associated with drug-resistant epilepsy (DRE). The major emphasis of our research is directed towards identifying aberrant epileptogenic networks at cellular level and its correlation with clinical findings. We have established a unique facility, where whole-cell patch clamp recordings can be performed on resected brain specimens obtained from patients with DRE. Our work on resected brain samples from patients undergoing epilepsy surgery, using a complementary and multi-disciplinary approach, has further highlighted the importance of neurotransmitter-mediated events in genesis of epileptiform activities in DRE. Our lab is involved in identifying pathology-specific alteration in synaptic transmission recorded from resected brain specimens obtained from the epileptogenic zone of patients with DRE and its correlation with the electro-clinical findings. Our lab also employs Golgi-Cox staining and immunohistochemistry-based experiments to study neuronal networks and its regulation at cellular and molecular level. We are using resected brain specimens obtained from patients undergoing epilepsy surgery and brain samples from animal models of DRE for our investigations. We have shown that the endogenous NMDA receptor activity plays a crucial role in generating hyperexcitable networks in patients with TLE, most common form of DRE. Spontaneous glutamatergic activity recorded from pyramidal neurons in the hippocampal and anterior temporal lobe of patients undergoing epilepsy surgery for TLE, as well as in animal model of TLE, helped identify two resting state networks. This was the first direct evidence of two independent networks at cellular level in TLE. We have further shown that brain levels of kynurenic acid, an endogenous NMDA receptor inhibitor, was significantly reduced in patients with TLE, suggesting possible reason for enhanced endogenous NMDA receptor activity in TLE. In case of focal cortical dysplasia (FCD), most common substrate of paediatric DRE, we found a tight association between GABAA receptor function and age-at-epilepsy-onset. In addition, we have shown that enhanced levels of benzodiazepine (BZD)-insensitive α4-containing GABAA receptors could be contributing to BZD resistance in resected brain samples obtained from patients with DRE. This suggests that selectively targeting α4-containing GABAA receptors may lead to improved seizure outcome in patients with DRE. We are also investigating the molecular mechanisms of alteration in synaptic transmission in animal models of DRE as well as patient samples. For this in addition to patch-clamp electrophysiology, we have been employing comparative transcriptomics (RNA sequencing), genomics (whole-genome sequencing), and lipidomics and proteomics (mass spectrometry) to identify molecular mechanisms of drug resistance and epileptogenesis in various DREs such as TLE, FCD, Rasmussen's' encephalitis, tuberous sclerosis complex, and glial and glioneuronal tumors. In case of dysembryoplastic neuroepithelial tumors (DNTs), we observed increased glutamatergic transmission and altered expression of glutamatergic synapse pathway genes in the epileptogenic cortical tissues resected from these patients. We also provided first report of

	epigenetic mechanism of aberrant activation of mTOR pathway in FCD.
Research Images	 Image showing morphological changes in neurons in slice preparations of brain samples of animal model of DRE using Golgi-Cox staining, immunohistochemistry and immunofluorescence techniques.

We are trying to bridge the gap between clinical and basic research to enhance our understanding of aberrant neuronal networks, better diagnosis and localization of the epileptogenic foci and to foster newer techniques for treatment of DRE.

