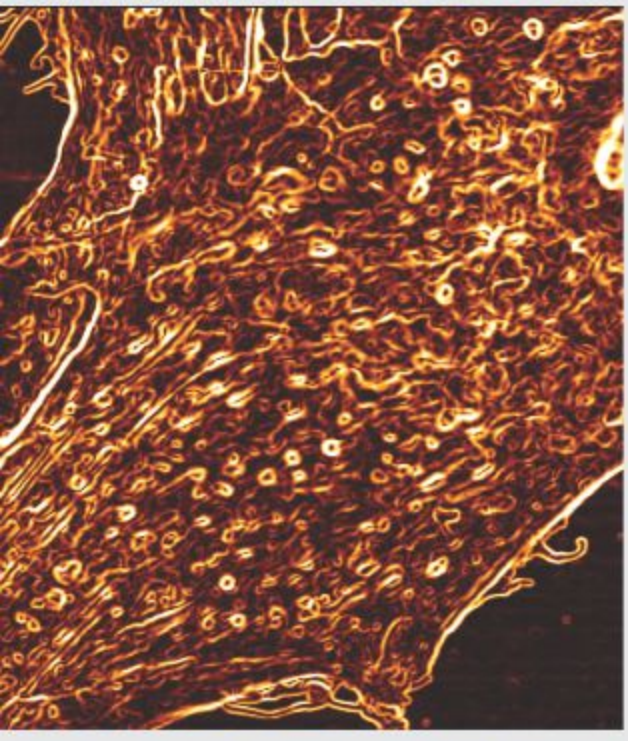
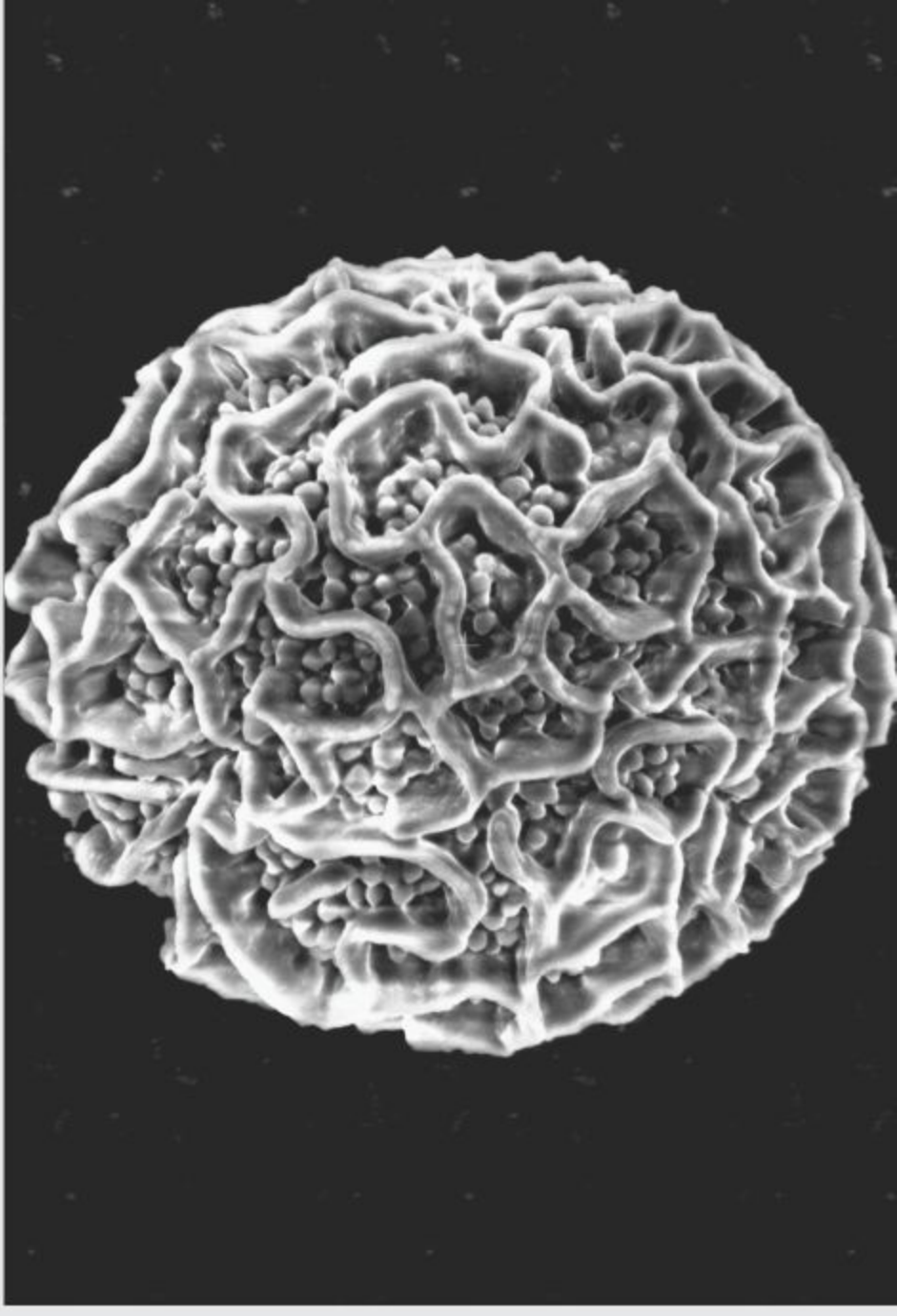
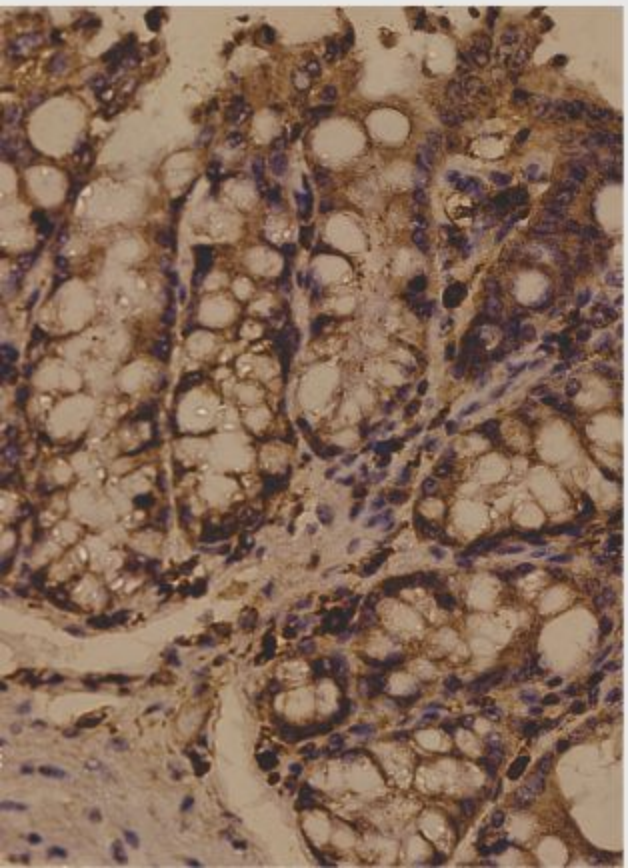
ANNUAL REPORT

2018 - 2019







United Nations
Educational, Scientific and
Cultural Organization

क्षेत्रीय जैव प्रौद्योगिकी केन्द्र
Regional Centre
for Biotechnology

CONTENTS

Mandate of the Regional Centre for Biotechnology

The mandate of the Regional Centre for Biotechnology (RCB) is to provide a platform for biotechnology education, training and research at the interface of multiple disciplines. The programs of the Centre are designed to create opportunities for students to engage in multi-disciplinary research where they learn biotech science while integrating engineering, medicine and natural sciences, to provide solutions for human and animal health, agriculture and environmental technologies. The vision is to produce human resource tailored to drive innovation in biotechnology, particularly in areas of new opportunities and also to fill talent gaps in deficient areas. The Centre is regarded as a "Category 2 Centre" in terms of the principles and guidelines for the establishment and functioning of UNESCO Institutes and Centres.

The objectives of the Regional Centre for Biotechnology are:

1. to disseminate and to advance knowledge by providing instructional and research facilities in such branches of biotechnology and related fields as it may deem fit including technology policy development,
2. to provide capacity-building through education, training, research and development in biotechnology and related academic fields for sustainable development objectives through regional and international cooperation,
3. to facilitate transfer of knowledge and technology relating to biotechnology at the regional level,
4. to create a hub of biotechnology expertise and to address human resource needs in the countries in the region,
5. to promote and strengthen international co-operation to improve the social and economic conditions and welfare of the people,
6. to promote and facilitate a network of satellite centres in the region as well as within India.

The functions of the Regional Centre for Biotechnology are:

1. to establish infrastructure and technology platforms which are directly relevant to biotechnology education, training and research,
2. to execute educational and training activities including grant of degrees in education and research in biotechnology and related fields,
3. to produce human resource tailored to drive innovation in biotechnology, particularly in areas of new opportunities and to fill talent gap in deficient areas,
4. to undertake research and development and scientific investigations in collaboration with relevant research centres in the region,
5. to hold scientific symposia and conferences within India or in the region or outside the region and to conduct short-term and long-term training courses and workshops in all areas of biotechnology,
6. to collect universally available information with a view to setting up data banks for bio-information,
7. to collect and disseminate, through networking, the relevant local knowledge in the field of biotechnology, ensuring protection of intellectual property rights of local stakeholder communities,
8. to develop and implement a policy for intellectual property rights which is equitable and just to the stakeholders involved in research in the Regional Centre,
9. to disseminate the outcome of research activities in different countries through the publication of books and articles,
10. to promote collaborative research and development networking programme in specific areas of biotechnology with national, regional and international networks and promote exchange of scientists, at the regional level having regard to issues pertaining to intellectual property rights of collaborating institutions promoting equitable sharing of benefits with collaborating institutions.

From the Executive Director's Desk

Education, training, and research in the broad area of biotech sciences are the three key verticals defining the mandate of the Regional Centre for Biotechnology (RCB). We have continued to strive hard towards achieving these objectives and have made considerable progress in each of these areas. RCB continues to be a category-2 institution of the UNESCO, the linkage providing an international reach to our academic and training programs. A detailed account of each of the RCB activities is provided in the various sections of this annual report with a summary in the following paragraphs.

Research-based learning is the hallmark of the RCB's education and training programs that include structured degree programs as well as short-term training programs in highly specialized areas of biotechnology and life science research. RCB offers doctoral degree programs in Biotechnology, Bioinformatics, and Biostatistics and over 80 students are currently working in the RCB laboratories towards their PhD degree. In the academic year 2018-19, RCB also initiated an integrated MSc-PhD degree program where students with bachelor's degrees are eligible to be admitted. The program received a lot of interest from the young students across the country and 10 students (including a foreign student) were admitted to the program. The RCB Act 2016 also empowers the Centre to recognize the institutions of higher learning for their various academic programs and in this direction, after the due diligence, RCB has granted academic recognition to the PhD programs at the Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad; National Institute of Animal Biotechnology (NIAB), Hyderabad; National Agri-Biotechnology Institute (NABI), Mohali; Centre for Innovative and Applied Biotechnology (CIAB), Mohali; and Institute of Life Sciences (ILS), Bhubaneshwar. A total of 130 students from these recognized centres have been registered for their PhD degree with RCB.

Towards human resource development in the advanced areas of life sciences and biotech sciences, RCB offers short-term innovative training programs for young scientists. In this direction, RCB conducted the 2nd Bioimaging School in March 2019 highlighting the popular imaging systems that are extensively used in biology and biomedicine. The other training workshops were in areas of genomics, proteomics and cell biology, introducing to the participants the latest methodology and instrumentation in these important areas of modern bioscience research. Participants for these training workshops included research scholars, doctoral students, and postdoctoral fellows selected from various institutions across India. The instructors and speakers included experts from prestigious academic research institutions and universities in India and Japan. Besides, RCB continues to provide the Indian researchers an access to the ESRF synchrotron radiation facility. This program has provided tremendous support to the Indian structural biologists and has benefited a large number of young research students.

During the 2018-19 reporting period, RCB organized an 'International Symposium on Infectious Diseases' which attracted speakers from several countries to share their findings in areas relevant to the Indian scenario. Another international meeting was convened on 'Structure-assisted Development of Novel Therapeutics' highlighting the latest developments in this key area of drug discovery and development. In March 2019, in association with UNESCO, RCB organized a 'Regional Training Program on Developing Effective and Inclusive Science' which was attended by representatives from the SAARC countries like Bhutan, Bangladesh, Nepal, and Sri Lanka. In pursuance to the Sustainable Developmental Goals of UNESCO, the training program focused on capacity building of the South-Asian policymakers. In February 2019, the Biosafety Support Unit of the Centre, in association with TERI, trained biosafety regulators from different African countries on the 'Food/Feed & Environmental Risk Assessment' as part of the Biotechnology and Biosafety study tour to India for African nationals.

The various scientific programs of RCB can be broadly grouped under the following heads: Structural Biology, Infectious Disease Biology, Molecular Medicine, Cancer and Cell Biology, Agricultural Biotechnology, and Systems and Synthetic Biology. Several advances were made in the various research areas being pursued at the Centre which are discussed in the scientific reports section of the annual report. Provided below are some of the research highlights of this year.

Dr. Avinash Bajaj's group has been working on the development of novel antimicrobials that are active against multi-drug resistant pathogens and can combat antimicrobial resistance (AMR). Their work demonstrated the broad-spectrum antimicrobial activity of membrane-targeting Cholic Acid Peptide conjugates (CAPs) in the murine wound and catheter infection models.

Dr. Deepti Jain's group determined the structure of the transcription factor that regulates biofilm to motility transition in Pseudomonas aeruginosa. The structural data showed that the activity of the regulator is maintained at low levels. This enables the bacterium to easily transition to the chronic biofilm mode of life. This finding is valuable for designing the anti-biofilm compounds against the pathogenic bacterium.

Dr. Divya Chandran's group identified key virulence proteins from the pea powdery mildew pathogen and functionally validated their role in disease development. These virulence proteins and their plant targets can serve as important tools for the development of biotechnological strategies for preventing powdery mildew infection in legumes of agronomic import.

Dr. Sam Mathew's group developed the first animal model for Freeman Sheldon Syndrome, a genetic disease that affects the muscle. Using this model, the group has identified the muscle defects in this disease, which should lead to new strategies to treat patients born with this disorder.

Dr. Prasenjit Guchhait's group has shown that Platelet Factor 4 (PF4) stimulates the replication of Dengue and Japanese encephalitis viruses in host immune cells. Inhibitors to PF4 or CXCR3 (receptor for PF4) abrogated the viral replication. The group is now developing small molecule inhibitors for the above molecules for antiviral therapy.

Dr. Deepak Nair's group has elucidated the mechanism utilized by DNA polymerases to prevent ribonucleotide incorporation in the genome. The study provides the possible cause of certain cancers and can also lead to novel engineered DNA polymerases for use as reagents in research and diagnostics. The group has also shown that the proofreading

domain of the DNA polymerase involved in duplication of the apicoplast genome of the malaria parasite protects the AT-rich genome from mutagenesis due to oxidized nucleotides. The study suggests that inhibitors of the proofreading activity may serve as powerful adjuvants that potentiate the activity of available antimalarials.

Additionally, RCB continues to participate in a multi-institutional research program aimed to understand the biology of preterm birth to identify possible biomarkers to predict the outcomes. A large cohort of pregnant women has been established by THSTI at the Gurgaon Civil Hospital and the scientists at RCB are conducting a comprehensive study on the proteome of the various tissue samples from these women.

RCB has established a Bio-Incubator with financial support from the BIRAC under the BioNEST (Bio-Incubators Nurturing Entrepreneurship for Scaling Technologies) scheme. The Bio-Incubator has been established to foster innovation, research and entrepreneurial activities in biotechnology related areas. During the reporting period 2 start up companies started to function from the Bioincubator and several more have shown keen interest. Through this mission, we contribute to spurring the economic growth in the region in the biotechnology sector.

Finally, I would like to thank my colleagues in the RCB faculty and administration for the excellent cooperation. I must place on record the immense support from DBT and UNESCO, the members of the RCB Board of Governors, the Programme Advisory Committee and the statutory committees in achieving the various scientific and academic goals of the Centre, and I look forward to their continued support in further advancing the RCB programs.

Jai Hind!

Sudhanshu Vrati
Executive Director

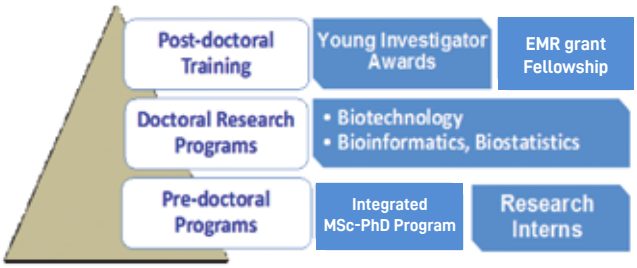

REGIONAL CENTRE FOR

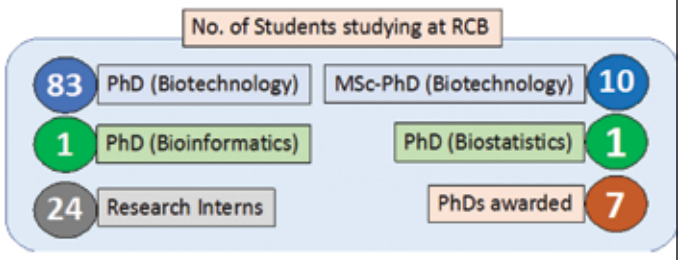
EXECUTIVE SUMMARY

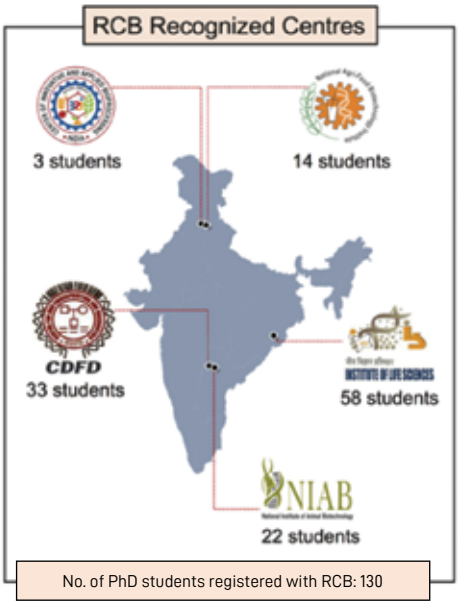
RCB Mandate

- Human resource development through education and training in the interdisciplinary areas of biotechnology
- To create a hub of biotechnology expertise in the SAARC region, and more generally in the Asian region
- To develop research programs of a global quality through international partnerships

Academic and Training Activities





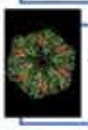


Date	Workshop / Symposium conducted
19 July 2018	INSPIRE Science Camp
24 September 2018	RCB Open Day
12-14 November 2018	International Symposium on Infectious Diseases
17-20 December 2018	RCB Mass Spectrometry & Proteomics Workshop
31 January 2019	Workshop on Science Communications & Careers in Science
12-16 February 2019	International Symposium on Structure-assisted Development of Novel Therapeutics
1 March 2019	2nd RCB Day Lecture by Prof. Balram Bhargava on Frugal Innovations in Heath Care
25-30 March 2019	2nd RCB Bioimaging School
6-8 March 2019	Regional Training Program on Developing Effective & Inclusive STI Policy

Research Areas


Infectious Disease Biology


Molecular Medicine


Structural Biology


Cancer and Cell Biology

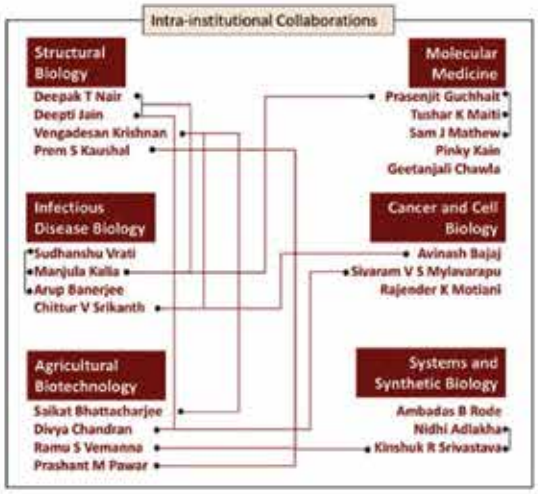

Agricultural Biotechnology

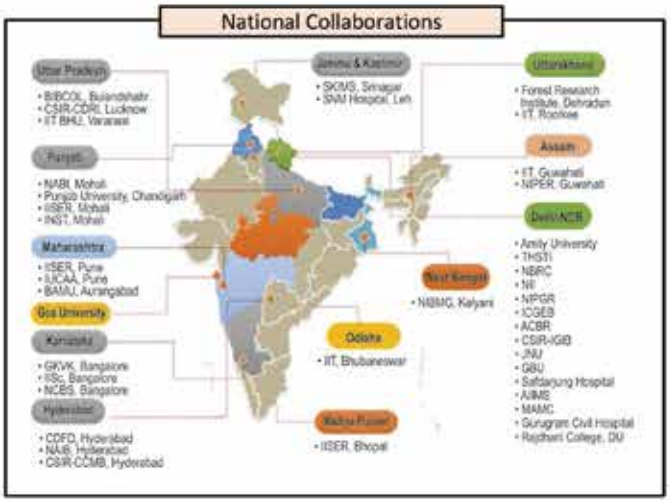

Systems and Synthetic Biology

Publications : 40
Patent Applications : 02

Research Highlights

- Engineered and developed novel antimicrobials that are active against multi-drug resistant pathogens and can combat antimicrobial resistance (AMR)
- Identified host factors crucial for Japanese encephalitis virus replication in epithelial and neuronal cells, some of which have the potential to be developed as antivirals.
- Platelet Factor 4 (PF4) was identified to stimulate the replication of Dengue and Japanese encephalitis viruses in host immune cells, and inhibitors to PF4 or CXCR3 (receptor for PF4) abrogated viral replication. These molecules could be attractive targets for development of antiviral therapy.
- Insights about mechanism (expose-ligase-seal) of pilus assembly have been revealed for the first time in a probiotic/beneficial bacterium. This knowledge advancement is helpful in targeting host-bacterial interface for combating infections and improving health.
- Using a model bacterial pathogen *Salmonella* Typhimurium, a novel cellular mechanism called SUMOylation was identified as a central player in several major forms of infectious and idiopathic gut illnesses. These findings would help development of strategies for combating drug-resistant infections and auto-immune disorders of gut.
- Determined the structure of the transcription factor that regulates biofilm to motility transition in *Pseudomonas aeruginosa*. This finding is valuable for designing the anti-biofilm compounds against the pathogenic bacterium.
- Described a novel chaperone mechanism of Parkinson's disease-associated protein DJ-1 where partially oxidized protein inhibited alpha-synuclein aggregation by its strong adhesive oligomeric surface. This will help in development of a therapeutic intervention for Parkinson's disease.
- Described novel molecular mechanisms by which human cells complete division and communicate with each other through tunneling nanotubes. These studies significantly advance the knowledge in these fields and could potentially be exploited for therapeutic intervention against cancer and other diseases.
- Elucidated the mechanism utilized by DNA polymerases to prevent ribonucleotide incorporation in the genome. The study provides the possible cause of certain cancers and can also lead to novel engineered DNA polymerases for use as reagents in research and diagnostics.
- Identified key virulence proteins from the pea powdery mildew pathogen and functionally validated their role in disease development. These are important tools for the development of strategies for preventing powdery mildew infection in legumes of agronomic importance.
- Developed the first animal model for Freeman Sheldon Syndrome, a genetic disease that affects the muscle. Using this model, we have identified the muscle defects in this disease, which should lead to new strategies to treat patients born with this disorder.





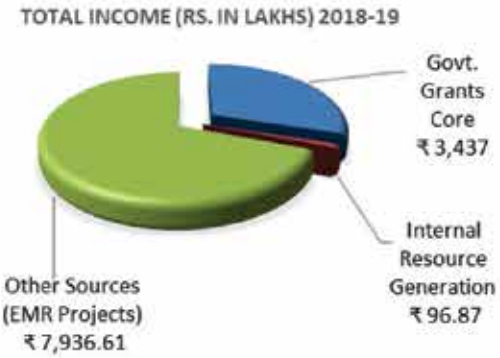
Infrastructure and Support Services

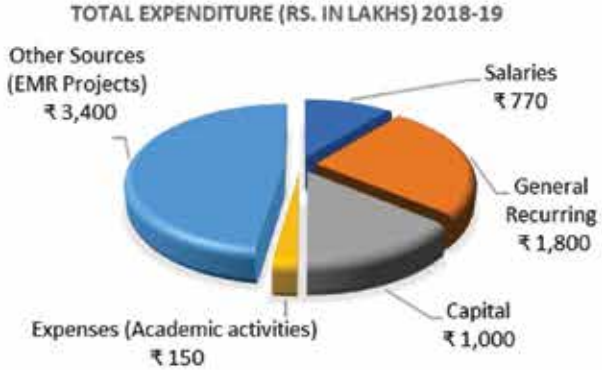
Advanced Technology Platform Centre

Biosafety Support Unit

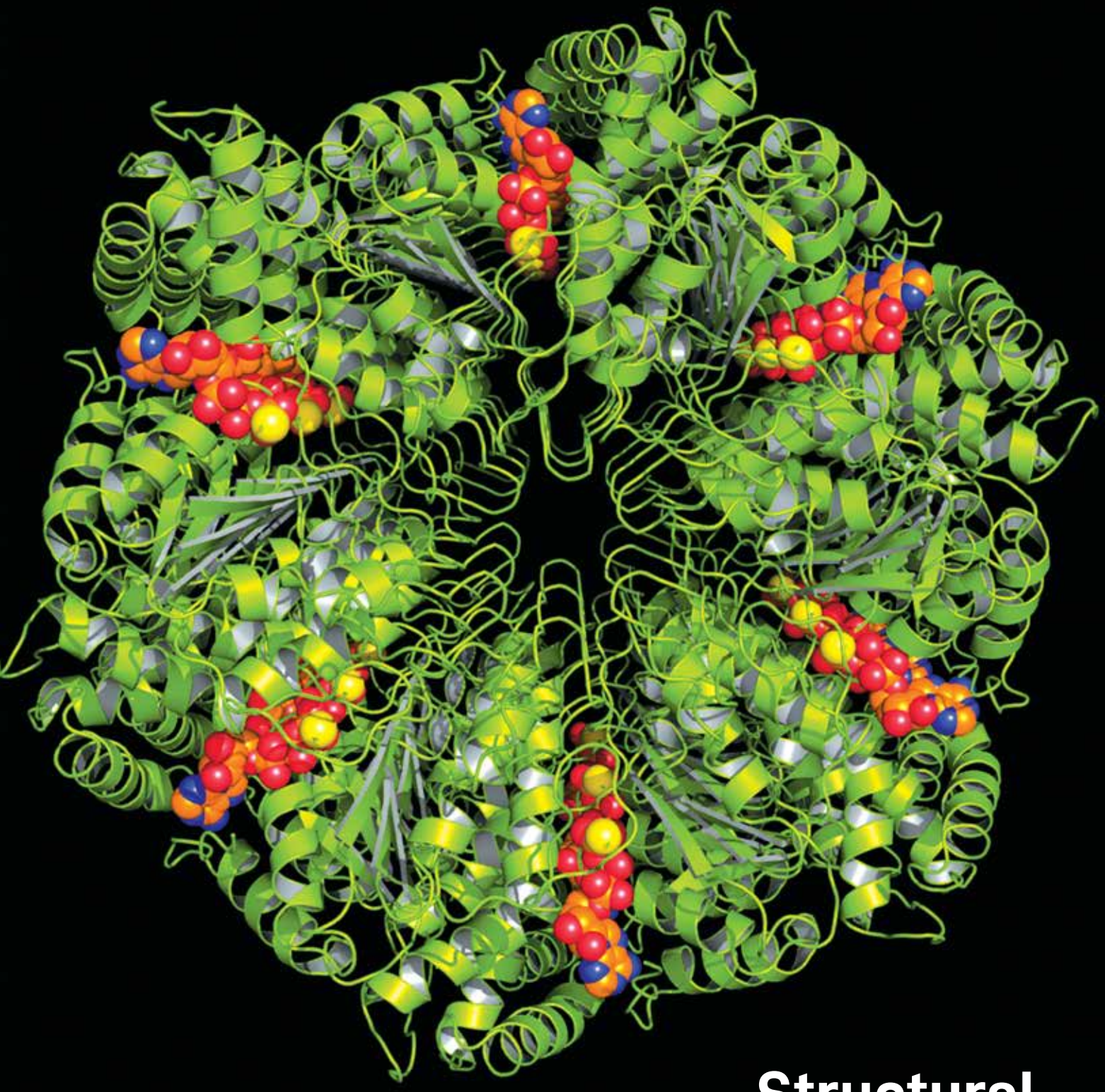
BSC BioNEST Bio-Incubator

Financial Figures





SCIENTIFIC REPORTS



Structural Biology

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Principal Investigator

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Molecular Determinants of Genomic Integrity and Plasticity

For all cellular processes to function optimally, the integrity of the genome has to be maintained. Conversely, plasticity in the genome can relieve selection pressures imposed by an adverse environment. These two conflicting requirements have led to the presence of molecules and pathways that either prevent or facilitate changes in the genome. In the case of pathogenic bacteria and viruses, genomic plasticity is implicated in the onset of drug resistance and reduction in vaccine efficacy. We aim to elucidate the structural mechanism utilized by various molecular determinants of genomic integrity and plasticity to achieve function. Within this broad aim, some of the biological processes under scrutiny in our laboratory are DNA replication, stress-induced epigenetic modification and transposition. The insights gained from studies conducted in the laboratory will shed light on how organisms evolve and also provide a robust platform for the development of novel therapeutic strategies against pathogenic bacteria and viruses.

DNA replication & translesion DNA synthesis

DNA polymerases (dPols) are the primary enzymes responsible for duplication of the genome. We study different dPols from various organisms to understand the mechanism utilized to achieve their role in replication and evolution. The formation of a phosphodiester bond between the α-phosphate of the incoming dNTP and the 3'- hydroxyl group of the terminal primer nucleotide is the primary chemical reaction catalyzed by the DNA polymerase enzyme and results in the release of a pyrophosphate moiety (PPi) as a byproduct. Using time resolved crystallography, we show that hydrolysis of PPi is an intrinsic and critical step of the DNA synthesis reaction. This observation was validated by biochemical studies and provides a solution for a long-standing conundrum regarding the energetics of tW#he DNA synthesis reaction (Fig. 1). The hydrolysis of PPi ensures that the DNA synthesis reaction is inherently energetically favorable without the need for additional pyrophosphatase enzymes, as believed previously (Kottur & Nair, 2018 *Nuc. Acids Res.*, 46:5875).