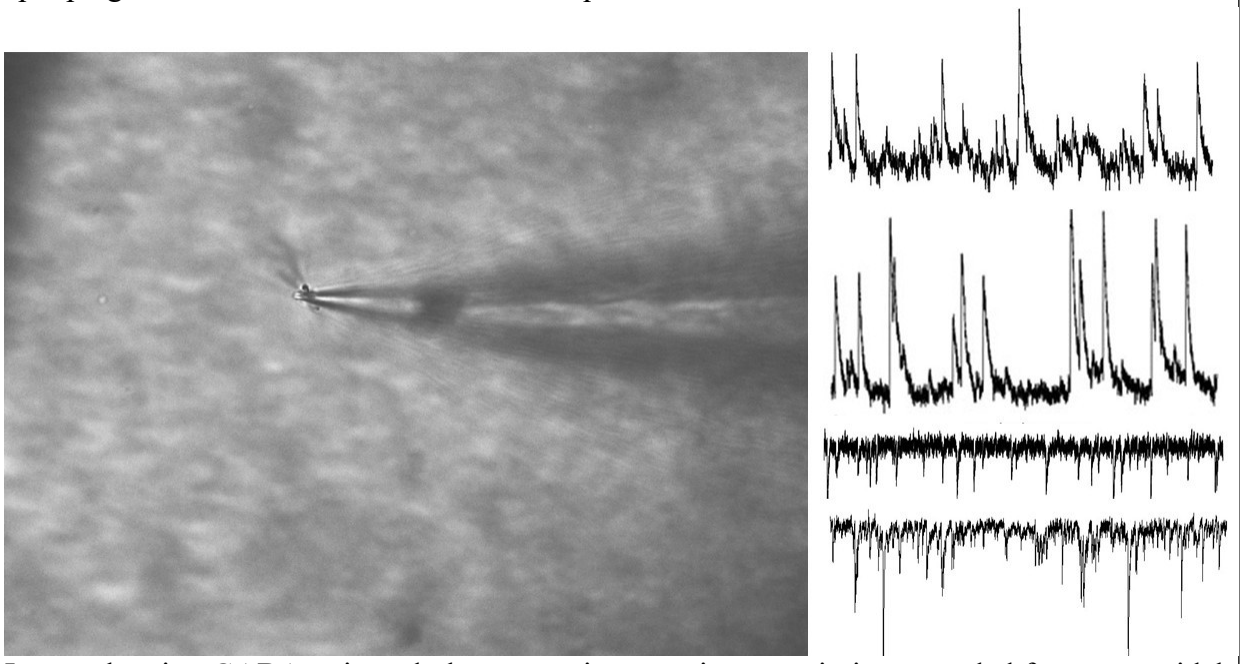


Image showing GABAergic and glutamatergic synaptic transmission recorded from pyramidal neurons in resected brain specimens obtained from patient with DRE.

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Left to right. Aryan, Shreesha Nambiar, Vivek Dubey, Mahendar Kumar, Yogesh Aggarwal, Dr. Jyotirmoy Banerjee

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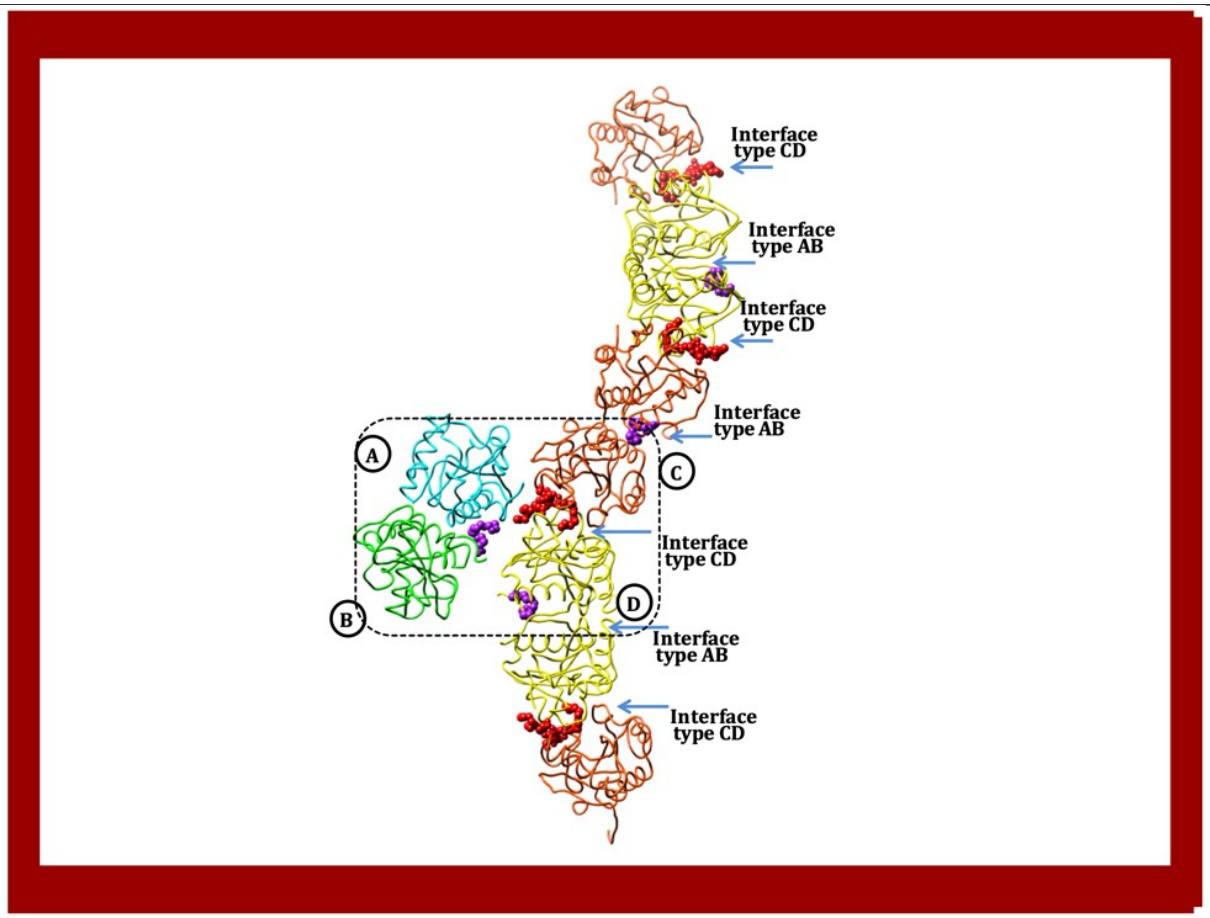
Dr. Pradeep Sharma	
Research	Our laboratory is currently working on proteins of metabolic pathways and infectious diseases (Mucormycosis and Covid-19) by combining tools of structural biology, bioinformatics, biophysical techniques. Bacteria, Plants and yeasts all have enzymes to synthesize Histidine (His). However it cannot be synthesized *de novo* in humans due to the absence of equivalent enzymes. Metabolic pathways are required for the maintenance of homeostasis for the survival of bacteria. The ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp*.) are the leading cause of nosocomial infections all over the world. Most of them are multidrug resistant, which is a greatest challenge to global public health. Understanding the resistance mechanisms of these bacteria is crucial for the development of novel antimicrobial agents. The ESKAPE pathogens causing multidrug resistance, makes Histidine in ten steps reaction, even a single histidine pathway gene knockout significantly affects bacterial growth. In this context, the 3-D structures of these enzymes (HisB, HisC, HisG, etc.) will be helpful in elucidating the molecular mechanisms and to design novel potential inhibitors through a structure-based approach. We have determined the crystal structure of ATP-phosphoribosyltransferase (HisG) from *Acinetobacter baumannii* which catalyses the enzymatic transfer of the phosphoribosyl group to the nucleotide base in the presence of Mg^{2+} ions. Over the past few years, we have determined high resolution crystal structure of Signalling protein-40 (SPX-40) and Peptidoglycan recognition proteins (PGRPs) as the protein antibiotics that can kill various pathogenic bacteria and help in boosting the immune system by binding to various pathogenic associated molecular patterns (PAMPs) in the human body. The X-ray intensity data collection of the diffractable crystals was done at synchrotron radiation sources ESRF, France and DESY, Germany. The ligand binding studies were performed in real time using surface plasmon resonance and fluorescence spectroscopic techniques. In order to establish the role of PGRP-S as potential antibiotic, the expression of various pro-inflammatory cytokines in the PAMPs augmented blood cells in either presence or absence of PGRP-S was studies with the help of flow cytometer and ELISA kits. The in-vivo beneficial effects of this protein were studied by injecting this protein in the mice experimental models.