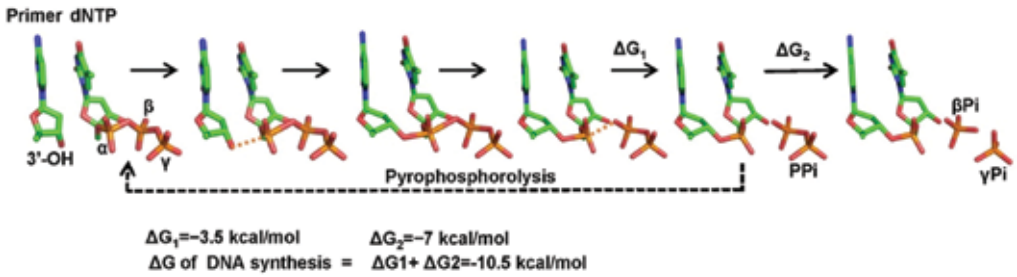

Figure 1. *Mechanism of DNA synthesis: The hydrolysis of PPi by dPols to phosphate ions is an intrinsic and critical part of the DNA synthesis reaction. This step ensures that the reaction is energetically favourable and moves in the forward direction.*

Stress-induced epigenetic modification

The gastric pathogen *Helicobacter pylori* is responsible for diseases such as ulcers and cancer. This pathogen possesses several DNA Methyltransferases (dMTases) that exhibit activity only in adverse conditions such as the highly acidic environment in the human stomach. Methylation of target sequences in the DNA genome by dMTases results in the alteration of transcriptional profiles and aids adaptation to environmental stress. We aim to elucidate the regulatory mechanisms that permit these enzymes to act only under specific environmental conditions. The expression of the dMTase coded for by the *hp0593* gene- named M.HpyAXI, is upregulated when the pathogen encounters low pH. Using a combination of structural, biochemical and biophysical tools, we have shown that the functional form of this enzyme is a tetramer that is

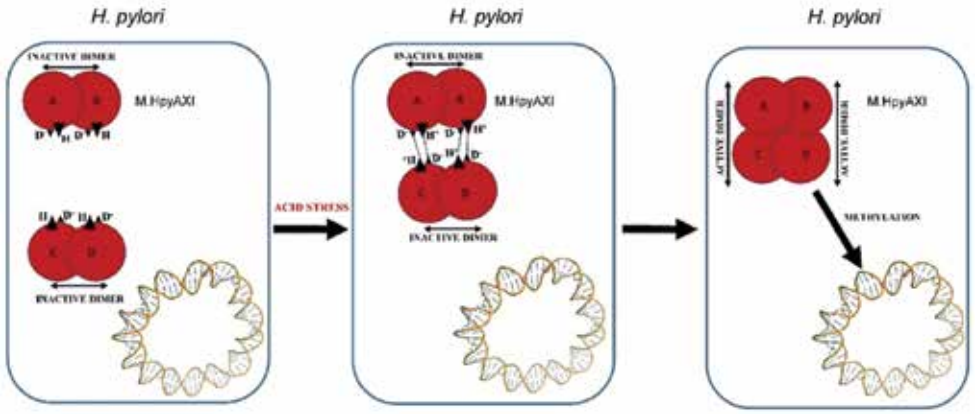

Figure 2. *Mechanism of activation of M. HpyAXI:The DNA MTase transitions from a non-functional dimer at alkaline pH to a tetramer with two functional dimers at low pH.*

formed only at low pH (Fig. 2). This property of M.HpyAXI ensures that it is licensed to act only when the organism is subjected to acid stress. The perturbation of the activity of this enzyme by specific inhibitors may render *H. pylori* more susceptible to available drugs.

Transposition

Transposons are mobile genetic elements that give rise to variation in the genome and can be responsible for horizontal gene transfer. The movement of transposons has been implicated in the onset of drug resistance since many transposons carry genes that endow resistance to antibiotics. The mobility of these genetic elements is primarily mediated by cognate enzymes known as transposases. We aim to understand the mechanisms employed by different transposases to achieve function. The piggyBac transposon was isolated from the cabbage looper moth, and its movement is mediated by the piggyBac transposase. We have shown that dimerization through the RING-finger domain (RFD) present toward the C-terminus of the transposase attenuates the excision activity (Fig. 3) of the piggyBac transposase (Sharma *et al*., 2018, *Biochemistry*, 57:2913).

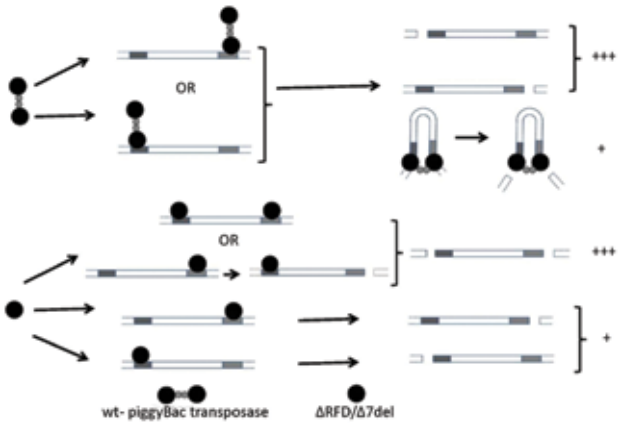

Figure 3. *Role of RFD in piggyBac transposase activity: Dimerization through the last seven residues of the RFD results in dimeric protein that exhibits reduced ability to excise the transposon.*

Deepti Jain
Principal Investigator

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Transcription Regulation: Structure and Mechanism

Resistance to antibiotics represents an escalating challenge in the treatment of bacterial infections. Pathogenic bacteria are known to switch phenotypes in order to reduce sensitivity towards antimicrobial agents. These phenotypic transitions are regulated at the level of transcription, which is an essential process responsible for gene expression. We employ an integrated approach, involving structural tools, biophysical techniques, biochemical methods and functional *in vivo* assays to investigate the molecular mechanisms of transcription regulation. The mechanistic insights obtained are exploited for the development of novel therapeutic agents against pathogenic bacteria and the development of novel inducible recombinant expression systems. The major model systems under study include the following

Regulation of flagellar and biofilm gene cascade in *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is an opportunistic pathogen and is a primary cause of nosocomial infections. The pathogen is known to transition from a motile to a sessile phenotype to evade antimicrobial agents. This ability is regulated by transcription modulators called bacterial enhancer-binding proteins belonging to AAA+ (ATPase associated with various cellular activities) family of proteins. The representatives of this class of proteins in *Pseudomonas* regulate the expression of genes involved in the assembly of a single functional flagellum and biofilms. Flagella is important not only for locomotion but also for adherence to the substrate, colonization of the host and biofilm formation. AAA+ proteins contain several conserved motifs such as the Walker A, Walker B motifs, sensor I and sensor II, etc.

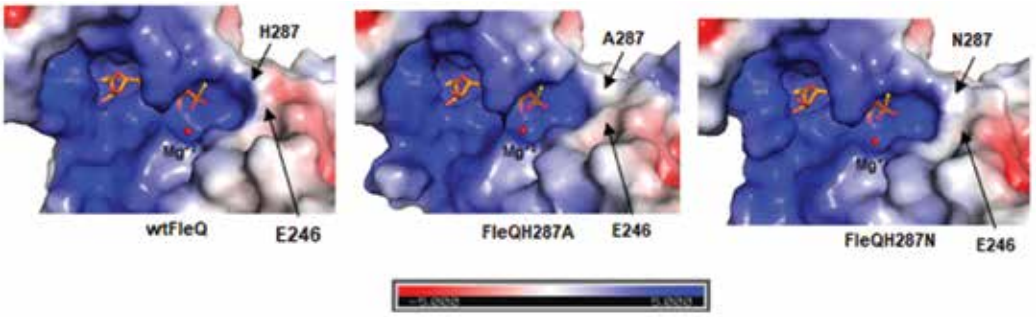

Figure 1. *Electrostatic potential surface of FleQ-Cent and mutants in complex with ATPγS*

The sensor I motif is a highly conserved motif among AAA+ proteins. Recent studies from the laboratory have delineated the role of the sensor I motif in regulating the efficiency of ATP hydrolysis, which in turn has a drastic effect on the flagellar phenotype of the organism (Fig. 1). In addition, we have demonstrated that the alteration of ATPase activity abolishes the ability of the bacterium to form biofilms. Our lab is currently exploiting this finding for *in silico* screening of databases of small molecules that can directly or allosterically inhibit ATP binding to FleQ and biofilm formation.

Another target under scrutiny in the laboratory is FleSR, a two-component system involved in bacterial motility, biofilm formation and antibiotic resistance. The knockout of FleSR is known to inhibit motility as well as biofilm formation in *Pseudomonas aeruginosa*. FleR is a response regulator which, upon phosphorylation, activates the transcription of late flagellar genes. We have initiated structural studies on FleR to understand the signal transduction mechanism in the flagellar cascade (Fig. 2).

Regulation of antibiotic resistance in *Staphylococcus aureus*

Antibiotic resistance in *S. aureus* is one of the leading causes of mortality and healthcare expenditure. Thus, understanding the regulatory networks mediating such resistance is very

Figure 2. *Left: Crystal structure of FleR-NTD dimer showing the conserved phosphorylation motif. Right: Homology model of FleR-Cent.*

essential. The GraXSR (Glycopeptide Resistance Associated) regulon, is essential for antibiotic resistance in *S. aureus*. We have determined the crystal structure of the adaptor protein whose knockout results in the downregulation of the genes necessary for resistance to antibiotics. Additionally, it was observed that the knockout of the adaptor protein results in increased susceptibility to vancomycin. The *in vitro* and *in vivo* work is currently ongoing. This work will aid in deciphering the putative network responsible for increase in glycopeptide tolerance in *Staphyloccocus*. The insights obtained from this study will be used to design and test small molecule inhibitors.

Regulation of arabinose metabolism in *Bacillus subtilis*

Another model system employed in the laboratory is important towards understanding the allosteric mechanism utilized by transcription factors responsive towards small metabolites. Allostery has been defined as the fundamental process wherein the binding of a ligand or the effector molecule alters the activity of the protein at a distant site. In the case of transcription modulators, effector binding can either increase the affinity (activation) or can decrease its affinity to the DNA (derepression) thereby altering the gene expression. Thus, transcription modulators serve as molecular switches, turning on and off the expression of genes. AraR protein is the key regulatory protein of the L-arabinose metabolism in *Bacillus subtilis*. AraR binds to eight different operator sequences governing five different promoters and has two different modes of transcriptional repression. Through our structural work on AraR, we have provided essential insights into long-standing fundamental questions in the field of regulation of gene expression. The structures shed light on the plasticity of transcription factors which endows them with the ability to tolerate differences in operator DNA sequences. The data uncovered the mechanistic details of the diverse approaches utilized by transcription modulators to bind different DNA sequences without compromise on specificity and affinity thereby regulating gene expression to different extents at different promoters. The structural data obtained is useful for the design of regulatory switches in bacteria.

Vengadesan Krishnan
Principal Investigator

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Vinay Sharma

Structural Biology of Host-Microbial Interactions in Health and Diseases

Microbial attachment to the host surfaces is the first and critical step in colonization regardless of whether it benefits or harms the host. The subsequent events in the pathogenesis or probiosis are highly dependent on this initial interaction or adherence. Interfering with the host-microbial interface (e.g. anti-adhesion therapy) is considered as one of the attractive approaches in improving health and combating infections. Since this approach does not directly kill bacteria, it is also recognized as a promising alternative to antibiotics which often results in the development of resistance. Such an approach requires detailed knowledge of how microbes attach to host, and how the adhesive strategies differ among microbes. Towards providing the essential foundations for this approach and understanding the mechanism by which microbes adhere to and interact with the host surfaces, we aim to generate structural knowledge by studying key molecules that establish the initial contacts between the host and microbes.

We currently focus on hair-like surface organelles called pili that enable bacteria to establish the initial contacts with the host surfaces for colonization and biofilm formation. Since the microbial surface adhesive molecules are often immunogenic, they are also considered ideal vaccine candidates. The ongoing structural investigation program covers beneficial strains from gut microbiota and pathogens for getting insights into tissue tropism and microbial interaction strategies in health and diseases.

Lactobacillus rhamnosus GG is a beneficial human gut microbiota isolate and a widely used probiotic because of its various health-promoting effects. Its genome contains loci for two different pilus operons (*spaCBA* and *spaFED*) for sortase-mediated pili formation. The spaCBA operon encodes a major pilin (SpaA), two minor pilins (SpaB and SpaC) and a pilin-specific or C-type sortase (SrtC1). Similarly, the *spaFED* contains genes for a major pilin (SpaD), two minor pilins (SpaE and SpaF) and a C-type sortase (SrtC2). The pili in *L. rhamnosus* GG are the major contributing factors in human gut adherence and colonization. The *L. rhamnosus* GG pili play a key role in persistence and immunomodulation in providing beneficial health effects. The *L. rhamnosus* GG utilizes pili to mediate interaction with intestinal mucus and components of the extra cellular matrix. Towards understanding the molecular mechanism by which this bacterium assembles pili and adheres to host surfaces, the structural investigation was begun for constituents of SpaCBA and SpaFED pilus including their respective sortases. Our earlier work on SpaA and SpaD which form SpaCBA and SpaFED pilus shaft respectively, has revealed new insights and mechanism of pilus shaft formation for the first time from a probiotic strain.

The recent structural analysis of basal pilin SpaE has revealed two-domain architecture with immunoglobulin-like CnaB fold (Fig. 1). Each domain displays an internal lysine-asparagine isopeptide bond with a proximal catalytic glutamate residue (Fig. 2). The mass spectrometric analysis showed that the isopeptide bond in the N-terminal domain is likely slow forming. Similar to the SpaD, the N-terminal domain of SpaE contains flexible AB loop that connects the first and second β-strand in the N-terminal domain and YPKN pilin motif at the linker region. The C-terminal domain shows an unstructured long C-terminal tail with an atypical sorting motif LPAMS. These observations suggest that the SpaE is incorporated into the SpaD pilus shaft in a similar way proposed in the expose-ligate-seal mechanism for connecting backbone pilins (Fig. 3). According to this, the mobile AB loop in the N-domain of SpaE leaves linking-lysine(K214) unprotected for favoring nucleophilic attack (*Expose*). This leads to sortase-mediated ligation between C-terminal LPMT-motif threonine (T487) of SpaD and N-terminal pilin motif linking lysine(K214) of SpaE (*Ligate*). Then, the mobile loop in the N-domain of SpaE undergoes a conformational change and becomes ordered by engaging in interaction with the adjoining C-domain of SpaD (*Seal*). The structural analysis of other pilins and sortases are in progress.

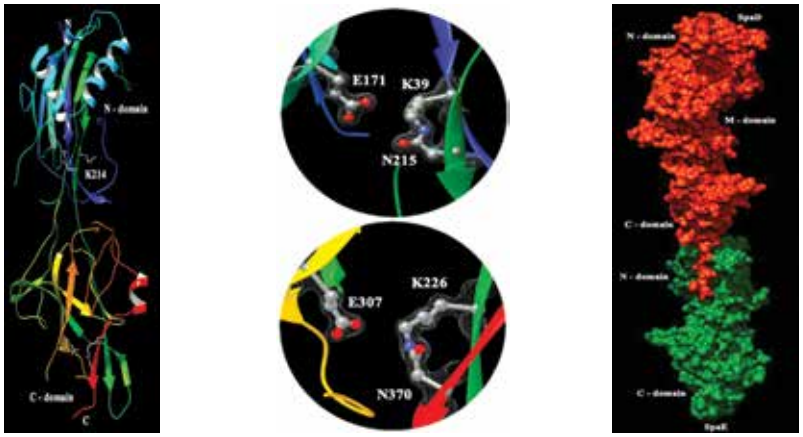

Figure 1 *(Left). Structure of SpaE in ribbon representation with a rainbow color style. SpaE consists of two structural domains with a CnaB fold, each with an internal isopeptide bond. Residues forming the isopeptide bonds are shown in stick representation. The YPKN pilin motif containing the linking lysine (K214) for intermolecular isopeptide bond formation is located near the domain linker that connects the N- and C-terminal domains.*

Figure 2 *(Middle). The electron density (2Fo-Fc) map contoured at 1.5 σ level showing the presence of internal isopeptide bonds in the N-terminal (upper) and C-terminal (bottom) domains of SpaE.*

Figure 3 *(Right). Surface representation of basal pilin SpaE incorporation into the SpaFED pilus. The N-, Middle, and C-terminal domains of SpaD are in orange, and the N- and C-domains of SpaE are in green. SrtC cleaves the bond between the threonine (T) and glycine (G) residues of the LPMTG motif peptide in SpaD and then catalyzes the formation of an intermolecular K-T isopeptide bond via the side chain of the linking lysine (K214) from the SpaE subunit. The C-terminal tail of SpaD inserts and encloses the groove-like hydrophobic pocket in the N-terminal domain of SpaE during the formation of the SpaD-SpaE complex through the expose-ligate-seal mechanism.*

Lactobacillus ruminis is another lactobacillus strain which was initially isolated from humans and subsequently from cattle, pigs, and birds. The *L. ruminis* has been described as an autochthonous microbiota present in the gastrointestinal tract with probiotic effects (immunomodulation, inhibition of pathogens, and maintenance of gut flora). Its genome contains pilus operon (*lrpCBA*), which encodes three pilins (LrpA, LrpB and LrpC) and one sortase (SrtC). The LrpCBA pilus type appears to be different from *L. rhamnosus* GG pili, and likely represents a third sortase-mediated pilus type in Lactobacillus species. The purification strategy has been optimized to recombinantly produce pilus components of LrpCBA pilus at a large-scale.

The oral cavity harbors the second most abundant microbiota followed by the gut. Certain streptococci bacteria (primary colonizers) can colonize the oral tissues through their pili for the formation of plaque which damages teeth and gums and leads to several periodontal diseases such as caries and gingivitis. The purification strategy has been optimized to recombinantly produce pilus components from these bacterial strains at a large-scale.

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Structural Aspects of Translation Regulation

Translation, the process of protein synthesis, in which genetic information present in the mRNA is decoded into a polypeptide, is the key step in the central dogma of molecular biology. Our laboratory's research goal is to unravel the structural basis of the functioning of macromolecular complexes involved in translation regulation, and thereby, to identify the potential drug targets. We are focusing on the structural aspects of protein synthesis in *Mycobacterium tuberculosis* (Mtb) and *Plasmodium falciparum*. MTb the causative agent of tuberculosis (Tb), causes one of humankind's deadliest diseases. MTb becomes dormant, nonreplicating and phenotypically drug-resistant when it encounters multiple stresses within the host macrophages. This condition is also known as latent tuberculosis infection (LTBI) or dormancy. Nearly, one-third of the world population possesses LTBI out of which 10% of LTBI infected individuals develop acute Tb infection. The eradication of tubercle bacilli in latent lesion by currently available drugs has proved to be inefficient. In order to mimic the host macrophage stress environment, different models have been developed and most widely accepted models are (1) Wayne hypoxia model, (2) Lobel nutrient starvation model and (3) multi stress condition model in which mycobacteria are grown in low oxygen content, low nutrient conditions and different stress conditions, respectively.

During dormancy mycobacteria, slow down cellular processes including translation however, 48 genes that appear to play crucial roles during dormancy are upregulated by the DosR regulon. Our long-term goal is to understand the life cycle of the Mtb pathogen in its dormancy sate, by illustrating the role of all 48 genes that are expressed during pathogen's dormancy. Initially, we are focusing on genes involved in translation inhibition such as RafH. The translation inhibition by RafH is a unique feature associated with Mtb ribosomes. It binds to the 70S ribosome which appears to be dramatically different from the one that occurs in enteric bacteria. In bacteria hibernating protein factor (HPF) binds to the ribosomes and forms the 70S of 100S ribosome dimers Fig. 1. During dormancy, the ribosome composition gets altered and some new proteins are expressed that bind to 70S ribosome and inhibit protein synthesis. We are also in the process of optimizing the growth of mycobacteria under different stress conditions.

Plasmodium faliciparum causes the most lethal form of malaria. Every year, malaria kills nearly half a million people worldwide, with the majority of victims being children under the age of five. Owing to the emergence of parasite resistance to front-line drugs, there is an urgent need to find new antimalarial drug targets. The *P. falciparum* has three sites of protein synthesis the

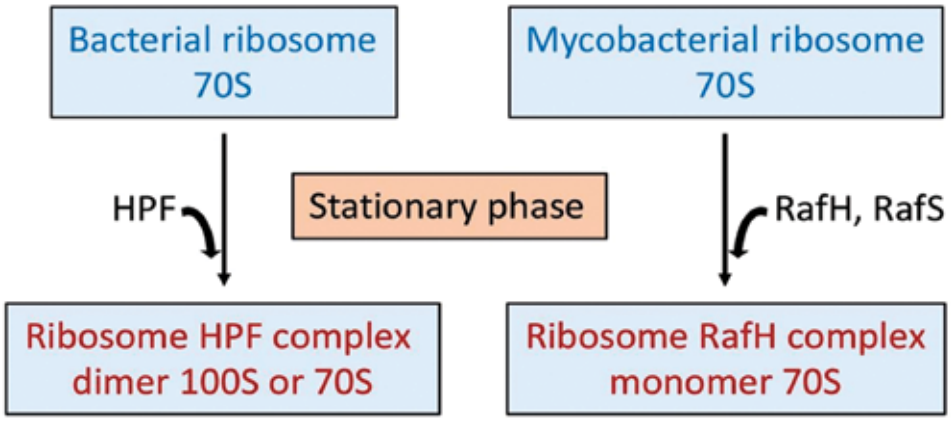


Figure 1. *Mechanisms of stationary phase ribosome inactivation. During the stationary phase in enteric bacteria the hibernation promotion factor (HPF) binds to bacteria and forms 100S ribosome whereas ribosome association factor under hypoxia (RafH) and (RafS) binds to 70S mycobacterial ribosomes.*

cytoplasmic ribosome and two organellar ribosomes, which reside inside the mitochondria and in a non-photosynthetic relict plastid, the apicoplast. Therefore, mitochondrial ribosome (mitoribosome) and apicoplast ribosome (apicoribosome) are of prokaryotic origin which makes them attractive targets for antimalarial drugs. Several antibiotics, such as Tetracycline, Doxycycline, and Clindamycin, etc. are currently used to treat malaria along with mainstream antimalarial drugs. However, these drugs show delayed-death drug response, where the blood-stage parasite dies only in the cycle next to the one in which it has been exposed to the drug. The organellar ribosomes possess several unique features. The mitoribosome have ~15 r-proteins in small ribosomal subunit (SSU), ~26 r-proteins in large ribosomal subunit (LSU) as compared to the bacterial ribosome (21 in SSU and 34 in LSU) and fragmented rRNA. One of the most distinctive features of mitoribosomes is that its rRNAs are highly fragmented with lengths ranging from 23 to 190 nucleotides and this is the highest fragmented ribosome known so far. What is the exact composition of the mitoribosome and how the fragmented rRNA provides a structural scaffold in the mitoribosome remains unknown. Similarly, the Pf apicoplast translational machinery also possesses several unique features, such as the apicoribosome contains a lesser number of ribosomal proteins (16 in the SSU, and 21 in the LSU), as compared to the bacterial ribosome (21 in SSU and 34 in LSU). In addition, the translation factors carry organelle-specific insertions and extensions which range from 8 to 115 amino acids.

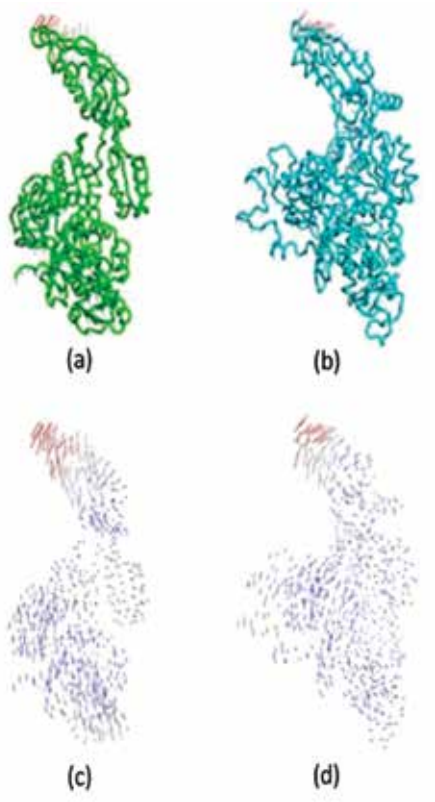
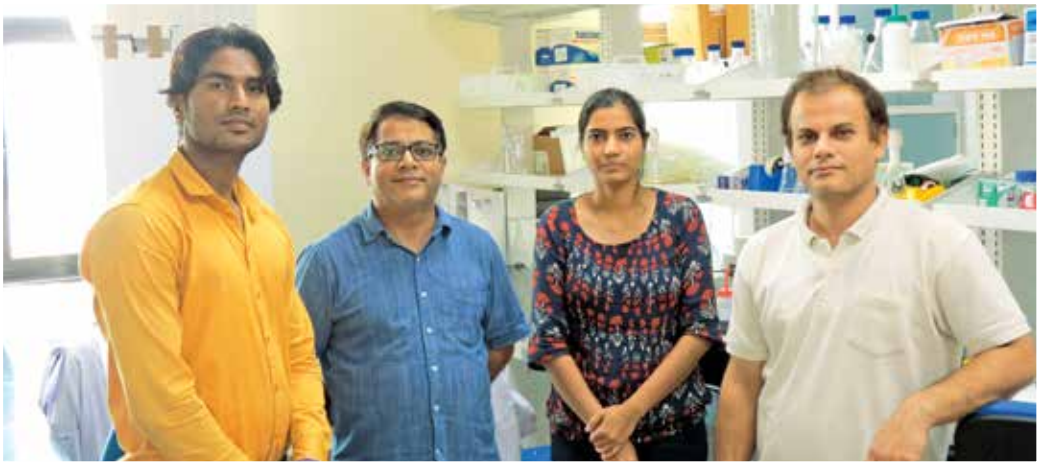
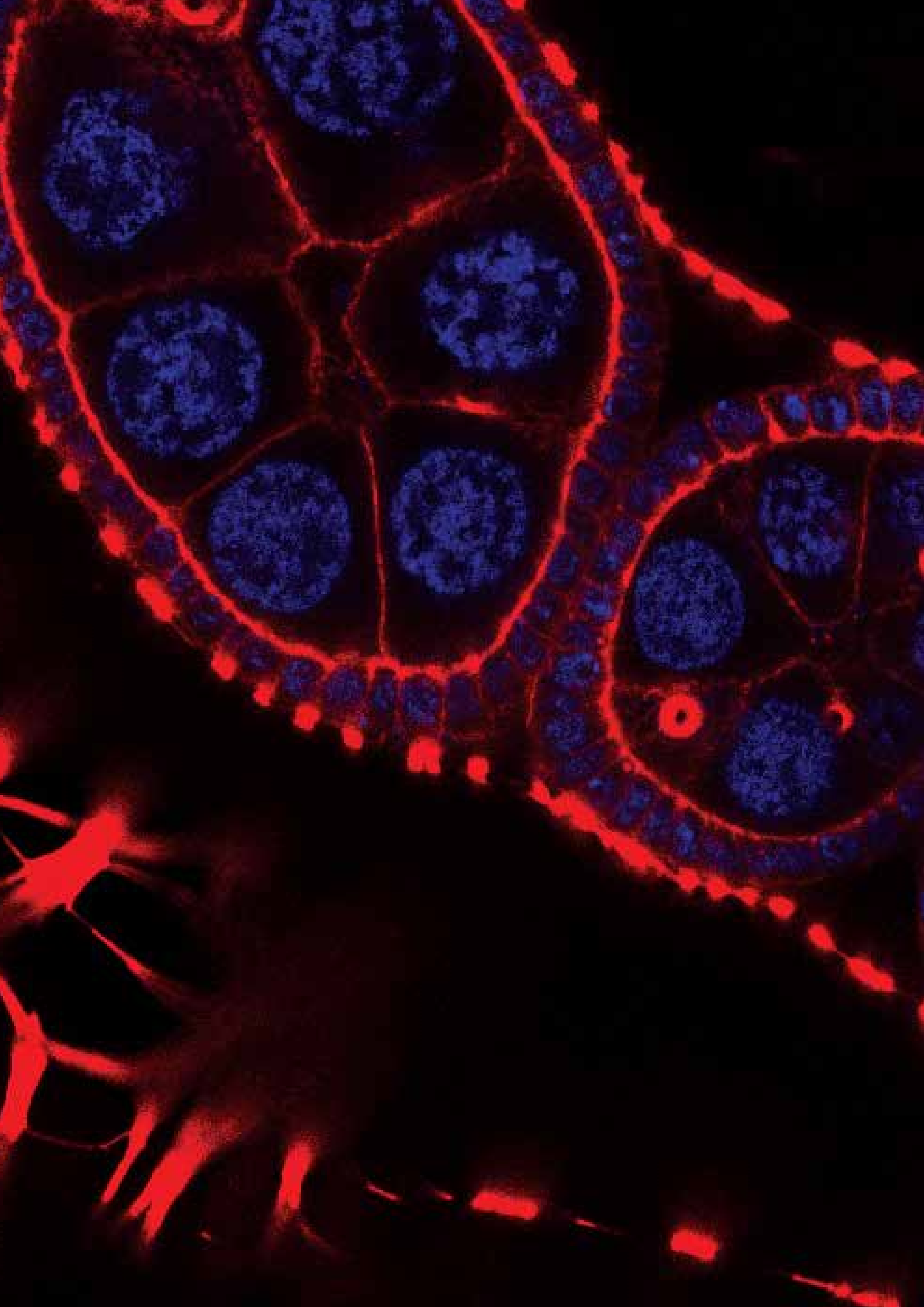


Figure 2. *Normal mode analysis (NMA) (a) P. Falciparum mitochondrial EFG model (cyan colour) (b) E. Coli EFG (green colour) (c) vector representation corresponding to panel a, (d) vector representation corresponding to panel b. Visualization is provided through vector field representation.*

We have initiated homology modeling and molecular dynamic (MD) simulation studies. Our MD studies on EF-G, a translation factor involved in translation elongation, from mitochondrial ribosome and *E. coli* ribosome show that the domain motion is substantially different Fig. 2. The homology modeling of apicoribosome is also in progress.





Molecular Medicine

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Role of Leukocytes – Platelet Crosstalk in the Pathogenesis of Systemic Inflammation in Human Diseases

The goal of this research program is to understand mechanisms by which leukocyte-platelet interactions contribute to 1) pathogenesis of systemic inflammation in hemolytic (PNH and SCD), metabolic (type 2 diabetes) and autoimmune (aHUS and SLE) disorders; 2) severity of inflammations in patients with acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE) at high altitude; 3) susceptibility of infection among natives of high-altitudes; and 4) replication and propagation of flaviviruses (Dengue and JEV) in host immune cells. We also aim to find biomarkers and molecular targets to develop potential therapeutics against these complications.

Systemic inflammation

In recent studies, we have shown that innate immune cells, including monocytes, are activated upon interaction with activated-platelets in the circulation of patients with hemolytic disorders such as paroxysmal nocturnal hemoglobinuria (PNH) and sickle cell disease (SCD). Circulating platelets in these patients are mainly activated by their interaction with free hemoglobin (Hb). Circulating monocytes become pro-inflammatory upon interaction with Hb-activated platelets and secrete elevated levels of pro-inflammatory cytokines. Another study from our lab has shown that like monocytes, neutrophils too show a high pro-inflammatory phenotype and function after engulfing Hb-activated platelets. As shown in Fig. 1, neutrophils isolated from PNH patients exhibit significant co-localization of Hb and platelets and are highly pro-inflammatory. We have also shown that the interplay between complement factor H (FH) and FH-related proteins (FHR), specifically (FHR1/3), plays a crucial role in the activation of monocytes, which induces them to mainly secrete pro-inflammatory cytokines. This correlates with the clinical phenotype of complement-mediated inflammation in patients with autoimmune disorders, including atypical hemolytic uremic syndrome (aHUS) and systemic lupus erythematosus (SLE). Furthermore, we have described the mechanism by which tissue necrosis at the site of injury develops systemic inflammation in about 17-20% of total accidental trauma patients.

Pulmonary edema

At high-altitudes, hypobaric hypoxia increases the risk of pulmonary and brain edema and intravascular clot formation among sojourners (travelers). Remarkably, Tibetans who live in high-altitude regions such as Leh (3500 meters), where the partial oxygen pressure is 40% lower than at sea level, do so without such clinical complications. Our recent collaborative work shows that the two novel mutations (C12G and G380C) in the *EGLN1* gene, which encodes Prolyl Hydroxylase-2 (PHD2, negative regulator of hypoxia-inducible factor HIF-1α, which is the master sensor of oxygen in the human body), protect the native Tibetan highlanders carrying $PHD2^{D4E/C127S}$ from polycythemia. Further, we found that these Tibetan highlanders with $PHD2^{D4E/C127S}$ are protected from an exaggerated immune response. However, patients with hypoxia-induced pulmonary edema (HAPE) show hyperimmune responses.