Research Images	
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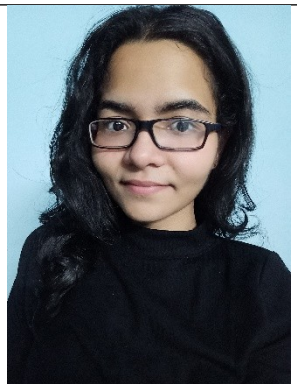

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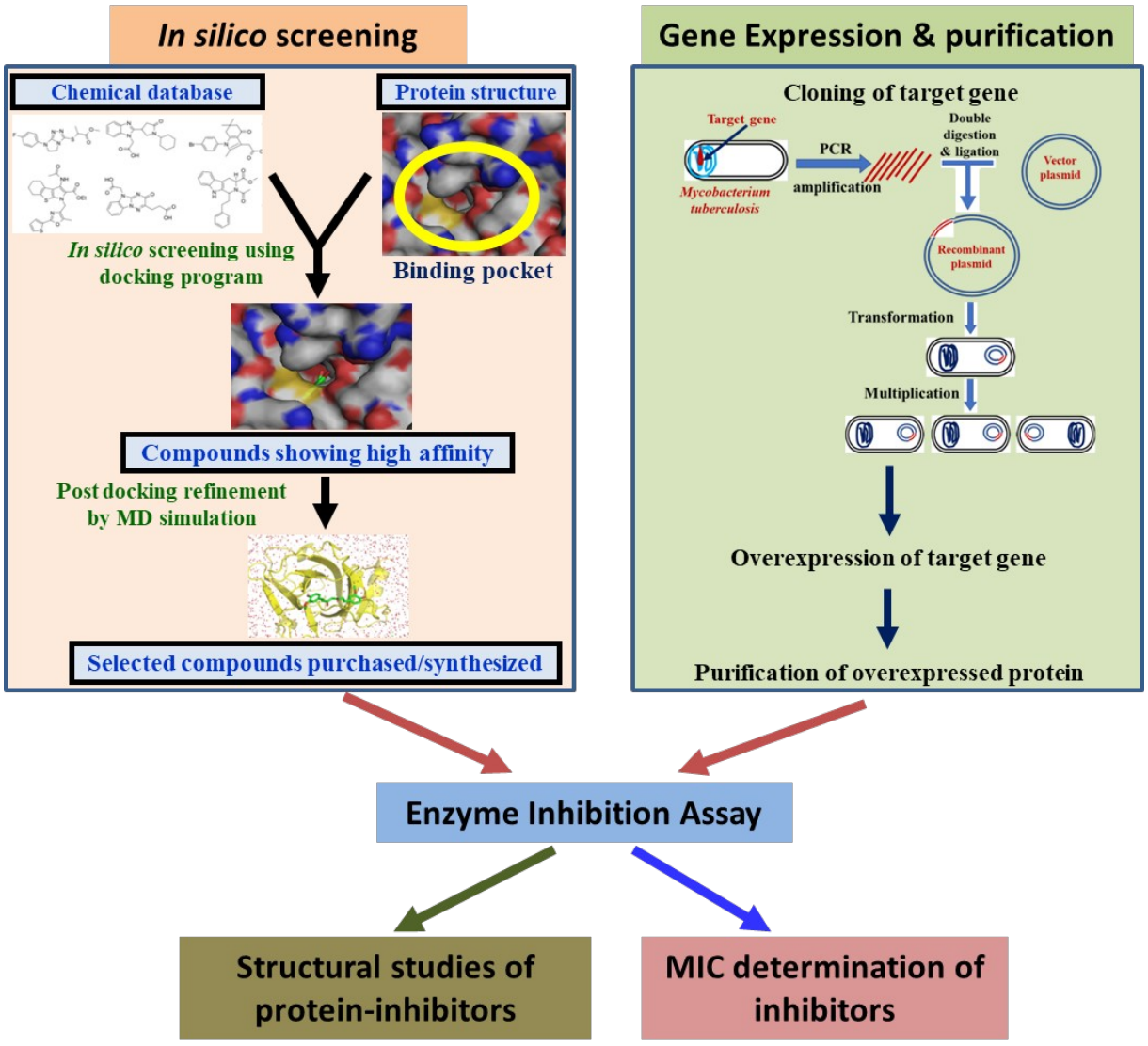
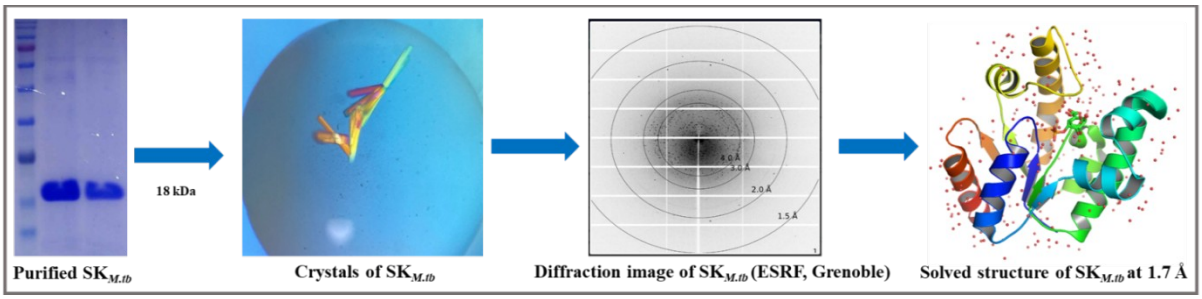
Dr. Manoj Kumar	
Research	The core area of my research group is discovery of drug leads for tuberculosis using rational drug design approach. Prolong treatment duration and lacks of effective drug for drug-resistant tuberculosis are the two major challenges in the tuberculosis therapeutics. Main focus of our group is to discover the lead molecules against potential drug targets of *Mycobacterium tuberculosis* using computational, biochemical and cellular approach. We identify the potential ligands using computational techniques (in silico screening and molecular dynamics simulations), express the target protein by molecular cloning and then evaluate the activity of potential ligands by inhibition assays. Potent inhibitors are crystallized with target protein to understand their binding mode that offers insight for enhancement of ligands activities. Simultaneously, MIC of potent inhibitors is determined in collaboration. Successful molecules would be tested in appropriate animal model of tuberculosis.

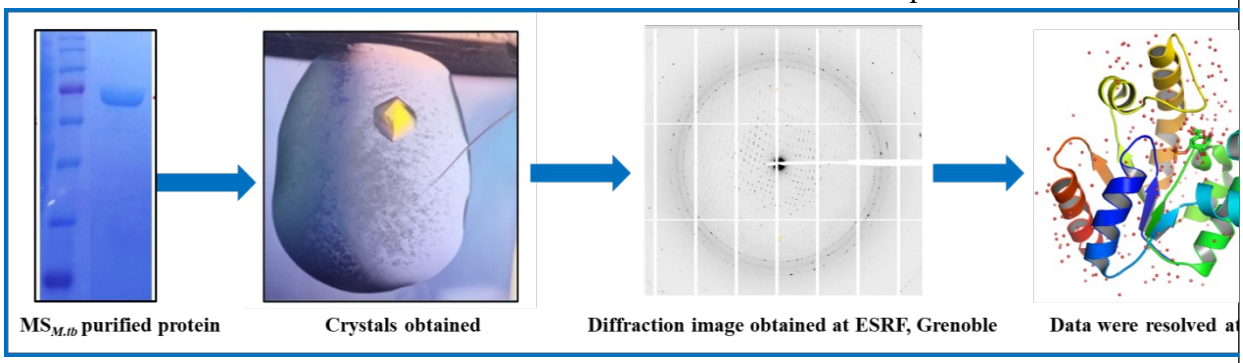


Shikimate kinase is a suitable drug target for the development of drugs to treat drug-resistant tuberculosis as it is essential for survival of *Mycobacterium tuberculosis*, absent in human and