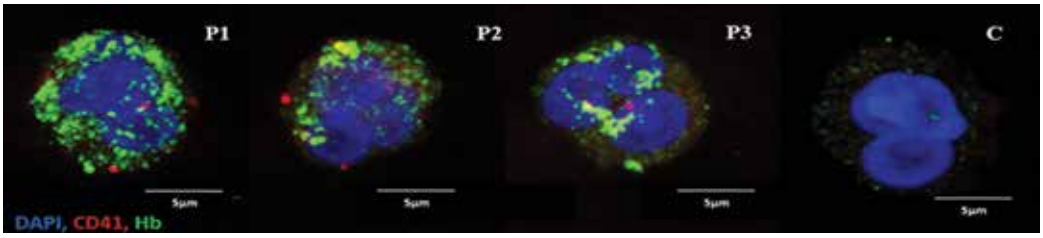

Figure 1. *The intracellular localization of platelets (red, CD42b), Hb (green, Hb), and nucleus (blue, DAPI) was analysed in neutrophils collected from peripheral blood of 3 PNH patients (P1-P3) and one healthy individual (C); 63X; scale bar, 5 µm.*

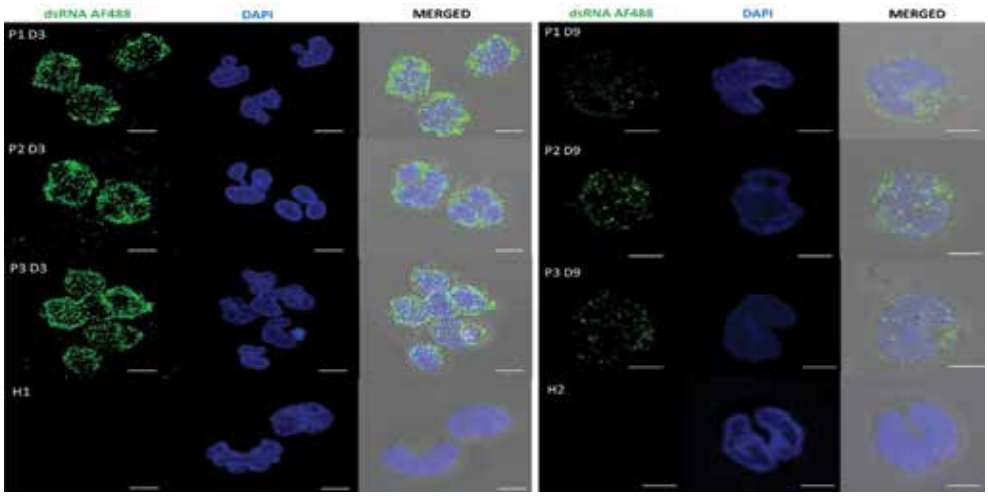

Figure 2. *Monocytes of Dengue patients (P1, P2, P3) on day-3 (left) and day-9 (right) were stained for intracellular viral dsRNA (green) nucleus (blue) and observed under a microscope. The monocytes of 2 healthy individuals (H 1-2) were used as controls; 63X; scale bar, 5 µm.*

Viral infection

In a recent study, we showed that Dengue virus (DV) replication is increased 5-fold inside monocytes in the presence of platelet factor 4 (PF4), a platelet cytokine secreted from activated-platelets. High plasma PF4 correlated with high DV replication in monocytes collected from peripheral blood of patients. Further, DV replication in monocytes was found to be higher at day-3 compared to day-9 of infection (Fig. 2).

Current focuses of our lab are: to investigate the role of leukocytes and platelets in the development of systemic inflammation in patients with type-2 diabetes. We wish to understand the mechanism by which necrotic tissue at the site of injury of an accidental trauma patient triggers systemic inflammation. We also wish to delineate the mechanism by which Tibetan highlanders with $PHD2^{D4E/C127S}$ are protected from an exaggerated immune response under extreme hypoxic conditions. We aim to search for chemical modifiers that can upregulate PHD2 enzyme function to diminish the hyper immune response in patients with HAPE. Finally, we wish to obtain more insights into the mechanism of PF4-mediated viral infection (with Dengue and JEV) using PF4-knockout as well as CXCR3-knockout mice and to develop inhibitors to PF4 and/or CXCR3 to abrogate viral infections.

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Proteostasis Mechanism in Neurodegenerative Diseases

Neurodegenerative diseases are characterized by progressive loss of structure and function of neurons in specific brain regions. The hallmark of neurodegenerative diseases is often associated with the abnormal accumulation of intracellular or extracellular protein aggregates in different parts of the brain. The impairment of protein quality control leads to the abnormal accumulation of disease-specific proteins. Our research program aims to understand the mechanism of protein aggregation and its toxicity that contributes to neurodegenerative diseases.

Parkinson's disease (PD) is the second most common neurodegenerative disorder, which is characterized by the death of dopaminergic neurons in the midbrain. Lewy body (LB) formation is the hallmark of PD pathology. PD is accompanied by shaking, rigidity, slowness of movement, difficulty with walking and ultimately death. Genetic factors, aging and excessive exposure to environmental toxins contribute to the etiology of PD. Recent studies have shown that more than 500 proteins are present in the LB and among them, 40 proteins are co-enriched with the α-synuclein protein. These proteins belong to the family of kinases (MAPKK1/MEK1, Protein kinase-C, and Doublecortin-like kinases), deubiquitinating enzymes (UCHL1 and OTUB1), ubiquitin ligases (KPC1 and FBXO2), chaperones (HSP90, Gelsolin, Spectrins, and DJ 1) and oxidative stress regulators (Carbonyl reductase-1, Peroxiredoxin-5 and protein disulfide isomerase). The functional role of a few such proteins has been studied. However, the precise role of these proteins in PD pathogenesis is still limited. Many of the identified proteins have not been investigated yet in the context of PD. Thus it is very pertinent to study their role in PD mechanism.

The cellular system is devised with various protective mechanisms to counteract the misfolded protein load. The ubiquitin-proteasome system, lysosomal degradation pathways, and autophagy are the molecular machineries that evacuate the misfolded protein load. Chaperones also play a critical role in protein refolding to attain proper conformation. However, a breach in any of these protective mechanisms leads to disease manifestation.

OTUB1, a deubiquitinating enzyme of the OTU family, is enriched with α-synuclein in LB of Parkinson's patients. However, its role in neuronal function and neurodegenerative diseases has not been investigated. OTUB1 is also majorly expressed in the brain and its presence in Lewy Body is intriguing to us. Here we have shown that OTUB1 forms amyloid structure in vitro. Like many other amyloid proteins, its oligomeric and fibril forms exhibit mitochondrial damage, cytoskeleton structure alteration, and neuronal cell death. OTUB1 forms inclusions in neuronal

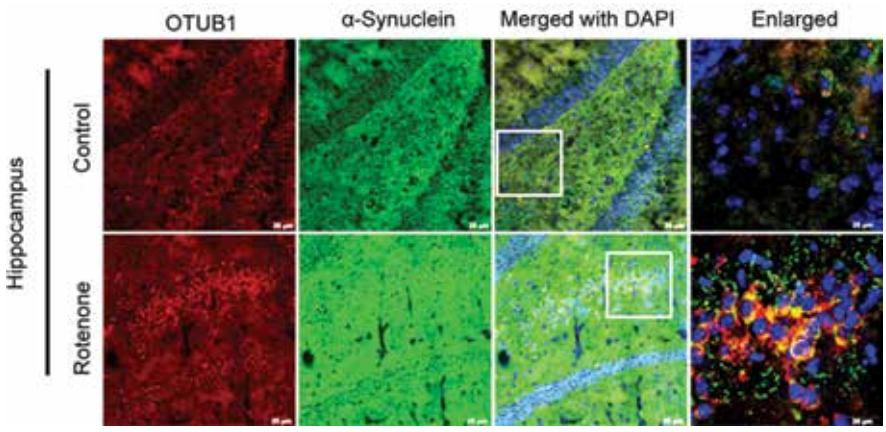

Figure 1. *OTUB1 aggregation in rotenone-induced PD mice model. Co-localization of OTUB1 and α-synuclein is shown in the rotenone-induced PD mouse hippocampus. Co-localization of both these proteins is more in rotenone condition than control. Images are acquired using Leica SP8 confocal microscope with the 10X dry objective. Scale bar is 20 µm.*

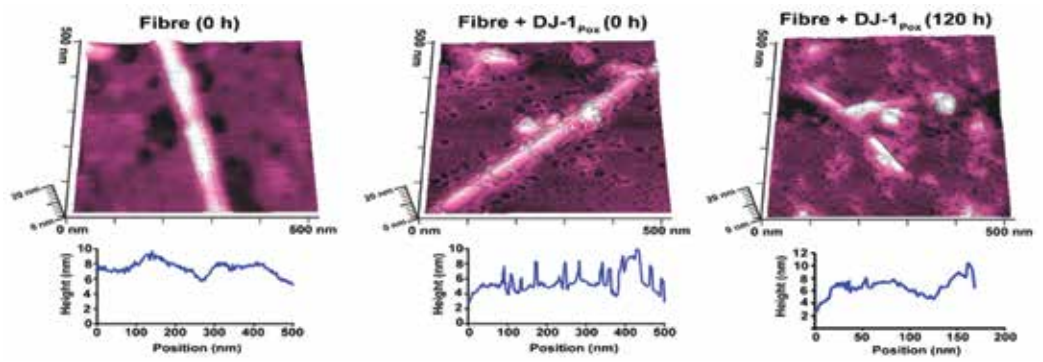

Figure 2. *Remodeling of α-synuclein at single fibril resolution. Atomic Force Microscopy images are taken after incubation of α-synuclein mature fibrils with DJ-1_{Pox} at 0 h and 120 h. The line profile is given below in the picture. The fiber periodicity is ~250 nm in α-synuclein fiber. Loss of periodicity is observed in both fiber+ DJ-1_{pox} (0 h) and fibre+DJ-1_{pox} (120 h) condition. Partially oxidized DJ-1 wraps α-synuclein as evident from the line profile and finally disintegrates into smaller fragments.*

cells and shows co-localization with α-synuclein in a rotenone-induced PD mouse model (Figure 1). In summary, our studies provide a piece of evidence that OTUB1 behaves as a novel amyloidogenic protein in LB in Parkinson's disease.

α-Synuclein is one of the major constituents of the LB. Genetic mutations, gene duplications and posttranslational modifications in α-synuclein induce oligomerization and beta-amyloid aggregate formation. Oligomeric α-synuclein is the major causative agent for neuronal toxicity and diseases spread through prion mechanism. Our group has demonstrated a new mechanism by which α-synuclein oligomers deface membrane nanostructure and promote S-nitrosylation induced neuronal cell death. Protein deglycase DJ-1 is identified in autosomal recessive early onset of Parkinson's disease and exhibits a redox-sensitive chaperone-like activity. The partially oxidized state of DJ-1 is active in inhibiting the aggregation of α-synuclein, but the underlying molecular mechanism remains unknown. Here we report that partially oxidized DJ-1 possesses adhesive surfaces compared to un-oxidized and hyper oxidized DJ-1, and sequesters α-synuclein monomers and blocks the early stages of α-synuclein aggregation. We have demonstrated for the first time that DJ-1 remodels α-synuclein fibrils into heterogeneous toxic oligomeric species (Figure 2).

The therapeutic strategies for managing Parkinson's disease mainly focus on the prevention of dopaminergic neuron loss. Currently, we have initiated a small molecule inhibitor screening, targeting protein aggregation pathways which would allow us to find potential compounds to combat PD.

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Signals that Regulate Skeletal Muscle Structure and Function

The skeletal muscle is one of the largest tissues in our body, required for movement, posture and metabolic regulation. We are interested in understanding how the skeletal muscle develops, how it regenerates during muscle injury, and the mechanisms underlying diseases that affect the skeletal muscle. One such disease is Freeman-Sheldon Syndrome (FSS), a genetic disease where patients exhibit musculoskeletal abnormalities such as joint deformities, bent fingers, club feet, curved spine and facial anomalies. FSS patients have compromised movement, respiratory, speech and feeding problems, delayed growth and development. Mutations in the MYH3 gene, a myosin family gene which helps in muscle contraction, is the primary cause of FSS. Interestingly, how mutations in the *MYH3* gene leads to musculoskeletal abnormalities seen in FSS patients is unclear. We found that the *MYH3* residues most frequently mutated in FSS patients, Threonine 178 (T178) and Arginine 672 (R672) are conserved evolutionarily from humans to *Drosophila myosin* (Fig. 1).

We have used the fruit fly *Drosophila melanogaster*, a genetic model, to understand the muscular abnormalities that occur in FSS patients. For this, we generated fruit flies expressing the FSS mutant myosins, T178I, R672C and R672H respectively, and characterized the abnormalities in muscle structure and function. The muscle is made up of numerous muscle fibers, which in turn contain sarcomeres, the functional contractile units of the muscle. We find that expressing the FSS mutant myosin leads to severe muscle defects such as shortening of the length and width of the sarcomeres and splitting of muscle fibers (Fig. 2). Functionally, we found that expression of FSS mutant myosins leads to aberrant muscle contraction and reduced climbing capability. Interestingly, these defects became more severe with age and muscle use. Thus, using the fruit fly, we have characterized what goes wrong in the muscle of Freeman Sheldon Syndrome patients. We are extending this work to understand the function of *MYH3* gene in mice, to obtain additional insights into FSS pathology.

Rhabdomyosarcoma is a type of cancer where the tumor cells exhibit characteristics of differentiated skeletal muscle cells and is thought to originate from the muscle stem cells. One pathway that is critical for proper skeletal muscle development is the receptor tyrosine kinase (RTK) signaling cascade, mediated by the MET receptor. MET is an oncogene associated with numerous types of cancers and mammalian muscle development.

We found that SPRY2, a bimodal regulator of receptor tyrosine kinase signaling, is a crucial MET interactor that regulates metastatic potential and differentiation in rhabdomyosarcoma. Knockdown of SPRY2 or MET led to similar functional outcomes in rhabdomyosarcoma, resulting in decreased migratory potential, and inducing differentiation. Thus, our study shows that SPRY2 is a key interactor and regulator of MET, functioning to stabilize the MET receptor to sustain downstream signaling, essential for the maintenance of migratory, metastatic and clonogenic capabilities, as well

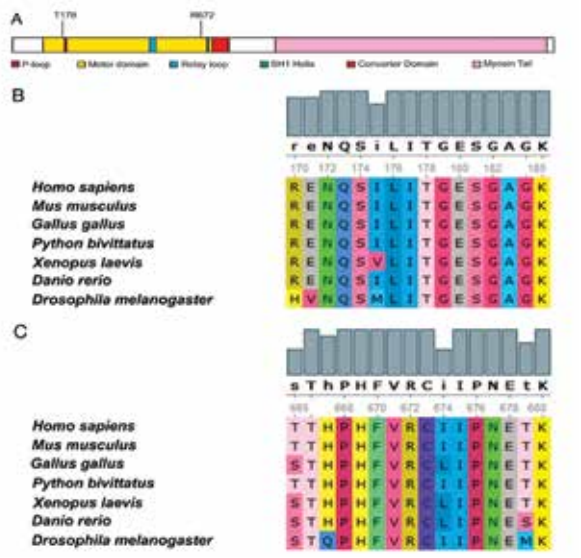

Figure 1. *The MyH3 residues mutated in Freeman-Sheldon Syndrome are evolutionarily conserved.Schematic showing MyHC-embryonic protein with the residues that have been found to be most frequently mutated in Freeman-Sheldon Syndrome (A). The residues T178 and R672 are conserved across evolution (B, C).*

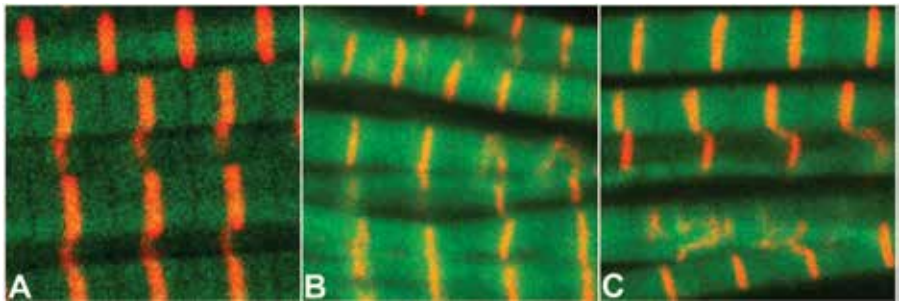

Figure 2. *Expression of myosin heavy chain with Freeman-Sheldon Syndrome mutations leads to sarcomeric defects in Drosophila.Indirect flight muscles of 20-day old wild type (A), R672H mutant (B) and T178I mutant (C) myosin heavy chain expressing Drosophila labeled by immunofluorescence for the Z-disc (red), thin filaments (green), and nuclei (blue).*

as to inhibit differentiation in rhabdomyosarcoma. These results identify a novel therapeutic intervention point in rhabdomyosarcoma.

Modulation of MET signaling and its role in myogenesis

Regulated cell signaling is fundamental to physiological processes such as organ morphogenesis, embryonic development, tissue homeostasis and regeneration. Consequently, aberrations in cell signaling underlie numerous human diseases including cancer. Signaling cascades transduced by receptor tyrosine kinases (RTKs) are essential components of cellular communication and are intricately regulated to fine-tune physiological processes. MET is one such proto-oncogenic RTK known to be important in normal embryonic development, and specifically critical for migration of skeletal muscle precursors during muscle development (myogenesis). MET signaling is crucial and redeployed in post-injury adult muscle regeneration. Intriguingly, MET signaling is known to be deranged in many cancers including Rhabdomyosarcoma (RMS) -a pediatric soft-tissue cancer where tumor cells resemble muscle precursors and fail to differentiate. Thus, MET signaling emerges as a connecting thread between muscle development, regeneration and disease. Nevertheless, the mechanisms underlying MET regulation during normal myogenesis remain to be understood. Therefore, my current work involves understanding modulation of MET signalingand significance of this regulation in developmental and regenerative myogenesis. For this work I am using mouse genetics based in vivo approach to address my questions. This work will be important in understanding differential regulation of MET signaling that underlies its diverse physio-pathological functions. The study should also provide a starting point for understanding the regulation of MET signaling, that is vital to development and homeostasis of other tissues types.

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RNA Biology of Aging and Dietary Restriction

Aging increases vulnerability to a number of non-communicable diseases including cancer, diabetes, neurodegenerative and cardiovascular diseases. Restricting nutrient intake without incurring malnutrition or dietary restriction is a robust intervention that can delay aging. This research program aims at assessing the role of post-transcriptional mechanisms in enhancement of lifespan and reducing risk factors associated with aging. Understanding how evolutionary conserved RNA mediated networks operate to affect the overall lifespan of an organism, will illuminate the basic principles underlying the aging process that can be applied to the development of therapeutic strategies to halt progression of age associated disorders.

The complex process of aging is characterized by organismal and cellular dysfunction and is associated with an increased risk of chronic diseases such as neurodegeneration, cardiovascular diseases and cancer. Dietary restriction (DR)-reduced nutrient intake that does not incur malnutrition - is a non-genetic intervention that extends lifespan and is associated with improved metabolic fitness and increased resistance to stress. The beneficial effects of this nutritional intervention are conserved across diverse species, indicating that the molecular mechanisms that underlie DR are evolutionarily conserved. Though, this anti-aging manipulation has been shown to direct profound changes in protein coding RNAs, its effect on non-coding RNA levels has not been explored extensively. Noncoding Ribonucleic acids (ncRNAs) are emerging as key regulators of gene expression, and are being recognized as key modulators of aging and late onset diseases. In contrast to the protein machinery that represents only ~2% of the transcribed genome, the expansion of the noncoding transcriptome in higher eukaryotes reflects greater regulation of cellular processes through control of protein function. Regulatory RNAs include a variety of evolutionary conserved classes of small noncoding RNAs [small interfering RNAs (siRNAs), microRNAs (miRNAs), small nuclear RNAs (snRNAs) and piwi interacting RNAs (piRNAs)] as well as the relatively newly evolved long noncoding RNAs (lnRNAs). Despite growing evidence that ncRNAs are altered during aging, there is little evidence on dietary restriction dependent positive effects on ncRNAs and their targets or the pathophysiological consequences of these alterations. This research program combines the genetically amenable fruit fly model with high throughput technologies such as RNAseq, proteomics and metabolomics to identify conserved miRNA-mediated networks that operate during aging and dietary restriction. This study is of direct relevance to the study of human age-associated diseases as inappropriate expression of miRNAs has been linked to a number of pathogenic states and molecules that alter the function or abundance of miRNAs are emerging as potential therapeutic agents to treat diseases. In addition, identification and characterization of conserved miRNAs that function during dietary restriction will likely lead to the discovery of circulating diagnostic biomarkers of age-related disorders in humans.

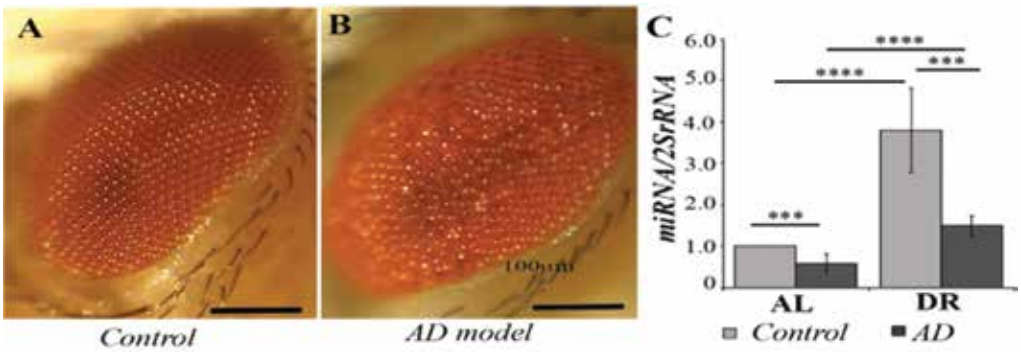

Figure 1. *Left panel: Heatmap showing miRNA abundances in adult fruit flies exposed to: "Ad libitum" diet (AL) for 10 days (Column 1), AL diet 40 days (Column 2) and dietary restricted diet (DR) for 40 days (Column 3). Right panel: Working model for characterizing age- and DR-modulated miRNAs and their downstream effectors.*

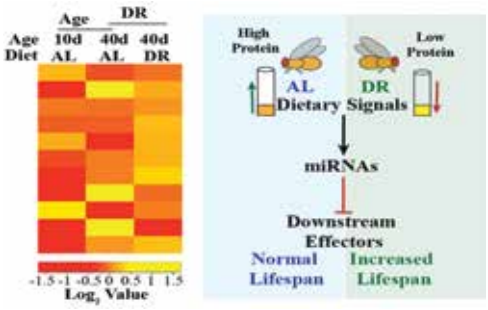

Figure 2. *MicroRNAs are altered in the Alzheimer's disease (AD) model. (A, B) Light micrograph of fly eyes from control (A) or AD model (B). Roughness in the eye in (B) indicates retinal degeneration due to pathogenic protein expression. (C) Changes in miRNA levels in AD flies that were fed "Ad libitum" (AL) and dietary restricted (DR) diet for 10 days.*

MicroRNA mediated mechanisms in aging and dietary restriction

MicroRNAs (miRNAs) are a class of small non-coding RNAs that negatively regulate gene expression by base-pairing to their target mRNAs. We are interested in using the fruit fly, *Drosophila melanogaster* as a model to study miRNA mediated post-transcriptional networks that operate during aging and late onset diseases. This model organism has yielded valuable insights into the molecular mechanisms underlying human aging owing to its' short lifespan (60-90 days), genetic feasibility, low cost and ease of handling. To assess whether miRNAs can mimic the effects of DR in animals that are fed a normal diet we performed high throughput RNA sequencing of small RNAs isolated from fruit flies exposed to dietary restricted and nutrient-rich diets (Fig 1). Since mutations in genes that do not respond to dietary restriction will serve as critical tools for understanding mechanisms underlying lifespan extension, we are analysing the lifespan of DR and age-modulated miRNA mutants or overexpression lines to identify miRNAs that contribute towards DR mediated lifespan extension. These studies will aid in defining miRNA mediated mechanisms that operate during aging and determine how targeted disruption, competitive inhibition or overexpression of miRNA network components modulates aging.

Illuminating microRNA mediated mechanisms that operate during the pathogenesis of late onset neurodegenerative disorders

Human neurodegenerative diseases are characterized by progressive and widespread loss of neurons in the central nervous system with aging being the major risk factor for disease onset. Recent studies have found that miRNAs are misregulated in neurodegenerative diseases (NDDs) such as Alzheimer's disease (AD). We are utilizing *Drosophila* neurodegenerative disease models to provide mechanistic insights into the roles of miRNAs in aging disease pathogenesis. Since, conserved miRNAs have been linked to AD, our system provides a tractable venue both to understand the molecular mechanisms underlying miRNA-mediated neurodegeneration and to explore miRNA-mediated therapies designed to ameliorate neurodegenerative symptoms. We have identified a few conserved miRNAs that are altered in a diet dependent manner in AD models (Fig 2) and are currently examining the effects of modulating these miRNAs on disease progression. Together these studies are aimed at developing RNA based therapeutic strategies to fine-tune conserved pathways that are able to provide broad spectrum health improvement and can aid in the development of treatments for late onset diseases simultaneously.

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Understanding Taste and its Modulation using Drosophila melanogaster as a Model System

Taste is extremely important for all organisms to evaluate and choose foods that are rich in calories and avoid bitter compounds that may be toxic. Like humans, *Drosophila* flies can differentiate various taste stimuli. By exploiting the taste system of flies, our lab is interested in understanding how flies make feeding decisions and how the taste information is wired and processed in the brain. My group is mainly interested in the gustatory system of *Drosophila* to understand the feeding behaviour, taste circuits and their modulation towards achieving the following main objectives: (1) how specific neuronal circuits influence-feeding behaviours, (2) how taste information at the periphery and central nervous system is modulated by physiological state and other factors that act on the taste cells and circuits, and (3) identifying the neuronal pathways that regulate satiety. When the balance between hunger and satiety is perturbed, food intake gets misregulated, leading to excessive or insufficient eating. In humans, abnormal nutrient consumption causes metabolic conditions like obesity (causing 3 million deaths/year) and eating disorders. Despite this burden on society, we currently lack enough knowledge about the neuronal pathways, circuits and genes that regulate appetite.

By using experimental strategies involving molecular, behavioural, genetic, calcium imaging and electrophysiological approaches, we are interested in dissecting the taste neural circuits (especially higher order taste neurons) that convey taste information to the brain and are involved in simple feeding behaviours like acceptance or rejection of food (Fig. 1A). To address this, we have screened around 150 promoter GAL4 lines by expressing GFP to identify taste circuits only in the brain (Fig. 1B). If the newly identified taste neurons are a part of appetitive taste circuits like sugar or low salt, artificial activation of these neurons by expressing the temperature-sensitive cation channel dTrpA1 leads to extension of the proboscis (PER- Proboscis extension response; first step in the appetitive behavior) at 32 0C. High PER responses (>50%) suggest that many of these taste neurons might be involved in the appetitive behaviour and are potential candidates for sugar or low salt sensing (Fig. 1C). We are now in the process of delineating these unmapped taste neural circuits in the brain with high cellular resolution and calcium imaging approaches to monitor taste-induced activity and understanding their physiological roles.

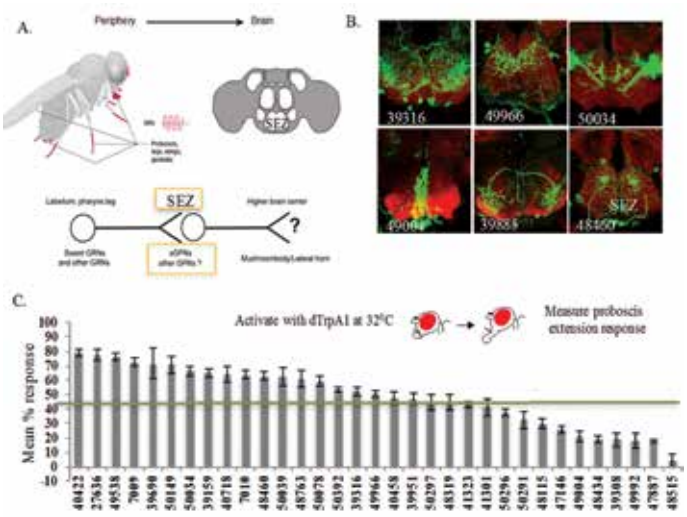


Figure 1. *(A) Drosophila peripheral and central taste organs. Gustatory receptors (GRs-red) are present on Gustatory receptors neurons (GRNs) which are distributed throughout the fly's body. The main peripheral taste organs of adult Drosophila are labellum, legs, wings and genitalia. GRNs send projections to brain in the sub esophageal zone (SEZ). SEZ is a first relay for taste information. The identity of second order gustatory projection neurons (GPNs) that respond to different taste modalities is still unknown except one sweet (sGPNs) and one bitter projection neuron (Kain and Dahanukar, 2015; Bohra et al., 2018). (B) Identification of neuronal pathways involved in the feeding behaviors. Expression pattern of some of the newly identified neurons only in the SEZ of the adult fly brain. GAL4 driven expression of UAS-mCD8::GFP in the SEZ for different GAL4 lines (visualized with anti-GFP- green). For all brain images, neuropil is stained with anti-nc82 (red). Various numbers indicate different GAL4 driver lines marking different set of neurons obtained from Janelia farm GAL4 collection. (C) Proboscis extension response (PER) of flies at 32°C by expressing Drosophila heat activated channel- dTrpA1 with various GAL4 lines. 21 GAL4 lines showed PER response around 50% and above that could be involved in the appetitive.*

The lab is also trying to understand how starvation state and neuronal activity in sensitized pharyngeal neurons induce modulation of salt taste behavior in *Drosophila*. Sodium present in salt is a fundamental nutrient that is required for many physiological processes. The most important ones include electrolyte homeostasis and neuronal activity in the body. In animals, including mammals and *Drosophila*, the detection of NaCl produces two different behaviours in a concentration - dependent manner: low-salt concentrations (< 100mM) act as an attractive cue and induce attraction, whereas high-salt concentrations (> 200mM) evoke aversive behavior (Fig. 2A-D). A complex code for salt taste at the periphery has been proposed recently in flies. How high salt diet affects the preferred level of salt and other taste preferences, and modulates the feeding behaviour is yet to be identified and has not been explored earlier. In our study, we identified that pre-exposing adult flies to high salt concentrations in the fly media for three days maintains their preferences towards high salt even later. Mated female flies show higher feeding preferences towards salt media and increase in body weight, as well as consume more water after high salt meals. Our results suggest that both Ionotropic receptor Ir76b and neurons are involved in the detection of low and high salt. Additionally, silencing neuronal activity of sweet and bitter neurons at the periphery changes sensitivity of flies towards salt, particularly in flies exposed to high salt previously, suggesting a role of intact pharyngeal neurons in regulating salt intake. Our study reveals that neuronal activity and starvation state in salt sensitized pharyngeal neurons play an important role in regulating salt intake and present a complex code even at the level of internal taste organ. In the future, we are interested in investigating the role of different physiological states like hunger and thirst that might alter the responses of newly identified candidate neurons and various gustatory receptors by performing calcium imaging on these neurons. The lab is also interested in exploring how hunger and satiety are achieved by identifying pathways, neurons and genes involved, and to relate our findings to homologous mammalian genes with similar functions to discover conserved pathways that regulate hunger and satiety. Disease-carrying and crop destroying insects use their senses of taste and smell to find hosts and food. Insect-borne diseases such as malaria, dengue fever and Chikungunya are transmitted via feeding behaviours. The results from simple model systems like *Drosophila* could potentially be applied to safe and cost effective pest control by improving insect trapping strategies and thus reduce pathogen transmission by insects and greatly benefit the agricultural industry and society as a whole.