it is a novel drug targets. We have identified potential inhibitors of *Mycobacterium tuberculosis* shikimate kinase among natural products and FDA approved drugs. Protein was overexpressed and purified. We developed an alternative enzyme assay which is simpler and cost-effective. Recently, we crystallized the protein and its high resolution structure was determined. Inhibition assay is in progress. Successful inhibitors would be lead molecules for development of drugs for the treatment of drug-resistant tuberculosis.



Presence of non-replicating and slow growing subpopulation of *Mycobacterium tuberculosis* during active tuberculosis is the primary reason behind sterilization phase of four months. Malate Synthase of *Mycobacterium tuberculosis* is essential for survival of such persistent population. We have identified potential inhibitors of malate synthase. Enzyme assay was optimized the enzyme assay using in-house produced malate synthase. Protein was crystallized and structure was determined. Inhibition studies with newly identified molecules are undergoing. Successful inhibitors could provide lead molecules for development of drugs to shorten the treatment duration in combination with isoniazid and rifampicin.



Our lab is also involved in drug discovery process for COVID-19. We have identified drug molecules that has potential to inhibit the SARS-CoV2 proteins (Mpro, PLpro & RdRp) in DrugBank) using the similar approach. Mpro was cloned, expressed, purified and an enzyme assay has been optimized. Enzyme assays with newly identified inhibitors are in progress.

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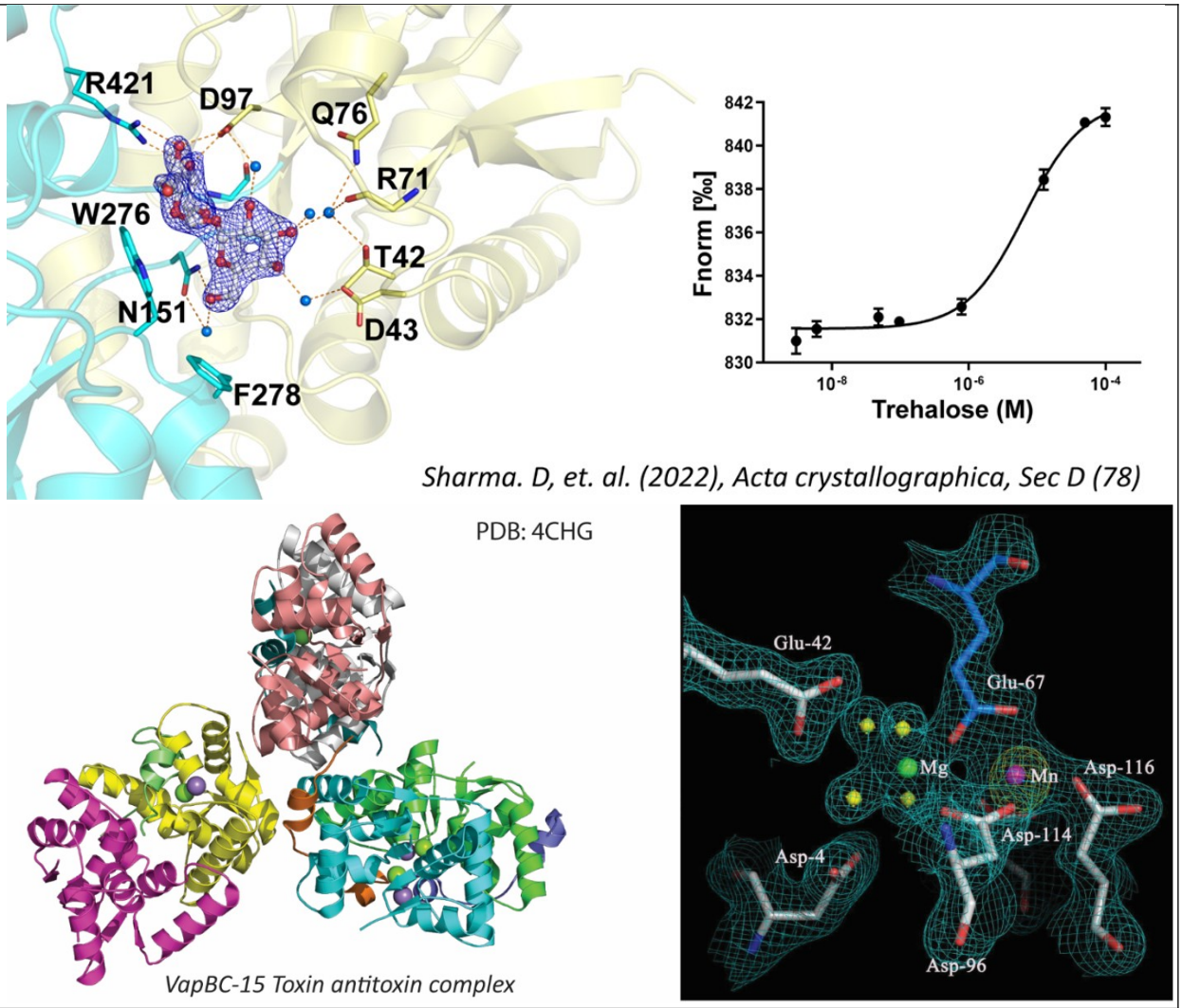
Dr. Uddipan Das	
Research	**ABC transporters:** Transporters are integral membrane proteins that transport molecules across cell membranes. We are interested in ATP-binding cassette (ABC) transporters, that are involved in various solute transport in *Mycobacterium tuberculosis*. These classes of transporters use the power of ATP as a driving force to transport molecules across the membranes. Based on the direction of transport, these transporters are classified as either importers or exporters. The importers are aided by an additional domain known as substrate binding protein that is located at the periplasmic part of the membrane in prokaryotes. With the help of X-ray crystallography and various biochemical and biophysical techniques, we deciphered the structure-function relationships of both the periplasmic (2022, *Acta Crystallogr Sect D Struct Biol* **78**, 835–845) and nucleotide-binding domain (2020, *Int J Biol Macromol* **152**, 109–116) of trehalose transporter from Mtb. Deciphering the intact structure of membrane proteins is a challenging area of structural biology, but with the emergence of new methodologies of solubilization and structure determination, there is a rapid growth in the number of new structures in PDB. Much of the credit goes to the development of Cryo-Electron Microscopy and various software for structure determination. Now it is possible to determine the structure of intricate membrane proteins/complexes which remained elusive for decades due to their resistance to crystallization to be studied by X-ray crystallography. We have incorporated Cryo-EM and Single particle analysis for studying the structure of membrane protein and protein complexes in our lab. Presently, much of the Cryo-EM project of the lab is with collaboration. **Toxin-antitoxin complexes:** Toxin-antitoxin (TA) systems are found in both bacteria and archaea and consist of a stable toxin and a labile antitoxin. Both components form a complex in which the activity of toxin is irreversibly inhibited by an antitoxin. Under favorable conditions the labile antitoxin is degraded by the host proteases, favoring the action of the toxin by the inhibition of essential cellular processes, such as replication, translation, ATP synthesis, and cell wall synthesis. The genome of pathogenic Mycobacterium tuberculosis encodes approximately 88 TA systems in contrast to 3 in the case of nonpathogenic *M. smegmatis*. This raises questions regarding the presence of such a high number of TA's and their role in virulence in Mtb. We were the first in our country to report the structure of VapBC TA complex from Mtb. The VapC-15 is a ribonuclease and without the inhibition of VapB-15, it readily degrades mRNA in the cell. Currently, we are exploring such interesting TA complexes from Mtb. We are working on the structural elucidation of these complexes by X-ray crystallography supplemented by various biophysical techniques.

Research Images	
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