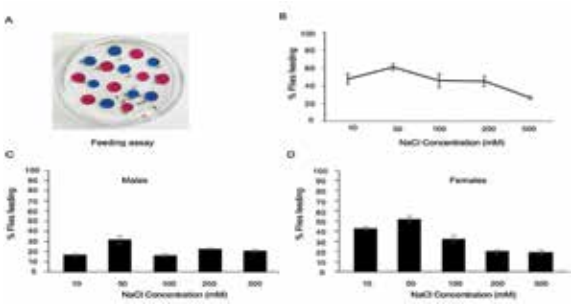
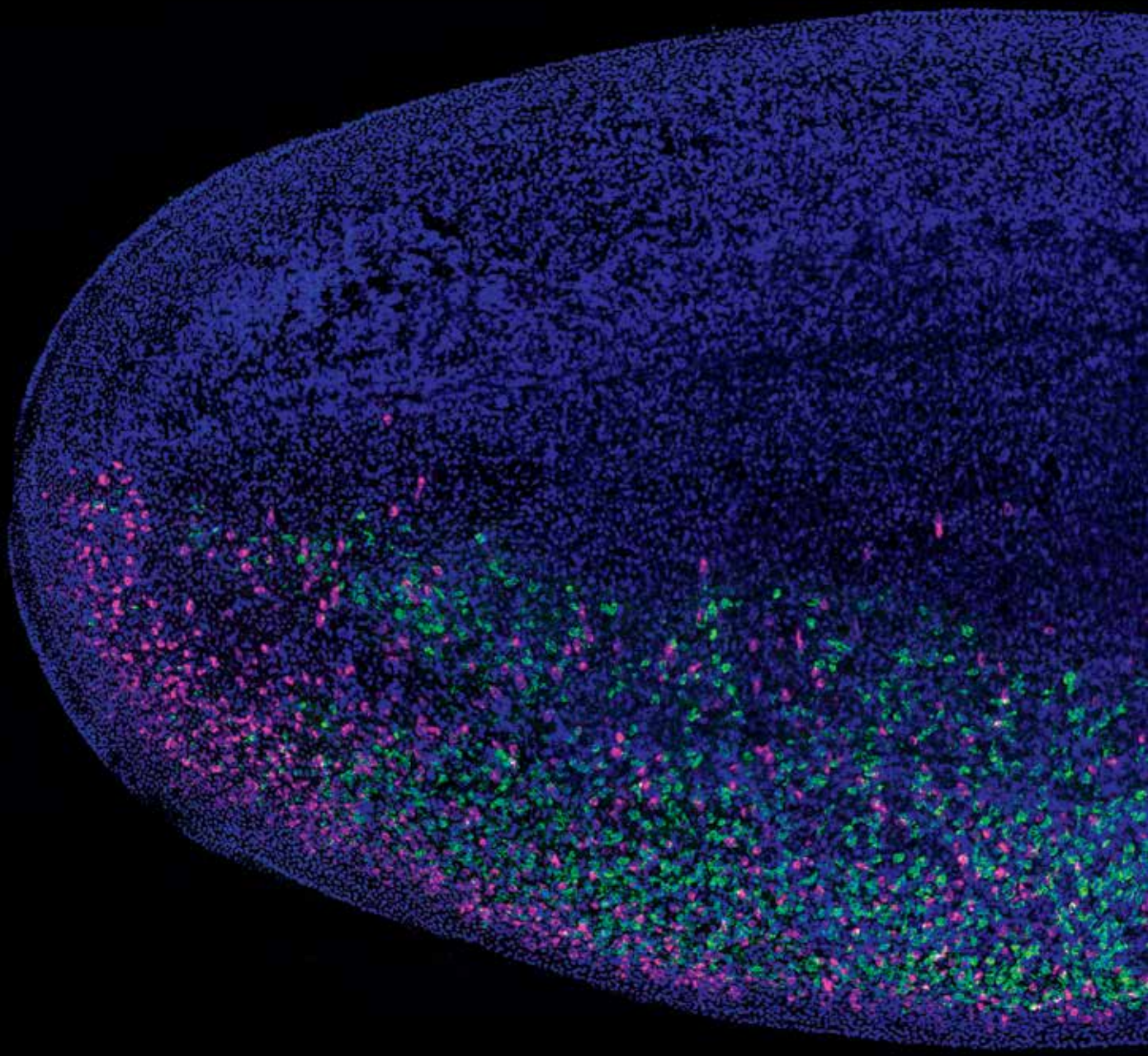
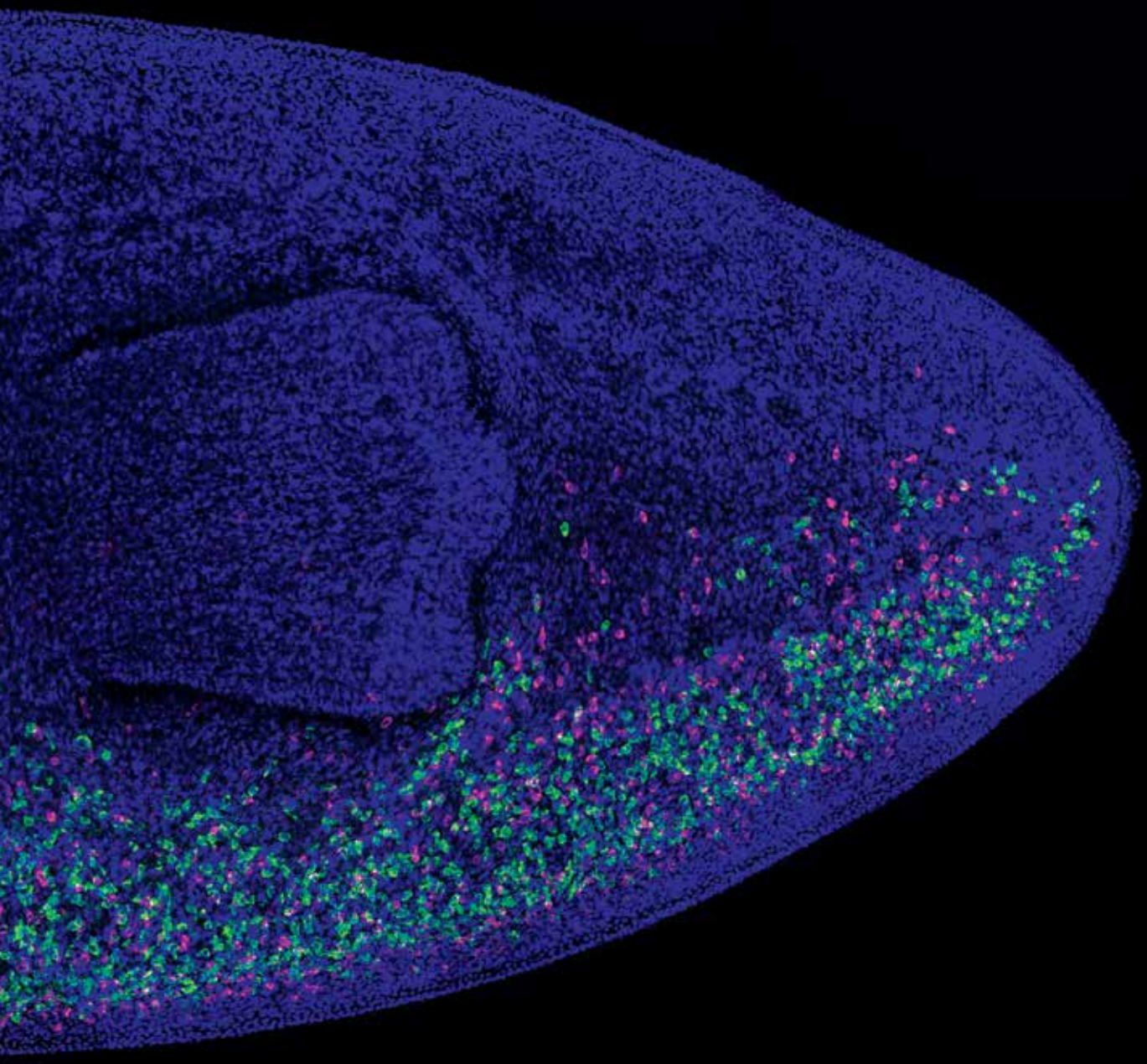


Figure 2. *(A) Two choice feeding assay for adult flies. In our two-hour assay, flies were allowed to make a choice between water and varying concentrations of salt in an unbiased manner in the dark. Blue is just water and agar. Red is salt added with agar and water. % flies that were eating salt was scored based on abdomen color. (B) Dose response curve for salt (N=6 plates for each concentration, 20 flies- 10 males and 10 females each plate). Wild type flies (CsBz) showed highest attraction towards salt at 50mM concentration and aversion at high salt concentrations. The similar trend in feeding is observed in males and females separately (C and D).*





Infectious Disease Biology

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Biology of Medically Important Viruses

Viruses pose an ever-increasing threat to the well-being of the human population at large and this scenario is particularly ominous in the Indian context, where epidemics of various viral infections are reported at regular intervals. Understanding the biology of virus infection and replication can help in designing novel antivirals for effective therapeutic and prophylactic interventions. This program aims to study the biology of mosquito-driven viruses relevant to India, such as Chikungunya (CHIK), Dengue (DEN) and Japanese encephalitis (JE) viruses, to understand their replication and pathogenesis with a view to design novel antiviral strategies. Provided below is a summary of some of the key projects under the program.

Identification of small molecule antivirals against CHIK and JE viruses

Efficacious and affordable antivirals against CHIK and JE viruses are urgently needed to deal with these medically important viruses. Two strategies are being followed to this end. In the first strategy, high throughput assays for testing the antiviral activity of small molecules are being developed and used to screen chemical compound libraries from commercial sources. In the second strategy, structures of viral proteins critical for the virus life cycle are used to in silico identify small molecules that have the potential to inhibit their activity and biological function.

We have constructed a recombinant CHIK virus that produces EGFP following the infection of the host cell. A high throughput assay in 96-well plate format was used to screen a small molecule synthetic chemical library (Spectrum collection from Microsource discovery) made up of 2560 compounds. We have identified some lead compounds that show significant inhibition of CHIK virus infection in 3 different cell types at 1 micromolar concentration, with at least one compound showing significant inhibition at 0.1 micromolar concentration. We have developed a mouse model of CHIK virus infection which will be used for testing the antiviral potential of the compounds in the animal model.

We have utilized bioinformatics tools to generate a computational model of the RNA-dependent RNA polymerase (RdRp) region of CHIK virus nsP4 (residues 285-577) in complex with substrate RNA and incoming CTP. The model was built using the coordinates of the functional complexes of the RdRps from Foot & Mouth Disease virus and the Norwalk virus. The model was analysed to identify interfaces that can be targeted for disruption by small molecules. *In silico* screening to discover potential binders that will interact with the identified surfaces is currently underway. In parallel, efforts are underway to obtain soluble RdRp (nsP4 protein) that will be used to assess the ability of the inhibitors unearthed by *in silico* screening to affect nsP4 activity.

Neutrophil activation in Dengue pathogenesis

Our work in the past had shown elevated levels of MPO and elastase in severe dengue cases and levels of these enzymes dropped during recovery. MPO and elastase are two important

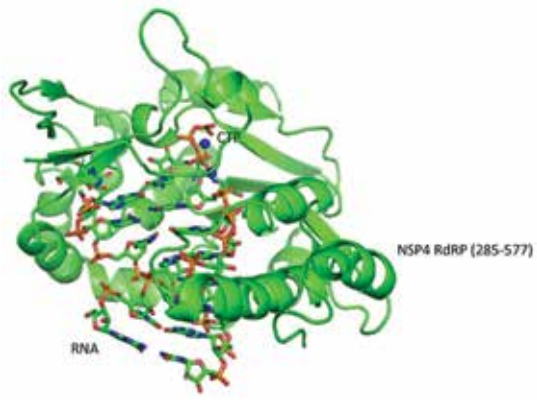

Figure 1. *Computational model of CHIK virus RdRp RNA:CTP complex*

neutrophil enzymes which play a very important role in neutrophil activation. Activated neutrophils release nuclear DNA into the extracellular milieu, forming a web-like structure and entrap invading pathogens, known as Neutrophil Extracellular Traps (NETs). Although NET release is considered a part of the host defence mechanism, aberrant or excessive NET production is involved in severe tissue injury, auto-antibodies and development of several chronic inflammatory diseases. Thus, countermeasures against the formation of NETs, or their effects, could be a useful approach for the prevention or treatment of many diseases, including dengue fever.

We are now extending our *in vitro* protocol for setting up a high-throughput screening system for identifying compounds involved in the modulation of neutrophil activation and modulation of NET release. Using HL-60 cells, we have developed an *in vitro* model for neutrophil activation.

Characterization of the replicase complex of JE virus

The NS5 protein of JE virus, containing the RdRp activity, associates with virus non-structural proteins and several host proteins to constitute the viral replicase complex. The identities of these host proteins and their role in virus replication is not well understood. The RdRp of JE virus has been purified from the recombinant *E. coli* and is being used to identify interacting proteins from mammalian cells using mass spectrometric analysis. We are also using a method called BioID, which is based on proximity-dependent biotinylation of proteins by a promiscuous biotin ligase mutant BirA (R118G), which is fused to the RdRp. After an overnight incubation with biotin, cells are subjected to harsh lysis and biotinylated proteins isolated and identified by mass spectroscopy to determine the proteins that had come into contact with the chimeric RdRp-BirA (R118G) protein. Both these methods have identified a number of common proteins involved with varied functions such as cytoskeletal architecture, RNA binding and energy metabolism. The role of these proteins in JE virus RNA synthesis and replication is under investigation.

Characterization of the distal gut virome through metagenome sequence analysis

Dr. Kanchan Bhardwaj
DBT Biocare Awardee

We have performed whole genome shotgun sequencing of DNA (from total community and purified VLPs) isolated from 10 healthy individuals and collected ~ 15 Gb data of paired end reads, average length of 150 bases per DNA sample, using Illumina (NGS) platform. After pre-processing, we have obtained an average of 12 gigabases (Gb) (20-30 million paired-end reads; read length of 36 to 150 bases) of high quality data for each sample. Further analysis is in progress for the taxonomic annotation of the recovered virotypes, identification of novel or unexpected viruses and describing the functional landscape. We will also describe inter-individual and temporal variability in the analyzed population and compare it with other populations.

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Molecular Biology of Infectious and Idiopathic Inflammation of the Gut

Modern ways of living have led to a sudden rise in abnormal immune function leading to auto-immune disorders. In this program we intend to look at gut inflammation particularly with relation to cellular SUMOylation, a post-translational modification (PTM) mechanism. SUMOylation is an inherent PTM pathway which is known to regulate several fundamental processes of the cell, though its connection to gut inflammation has not been well studied. Inflammatory bowel disease (IBD) is an inflammatory autoimmune disorder of the gut involving chronic abnormal immune activation. Symptoms that include recurrent diarrhea, abdominal cramps and weight loss lead to a compromised 'quality of life'. Several molecular pathways have been tested for therapeutic intervention but none have been found fully successful. Even the presence of certain gastric pathogens such as *Salmonella* Typhimurium have been linked to IBD. In our study, we have investigated a possible role for SUMOylation in epithelial signalling and its crosstalk with the immune system. Using a mouse model and human patient samples, we demonstrate the existence of an aberrant SUMOylation pathway linked to immune over-activation. These findings, the first of their kind in gut inflammation, connect immune cell conditioning to SUMOylation and highlight its importance for therapeutic interventions.

A SUMOylation dependent switch of Rab7 controls Salmonella infection

We tested SUMOylation in gastroenteritis, a diarrhoeal disease caused by the gastric pathogen *Salmonella* Typhimurium (hereafter *Salmonella*). Such food borne illnesses pose a significant health challenge in the developing and developed world. The emergence of multidrug resistant strains of Salmonellae has led to several manifestations of the disease that are more difficult to treat. Remarkably, certain cellular, molecular and pathological markers of *Salmonella*-induced gastroenteritis have deep-rooted similarity with those of IBD. After infection, *Salmonella* thrives in a membranous vacuole called SCV and it takes complete control of the transcriptional and signalling machineries of the host cell. Details of the mechanisms that stabilize the SCV and enable the pathogen to hijack the host cell are not fully understood. Our experiments using cell culture model and a mouse model demonstrated a critical role for SUMOylation in *Salmonella* infection and induced inflammation. It was observed that *Salmonella* targets multiple components of the SUMOylation pathway to alter the SUMO-modified proteome (SUMOylome). In the current year, the connection between the changes in the SUMOylome and *Salmonella* intracellular life was probed in greater detail. One such component of the SUMOylome was Rab7, an intracellular trafficking regulator known to be important for SCV stability. Using mass-spectrometry, *in silico* docking and biochemical assays, SUMO-modification of Rab7 was confirmed. The exact location of Rab7 SUMO-modification was identified to be a lysine residue at position 175 (Fig. 1). This lysine was mutated to disallow SUMO-modification and the mutant form was called as $Rab7^{SD}$. Cells bearing gene constructs encoding wildtype ($Rab7^{wt}$) or mutant ($Rab7^{SD}$) were transfected, followed by *Salmonella* infection and microscopy. Surprisingly, the non-SUMOylable Rab7 ($Rab7^{SD}$) displayed several features that appeared to be beneficial to the bacteria, such as enhanced interaction with PLEKHM1. Activity assessment revealed decreased GTPase activity and altered subcellular localization of $Rab7^{SD}$ during infection. Together these results indicate that a SUMOylation-dependent mechanism controls the stability, localization and function of Rab7 and thereby modulates intracellular *Salmonella* biology.

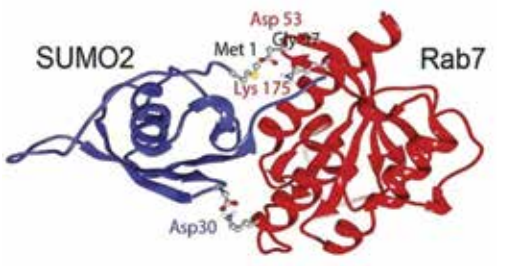

Figure 1. *SUMOylation of Rab7 at Lysine-175: Computational molecular docking of available protein structures of SUMO2 and Rab7 from the Protein Data Bank (PDB) examining possible interaction using the ClusPro programme, showing the ribbon structures of SUMO2/3 (blue) and Rab7 (red). The juxtaposed C-terminal Glycine-97 of SUMO2/3 and Lysine 175 of Ra7 are represented in the structure.*

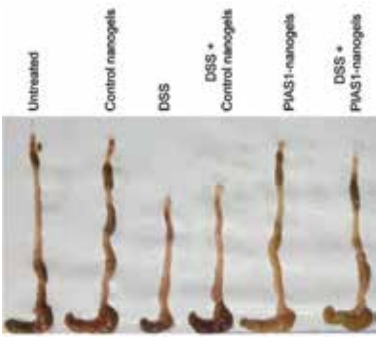

Figure 2. *Delivery of PIAS1-encoding DNA with nanogel in mice relieves inflammation. Analysis of gross morphology of the colon and caeca of mice treated as indicated, showing the rescue of animals treated with PIAS1-nanogel.*

Targeting SUMOylation pathway genes to combat intestinal inflammation

Interestingly our investigations have also revealed the involvement of SUMOylation in Crohn's Disease (CD) and Ulcerative Colitis (UC), the two major forms of IBD. The chronic and relapsing nature of inflammation in IBD is thought to result from an inappropriate and continuing inflammatory response to commensal microbes in a genetically susceptible host. While several genetic loci have been linked to IBD, the precise etiology remains unknown. In our investigations, a dramatic lowering of SUMOylation resulting from a decrease in SUMO-enzymes Ubc9 and PIAS1 in the intestinal epithelium was observed. In a mouse model of IBD, induced by treatment with dextran-sulphate sodium (DSS-mice), a comparative SUMO-proteome analysis of the intestine revealed a distinct SUMOylome. A critical alteration of SUMOylated forms of key cellular regulators was observed in epithelial cells, which could be attributed to inflammatory signalling. To probe this further, the expression dynamics of SUMOylation pathway genes and inflammatory markers were investigated in DSS-mice. Expression of inflammatory markers began on day 5 post treatment with DSS, while SUMO-pathway enzymes PIAS1 and Ubc9 showed alteration much earlier (day 3). To confirm the relevance of these findings to human IBD patients, expression analysis of PIAS1 was performed using endoscopic biopsy samples of human IBD patients. Compared to the control group, UC and CD patient samples showed a dramatic lowering of expression of SUMO pathway genes. Patients with severely lowered SUMO pathway genes displayed a heightened expression of pro-inflammatory cytokines and higher disease severity. Together, these observations led us to hypothesise that the SUMOylation pathway may be a crucial regulator of inflammation and could be targeted for combating colitis. In collaboration with nanotechnologists, a polymer-based nanoparticle formulation (TAC-6) was generated to deliver PIAS1-encoding nucleic acids in mice. The idea was to enhance the levels of PIAS1 during DSS treatment and examine the outcome. While the treatment of nanogel mixed with the PIAS1-encoding gene (PIAS1-nanogel) did not alter the body weight or any other discernible phenotype in animals, their gut inflammation was significantly reduced as revealed by detailed histopathological analysis (Fig. 2). Interestingly, the PIAS1-nanogel treated mice showed significant downregulation of pro-inflammatory cytokines, while anti-inflammatory cytokines were upregulated. Together these results confirmed successful delivery of the PIAS1 gene in vivo and demonstrated PIAS1 as a target for combating intestinal inflammation.

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Host-Pathogen Interactions of Flaviviruses

Japanese encephalitis virus is spread through mosquito bites, with several cases reported from across India every year. The virus infection leads to acute brain fever (encephalitis) and causes several deaths. Though vaccines are available, no drugs or therapeutics against JEV have been developed. Treatment for the disease is only supportive and hence there is an urgent need for the development of effective anti-virals or therapeutics. We are trying to understand how the virus invades the different cells of the human body including the brain and how it exploits the cellular machinery to grow and spread. We also look at how the body mounts an immune response and what parameters are essential for blocking/killing the virus. This gives us clues to design and/or test drugs that can block the infection and/or enhance immunity.

We aspire towards identification and development of anti-viral strategies and drugs. We are working on the following objectives:

(a) Characterization of JEV trafficking in neuronal cells,

(b) Elucidating mechanisms of the anti-viral role of autophagy during JEV infection and

(c) Pharmacological modulation of autophagy as a potential therapeutic target for JE.

Studies from our lab have shown that JEV utilizes distinct entry pathways for establishing infection depending on the cell type - neuronal or epithelial. We recently completed and validated an RNA interference based screen of a set of 136 human genes implicated in membrane trafficking in two cell lineages - epithelial and neuronal. This study has identified several host-factors crucial for virus replication and/or egress (Fig. 1). Some of the hits in the study are established drug targets. We propose to validate these drugs in vitro and in an animal model of JEV.

Autophagy is a cellular pathway that occurs at a basal level in all cells, but is up-regulated in response to stress and pathogen infection. Previously, we have characterized autophagic progression during JEV infection and have shown that autophagy is primarily anti-viral. Autophagy is functional during early stages of infection; however it becomes dysfunctional as infection progresses, leading to cell death. Autophagy induction in JEV infection is mediated primarily through the activation of ER and oxidative stress.

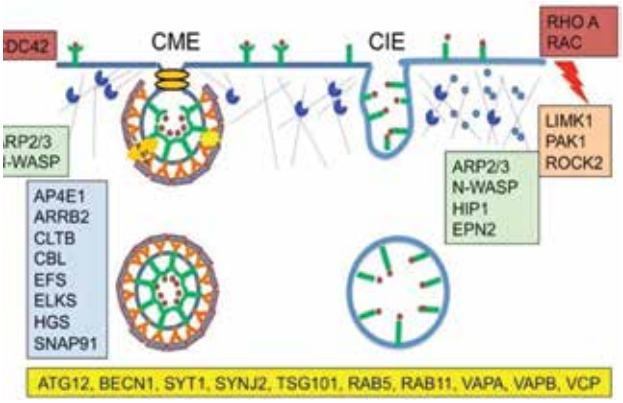

Figure 1. *JEV utilizes lineage-specific entry portals for establishing infection in mammalian cells. JEV entry is through a strict clathrin-mediated endocytic (CME) pathway in epithelial cells (left). The pathway is dependent on CDC42 and ARP2/3 mediated actin rearrangements. Entry in neuronal cells (right) can take place through clathrin-independent endocytosis (CIE) and is dependent on RHOA and RAC. This mechanism, in addition to the ARP2/3 complex, also requires additional signaling molecules such as LIMK1, PAK1 and ROCK2. Several essential common host factors were also identified in our study (highlighted in yellow).*

To study the impact of dysfunctional autophagy on the cellular proteome during JEV infection, we performed TMT based mass spectrometry and compared the level of protein abundance between wild-type and autophagy-deficient fibroblasts in the context of JEV infection. We observed that the levels of proteins related to cell adhesion, metabolic processes, transport, cell differentiation and immune pathways were highly affected due to the lack of autophagy. Metabolic processes, lysosomal organization and various innate immune responses were compromised while cell adhesion, cell development and differentiation processes were elevated in autophagy defective cells. The autophagy deficient cells had

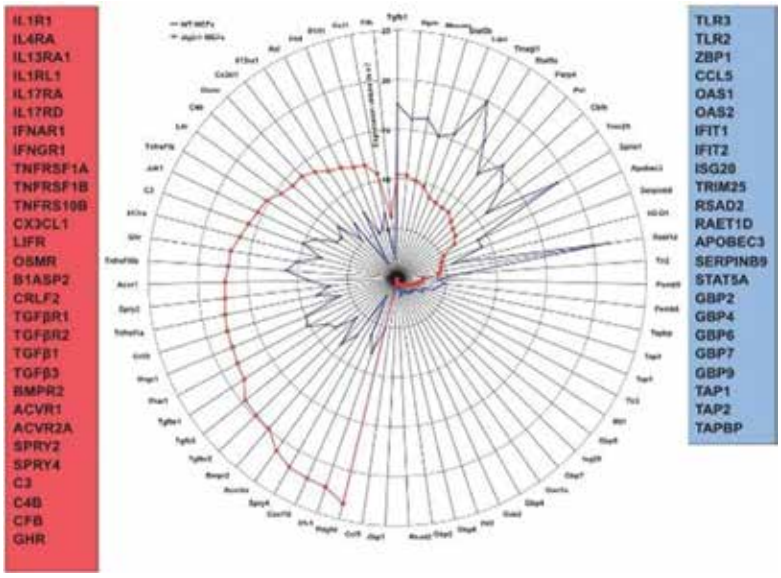

Figure 2. *Autophagy-deficient fibroblasts show dysregulation of several immune related proteins. Radar plot representing the expression values of the listed immune proteins in wild-type (WT) and autophagy deficient cells. Proteins listed in red show higher levels in autophagy deficient cells, while those in blue are enriched in WT cells.*

lower levels of key immune sensors and effectors (Fig. 2). This study has given us crucial insights into the protein landscape of JEV infection, which is currently under validation. The role of autophagy in determining the host immune responses to JEV infection is also being actively pursued in our laboratory.

Several FDA approved drugs have been shown to enhance autophagy, and this has the potential to be repurposed for the treatment of infectious diseases. We plan to test the potential of approved autophagy inducing drugs in blocking virus replication, preventing cell damage and inflammation, and enhancing survival in a mouse model of disease. As a first step towards this goal, we have generated a reporter cell line to measure autophagy flux in a high-throughput imaging platform. Using this reporter system, we have performed a primary screening of "The Spectrum Collection" comprising of 2560 biologically active and structurally diverse compounds. In the primary screen, 104 autophagy inducers were identified, of which 65 compounds are novel. In further studies, the autophagy inducing potential of these drugs will be validated, following which they will be utilized for studying their effect on JEV infection.

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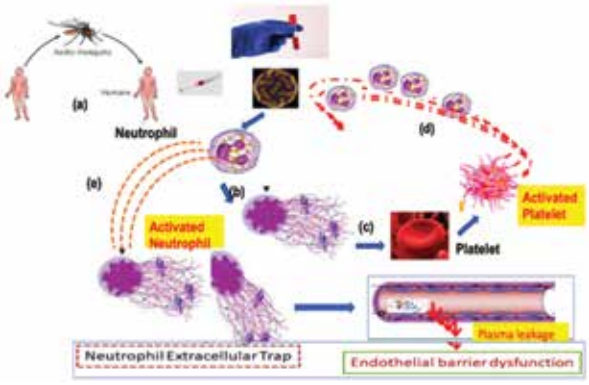
Understanding Viral Pathogenesis and Development of Therapeutic Measures against the Flaviviruses Prevalent in India

Dengue fever is the most common mosquito-transmitted viral disease caused by Dengue virus. The infection can become dangerous since it may cause rash and bleeding. As a result, there is less blood circulation in our organs and patients ultimately die due to shock. Our group is interested in understanding the factors that trigger dengue severity. This knowledge will help to develop a scientific basis for managing dengue disease progression by targeting specific factors responsible for disease severity. Like Dengue, Japanese Encephalitis Virus (JEV) infection is transmitted through mosquito bites and causes brain infection. Children are most susceptible to JEV infection and develop a permanent neurological problem. Our group is interested in identifying alternative therapeutic options for controlling virus-induced brain damage.

Dengue is a mosquito-borne flavivirus that is spreading explosively in many parts of the world. Clinically, dengue can present as a febrile illness or a severe, life-threatening disease known as Dengue Haemorrhagic Fever (DHF). The hallmark of DHF is increased vascular permeability and consequent plasma leakage, leading to rash, bleeding, circulatory collapse and shock. The morbidity and mortality of DHF are largely driven by vascular leakage and its resulting complications. The molecular mechanisms of endothelial barrier dysfunction that lead to vascular leakage syndrome during dengue disease progression are ill-understood. My group studies the immuno-pathogenic mechanisms in symptomatic versus asymptomatic disease and tries to identify the key factors associated with the development of dengue severity. Based on our previous study, we hypothesize that in response to virus infection two important immune cells, activated platelets and neutrophils interact in circulation, which results in the release of toxic factors. Deposition of toxic factors on the blood vessels causes plasma leakage, leading to the development of haemorrhagic fever (Fig. 1).



a) Dengue virus transmitted through mosquito bites.
b) Neutrophils are the first immune cells that reach at the site of infection. Upon interaction with dengue virus neutrophils get activated and release several toxic proteins and dsDNA in the circulation.
c) Circulating platelets simultaneously undergo activation and
d) recruit more and more neutrophils at the site of inflammation.
e) These neutrophils release more and more toxic materials and form a net like structure, called Neutrophil Extracellular trap (NET). NETs deposit inside the blood vessels and cause excessive damage,leading to plasma leakage

Figure. 1. *Neutrophil-platelet interaction in the development of Dengue pathogenesis. The figure shows hypothetical model for studying dengue pathogenesis.*

Japanese Encephalitis is a serious neurologic disease characterized by massive inflammation of the central nervous system. Children are particularly susceptible to neurotropic virus infections and higher incidence of neurological sequel is reported in children compared to adults. Even though vaccines for JE are available, the existing vaccines do not confer long term protection. When patients come to the hospitals, the virus is about to reach the brain and therefore it is difficult to restrict viral replication and brain damage. As no antivirals are available to limit viral replication, there is a large unmet need for the development of countermeasures to combat

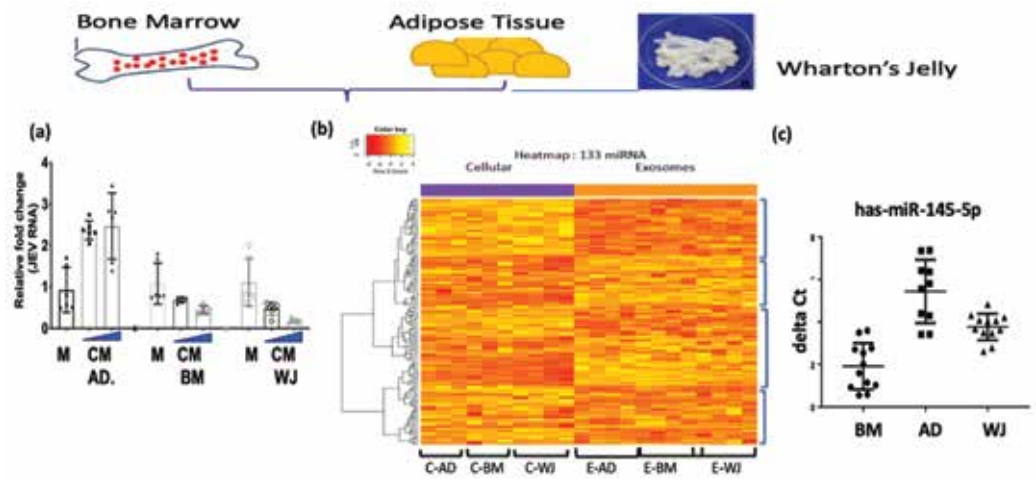
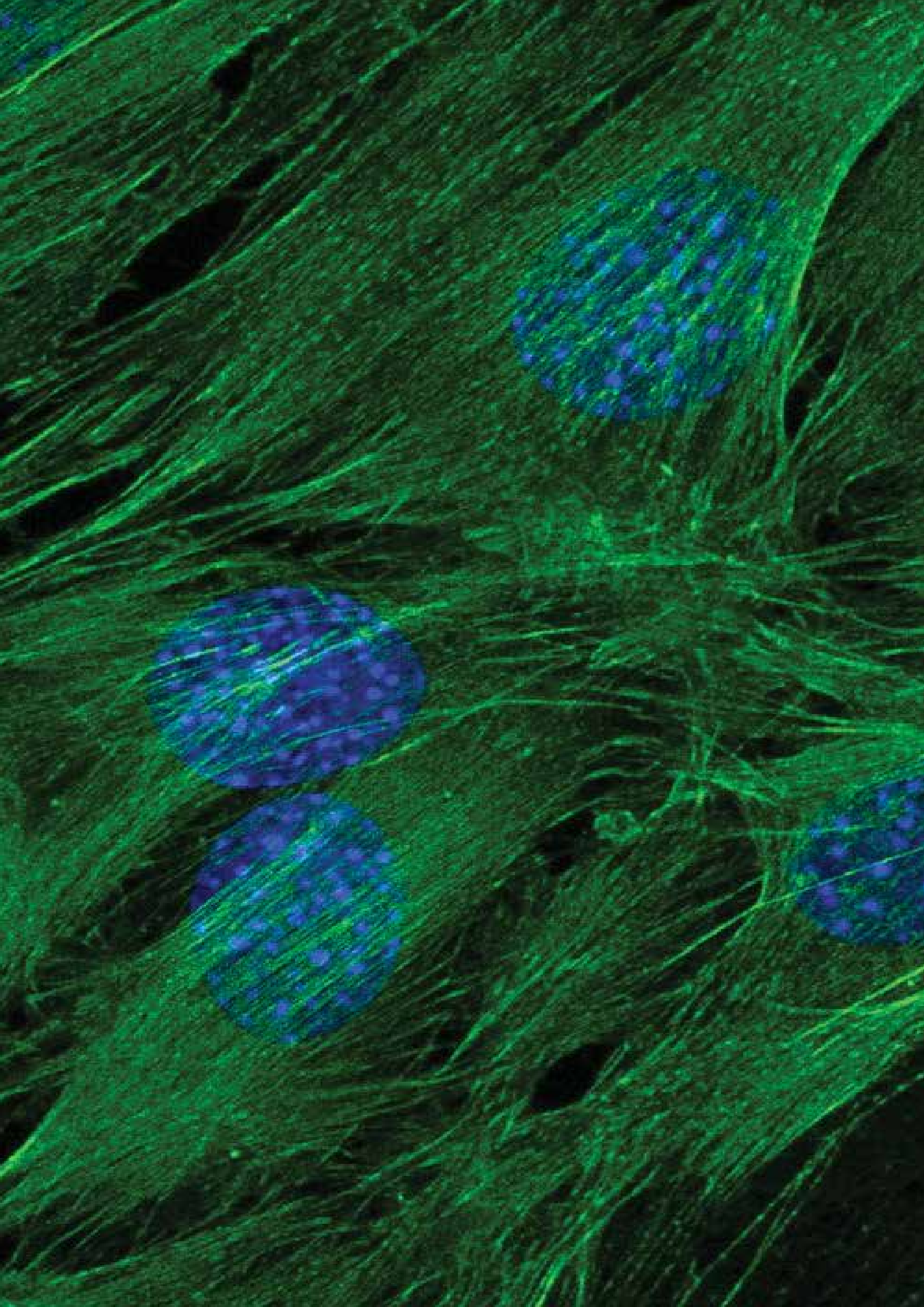
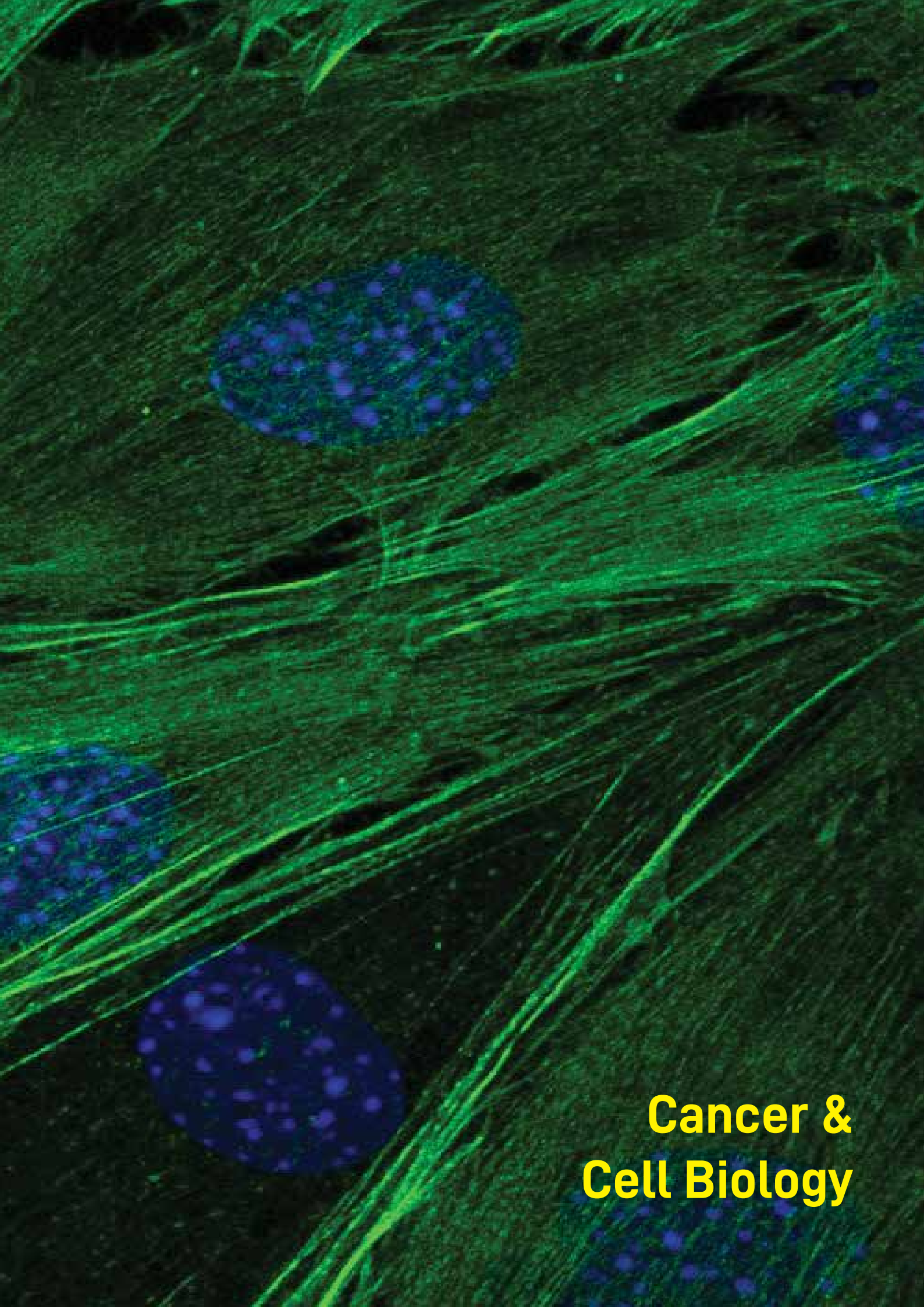


Figure 2. *(a) Effect of different stem cell derived conditioned media on JEV replication in C17 neuronal stem like cells. M = normal media; CM = Conditioned Media. (b) Heatmap of 133 common microRNAs' expression profile in different stem cells and in the exosomes, C = Cellular RNA; E = Exosome RNA. (c) Validation of miR-145 in three different stem cells, BM = Bone Marrow; AD = Adipose Tissue; WJ = Wharton's Jelly.*

disease progression. It is important to note that JEV survivors also develop long term neurologic sequel. Thus, we need drugs/therapies which on the one hand eliminate viruses from infected cells, and on the other hand, will help in neurogenesis to minimize the damage caused by the viruses. To address both issues simultaneously, our lab collaborates with two institutes, AIIMS New Delhi and NBRC Manesar. Together we are trying to explore a different approach to combat disease progression. We are using adult stem cell-derived exosomes (*in vitro* and in the animal model) to inhibit viral replication as well as inducing neurogenesis in the brain. The adult stem cells, e.g. Mesenchymal Stem Cells (MSCs) will be isolated from different sources (bone marrow, adipose tissue, cord blood Wharton's Jelly). These cells have different regenerative properties, thus showing great promise for different diseases. So far, we have isolated and cultured MSCs *in vitro* and purified the exosomes from different sources. We are now in the process of testing their antiviral and neurogenic properties in cell culture and in a JE animal model (Fig. 2). Overall, our continuous effort is to understand disease pathogenesis and develop alternative strategies to combat vector-borne viral diseases prevalent in India.




Cancer &
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Engineering of Nanomaterials for Biomedical Applications

We at the Laboratory of Nanotechnology and Chemical Biology (LNCB), are a unique group of people from diverse academic backgrounds including chemistry, biology and materials science closely working together on two major health challenges, cancer and infectious diseases. Microbial infections caused by gram-negative bacteria pose a serious healthcare challenge due to the emergence of multi-drug resistance towards existing antibiotics. *Escherichia coli* (*E. coli*) is one of the major causative agents for skin and soft tissue infections, especially in the case of neonatal omphalitis, surgical site infections and infections after burn injuries. *E. coli*-mediated nosocomial catheter-associated infections caused by drug resistant bacteria are a serious burden in medical settings. To combat these challenges, we synthesized twenty cholic acid-peptide conjugates (CAPs) with the general chemical formula of CA-(G-X)3 (referred to as CA-X_3), where X is any natural amino acid conjugated to cholic acid through a glycine linker (Fig. 1). SAR studies revealed that valine-derived CAP 3 (CA-V_3) and isoleucine-derived CAP 4 (CA-I_3) are the most active with MIC_{99} of 8 μM. The hemolytic activity of CAPs against human red blood cells (RBCs) and cytotoxicity against epithelial cells (A549) revealed that CAP 4 is highly toxic towards RBCs and epithelial cells without any selectivity for bacterial membranes. In contrast, CAP 3 is about 6-7 fold selective for E. coli over RBCs and epithelial cells. To understand this SAR, we selected the most active hydrophobic valine-derived CAP 3 andthree inactive CAPs based on polar hydrophobic tryptophan (CAP 10), acidic glutamic acid (CAP 15) and basic lysine(CAP 18) amino acids. Comparison of permeation assays showed that CAP 3 is more effective in permeabilization of outer bacterial membranes over the other CAPs (Fig. 2A). Comparative analysis of the CAPs confirmed CAP 3-mediated increase in fluorescence of $DiSC_2(5)$, thereby making it most effective in depolarization of bacterial membranes (Fig. 2B). Quantification of the uptake of membrane impermeable dye propidium iodide (PI) by bacteria on treatment with different CAPs revealed that CAP 3 induced a significant increase in the number of PI positive cells (Fig. 2C). We did not observe any colony after 6 h of CAP 3 treatment at 1X MIC_{99} and 90 minutes of CAP 3 treatment at 4X MIC_{99} was sufficient to kill most of the bacteria (Fig. 2D).

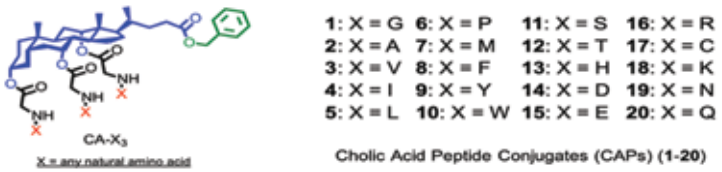

Figure 1. *Molecular structures of cholic acid-peptide conjugates screened for antimicrobial activities.*

To assess the impact of CAPs on membrane rigidity, we first prepared diphenylhexatriene (DPH)-doped model gram-negative bacterial vesicles using LPS, DPPE and DMPG lipids and measured the change in DPH anisotropy on incubation with CAPs. We observed an approximately 2-fold increase in the fluidity of membranes on incubation with CAP 3, whereas no significant change in rigidity was observed on incubation with other CAPs (Fig. 3A). Increase in fluorescence of dansyl-polymyxin B due to its displacement from LPS complexes confirmed the strongest affinity of CAP 3 for LPS over the other CAPs (Fig. 3B). Similarly, an increase in fluorescence on titrations of CAPs with fluorescent boron-dipyrromethene conjugated LPS (BODIPY-LPS) established that CAP 3can bind and disintegrate the LPS aggregates more effectively than other CAPs (Fig. 3C). We then assessed the relative membrane binding affinities of CAPs using Surface Plasmon Resonance (SPR), where CAP 3 showed the highest binding response with irreversible binding among all the CAPs (Fig. 3D-F). We tested the ability of *E. coli* to develop resistance against CAP 3 and observed that *E. coli* was unable to develop resistance against the CAP 3 whereas there was multi-fold increase in MIC_{99} of neomycin. The antimicrobial activity of CAP 3 against stationary and persistent *E. coli* cells established that CAP 3 was able to kill the stationary and persistent bacteria whereas ampicillin was ineffective. Antibacterial activities

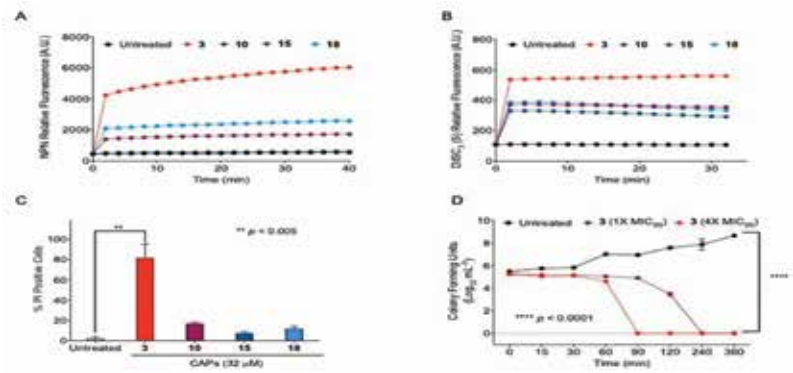

Figure 2. *A) Change in fluorescence of N-phenyl naphthylamine (NPN) showed enhanced ability of CAP 3 to perturb the outer bacterial membranes as compared to other CAPs. B) Time dependent change in DISC2(5) fluorescence in E. coli showed better ability of CAP 3 to permeabilize the inner bacterial membranes than other CAPs. C) Percentage of Propidium iodide (PI) positive E. coli cells showed maximum number of dead cells on CAP 3 treatment. D) Time kill assay confirmed the bactericidal effect of CAP 3 on E. coli as no colonies were observed upon treatment.*

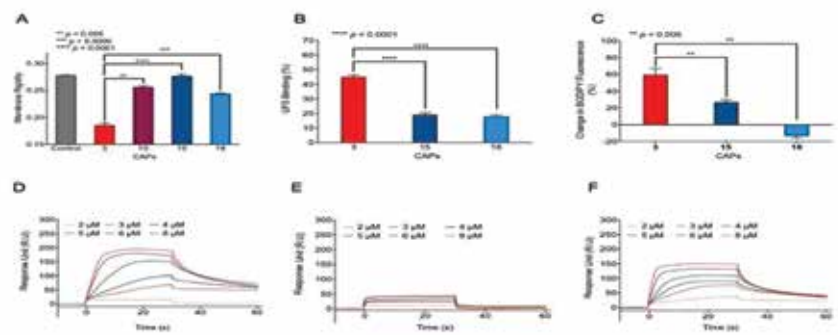

Figure 3. *A) Change in anisotropy of diphenylhexatriene (DPH) confirmed the ability of CAP 3 to disrupt the membranes more effectively than other CAPs. B) LPS binding ability studiesshowed strongest binding of CAP 3 over other CAPs. C) Change in fluorescence of BODIPY showed the strong interactions of CAP 3 with LPS, causing its disintegration. D-F) Surface Plasmon Resonance based sensorgrams of CAPs 3(D), 15 (E) and 18 (F) confirm irreversible and strong binding of CAP3 over other CAPs.*

at different CFUs of *E. coli* validated that CAP 3 was also able to clear the bacterial growth even at CFUs of 10^{12}/ml, making it a highly potent antimicrobial.Confocal laser scanning micrographs (CLSM) of untreated biofilms stained with SYTO9-PI showed a thick biofilm mass of viable SYTO9-stained green fluorescent *E. coli* bacteria without any visible PI-stained red bacteria. CAP 3 treatment resulted in increase of PI-stained *E. coli*, establishing the bactericidal and biofilm disrupting effect of CAP 3. In animal studies, CFU analysis confirmed that there was no adherence of any bacteria on CAP 3-coated catheters after three days, unlike uncoated and control catheters establishing the ability of CAP 3 in preventing bacterial growth in murine models. In wound infection studies on mice, CFU analysis on day 5 showed significant reduction in bacterial load on the wound, whereas ampicillin was less effective. These results therefore establish that CAP 3 can act as a bactericidal in clearing wound infections.

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Molecular Mechanisms of Cell division, Intercellular Communication and Cellular Dynamics

Cells are highly dynamic entities that proliferate and communicate with each other to enable the complex functions of the body, with malfunctions in these processes leading to deadly diseases. Our group works towards elucidating mechanisms of cell duplication and cell-cell communication. As part of this broad objective, we wish to understand the regulation of cell division by the intracellular transport motor proteins and through vesicular traffic. We also aim to elucidate the mechanisms of formation and function of novel modes of cell-cell communication through enigmatic structures called tunneling nanotubes, and aim to understand the host cell biology of pathogenic microorganisms. The broad objective is to obtain a holistic understanding of the molecular mechanisms that govern these processes through multi-disciplinary approaches.This knowledge could be exploited for future therapeutic intervention against major diseases.

A novel role for the endoplasmic reticulum in tunneling nanotube formation

Tunneling NanoTubes (TNTs) are membrane conduits that mediate long-distance cell-cell crosstalk in several organisms and play vital roles during development, pathogenic transmission and cancer spread. We wish to understand the molecular mechanisms of TNT formation and function. The protein MSec is essential for TNT formation in multiple cell types. We determined the protein interaction partners of MSec from a human osteosarcoma cell line (U2OS) by mass spectrometric analysis. Here, we characterized the function and mechanism of the novel MSec interactor ERp29, a protein chaperone, and demonstrated that it is required for the induction of TNT formation. ERp29 interacted specifically with MSec, which enriched strongly at the ER. Confocal microscopic analysis revealed that ERp29 depletion led to a significant loss in the number of TNTs, while exogenous expression of ERp29 induced the formation of a higher number of TNTs, but only when MSec was present in the cell. Our further experiments confirmed that ERp29 acted as a chaperone for MSec (Fig. 1). We suggest a model in which the largely ER-lumen-resident ERp29 could interact with ER-surface-localized MSec through unknown bridging transmembrane-ER protein(s). Our studypostulates a generic mechanism that could be employed by ERp29 to stabilize a host of developmentally important proteins and could be exploited to modulate TNT numbers in specific disease conditions. Based on strong clues from our list of MSec interacting proteins, we are now studying the potential role of localized production of specific proteins in TNT formation and stabilization.

Exocytic endocytic cross talk in cytokinesis, the final step of cell division

Mis-regulation of cell division leads to aneuploidy and chromosomal instability, well-established precursors to cancer. Cytokinesis is the final step of cell division following DNA segregation

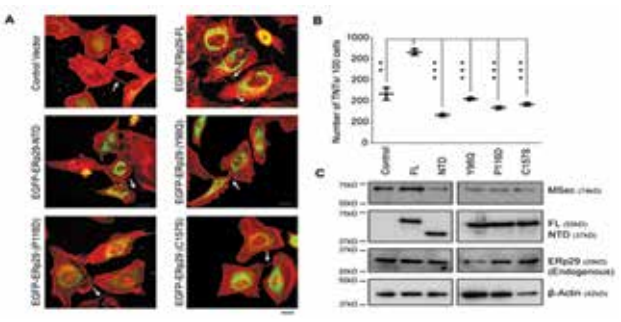

Figure 1. *The chaperone activity of ERp29 is required for TNT formation. A) Confocal microscopy images of cells expressing either luminal-EGFP (control) or the various chaperone point mutants of EGFP-ERp29 and co-stained in red (to visualize F-actin) and gree, (to visualize the EGFP/ EGFP-ERp29 proteins). Arrows indicate TNTs connecting neighbouring cells. Scale bar, 20μm. B) Quantification of the number of TNTs per 100 cells from the confocal images. C) Immunoblots showing expression levels of endogenous MSec, EGFP-ERp29 constructs and endogenous ERp29 probed with the respective antibodies as indicated upon expression of the EGFP-ERp29 wild type and various mutant constructs.*

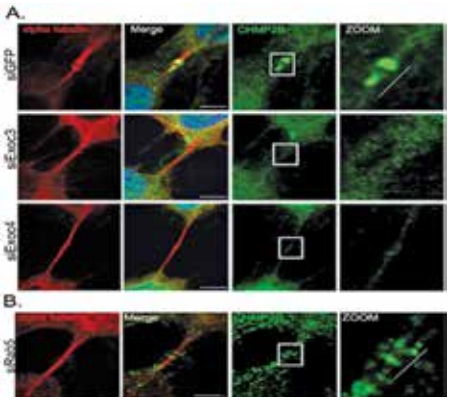

Figure 2. *The Exocyst complex and Rab5 deliver ESCRT III subunits to the cytokinetic bridge. A, B: Representative confocal micrographs of HeLa cells treated with control (GFP), Exoc3, Exoc4 and Rab5 siRNAs, fixed and stained for α tubulin (red) and CHMP2B (green) and chromatin (DAPI, blue). Scale bar: 10 µm.*

that separates the daughter cells, a process for which the Exocyst complex is required. Despite the clear evidence for the requirement of the Exocyst, its precise function in cytokinesis was unknown. Our experiments identified the master early endocytic regulator Rab5 as a novel interactor of the Exocyst. Using multiple strategies, we demonstrated the interaction of the Exocyst complex with Rab5-positive endosomes, a marked increase in endocytic activity and increased engagement of the Exocyst with the early endocytic machinery during cytokinesis. We also observed that the Exocyst in the roundworm *C elegans* is required for endocytosis of yolk during development, thus establishing a novel functional crosstalk between the Exocyst complex and Rab5. A striking observation from our study was that the Exocyst complex and Rab5 were essential for the delivery of the membrane-abscising ESCRT III machinery to the cytokinetic bridge to ensure successful cytokinesis (Fig. 2). We envision that ESCRT III is cytoplasmically recruited by Rab5- and Exocyst-positive early endosomes and delivered to the bridge. Based on our studies, we postulate that the Exocyst anchors at least three distinct kinds of intracellular vesicles in the bridge, potentially explaining its critical requirement for cytokinesis. In summary, this study reveals the novel function of the evolutionarily conserved Exocyst complex and Rab5 in cytokinesis andsuggests that the Exocystcomplex is an attractive target for further investigation and for potential therapeutic intervention to stall cell division. It is also attractive to test the hypothesis that other novel branches of intracellular traffic could be involved in mediating cytokinesis.

Novel mechanism of Notch regulation during *C elegans* germline development

Dr. Pushpa Kumari
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In the round worm, *Caenorhabditis elegans*, germline stem cells (GSCs) receive vital signals from their surrounding niche through the Notch surface protein to maintain "stemness". Either sub-optimal or excessive Notch signaling leads to drastically reduced gamete numbers, thus compromising fertility. We have discovered that Notch is largely maintained in cell surface reservoirs facing away from the niche, with a much smaller number present on the niche-facing signaling surface. We demonstrate that the Exocyst complex redistributes Notch from these distant reservoirs to the signaling hotspots. Given their high degree of conservation, this mechanism of Notch signaling modulation may occur in other stem cell types also. The strong association of these proteins with cancers suggests that the Notch-Exocyst crosstalk could be an attractive target for future investigation.

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Understanding Molecular Mechanisms Regulating Calcium Signaling and their role in Human Pathophysiology

Cancer is one of the leading causes of death. Most cancer-associated deaths are due to its spread within the body. It is important to note that cancer incidence is on the rise in the Indian population. Similarly, skin diseases like allergies and skin pigmentary disorders are on the rise in India. Our laboratory is focused on understanding the molecular reasons leading to cancer spread and skin pigmentary disorders. Our efforts have suggested that issues with cellular calcium signaling contribute to these diseases. Currently, we are generating a knowledge base that could be used in the future for better management and treatment of these conditions. Ca^{2+} signaling regulates a plethora of cellular functions and thereby plays an integral role in maintaining tissue homeostasis and health. Furthermore, Ca^{2+} homeostasis is essential for the proper functioning of organelles important for metabolism, protein synthesis & trafficking (mitochondria, endoplasmic reticulum, Golgi complex, endolysosomes). Thus, Ca^{2+} regulates specialized organellar functions via inter-organelle communications and by driving gene expression, calibrating enzyme activity and inducing protein conformational changes. Perturbation in Ca^{2+} dynamics causes impairment of cellular physiology eventually leading to diseases. The focus of our group is to understand the role of Ca^{2+} signaling in skin pigmentation, tumorigenesis and cancer metastasis. We aim to: 1) Delineate the role of organellar Ca^{2+} dynamics in these pathophysiological conditions, 2) Elucidate detailed molecular mechanisms connecting dysregulated Ca^{2+} signaling to cancers and pigmentary disorders, and 3) Eventually, utilize this knowledge for devising strategies for better management and treatment of these pathophysiological conditions.

Calciomics of Skin Pigmentation

Skin pigmentation plays a vital role in protection against harmful ultraviolet (UV) rays. Indeed, tanning is a protective response of melanocytes for guarding skin from UV induced cancers. Perturbations in pigmentation pathways result in pigmentary disorders like solar lentigo, melasma, and vitiligo. These disorders are considered as social stigmas; they impart long-term psychological trauma and are a huge economic burden on the health care system. The current therapeutic regimes are not efficient in alleviating pigmentation defects. Therefore, it is critical to identify the novel molecular players regulating pigmentation and devise strategies to target them for calibrating pigmentation. For identifying novel regulators of pigmentation, we performed microarray analyses on hyperpigmented and hypopigmented primary human melanocytes. Interestingly, we observed significant deviations in the Ca^{2+} homeostasis in these differentially pigmented cells (Fig. 1). Therefore, we aim to delineate the Calciomics (studies of Ca^{2+} handling proteins, interactome and downstream effector proteins) of skin pigmentation. In one such study, we have recently identified an ER Ca^{2+} sensor protein STIM1 as a novel regulator of pigmentation.

Targeting calcium signaling for curtailing tumor growth and metastasis

During transformation of normal healthy cells to cancerous cells, there are perturbations

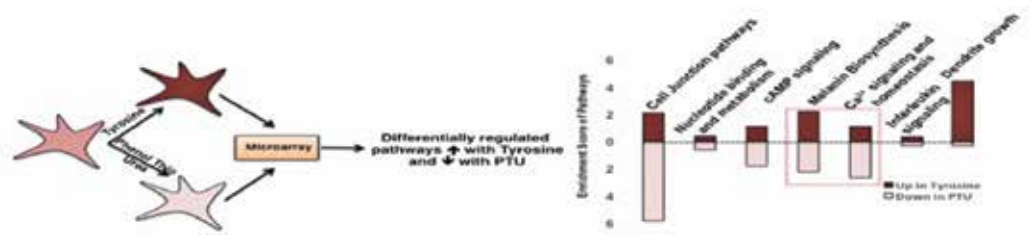


Figure 1. *Microarrays on hyperpigmented and hypopigmented primary human melanocytes. Primary melanocytes were treated with either tyrosine to enhance pigmentation or Phenol thio-Urea for decreasing pigmentation. RNA samples from these melanocytes were subjected to microarrays. Ca^{2}+ homeostasis emerged as one of the most differentially regulated signaling module in response to pigmentation changes (adapted from Motiani et al. EMBO J, 2018).*

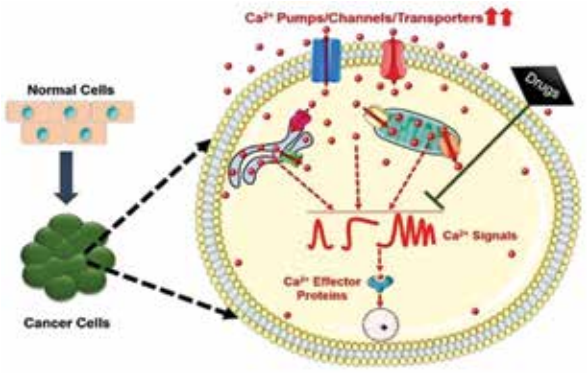


Figure 2. *Dysregulated Ca^{2}+ homeostasis in Cancers.The transformation of healthy cells to cancerous cells is associated with perturbations in the expression and function of Ca^{2}+ handling proteins. This in turn results in changes in the cellular as well as organelle-specific Ca^{2}+ signals eventually leading to enhanced proliferation, invasion and resistance to apoptosis.*

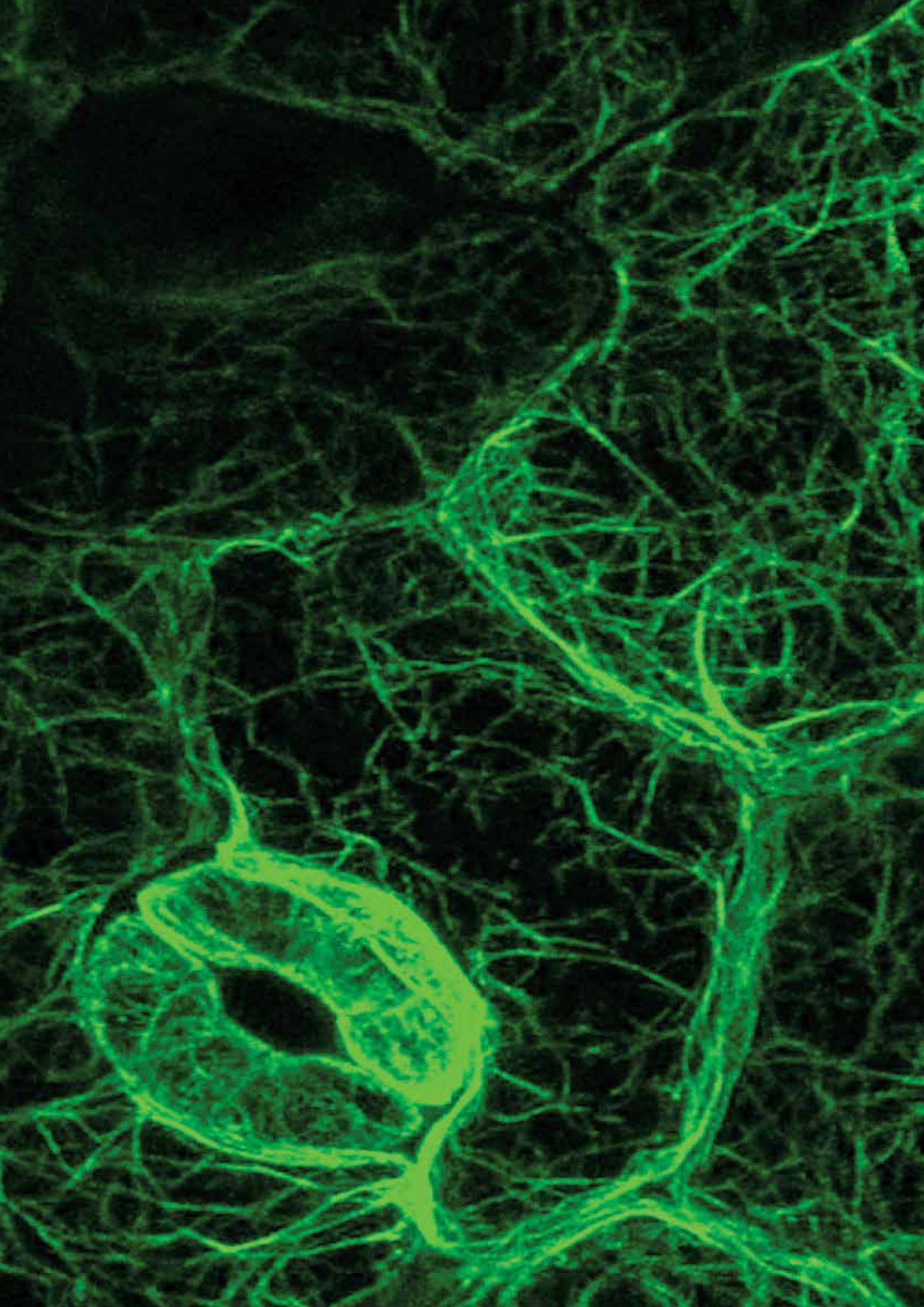
in the expression and function of Ca^{2+} handling proteins such as Ca^{2+} channels, pumps and transporters. This, in turn, results in changes in cellular as well as organelle-specific Ca^{2+} signals eventually leading to enhanced proliferation, invasion and resistance to apoptosis (Fig. 2). Further, there are several FDA approved drugs that target Ca^{2+} channels and transporters. However, currently, to the best of my knowledge, none of these drugs are used for managing cancers. Therefore, we aim to perform proof of concept studies with these drugs using *in vitro* and *in vivo* model systems.

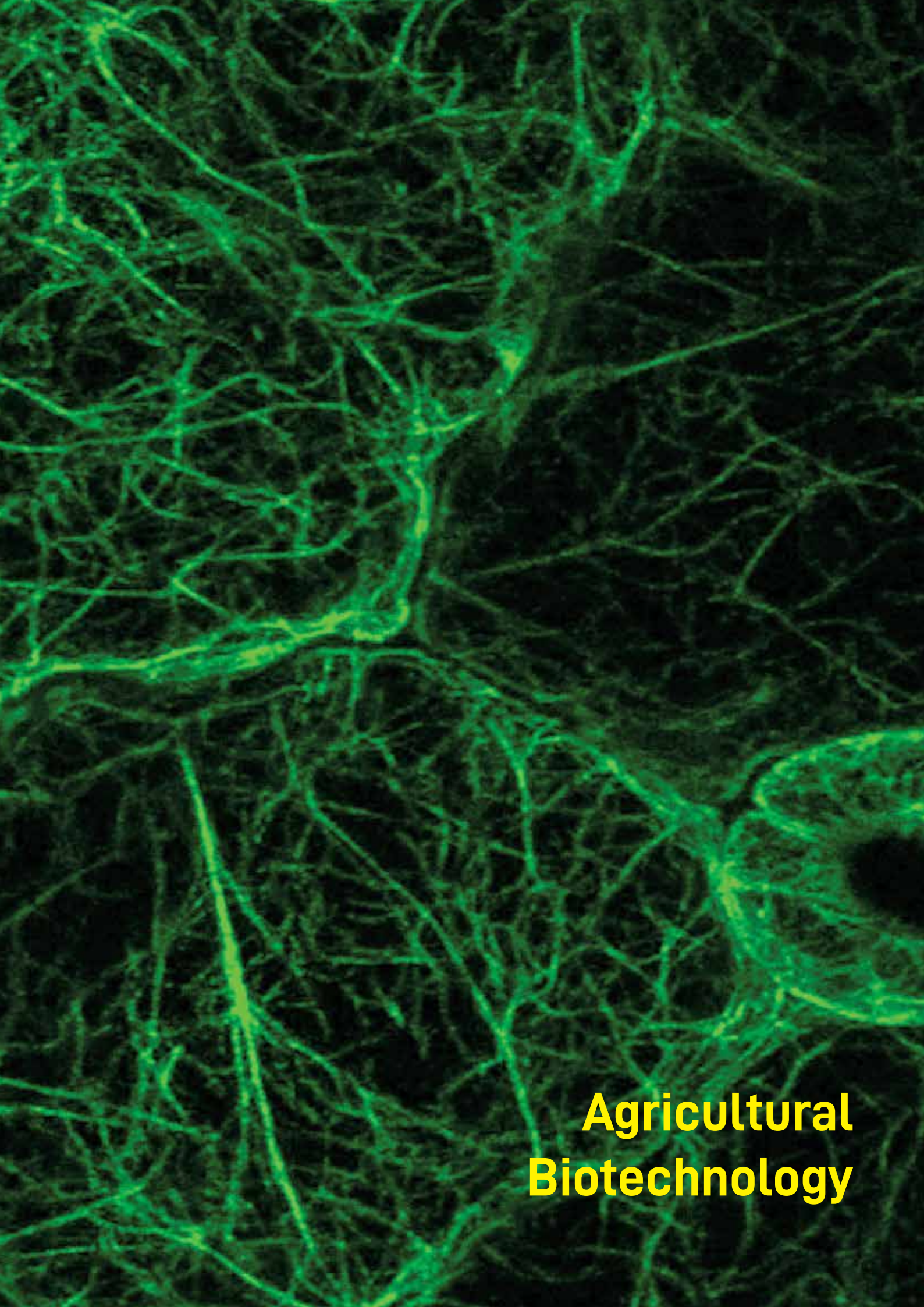
Orai3's role in tumorigenesis

Currently, we are focusing on the highly selective and mammalian specific plasma membrane Ca^{2+} channel Orai3. We previously reported that: a) Orai3 forms a functional Ca^{2+} influx channel in breast cancer, b) it regulates breast cancer development in mice models, and c) its expression is higher in cancerous tissues in comparison to patient match non-cancerous tissues. Our current efforts are directed towards understanding the mechanisms regulating its expression in cancerous tissue as Orai3 becomes functional only upon its overexpression. Thus, Orai3 can be selectively targeted in cancerous cells without any significant side effects on healthy tissues.

Cancer metastasis and inter-organellar Ca^{2+} signalling

Most of the cancer-associated deaths are due to metastasis of the primary tumor. Cancer metastasis is a complex phenomenon that involves tumor angiogenesis and loss of endothelial barrier function both at the site of primary tumors (intravasation) and at the secondary sites (extravasation). Although tumor metastasis is widely studied, the critical step of intravasation remains poorly understood. Moreover, the key targetable regulators of intravasation are particularly inadequately defined. Inter-organellar communication via Ca^{2+} signaling plays a critical role in regulating cellular physiology. However, its influence on endothelial function remains under-appreciated. Therefore, our aim is to examine the role of inter-organellar Ca^{2+} signaling in endothelial cell function and to identify key proteins regulating tumor cell intravasation. The long-term goal of this program is to identify targetable proteins and devise strategies for therapeutically managing them for abrogating tumor cell metastasis.





Agricultural Biotechnology

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Deciphering Signaling Pathways and Pathogen-mediated Perturbations in Innate Immune System of Plants

Plants, under the constant risk of pathogen attacks, have evolved a sophisticated defense system that balances energy requirements of a transitory immune response through a proportional adjustment of growth and developmental functions. At a molecular level, this involves recruiting proteins that serve the dual function of associating with defense mediators and coordinating with cellular homeostasis processes. We explore the characterization of these signaling routes with a broad aim to improve plant immunity. Intricacies of the plant defense network and the pathogen's constant efforts to evade them have shaped counter evolution of both host and pathogen. Engineering durable resistance therefore necessitates a comprehensive understanding of both processes. Our research program dissects immune crosstalks at three nodes: Regulation, Trigger and Signaling. We utilize the model plant system *Arabidopsis thaliana* and the hemi-biotroph *Pseudomonas syringae pv* tomato (*Pst*) pathosystem for our investigations. Pathogen effectors thwart a plant's first line of defense (termed PAMP-triggered immunity; PTI) mediated by pattern-recognition receptors (PRRs) deployed to recognize conserved determinants such as bacterial flagellin, fungal chitin, bacterial lipopolysaccharides, etc. This activity is termed as virulence. However, virulence functions of an effector in some instances betray the pathogen's presence to the host by activating a component of the second layer of immunity (termed effector-triggered immunity; ETI) mediated by distinct classes of resistance (R) proteins. These R proteins, upon activation, initiate massive transcriptional reprogramming for defense that also crosstalks with physiological and developmental pathways to minimize fitness costs. Mutants with constitutive activation of R proteins hence are often developmentally compromised. How such a tight orchestration is achieved remains unknown.

A significant clue is obtained from altered pathogen susceptibilities of mutants regulating post-translational modification (PTMs) of targets. Most pathogen effectors also in turn are endowed with modulation of PTMs of plant targets. We are investigating the role of covalent attachment of Small Ubiquitin-Like Modifiers (SUMOs) in pathogenesis. We identified that an *Arabidopsis SUM1* mutant exhibits enhanced resistance to *Pst*. *SUM1* encodes SUMO1, one of the 4 SUMO paralogs expressed in *Arabidopsis*. In contrast, a *sum3* mutant exhibits enhanced susceptibility to *Pst*. This suggests that SUMO paralogs may function antagonistically. Indeed today, developmental defects of *sum1* are partially rescued in the *sum1 sum3* double mutant (Fig. 1a & b). The loss of *SUM3* also down-regulates elevated levels of the defense marker Pathogenesis Related Protein1 (PR1) that confers enhanced immunity in *sum1* plants (Fig. 1c). With these assays we report the first evidence of SUMO-antagonism in plant immunity. We aim to identify plant targets, especially defense-modulators, that overlap or are distinct candidates for SUMOylation by SUMO1 and/or SUMO3. Signaling networks are orchestrated through strategically deployed 'hub proteins' which often are targets for most characterized pathogenic

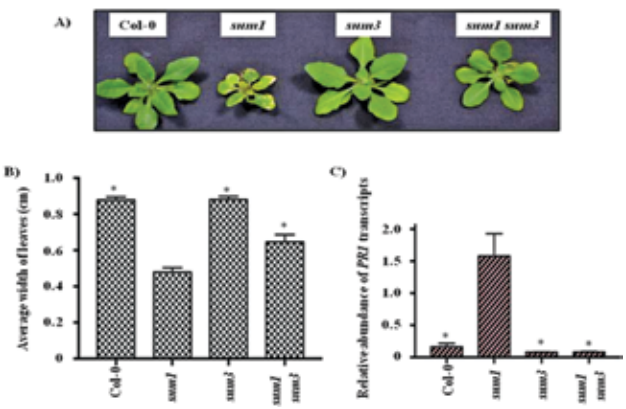

Figure 1. *Phenotypic defects and enhanced defenses of sum1 are partially dependent on SUM3. A) Plant growth phenotype comparison demonstrates that smaller stature of sum1 is partially restored in the sum1 sum3 double mutant. B) Measurement of leaf width indicates that loss of SUM3 partially increases the smaller leaf widths of sum1 plants. N= 20-30. C) Enhancement of PR1 transcript levels in sum1 is completely abolished in the sum1 sum3 double mutant. Asterisks indicate statistically significant difference to the sum1 plants.*

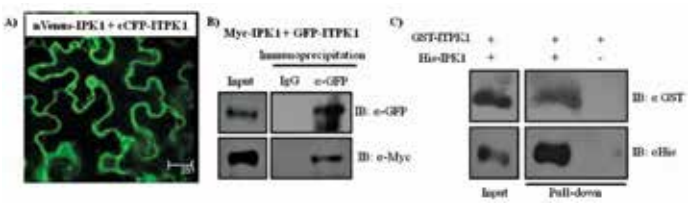

Figure 2. *IPK1 and ITPK1 interact in vivo and in vitro. A) Bi-molecular Fluorescence Complementation (BiFC) to test for IPK1 and ITPK1 demonstrate in planta interactions localized to nucleus and cytoplasm. B) Co-immunoprecipitation of Myc-IPK1 and GFP-ITPK1 via transient expression in N. benthamiana demonstrate ITPK1 and IPK1 interact in vivo. C) E. coli expressed His-IPK1 and GST-ITPK1 when subjected to Nickel-affinity purification enriches GST-ITPK1 as an interactor of His-IPK1.*

effectors. Major immune players associate with these hubs to rapidly perceive threat and connect to downstream defense signaling pathways. Lipid-conjugated inositol phosphates (Phosphatidylinositol phosphates; PtdInsPs) stabilize macromolecular protein assemblies at distinct cellular locales, and their perturbations generate soluble inositol phosphates (InsPs) as signaling messengers. To test whether selective InsPs transduce defense signaling, we tested the immune responses in various InsP-mutants towards *Pst*. We identify that IPK1 and ITPK1, two InsP-biosynthesis proteins genetically function as negative regulators of defenses against *Pst*. Enhanced immunity in *ipk1* and *itpk1* mutants are mediated through the defense hormone salicylic acid (SA)-regulated signaling sectors. Indeed the loss of ICS1, an enzyme responsible for SA-biosynthesis, abolishes enhanced resistance of *ipk1* and *itpk1* mutants. We further show that IPK1 and ITPK1 proteins interact *in vivo* and *in vitro*, thus supporting their involvement in a common pathway (Fig. 2). Our results suggest that InsPs intersect on SA-regulatory networks to modulate defenses. We are currently identifying targets of IPK1 and ITPK1 to obtain deeper insights into their immune-associated functions.

In order to gain better insights into perception or evasion of defense, we utilize two closely-related effectors differing in defense elicitation in a common host. HopA1 effectors in *Pseudomonas* pathovars confer expanded host range to the pathogen, thereby increasing its threat on economically important crops. Curiously, HopA1 from pv syringae ($HopA1_{pss}$) elicits resistance whereas HopA1 from pv tomato ($HopA1_{pst}$) does not on *Arabidopsis*. In order to identify distinct cellular targets that may contribute to differential perception of these effectors, we generated chemical (Dexamethasone; Dex)-inducible transgenic plants expressing cMyc epitope-tagged $HopA1_{pss}$ (Dex-$HopA1_{pss}$-Myc). We detected HopA1pss protein 24 hrs post-Dex application. Interestingly, we note progressive increase in necrosis (termed hypersensitive response; HR) upon Dex treatment in the transgenic line. Endogenous *PR1* was significantly increased upon $HopA1_{pss}$ expression in the transgenic line, suggesting upregulation of defenses in these plants. We measured the electrolyte leakage from untreated/treated leaves using conductance assays. Clearly, increased kinetics of electrolyte leakage as a function of time was noted only in the Dex-treated leaves. The transgenic line provides an excellent system to identify targets of $HopA1_{pss}$ and is being currently pursued.

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Investigations into the Molecular Mechanisms underlying Legume-Powdery Mildew interactions

Powdery mildews are significant fungal pathogens that cause yield losses of ~25-60% in agronomically relevant grain legumes such as pea, lentil and mung bean. The goal of our research program is to develop legume crops with broad-spectrum and durable resistance to the pea powdery mildew *Erysiphe pisi* (*Ep*). To achieve this, we aim to uncover the molecular interplay between *Ep* and two legume hosts, *Medicago truncatula* and pea.

Powdery mildew (PM) fungi are true obligate biotrophs, which means that they depend entirely on living plants for their survival. To establish biotrophic relationships with their host, these fungi secrete a plethora of effector molecules primarily through specialized infection structures termed haustoria. To identify *Ep* effector candidates, a cDNA library of enriched haustoria was sequenced, from which 167 candidate secreted effector proteins (*Ep*CSEPs) were predicted (Fig. 1). Phylogenetic analysis revealed that *Ep*CSEPs are highly diverse, but unlike cereal PM-CSEPs, exhibit extensive sequence similarity with effectors from other PMs. The functional role of two effector candidates was probed via a double-stranded (ds) RNA-based RNA interference approach. Foliar application of individual *EpCSEP*-dsRNAs resulted in a marked reduction in disease symptoms, suggesting that these *Ep*CSEPs play important roles in pea PM pathogenesis. Homology modeling revealed that both *Ep*CSEPs are analogous to fungal ribonucleases and may possess RNA cleavage activity. To obtain deeper insights into their role as virulence factors, future investigations will focus on the identification of their plant targets.

Legumes are rich in isoflavonoids, which are secondary metabolites known to exhibit antimicrobial activity. We found induced expression of isoflavonoid biosynthesis genes, as well as the accumulation of pathway metabolites, upon *Ep* inoculation in a resistant *Medicago* genotype, suggesting that these metabolites may contribute to PM resistance. Exogenous application of the end product of the isoflavonoid pathway in leaves of a moderately resistant *Medicago* genotype resulted in enhanced penetration resistance against *Ep*. Further, transient over expression of a putative positive regulator of this pathway in *Medicago* enhanced the expression of several isoflavonoid biosynthetic genes and significantly reduced *Ep* growth. Interestingly, enhanced *Ep* growth was observed in R-gene-silenced leaves of the resistant *Medicago* genotype, in which the expression of isoflavonoid biosynthetic genes was repressed. We are currently elucidating the exact mechanism by which this metabolite confers penetration resistance against *Ep*.

PM infection typically creates an additional sink in infected tissues, which can lead to significant changes in sugar transport and partitioning within the plant. Consistent with this idea, plant sugar transporters have been shown to play significant roles during plant-pathogen interactions. We found a *Medicago* hexose transporter that shows *Ep*-induced expression. We confirmed that the protein is plasma membrane localized and functions as a broad range hexose transporter. When this gene was silenced in *Medicago* leaves, enhanced *Ep* growth was observed, suggesting a role

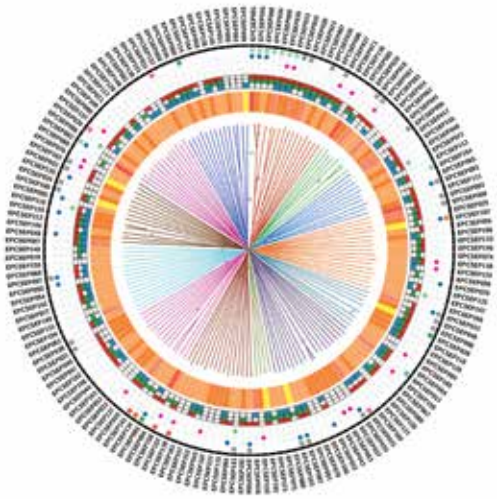

Figure 1. *Circos plot depicting key features of the Ep effector repertoire. From perimeter to centre: EpCSEP identifier; MCL family clustering; Presence of conserved Y/F/W-x-C motif (Blue, YxC; Pink, FxC; Green, WxC); Homologous sequences in powdery mildew infecting grape (red), Arabidopsis (green) and barley (blue); Heat map (Yellow to red = low to high expression; log_2 scale); Radiating Neighbor-Joining tree clustering the 167 EpCSEPs into 13 clades. Bootstrap support values >50% are shown next to the branches.*

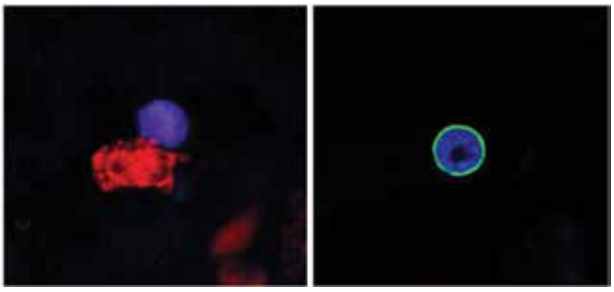

Figure 2. *Left panel: Host epidermal cell nucleus (shown in blue) is closely associated with the primary Ep haustorium (shown in red) during a susceptible pea-Ep interaction. Right panel: Subcellular localization of PsSUN1-GFP at the nuclear envelope.*

for this transporter in defense. By contrast, transient overexpression of the transporter in *Medicago* resulted in reduced *Ep* growth compared to control leaves, suggesting that altered hexose/sucrose levels at the host-biotroph interface, resulting from the over expression of this transporter, contributes to PM resistance. We are currently investigating whether sugar signaling-mediated activation of defense gene expression is impacted in these silenced/ overexpression lines.

PM haustoria are the primary sites of nutrient uptake and effector delivery. We observed that the host cell nucleus moves towards the site of fungal penetration and closely associates with the *Ep* haustorium (Fig. 2). The actin cytoskeleton is known to regulate nuclear migration in conjunction with LINC (linker of nucleoskeleton and cytoskeleton) complexes, which are formed by SUN and KASH-like nuclear envelope proteins. We found that disruption of pea F-actin organization via cytochalasin-D inhibits host nuclear repositioning, primary haustorium formation and *Ep* growth, suggesting that nuclear repositioning may serve as an important susceptibility factor required for early *Ep* colonization. We are currently investigating the role of the inner nuclear envelope protein *Ps*SUN1 (Fig. 2) in host nuclear positioning and immunity.

Functional characterization of HY5 homolog in rice

Light is an important environmental signal that is perceived by plants by photoreceptors. Photoreceptors pass on the signal to master regulators, which in turn bring about changes in downstream components, leading to changes in gene expression. HY5 is one such master regulator with an important role in photomorphogenesis. In the dark, HY5 interacts with COP1/SPA1 and is constitutively degraded by COP9 signalosome complex. However, as soon as the cell perceives light, phytochrome moves into the nucleus where it inhibits COP1 activity by excluding it from the nucleus. As a result, HY5 is able to activate downstream light-responsive genes involved in photomorphogenesis. Most of the work on HY5 and its interacting partners has largely focused on *Arabidopsis*. In our endeavour to characterize HY5 from monocots, we have identified three orthologs in rice and have functionally characterised one (OsbZIP48). We are now investigating how these three genes work in tandem as well as independent of each other.

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Biotechnological Approaches to improve Stress Adaptation of Crops

Plant adaptation to changing climatic conditions is crucial to improve crop productivity. Plants are continuously exposed to diverse stresses like drought, heat, bacteria, fungal and viral infections. Under stress conditions, protein turnover mechanisms are affected, including protein synthesis and degradation. In this context, our studies focus on DNA repair and protein turnover mechanisms. We aim to identify genes and genetic networks associated with protein turnover, and functionally characterize relevant genes using genome editing tools and chemical genomic approaches. The emphasis is on ribosomal proteins and E3 ligases involved in protein degradation mechanisms to improve protein turnover. In particular, the extra-ribosomal function of ribosomal proteins in abiotic stress will be studied. Further, the role of E3 ligase in combined drought and bacterial blight (*Xanthomonas*) infection in rice will be studied to understand pathogenicity and improve plant health.

Rice plants are exposed to multiple stresses in field conditions, such as drought and bacterial infection, that affect productivity. Over the years, significant overlapping mechanisms have been identified in response to pathogen and drought. One of the objectives of this study is to identify differentially expressed ribosomal proteins, bacterial effectors, and their host target genes under combined stress conditions and manipulate them using genome-editing technology. To identify differentially expressed genes, RNA sequencing data was generated from contrasting rice genotypes BPT5204 (resistant) and TN-1 (sensitive) exposed to drought, pathogen, or combined stress. The methods for drought stress imposition and bacterial inoculation were standardized and samples submitted for RNA sequencing. The RNA sequencing data revealed that unique sets of genes were differentially regulated in each stress in both genotypes. In-depth analysis was performed to identify the common and unique genes from both up and downregulated gene sets (Fig. 1). Several genes showed shared responses during the combined stress treatment whereas a few of them were unique to individual stresses. The ribosomal protein-encoding genes *RPS6, RPS10a, RPS9, RPS4, RPL10* and *RPL23* were commonly upregulated in response to the combined stress treatment. Interestingly, temporal gene expression analysis indicated that these ribosomal protein-encoding genes were upregulated at earlier time points in the resistant genotype compared to the susceptible one. To characterize the function of these genes in rice using CRISPR Cas9, suitable guide RNA (gRNA) was

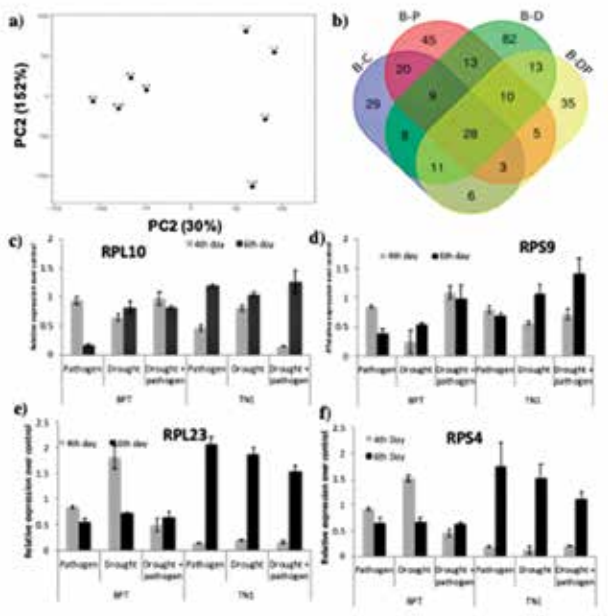

Figure 1. *Differential response of rice transcripts and ribosomal protein encoding gene transcripts in drought, pathogen and combined stress. a) Principal component analysis (PCA) of RNAseq data showing the differential response of transcripts in response to different stresses. B-BPT52014, T-TN1, C-control, D-drought, P- pathogen, DP-drought and pathogen, b) Venn diagram showing the common and unique genes upregulated in BPT rice genotypes under different stresses. c-f) qRT-PCR analysis of ribosomal protein encoding genes at different time intervals after stress imposition.*

Figure 2. *The altered phenotype of rice plants transformed with A. tumefaciens carrying MSH1 gRNA. (a) Non-transformed/ wild type plant at flowering stage. (b) Mutant plant showing difference in tillering habit. (c) Wild type plant and mutant plant showing difference in plant height. (d) Wild type plant and mutant plant showing difference in days to flowering. (e) Altered plant stature- broad growth pattern.*

developed for individual genes by analyzing their gene structures. The gRNAs were synthesized and integrated into pRGEB32 binary vector using the Golden Gate assembly kit and are currently being transformed into rice. We also identified a salt and drought induced RING finger 1 (SDIR1), an E3 ligase that is upregulated during drought and pathogen stress. We have identified a new interacting protein JAZ9 and characterized its role in pathogenicity in *Arabidopsis*.

Disruption of genome integrity to create genetic variability by editing (using CRISPR-CAS9) the genes associated with DNA mismatch repair and characterization of their relevance in crop improvement

The aim of this project is to develop a diverse mutant population by disturbing the integrity of the genome through the silencing of mismatch DNA repair associated genes. We used the CRISPR Cas9 system to edit the genes involved in DNA mismatch repair such as MSH1, MSH2 and MLH1. Guide RNAs (20 bp) specific to MSH1, MSH2 and MLH1 genes were designed using the CRISPOR software and each pair of DNA oligonucleotides were annealed, PCR amplified, and cloned into pRGEB32 binary vector through the Golden Gate assembly method. Further, Agrobacterium-mediated tissue culture and in planta transformation methods were used to generate mutant rice plants in the IR-64 background. Following Hygromycin selection, T0 generation seedlings were allowed to pollinate naturally and set seeds. T0 plants were tested for the integration of transgene by PCR. Notably, phenotypic variations in plant height, stature, tillering habit and days to flowering were observed in MSH1 reprogrammed plants when compared to wild type plants (Fig. 2). We reasoned that this phenotypic variability may have arisen from the genome reorganization-induced mutations in the MSH1 gene. Similarly, variable plants were developed with MSH2 and MLH1 independently. To bring in stability in the traits and further bring in native MSH genes, the T1 generation plants are being grown in the greenhouse along with wild type IR64 rice for crossing.

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Unravelling the Plant Cell Wall Biosynthesis and Architecture for Bioenergy Applications

Plant cell wall, which is the outermost layer of the cell, has a complex and dynamic structure, and is composed of energy rich sugars and polymers. In our research program, we study plant cell wall biosynthesis, and aim to fine-tune its structure to produce sustainable bioenergy and bio-based products.

The burning of fossil fuels as a source of energy has contributed to global climate change. As an alternative, plant lignocellulosic biomass generated either from fast growing trees or agricultural waste can be utilized to produce bioenergy in the form of biofuel. However, this biomass is composed of a complex and recalcitrant plant cell wall matrix, which is difficult to degrade during biofuel production. This is because, not only are the structures of the individual components of the cell wall rigid, associations between these components via hydrophobic, hydrophilic and covalent interactions makes the cell wall less amenable to degradation during bioethanol production. By altering the crystallinity of cellulose, modifying the composition/content of lignin, altering pectin methyl esterification, reducing xylan chain length/content and O-acetylation, these polysaccharides can be made labile to enzymatic treatment. However, alterations in these components often have negative effects on plant growth, development, and pathogen resistance, which reduces the overall yield of lignocellulosic biomass used for bioethanol production. We study plant cell wall biogenesis and its role in plant growth and development. This knowledge will be used to fine-tune the plant cell wall structure to develop easily degradable plant lignocellulosic biomass without compromising plant growth.

The plant cell wall matrix is composed of cellulose, matrix polysaccharides, lignin and structural proteins, with each component having its own unique composition and properties. Cellulose is a linear polysaccharide of β, 1-4 linked glucose subunits. Lignin polymer is composed of end products of the phenylpropanoid pathway, which are the aromatic alcohols: coumaroyl (H), sinapyl (S) and coniferyl (G). Matrix polysaccharides are branched polysaccharides of different types- xylan, xyloglucan and pectin, which are often acetylated. The acetyl or ester groups are decorated on the sugar backbone or side chains of polysaccharides. The distribution, position, and composition of O-acetyl groups decides the physio-chemical properties of the polysaccharides and the cell wall in general. Therefore, perturbing O-acetylation has an impact on plant growth, cell wall structure and processing of lignocellulosic biomass. However, the reasons behind such diverse implications of altered acetylation on plant phenotype is poorly understood. In one of the projects, we are investigating the role and mechanism of O-acetylation of polysaccharide in plants. Simultaneously, we are also assessing the effect of altered cell wall acetylation on plant cell wall organization, polysaccharide digestibility and ethanol production.

O-acetylation process occurs in the Golgi, and acetyl CoA is a potential donor substrate. According to the current hypothetical model for Arabidopsis, acetyl CoA is transported from the

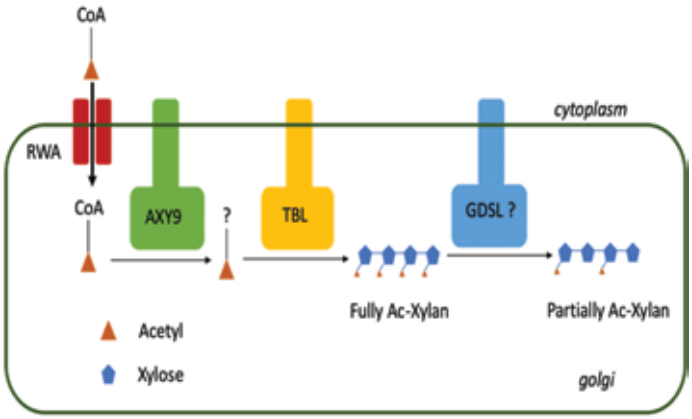


Figure 1. *Proposed model of polysaccharide O-acetylation in Arabidopsis. Reduced Wall Acetylation (RWA) proteins have transmembrane domains which translocate/transfer acetyl-CoA from cytoplasm to Golgi. AlteredXYlann (AXY9), which is an acetyl transferase and a single member protein, transfers acetyl group to an unknown substrate. Trichome Birefringence Like (TBL) is polysaccharide specific acetyl transferase. GDSL lipase/esterases are putative polysaccharide esterases, which are yet to be identified in Arabidopsis.*

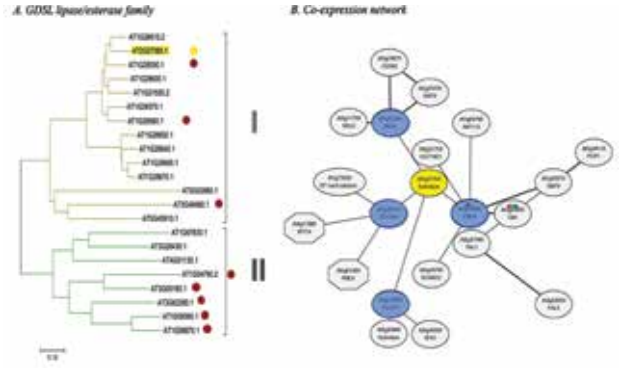
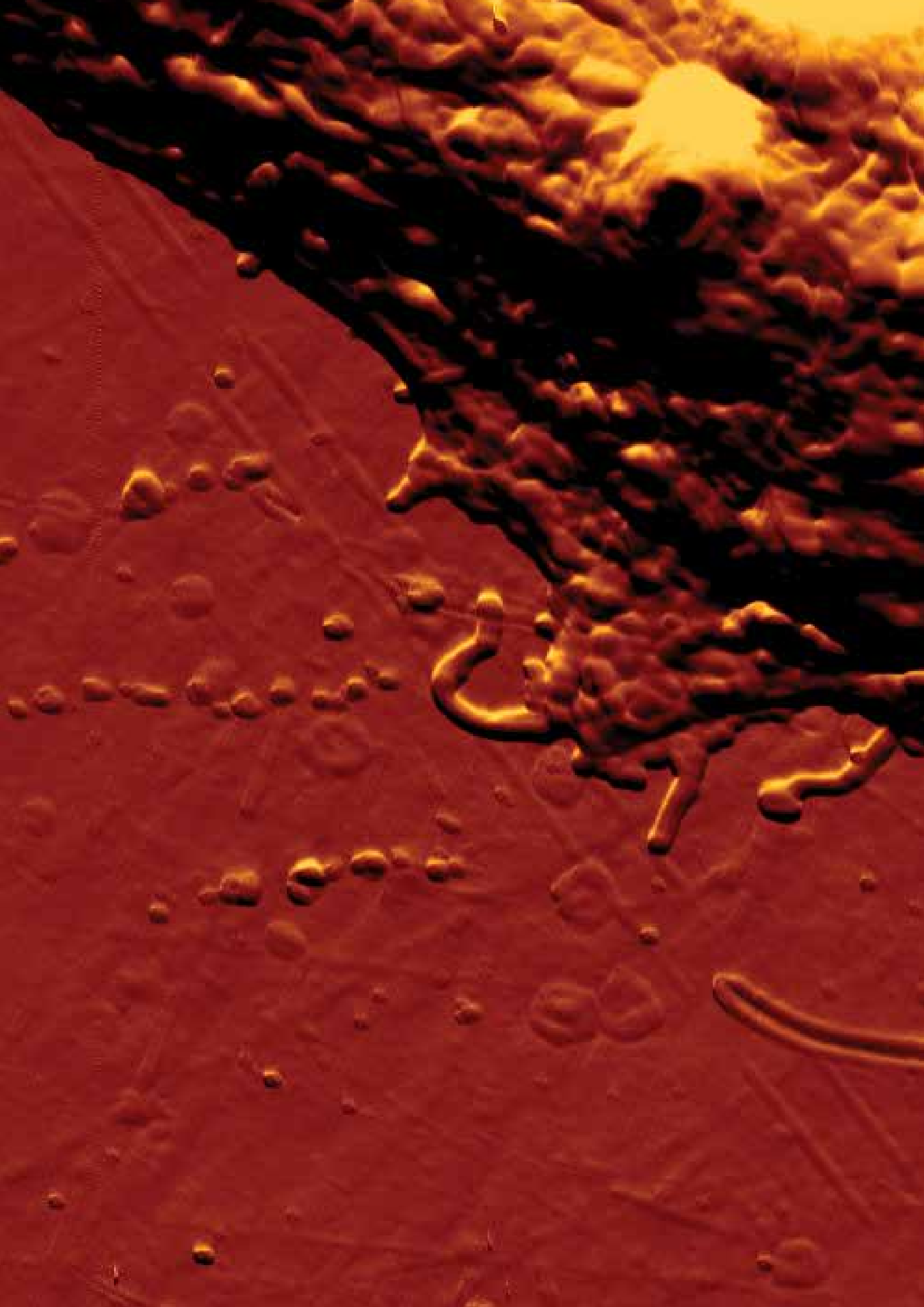
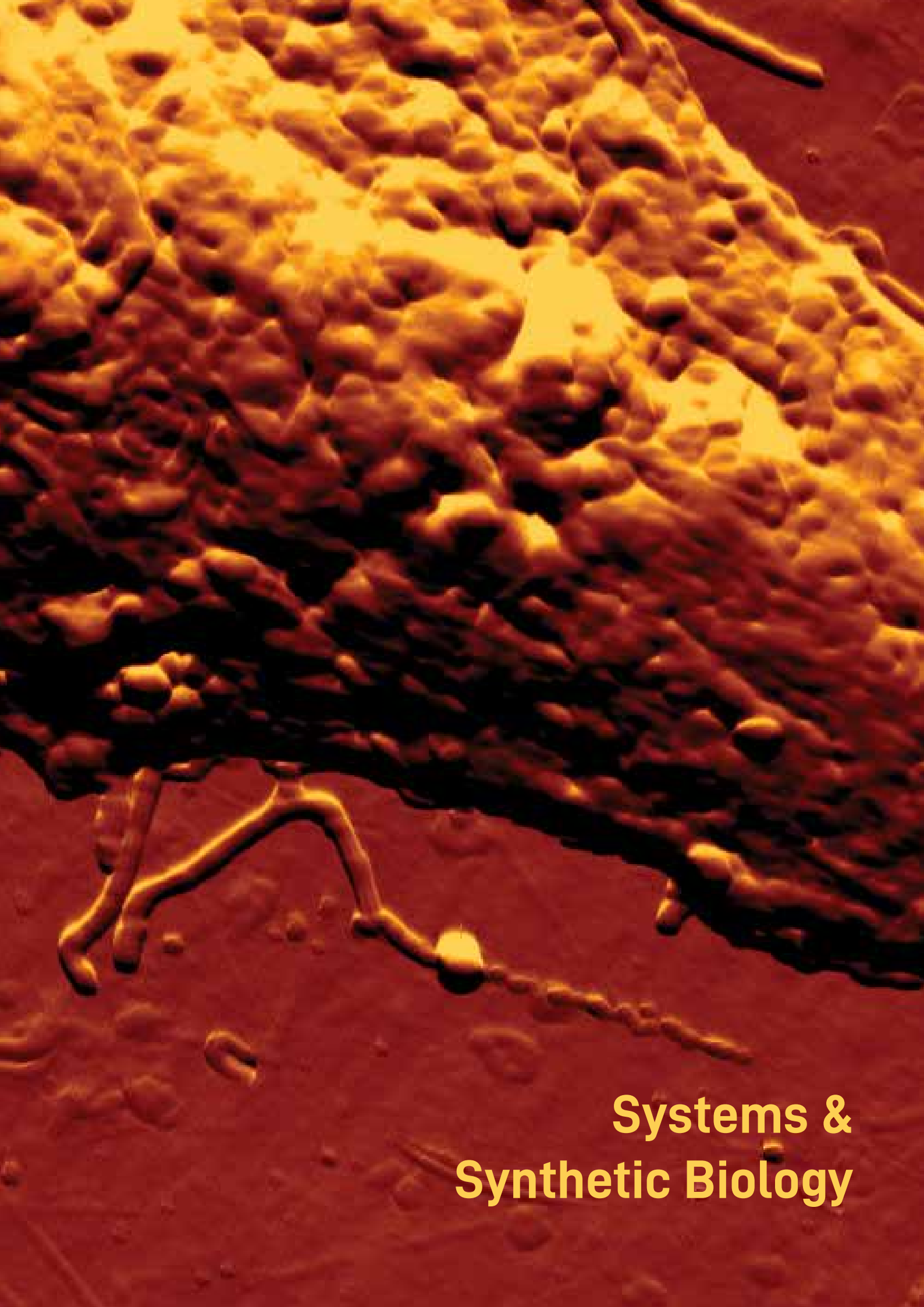


Figure 2. *Identification of a putative polysaccharide acetyl esterase. A. Phylogenetic tree of GDSL lipase/ esterase subfamily B generated by MEGA software. The genes co-expressed with plant cell wall biosynthetic genes are marked with a red circle. B. A representative co-expression network of a GDSL gene (yellow), which is co-expressed with plant cell wall biosynthetic genes (blue).*

cytoplasm via Reduced Wall Acetylation (RWA) proteins to the Golgi membrane, and proteins from AlteredXYlan (AXY) and Trichome Birefringence-Like (TBL) transfer the acetyl group onto the polysaccharides. The GDSL proteins involved in de-esterification of extra acetyl groups maintain the homeostasis of polysaccharides (Fig. 1). Two polysaccharide esterases recently identified in rice belong to the GDSL lipase/esterase family. We aim to identify and characterize Arabidopsis polysaccharide esterases to understand the overall mechanism of polysaccharide acetylation in Arabidopsis. The Arabidopsis GDSL lipase/esterase is a large family containing 106 gene members, divided into 3 subfamilies - A, B and C. Few members of this family have been functionally characterized in Arabidopsis and shown to possess diverse functions in plant growth, development, biosynthesis of secondary metabolites and defense.

The Arabidopsis GDSL lipase/esterase subfamily B is divided into two clades. Most of the genes from clade II are co-expressed with plant cell wall biosynthetic genes (Fig. 2). Based on phylogenetic and co-expression analysis, we hypothesise that 14 proteins from this family have a role in polysaccharide acetylation. We have a collection of T-DNA SALK mutant Arabidopsis lines for each member of the GDSL family, and are currently genotyping these lines to isolate homozygous mutants. Simultaneously, biochemical characterisation of the selected GDSL candidates is under progress to understand how esterases play a role in the biosynthesis of O-acetylation. We are performing stable and transient expression of these GDSL genes (Fig. 2)in Arabidopsis and *Nicotiana benthamiana*, respectively. All mutant and transgenic lines will be analysed by measuring acetylation levels in the following polysaccharides - xylan, pectin and xyloglucan. Additionally, we will analyse the phenotype of altered acetylation mutants since an alteration in polysaccharide O-acetylation levels is known to negatively impact growth. We will investigate plausible reasons for these changes by examining several plant cell wall properties. We will use wet chemistry methods, Nuclear Magnetic Resonance (NMR), and Gas Chromatography-Mass Spectroscopy (GC-MS) to understand the plant cell wall structure in transgenic GDSL lines and mutants. The final goals of this project are to (1) identify polysaccharide-specific esterases, which are either localised in the Golgi or the plant cell wall, (2) comprehend how esterases maintain homeostasis of acetyl groups on specific polysaccharides, and (3) tailor polysaccharide O- acetylation for the improvement of lignocellulosic biomass.





Systems & Synthetic Biology

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Targeting and Tuning Nucleic Acid Structures for Therapeutic and Biotechnology Applications

Antimicrobial resistance (AMR) occurs when bacteria develop mechanisms to escape from antibiotics rendering them ineffective. AMR is a threat to public health and is estimated to cause 10 million deaths annually by 2050. Thus it is important to find novel antibiotics that use new targets to kill bacteria. Riboswitches have emerged as a novel and unexplored antibacterial drug target due to their role in bacterial survival and pathogenesis. In our laboratory, we are synthesizing chemical compounds that interact with riboswitches to inhibit bacterial growth. In addition, we are using riboswitches as tools for control of gene expression for biotechnology applications.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are the basic molecules of life. Besides serving as genetic repositories, they also form non-canonical structures (e.g., G-quadruplexes, stem loops, riboswitches and three-way junctions; Fig. 1), which are diverse and remarkably involved in a broad spectrum of biological processes. Thus, these structures have gained attention as synthetic biology tools. Riboswitches are natural regulatory elements found in pathogenic and biotechnologically important bacterial strains. We specifically seek to (1) design and synthesize new synthetic molecules to target riboswitches for antibacterial treatment, and (2) rationally develop synthetic riboswitches for precise control of gene expression for various applications.

Riboswitches are naturally occurring RNA regulatory elements found in bacteria and some eukaryotes. A riboswitch consists of an aptamer domain that binds to a target ligand and transduces the binding signal into a gene expression output. Several interesting features of riboswitches have inspired researchers to develop synthetic riboswitches. To date, several synthetic riboswitches have been constructed. However, one of the biggest hurdles while using these synthetic riboswitches in vivo is the unsuitability of the aptamer domains and regulator ligands. RNA aptamers for constructing artificial riboswitches have been mainly selected in vitro using an iterative process called systematic evolution of ligands by exponential enrichment (SELEX). Although the SELEX method generates aptamer domains with high binding affinity (lower equilibrium dissociation constant KD) for the chosen ligand, these aptamers have several limitations as discussed below. To date several aptamers have been selected by SELEX, however only few aptamers i.e. theophylline, neomycin and tetracycline have been found suitable for in vitro applications The requirement of high ligand concentration (in the millimolar range) and antibiotic property generally limits their use due to toxicity and poor cell permeability. Furthermore, a switching sequence is required that transduces the aptamer-binding signal to the functional moiety, and obtaining an efficient switching sequence is difficult in SELEX-selected aptamers. Finally, one of the most challenging factors is the kinetics of ligand binding and RNA folding, which cannot be controlled in SELEX-selected aptamers. These limitations clearly indicate a need for the development of a new method for aptamer domain selection for advanced applications. The use of naturally existing riboswitch

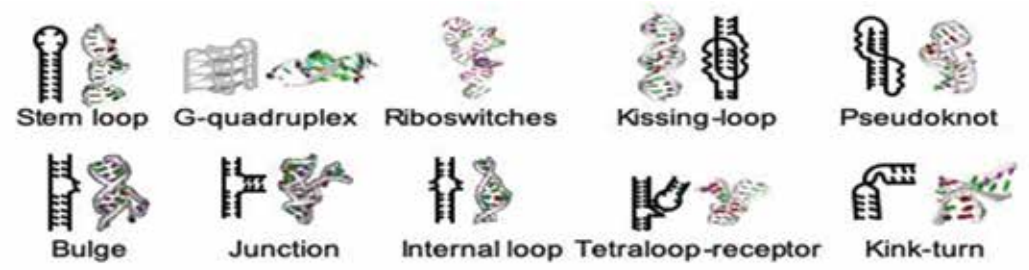

Figure 1. *Functional non-canonical DNA and RNA structures.*

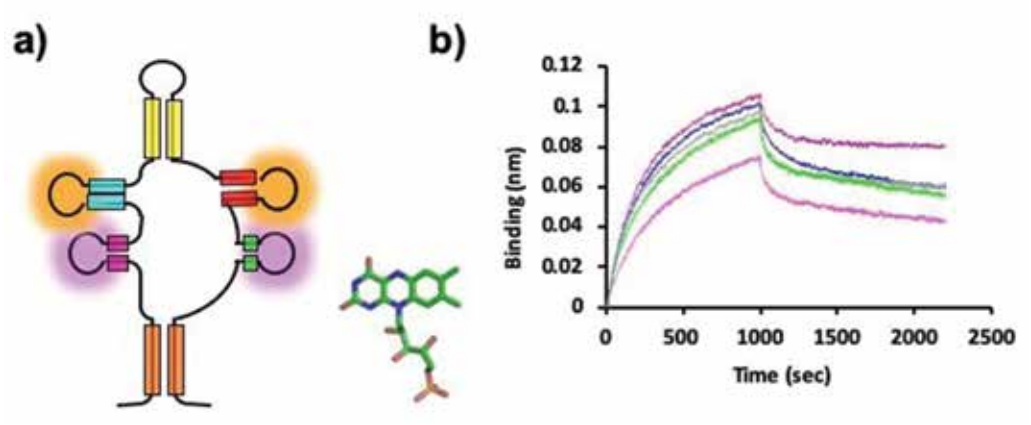

Figure 2. *Secondary structure of aptamers and its effector ligand. (a) FMN aptamer derived from F. nucleatum and FMN ligand. (b) Binding analysis of the reengineered FMN aptamers with diverse synthetic ligands using Biolayer interferometry (BLI).*

aptamer domains is a promising strategy to overcome these limitations. Although promising, to date only few natural riboswitches have been engineered to recognize synthetic ligands. Here, we have reengineered a natural Flavin mononucleotide (FMN) riboswitch (Fig. 2a) and confirmed its binding using biolayer interferometry (BLI) (Fig. 2b).

The insights gained from our biophysical studies with natural FMN riboswitch aptamers have been used to reengineer orthogonal aptamers. Structure-guided mutagenesis was performed on the FMN riboswitch by randomizing conserved residues to generate various riboswitch aptamers. These sequences were subjected to a binding screen using BLI with synthesized analogs. The unnatural riboswitch aptamer-ligand pairs exhibited desirable orthogonality to the parent FMN riboswitch aptamer in vitro.

The rise of drug resistance in human pathogenic bacteria is a major global health concern. Hence, there is an urgent need for the development of novel antibiotics that employ new molecular targets. Riboswitches have emerged as promising targets as they are involved in the regulation of genes essential for bacterial survival or pathogenesis. Targeting riboswitches for antibacterial therapy is an emerging research area and the compounds identified for targeting riboswitches to date show minimum inhibitory concentration (MICs) in the high micromolar to low millimolar range. Thus, further improvement is necessary to reach therapeutically relevant values. We have used a structure based drug design approach to develop antibacterial drugs. A small library of compounds was synthesized, purified and characterized by nuclear magnetic resonance (NMR) and mass spectroscopy. We have tested these against several bacterial strains. Some of these synthesized compounds showed significant mean zone inhibition against all tested bacterial strains. To further evaluate antimicrobial potential, we are currently determining the minimum inhibitory concentration (MIC) for the active compounds.

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Development of Synthetic Biology Platforms and Bioprocessing Strategies for Generation of Bioproducts

Overall, the research group is focussed on developing superior biocatalysts for pharma, food, and agro-based industries. The research programme aims to develop biocatalysts using a systems and synthetic biology approach. These biocatalysts can be either enzymes from biological sources or whole cells, which accelerate the rates of reactions resulting in economical bioproduct synthesis. A better understanding of the catalytic mechanism will certainly aid in the development of exceptional biocatalysts.

Lignocellulosic biomass is the most abundant source of organic carbon on earth. It mainly consists of three major biopolymers: cellulose, hemicellulose, and lignin, which are present in interwoven linkages resulting in a natural recalcitrant composite. This complex structure of biomass makes it resistant to enzymatic decomposition, serving as the biggest technical and economic hurdle to cost-effective release of fermentable sugars for biorefineries. In order to achieve sustainable biomass deconstruction into fermentable sugars, it is necessary to overcome the chemical and structural complexity of biomass through the development of more efficient enzyme preparations. The hydrolytic enzymes used today are basically fungus based preparations owing to their potential to secrete copious amounts of enzymes when grown in cellulose-rich medium. Therefore, insoluble substrates such as cellulose, hemicellulose, or mixtures of plant polymers are considered the best inducers for upregulating the expression of plant cell wall-degrading enzymes by filamentous fungi. However, the use of insoluble substrates to induce enzyme secretion is not ideal for industrial processes, because these naturally inducing substances cannot enter fungal cells and are thus observed to take longer time for induction. Moreover, complex cellulose tends to choke the bioreactor making it unavailable for the next run.

It is believed that oligosaccharides released from polymers and their derivatives function as the actual molecules that trigger enzyme induction. One such example is cellobiose, the major soluble end product of cellulose hydrolysis, which moderately induces cellulase gene expression and activity in *Hypocrea jecorina* (*Trichoderma reesei*) and Aspergillus species, two commonly used fungi for high-level enzyme production. However, in another study, it was pointed out that cellobiose was unable to induce cellulase gene expression in these fungal strains; instead they responded to cellotriose or cellotetraose. Thus, the precise nature of the "true inducer" responsible for overexpression of cellulolytic enzymes is still unknown. We aim to unravel the global inducer and anticipate that an understanding of its mode of action will certainly aid in the development of a robust platform for the production of an array of hydrolytic enzymes. Under this objective, we will cultivate the fungus on 13C-enriched wheat straw, and the intracellular labelled metabolite generated upon hydrolysis will be then analyzed at

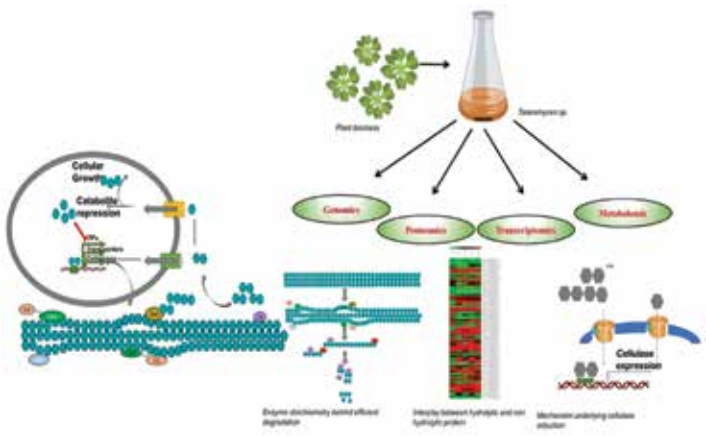

Figure 1. *Schematic of platform developed for inducer identification*

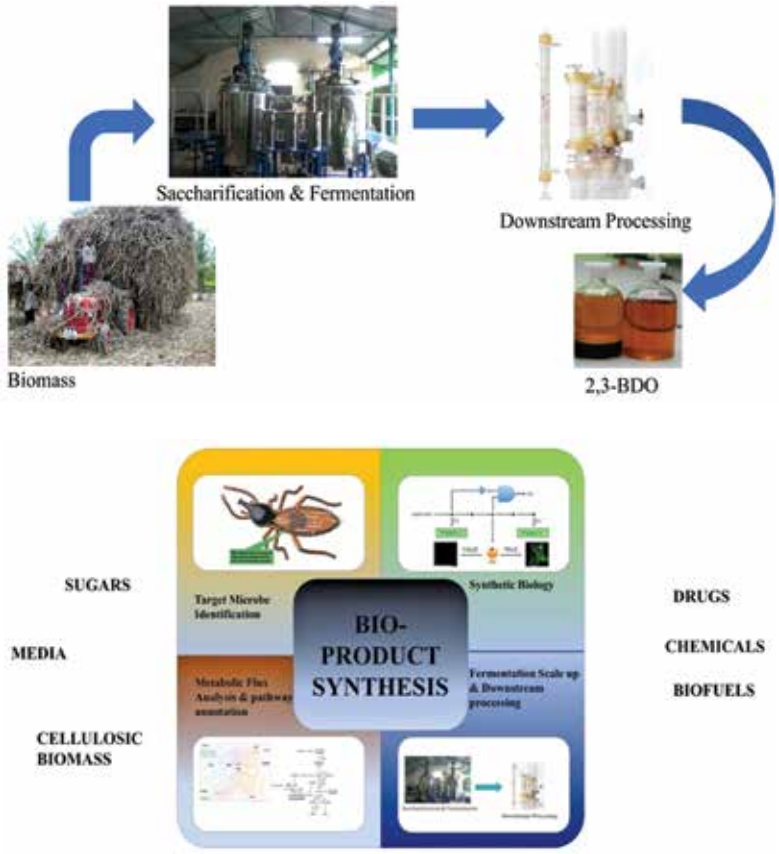

Figure 2. *Process developed for bioproduct synthesis.*

different time intervals. Analysis of the metabolites will give insight into the identity of the inducer required for enzyme overexpression (Fig. 1). Further, we aim to decipher the regulatory mechanism of enzyme production using this inducer. In the future, we will develop a platform for heterologous enzyme production using the inducer regulated promoter system in fungal sp.

Additionally, the lab is working towards the utilization of processed biomass for bioproduct synthesis. The research group previously developed a platform for exploiting lignocellulosic biomass for 2,3- butanediol production using a commercial hydrolytic enzyme cocktail (Fig. 2). Based on the knowledge gained, we propose to utilize the in-house developed enzyme system for fermentative production of other valuable bioproducts such as methyl ethyl ketone, isobutanol, etc. Methyl ethyl ketone is widely used as an antifreeze agent. Branched chain alcohols, such as isobutanol and isopentanol, have an energy density close to gasoline and, unlike ethanol, are not corrosive and do not absorb water. Therefore, they can be utilized as a highly efficient drop-in fuel.

Kinshuk Raj Srivastava
Principal Investigator

Lab Member
Sunny

Development of Biocatalyst and Biocatalytic Process for the Synthesis of High-value Products

Enzymes are nature's catalysts that accelerate reactions to produce the desired product. However, in their native form, enzymes are not suitable to carry out the desired transformation. Therefore, enzymes need to be engineered to work efficiently in industrial operational conditions. My research program is focused on developing a molecular level understanding of structure, dynamics, function, and spatio-temporal communications of enzymes present in specific metabolic network/synthetic cascades. We will exploit the gained knowledge to engineer efficient biocatalysts and develop biocatalytic processes for the production of pharmaceuticals and fuel. Biocatalytic processes have significant advantages over chemo-catalysis methods, due to their high selectivity, compatibility between enzymes for multi-enzyme catalysis, and mild operational conditions. However, industrial use of biocatalytic process are greatly hampered by the native enzyme's narrow substrate scope, poor stability and efficiency, and the lack of understanding about coordination and organization of multiple enzymes in native biochemical cascades. Therefore, my research group will be addressing such limitations by a) first developing the mechanistic understanding about physiochemical factors governing the enzyme's structure, stability, and activity, and spatio-temporal communications between multi-enzymatic systems, and b) further exploiting the gained knowledge to engineer single enzyme and/or multi-enzyme cascades for biocatalytic synthesis of high value chemicals. The proposed work flow with details are presented in Fig. 1. We believe that our efforts will expand the available repertoire of efficient biocatalysts, and synthetic enzyme cascades, for industrially important manufacturing process.

Harnessing enzyme engineering for efficient biocatalytic synthesis of cyclic peptide derivatives for diverse biological applications

Cyclic peptides constitute a large class of microbial natural products and display a broad variety of biological and pharmacological activities, which include antibacterial, antitumor, antifungal, antiviral, antitubercular, cell-to-cell communication, and blood-brain barrier transport. Their anticancer, and neuroprotective activities are currently under investigation. The exceptional stability and bioactivities of this class of compounds makes them attractive structural scaffolds for medicinal chemistry and drug discovery applications. Generating diversity along this cyclic peptide scaffold is an attractive strategy to improve and further expand the bioactivities exhibited by this class of compounds. My research group is involved in genome mining based discovery of enzymes, structure-function characterization, and engineering of biosynthetic enzymes to evolve a better enzyme candidate with altered specificity and promiscuity towards a broad range of cyclic peptides. Application of these engineered biocatalysts will enable us to synthesize structurally and chemically diverse cyclic peptide derivatives for diverse drug discovery applications.

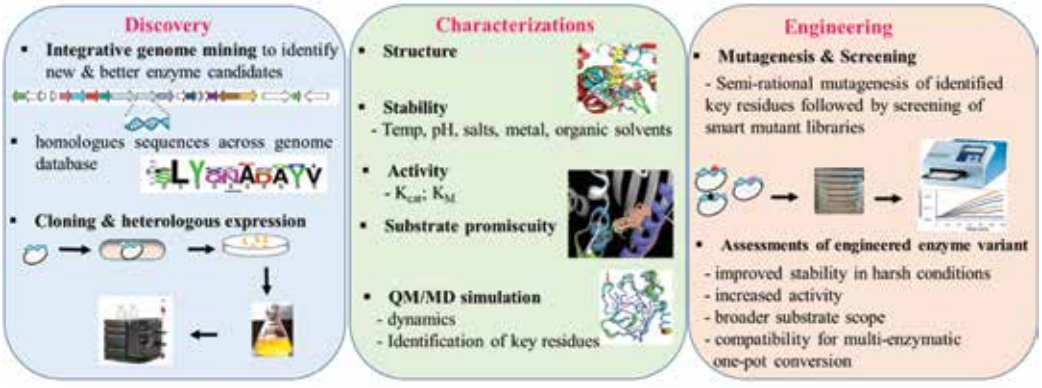

Figure 1. *Schematics of work flow for discovery and development of biocatalyst.*

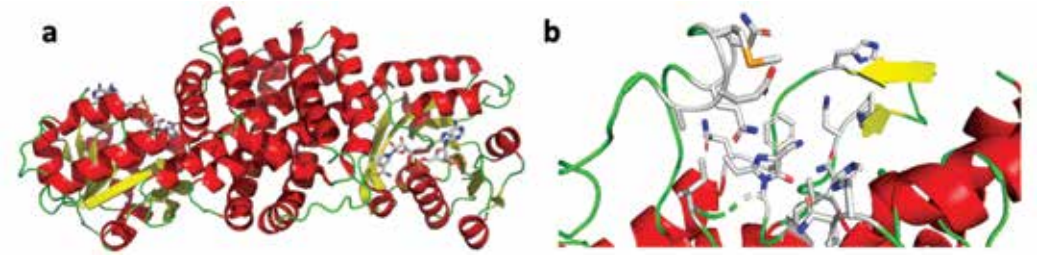

Figure 2. *(a) Dimer structure of AoIRED illustrating the canonical IRED fold, (b) zoomed-in view highlighting the active site of PAL from R. toruloides.*

Integrative genome-based discovery, characterization and engineering of biocatalyst for the synthesis of chiral amines precursor for pharmaceuticals

Chiral amines are the most valuable building blocks in the pharmaceutical, fine chemicals and agrochemical industries. The majority of the drugs approved by FDA in recent years constitute amine intermediates, and about 40% of the active pharmaceutical ingredients (APIs) contain the chiral amine moiety. Chemical synthesis of chiral amines industrially is very inefficient and involves the application of expensive toxic metals. Furthermore, it is very difficult to control the stereoselectivity in chemical synthesis. The product contains a mixture of enantiomers, which necessitates a next round of purification to achieve chiral amine compounds. Enzymes such as transaminases (TA), monoamine oxidases (MAOs), amine dehydrogenases (AmDHs), phenylalanine ammonia lyases (PALs), imine reductases (IREDs), lipases, and monooxygenases are some of the classes of enzymes that are targeted for biocatalytic synthesis of chiral amines. My research group will engineer PALs and IREDs to evolve superior catalysts with high stability, activity, promiscuity and cofactor specificity, which could be applied for the sustainable production of chiral amines of industrial interest. Fig. 2 illustrates the overall topology and active sites for PALs and IREDs. Using data-driven engineering, the enzyme scaffold would be mutated to obtain biocatalysts for specific transformations. Furthermore, we intend to evaluate the applicability of whole cell biocatalysts (recombinant *E. coli* heterologously expressing the enzymes) to simplify its preparation, making the biocatalyst particularly cost-effective.

Investigation of substrate channeling during biosynthesis of natural products

To realize the full potential of multi-enzyme cascade catalysis, or metabolic engineering, we need to develop a molecular-level understanding about transient physical interactions of enzymes with myriads of their interacting partners in the metabolic network. Towards this end, we aim to investigate enzyme-enzyme interactions, and structure-function characterization of enzyme supramolecular complexes (metabolons) from tirandamycin, cellulose degradation, and phenylpropanoid biosynthetic pathways. This will provide evidence and an understanding about the spatial and functional orchestration among multiple enzymes in natural metabolic pathways. The gained understanding will be exploited to develop self-sufficient, spatially organized, multi-enzymatic cascades for the production of desired high-priced molecules such as active pharmaceutical and fuels.

Contents lists available at ScienceDirect

Journal of Structural Biology

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Crystal structure of basal pilin SpaE reveals the molecular basis of its incorporation in the lactobacillar SpaFED pilus

Journal of Neurochemistry JNC

JOURNAL OF NEUROCHEMISTRY | 2019 | 149 | 518-534

doi: 10.1111/jnc.14645

Journal of Neurochemistry

ORIGINAL ARTICLE

Japanese Encephalitis Virus–induced *let-7a/b* interacted with the NOTCH–TLR7 pathway in microglia and facilitated neuronal death via caspase activation

Journal of Clinical Immunology (2019) 39:336–345
https://doi.org/10.1007/s10875-019-00619-2

Journal of Clinical Immunology

ORIGINAL ARTICLE

Altered Peripheral Blood Leucocyte Phenotype and Responses in Healthy Individuals with Homozygous Deletion of *FHR1* and *FHR3* Genes

The Journal of Physical Chemistry Letters

Letter

Cite This: J. Phys. Chem. Lett. 2019, 10, 754−760

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Distinct Intramolecular Hydrogen Bonding Dictates Antimicrobial Action of Membrane-Targeting Amphiphiles

Journal of Medicinal Chemistry

Article

Cite This: J. Med. Chem. 2019, 62, 1875−1886

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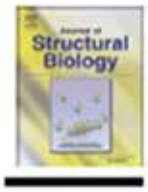
eciphering the Role of Intramolecular Networking in Cholic Acid–eptide Conjugates on the Lipopolysaccharide Surface in ombating Gram-Negative Bacterial Infections



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RESEARCH ARTICLE

Journal of Cell Sciences

The exocyst complex and Rab5 are required for abscission by localizing ESCRT III subunits to the cytokinetic bridge

ACS Chemical Biology

Articles

Cite This: ACS Chem. Biol. 2019, 14, 1515−1527

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JBC ARTICLE

Journal of Biological Chemistry

The chaperone ERp29 is required for tunneling nanotube formation by stabilizing MSec

Nanoscale

PAPER

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Bioconjugate Chemistry

Article

Cite This: Bioconjugate Chem. 2019, 30, 721−732

pubs.acs.org/bc

Oral Delivery of Cholic Acid-Derived Amphiphile Helps in Combating *Salmonella*-Mediated Gut Infection and Inflammation

Publications & Patents

Peer-reviewed Publications

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2. Ghodke, P P, Bommisetti, P, Nair, D T, Pradeepkumar, P I. (2019) Synthesis of N(2) Deoxyguanosine Modified DNAs and the Studies on Their Translesion Synthesis by the E. coli DNA Polymerase IV. J Org Chem. 84:1734.
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Patent Applications

1. Eswaran SV and Guchhait P. Water Soluble Fullerene C60 Adducts for Nano-Medicine & Materials Science. Indian patent application No. 201811020894.

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ACADEMIC & TRAINING ACTIVITIES

Academic Programs

PhD Program in Biotechnology

Regional Centre for Biotechnology offers a PhD programme in Biotechnology for students who have interest in work ing at the interface of multiple disciplines in the areas related (but not limited) to structural, systems, synthetic and chemical biology, analysis of complex diseases for identification of intervention points, development of knowledge-based drug discovery strategies, plant biotechnology, enzyme engineering, and fermentation among others. Presently, there are 83 students working at RCB for the PhD degree in Biotechnology. During the period of the report, 7 students were awarded PhD degree.

PhD Programs in Biostatistics and Bioinformatics

RCB is offering interdisciplinary doctoral programs in Biostatistics and Bioinformatics in partnership with other institutions by creating a virtual faculty pool. These programs are being supported through a collaboration with the global pharmaceutical giant, Glaxo Smith Kline Pharmaceuticals India Private Ltd. (GSK) and are subject to RCB statutes, ordinances and regulations. In addition to RCB faculty members, faculty from partner institutions like IIT Delhi, NII New Delhi, ICGEB New Delhi, NIBMG Kalyani, holding an adjunct faculty position with RCB, act as mentors for the students admitted to the programme. Students receive a consolidated fellowship of Rs. 45000 per month for the first two years and Rs.50000 for the next three years. Presently, there are a total of 2 students registered with RCB for PhD in these programs.

Integrated MSc-PhD Degree Program in Biotechnology

In 2018-19, RCB introduced an Integrated MSc-PhD Programme in Biotechnology with focus on research-based learning. The program in its first year provides extensive learning opportunities in the broad field of life sciences and biotechnology through rigorous class room study and hands-on laboratory experiments. In the second year, the students work in a research lab under the supervision of a research guide in an area of mutual scientific interest, and submit a dissertation by the end of the fourth semester. The student may exit the programme with a Master's degree or continue in the program for pursuing the PhD program. The students admitted to the program receive the RCB Ramachandran-DBT fellowship of Rs. 16000 per month for the first two years, after which, the Indian students continue in the PhD component with a fellowship from a national funding agency while the foreign students receive the RCB-DBT International Doctoral fellowship. Ten students were registered with RCB for the program in July 2018 including one foreign student.

Research Training Programs for Post-graduate Students

RCB offers research training to post-graduate students of biotechnology related areas from various universities/ institutions/ colleges of repute to carry out their project work towards partial fulfilment of their post-graduate degrees. It also offers short-term summer trainings/ internships for students interested in research areas of specialization in RCB. Selection is based on the strength of resume and evaluation of write-up on their research interests. Selected candidates under go research training under the mentorship of RCB faculty. They learn to carryout their own research projects in collaboration with other group members. Trainees get a realistic experience of several facets of conducting modern biological research and embarking ona research career. The training programs range from two to six months' duration. In the past year, 8 research trainees joined for six months' duration and 16 research interns joined for two months' internship in the summer.

Academic Programs at the RCB's Recognized Centers

RCB has given academic recognition to the various institutions of excellence as per Clause 10(1) for the RCB Act and RCB Ordinance for their academic programs. Students admitted to these programs are registered at RCB for their degrees. At present, following institutions and their academic programs are recognized by RCB. The number of students registered under the various programs are provided below.

Name of Recognized Centre	Courses Recognized	No. of students
Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad	PhD (Biotechnology)	33
Center of Innovative and Applied Bioprocessing (CIAB), Mohali	PhD (Biotechnology)	3
National Institute of Animal Biotechnology (NIAB), Hyderabad	PhD (Biotechnology)	22
National Agri-Food Biotechnology Institute (NABI), Mohali	PhD (Biotechnology)	14
Institute of Life Sciences (ILS), Bhubaneswar	PhD (Biotechnology)	58

Distinguished Lectures

Date	Speaker	Title
October 08, 2018	Dr. Rajesh Gokhale, National Institute of Immunology	Renewing the Romance in the Love-Lost Marriage: Bioentrepreneurship in India
March 1, 2019	Dr. Balram Bhargava, Indian Council of Medical Research	Frugal Innovations for Healthcare

Invited Seminars

Speaker	Title	Date
Prof. Kaoru Katoh Biomedical Research Institute, AIST Japan	Observation of Fine Structures of the Cell with Super Resolution Microscopy	March 30, 2019
Dr. Nitin Mohan IIT Kanpur	Illuminating autophagy regulations by tubulin post-translational modifications using super-resolution microscopy	March 29, 2019
Dr. Akash Gulyani InSTEM	Imaging protein activation and cellular dynamics using novel FRET and environment-sensitive fluorescent biosensors	March 28, 2019
Dr. Ravi Manjithaya JNCASR	Autophagy in health and disease	March 28, 2019
Dr. Ananda Sarkar National Institute of Plant Genome Research	Laser Capture Microdissection: method and important applications in plant science	March 27, 2019
Dr. Anindya Ghosh Roy National Brain Research Centre	Femtosecond laser and live imaging meet the power of genetics in transparent nematode: Intrinsic control of axon and dendrite regeneration	March 25, 2019
Dr. Shailendra Mani Duke-NUS, Graduate Medical School, Singapore	Novel serological platform in biomedical research	March 20, 2019
Dr. Rohit Jangra Albert Einstein College of Medicine	Screening for host factors and neutralizing mAbs: a story of two viruses	March 12, 2019
Prof. Joel Sussman Weizmann Institute of Science, Israel	Acetylcholinesterase: A model enzyme for drug discovery	February 16, 2019
Prof. B. Gopal IISc, India	Targeting protein interactions and networks that govern transcriptional changes and adaptation in Mycobacterium tuberculosis	February 16, 2019
Prof. S. Ramaswamy inStem, India	Drug Discovery across Molecular Scales	February 16, 2019
Prof. Aneel K. Aggarwal Mount Sinai Medical Center, USA	Targeting DNA and RNA metabolism	February 15, 2019
Prof. Edward Arnold Rutgers University, USA	Successful structure-based design of drugs targeting HIV-1 reverse transcriptase	February 15, 2019
Prof. Ming-Hon Hou National Chung Hsing University, Taiwan	Structure-based virtual screening and experimental validation of novel human coronavirus nucleocapsid protein antiviral inhibitors	February 15, 2019
Dr. R. Ramachandran CDRI, India	Characterization of DNA Base Excision Repair complexes and implications for new therapeutic strategies	February 15, 2019
Prof. T. P. Singh AIIMS, India	Structural basis of antibiotic activity of innate immune peptidoglycan recognition proteins	February 15, 2019
Prof. S. Gourinath JNU, India	Structural & functional studies, inhibitor development against cysteine biosynthetic pathway enzymes of E. histolytica.	February 15, 2019
Prof. Seth A Darst Rockefeller University, USA	Teaching old dogs new tricks; Inhibiting rifampycin-resistant M. tuberculosis RNA polymerase	February 14, 2019

Prof. Christoph Stein Freie University, Germany	Opioid Receptors – Structure, Function and Plasticity	February 14, 2019
Prof. Sir Tom Blundell Cambridge University, UK	Structure-guided drug discovery in industry and academia: cancer, tuberculosis and the emergence of Resistance	February 12, 2019
Prof. R. Sowdhamini NCBS-TIFR, India	Lessons learnt from modelling and virtual screening towardsdrug design	February 12, 2019
Dr. Shailly Tomar IIT-Roorkee, India	Structure-assisted discovery of antivirals targeting chikungunya viral protease	February 12, 2019
Dr. Sarel Fleishman Weizmann Institute of Science, Israel	Automated design of enzymes, antibodies, and vaccine immunogens.	February 12, 2019
Dr. Ramchand CS Saksin Technologies, India	Discovery and Development of a novel epitope binding Anti-VEGF Fab for age related macular dystrophy: A structure based approach.	February 12, 2019
Dr. Ramesh Thimmappa The John Innes Centre, UK	Probing hidden functional diversity in oxidosqualenecyclases; towards novel triterpenes discovery and metabolic engineering.	January 18, 2019
Dr. Kalpana Bhargava DRDO, India	Post Translational Modifications: A tool to study Protein Structure-Function Relationship	December 20, 2018
Dr. Inderjeet Kaur ICGEB, India	Decoding post translational modifications in malaria parasite biology	December 20, 2018
Prof. Subhra Chakraborty NIPGR, India	Proteomics of abiotic stress responses in plants	December 19, 2018
Dr. Mahesh J. Kulkarni NCL, India	Quantification of post translational modification- a special reference to protein glycatiin"	December 19, 2018
Dr. S. Sudarslal Amritha University, India	Impact of guggulsterone on diabetes-related complications: An investigative analysis using quantitative mass spectrometry	December 18, 2018
Dr. Shantanu Sengupta IGIB, India	Vitamin B12 deficiency: Time for a reality check?"	December 18, 2018
Dr. Devin Sok International Aids Vaccine Initiative, USA	Antibody discovery against variable pathogens and diseases	November 14, 2018
Dr. Debashis Mitra Centre for DNA Fingerprinting and Diagnostics, India	Cellular stress proteins as potential targets for HIV-1 infection	November 14, 2018
Kuldeep Sachdeva National Centre for Biological Sciences, India	Dual modulation in the endo-lysosomal system driven by the host heterogeneity and mycobacterial lipid defines the homeostasis of Mycobacterium tuberculosis infected macrophage	November 14, 2018
Dr. Jorge E Galan Yale University School of Medicine, USA	Typhoid toxin: a window into the unique biology of Salmonella Typhi	November 14, 2018
Dr. Mahak Sharma Indian Institute of Science Education and Research, Mohali, India	How to do business with lysosomes: Salmonella leads the way	November 14, 2018
Dr. Suresh Mahalingam Griffith Universtity, Australia	Alphavirus-inflammatory diseases: New insights into disease mechanisms, vaccine development and therapeutic approaches	November 12, 2018

Dr. AnirbanBasu National Brain Research Centre, Manesar, India	Host MicroRNA: An important modulator of antiviral immunity in Japanese Encephalitis virus infection	November 12, 2018
Dr. Subhash Vasudevan Duke NUS, Singapore	Dengue antiviral discovery and development	November 12, 2018
Dr. Arvind Sahu National Centre for Cell Sciences, India	Species specificity of vaccinia virus complement control protein towards bovine classical pathway is governed primarily by direct interaction of its acidic residues with protease factor	November 12, 2018
Dr. Qiuwei Abdullah Pan Erasumus MC, Netherlands	Virus-host interactions and antiviral drug development against hepatitis E virus infection Virus-host interactions and antiviral drug development against hepatitis E virus infection	November 12, 2018
Dr. Kavita Lole National Institute of Virology, India	MicroRNA-122 facilitates Hepatitis E virus replication by directly interacting with the viral genome	November 12, 2018
Dr. Javed Iqbal Jamia Millia Islamia, India	Osteopontin regulates hepatitis C Virus replication and assembly by interacting with viral proteins and lipid droplets	November 12, 2018
Dr. Manikandan Karuppaswamy EMBL, Grenoble, France	Cryo-EM Structure of Saccharomyces cerevisiae Target of Rapamycin Complex 2	September 7, 2018
Dr. Sandip Kaledhonkar Columbia University Medical Cenre, New York	Structural Dynamics of Biomolecules Captured by Time-Resolved Cryo- Electron Microscopy	August 10, 2018
Dr. Ullas Kolthur-Seetharam Tata Institute of fundamental Research, India	Un-holy link between Diet and Protein-Structure/Function: Relevance in Aging and Age related diseases	July 10, 2018
Dr. Hemchand Tummala Associate Professor, South Dakota State University, USA	Pathogen mimicking vaccine delivery System (PMVDS) designed with a novel Toll-Like Receptor-4 agonist	June 20, 2018
Dr. Girish Ratnaparkhi IISER, Pune	SOD1 activity threshold and TOR signalling modulate VAP(P58S) aggregation via ROS-induced proteasomal degration in a Drosophila model of Amyotrophic Lateral Sclerosis	June 18, 2018
Dr. Ananda Chowdhury National Cancer Institute, National Institutes of Health, USA	Recombinant "Target" and "Effector" Proteins: Production Strategies and Pharmacological Evaluation	June 6, 2018
Dr. Harshini Mukundan Los Alamos National Laboratory, USA	A Universal Bacterial Sensor for Point of Care Diagnostics	May 28, 2018
Dr. Anita Roy Universite Catholique de Louvain, Belgium	Megakaryopoiesis: normal development and myeloproliferation	May 15, 2018
Dr. Indrajit Lahiri University of California, USA	Unravelling fundamental nucleic acids processes: the role of cryo-EM	April 10, 2018
Dr. Basudeb Maji Harvard Medical School, USA	Small Molecule Controlled CRISPR-Cas9 towards Genome-engineering in Cells	April 6, 2018
Prof. Jeffrey Murray Bill & Melinda Gates Foundation, USA	Omics approaches to newborn traits and diseases	April 5, 2018
Dr. Rinku Jain Mount Sinai School of Medicine, USA	Structural Studies on Zika and Cancer Targets	April 4, 2018

Symposia, Conferences, Workshops and other Events

International Symposium on Infectious Diseases

Regional Centre for Biotechnology and Jamia Hamdard, New Delhi jointly organized an International Symposium on Infectious Diseases from 12th to 14th November 2018. With the evolution of bacterial and viral superbugs, infectious diseases have re- emerged to be a major threat to mankind and nature. This conference was aimed to cover contemporary areas related to viral and bacterial pathogens. Particular emphasis was laid on Japanese encephalitis virus (JEV), Dengue virus, Salmonella typhimurium, Salmonella typhi and Staphylococcus aureus which have posed health challenges in the recent past in India. The three-day symposium was planned such, that the sessions of day 1 and day 3 were held at RCB and day 2 sessions at Jamia Hamdard allowing wider audience and varied ambiance. Eighty-two enthusiastic students from various institutions and universities of India participated in the symposium along with 52 reputed scientists from across the globe. The sessions covered invited seminar presentations from scientists with distinguished eminence, oral presentation from selected young researchers and poster presentations of participants. On the day 2, after the scientific sessions, a cultural program showcasing Indian heritage was also held. The multi-institutional and trans-disciplinary nature of the symposium was scientifically fruitful as it not only enabled development of newer collaborations, but also generation of ideas and questions across the spectrum of infectious diseases.

International Conference on Structure-Assisted Development of Novel Therapeutics

Recent viral outbreaks and the increasing incidence of antimicrobial resistance in India represent public health problems of escalating intensity. New therapeutic strategies are urgently required and to accelerate research towards this end, the Regional Centre for Biotechnology held an International Conference on Structure-assisted development of novel therapeutics from February 12-16, 2019. The meeting discussed structural methods available to identify lead molecules for drug development and also dwelt on all aspects of the drug discovery pipeline. The event involved a one-day hands-on workshop that educated participants about computational methods utilized for discovery of lead molecules using structural information. This was followed by a four-day conference with seminars by international and national speakers from academia and industry on strategies and successful examples of drug discovery.

The conference was inaugurated by Dr. Renu Swarup (Secretary, DBT) and speakers included Prof. Sir Tom Blundell (Cambridge University, UK), Prof. R Sowdhamini (NCBS, Bangalore),

Dr. Shailly Tomar (IIT-Roorkee), Dr. Sarel Fleishman (Weizman Institute of Science), Dr. Ramchand CS (Saksin Technologies, Chennai), Prof. Seth A. Darst (Rockefeller University, USA), Prof. Christoph Stein (Freie University, Germany), Prof. Aneel K. Aggarwal (Mount Sinai Medical Center, USA), Prof. Edward Arnold (Rutgers University, USA), Prof. Ming-Hon Hou (NCHU, Taiwan), Dr. R. Ramachandran (CDRI, Lucknow) , Prof. T. P. Singh (AIIMS, New Delhi), Prof. S. Gourinath (JNU, New Delhi), Prof. Joel Sussman (Weizmann Institute of Science, Israel), Dr. Bichitra Biswal (NII, New Delhi), Prof. B. Gopal (IISc, Bangalore) and Prof. Ramaswamy (inStem, Bangalore). In addition to seminars, the conference also involved a poster session and a panel discussion on different aspects of drug discovery. It was observed that the delegates, many of whom were young researchers participated in intense discussions with the distinguished speakers and between themselves. Six young researchers were awarded for their posters by the jury. Overall, the academic event involved about 130 participants from 10 countries and 40 different institutions/universities/companies from around the world, providing a strong impetus to the structure-based drug discovery and medical biotechnology research in India.

Regional Training Program on Developing Effective and Inclusive Science, Technology and Innovation Policy

The United Nations Organisation for Education, Science and Culture (UNESCO), the UNESCO Institute for Statistics (UIS), and the Regional Centre for Biotechnology (RCB) organized a



Regional Training Programme on Developing Effective and Inclusive Science, Technology and Innovation Policy (STIP) from 6-8 March, 2019 which was inaugurated by Mr. Eric Falt, Director, UNESCO, New Delhi. Mr. Alessandro Bello and Ms. Angela Sarcina from UNESCO, Paris were the main instructors. The training participants included representatives from SAARC countries like Bhutan, Bangladesh, Nepal and Sri Lanka, in addition to participants from all over India. In pursuance to the Sustainable Developmental Goals of UNESCO, the training program focused on building capacity of South-Asian planners and policy makers. The modules included STI indicators for effective and inclusive policy formulation, monitoring tools for identifying gaps in policy data, GOSPIN and SAGA methodologies and national STI inventories.

Workshops on Science Communication and Careers in Science

Regional Centre for Biotechnology and IndiaAlliance organized a workshop on Science Communication on 31 January 2019. More than eighty students from the NCR region and outside attended the workshop. The eminent speakers from IndiaAlliance trained the participants in basics of Science Communication, writing a manuscript, presentation skills, writing grants, preparing CVs and for interviews etc. Regional Centre for Biotechnology and IndiaBioscience organized a seminar on Careers in Science on 1 February, 2019 wherein accomplished science professionals from different scientific arenas shared their life journeys. The said professionals included Dr. Suman Govil, Ms. Shubhra Priyadarshini, Dr. Puneet Gupta, Dr. Deepak T. Nair, and Mr. Syed Tarique Abdullah. This was followed by a workshop on "Crafting your Career" conducted



by IndiaBioscience for PhD and MSc students. The workshop aimed to equip life science students with basic skills and knowledge to select a career path and to prepare themselves for embarking upon it.

The 2nd RCB Bioimaging School

This imaging workshop was started in the year 2018 and has seen a second year running as a highly popular and successful workshop for the benefit of the research community aiming to address important biological and biomedical research questions using high resolution microscopy as

a major tool of investigation. This year, a mix of 21 doctoral students and postdoctoral fellows from across India were trained in the basic principles of optical microscopy, spanning sample preparation, experimental design, imaging at the microscopes and in quantitative data analysis and interpretation. Expert faculty from both within RCB and across academic research institutions of excellence in India delivered academic research lectures and participated as instructors. They were complemented by talks and hands-on demonstrations from technical experts from the best high-resolution microscopy companies globally. The technologies covered included brightfield, widefield fluorescence, confocal microscopy, super resolution microscopy, laser capture microdissection, atomic force microscopy and high throughput imaging. The students also presented posters on their ongoing research work. The RCB Bioimaging School has begun to create an expanding network of bioimaging researchers across India, thus helping to spread knowledge of these cutting-edge technologies across the nation for their intended use in producing globally competitive scientific discovery across diverse disciplines.

RCB Mass Spectrometry and Proteomics Workshop

A four-day workshop on Mass Spectrometry and Proteomics was conducted during December 17-20, 2018. The aim of the workshop was to provide basic understanding of the mass spectrometry and proteomics including sample preparation, workflow, data analysis and basic troubleshooting, via a series of lecture and practical sessions. A total of 12 field experts from reputed institutes like National Institute of Plant Genome Research, International Centre For Genetic Engineering and Biotechnology, Delhi University, National Chemical Laboratory, and Translational Health Science and Technology Institute were invited for delivering lectures. The 15 participants were shortlisted across the country and trained for mass analysis on MALDI-TOF plus 5600, protein digestion, peptide extraction, fractionation strategies, quantitation and data analysis.

RCB Open Day

Regional Centre for Biotechnology conducted its Open Day on September 24, 2018 as an Outreach Programme under the banner of India International Science Festival (IISF) on behalf of Ministry of Science & Technology and Ministry of Earth Sciences in association with

Vijnana Bharati. The objective of the programme was to provide an insight into the work life of researchers and showcase achievements of RCB scientists and research facilities at RCB. The programme attracted over 250 students from schools and colleges, including forty students from aspirational district of Mewat, Haryana. The programme included a talk on motivation towards science and a brief of research initiatives and achievements of RCB by Dr. Avinash Bajaj, Associate Professor at the Centre. A talk about the newly established Bioincubator facility at RCB was delivered by Ms. Suman Gupta. The programme included Research Displays as Scientific Research Videos, Research Exhibits and Research Posters by RCB faculty and students. There were competitive events for the visiting students like debate competition with topic 'Personalized Medicine Promises Sustainable Healthcare', Model making competition on 'Futuristic Biotechnological Innovations', sketching of Sci-toons and Science questionnaire. Students have deeply appreciated the entire initiative and felt very motivated towards science and taking up a research career in future.

INSPIRE Science Camp

On 19th July 2018, the Centre hosted 70 students of INSPIRE Science camp (Innovation in Science Pursuit for Inspired Research (INSPIRE), an initiative of the DST launched by the Government of India to inspire intelligent and inquisitive school students who have passed class 10 with 95 % marks and above. The students were accompanied by their teachers and other supporting staff. The scientists of RCB gave presentations regarding research initiatives of RCB. The students visited various research laboratories where they were given live demonstrations by the scientists/ research fellows as part of hands–on–training sessions. Students also visited ATPC and Bio-incubator facilities of RCB.

RCB Foundation Day

In 2016, RCB was ordained with the status of an "Institution of National Importance" through an Act of the Parliament. It was brought into effect by a Gazette notification on 1st March, 2017. To commemorate this momentous occasion, 1st March has been adopted as the RCB Day. The second RCB Day was observed on 1st March 2019 and was celebrated with a blend of scientific and sports events. The day began with the final year PhD students presenting their research work in front of a panel of judges from various walks of research. The RCB Day oration was given by Prof. Balram Bhargava, DG ICMR & Secretary, DHR, on "Frugal Innovations for Healthcare". The Executive Director, RCB felicitated Prof. Balram who also presented the awards for best scientific presentations by the students and became a part of the RCB Day festivities.

Sports Day 2018

Sports at RCB is a month-long activity which includes outdoor and indoor sports competitions like badminton, table tennis, cricket, volley ball, chess, carrom etc., signifying the importance of physical and mental health being as important as intellectual health. The prize distribution for the winners of all the events was done on 1st March 2019 on the occasion of RCB Foundation day.

Memberships of Professional Bodies

Prof. Sudhanshu Vrati

1. Life Member, Indian Society for Cell Biology
2. Life Member, Society of Biological Chemists, India
3. Life Member, Association of Microbiologist of India
4. Life Member, Indian Immunology Society
5. Life Member, Indian Virology Society
6. Member, Scientific Advisory Committee, ILS, Bhubaneswar
7. Member, Scientific Advisory Committee, NIBMG, Kalyani
8. Member, Academic Council, South Asian University, New Delhi
9. Editorial Board Member, Therapeutic Advances in Vaccines (SAGE, UK)
10. Independent Director, BIBCOL, Bulandshahar

Prof. Prasenjit Guchhait

1. Scientific advisory committee member for reviewing new platelet research center of ICMR
2. Review committee member for scientific proposals of Ramalingaswami Fellows, DBT

Dr. Deepak T. Nair

1. Member, Guha Research Conference
2. Member, Indian Crystallography Association
3. Member, Society of Biological Chemists
4. Member, Indian Biophysical Society
5. Member, Board of Studies, Regional Centre for Biotechnology
6. Co-Opted Member of the Program Advisory Committee on Interdisciplinary Biological Sciences of the Science & Engineering Research Board

Dr. Arup Banerjee

1. Contributing member of the F1000 Faculty Infectious Diseases of the Nervous System Section in F1000Prime (https://f1000.com/prime)
2. Member of World Society for Virology (WSV)

Dr. Deepti Jain

1. Member, Indian Crystallography Association
2. Member, Electron Microscope Society of India
3. Member, Society of Biological Chemists

Dr. Manjula Kalia

1. Member, Editorial Board of Virus and Host, Frontiers in Cellular and Infection Microbiology

Dr. Sam Jacob Mathew

1. Member, Indian Society for Developmental Biology (InSDB)

Dr. Sivaram V.S. Mylavarapu

1. Life member, Indian Society for Cell Biology
2. Life member, Society of Biological Chemists, India
3. Reviewer for Scientific Reports

Dr. C.V. Srikanth

1. Member of American Society for Microbiology

Dr. Tushar Kanti Maiti

1. Executive Council Member of Proteomics Society of India
2. Editorial Board member of Scientific Reports, Nature Publishing Group

Dr. Vengadesan Krishnan

1. Member, Indian Crystallographic Association (ICA)
2. Member, Indian Biophysical Society (IBS)
3. Member, International Union of Crystallography (IUCr)

Dr. Ambadas B. Rode

1. Member, Indian Biophysical Society
2. Member, Society of Biological Chemists
3. Member, Indian JSPS (The Japan Society for the Promotion of Science) Alumni Association

Dr. Divya Chandran

1. Member, National Selection Committee for the 2019-2020 Fulbright-Nehru Doctoral Research Fellowships (STEM)
2. Review Editor, Frontiers in Plant Science: Plant Biotic Interactions, Frontiers Publishing Group

Dr. Nidhi Adlakha

1. Ad hoc reviewer, Biotechnology for biofuels
2. Ad hoc reviewer, Scientific Reports

Dr. Prashant M. Pawar

1. Reviewer of Molecules, International Journal of Molecular Sciences

Dr. Prem Singh Kaushal

1. Member, Indian Crystallography Association (ICA)
2. Member, Electron Microscope Society of India (EMSI)
3. Member of screening committee (Membrane Structural Biology), Department of Biotechnology

Dr. Rajender K. Motiani

1. Ad-hoc reviewer for following Journals: Journal of Biological Chemistry, Cellular Physiology and Biochemistry, Molecular Oncology, Onco-Targets and Therapy, Scientific Reports, Cancer Epidemiology, Cell Calcium, EBio Medicine

Dr. Ramu S. Vemanna

1. Project Proposal reviewer: Central Sericultural Germplasm Resources Centre, Central Silk Board, Bangalore
2. Reviewer for Journals: Frontiers in plant sciences, Applications in Plant Sciences, Current science, PNAS-India, Plant Physiology (India), Plos One

Dr. Saikat Bhattachajee

1. Member, Expert Evaluation Group, BioCARE proposal
2. Member, International Society-Molecular Plant Microbe Interactions (MPMI)

Dr. Geetanjali Chawla

1. Adhoc reviewer for Scientific Reports, MicroRNA and Parasites and Vectors
2. Associate Editor for Journal of Experimental Research on Human growth and aging (JERHA), MedWin Publishers

Dr. Pinky K. Sharma

1. Associate Editor- Journal of Experimental Neuroscience

Distinctions, Honours and Awards

Prof. Sudhanshu Vrati

1. Elected Fellow, National Academy of Sciences, India
2. Elected Fellow, Indian Academy of Science, Bangalore
3. Elected Member, Guha Research Conference

Dr. Sam Jacob Mathew

1. Cover image and featured article status for the manuscript "Myosin heavy chain mutations that cause Freeman-Sheldon syndrome lead to muscle structural and functional defects in Drosophila", Das et al, Developmental Biology, 2019.

Dr. C. V. Srikanth

1. Awarded Wellcome Trust-DBT IndiaAlliance Intermediate Fellowship

Dr. Prashant M. Pawar

1. DST-INSPIRE Faculty fellowship
2. DBT-Energy Bioscience Overseas Fellowship (Relinquished)

Dr. Ramu S. Vemanna

1. Ramanujan Fellowship awarded by SERB, India
2. Innovative Young Biotechnologist Award, DBT, India

Dr. Geetanjali Chawla

1. Wellcome Trust-DBT IndiaAlliance Intermediate Fellowship
2. Invited to serve as a member of the consultative group/s of researchers being formed by the Principal Scientific Advisor to Govt. of India to advise government on policy matters.

Dr. Pinky K. Sharma

1. Story of Science Image award (Wellcome Trust-DBT IndiaAlliance)
2. IndiaAlliance Fellow in Spotlight, Wellcome Trust-DBT IndiaAlliance, India
3. Wellcome Trust-DBT IndiaAlliance Intermediate Fellowship

Lectures, Visits and Outreach

Dr. Deepak T. Nair

1. Seminar titled "New answers to old questions regarding DNA synthesis by DNA polymerases" at IIT-Roorkee on March 22, 2019.
2. Seminar titled "Interaction, Replication and Evolution: A journey in Science" at the Careers in Science Workshop held at the Regional Centre for Biotechnology on February 1, 2019.
3. Seminar titled "Chemistry and Biology of a DNA polymerase" at NCR Bio-cluster meeting held at ICGEB, New Delhi on January 25, 2019.
4. Seminar titled "Pyrophosphate hydrolysis is an intrinsic and critical step of the DNA synthesis reaction catalysed by DNA polymerases" at the 5th DNA polymerase meeting held at Leiden, the Netherlands from September 23-26, 2018.
5. Local Coordinator of the European Synchrotron Access program of the Regional Centre for Biotechnology. The program provides access to high intensity synchrotron radiation to scientists from India and the Regional Centre for Biotechnology runs this program on behalf of the Department of Biotechnology.
6. Member of Expert Committee for selection & promotion of faculty for the discipline of Biosciences & Biomedical Engineering at IIT-Indore.
7. RCB Nominated Member of the Committee to review Zero Draft proposal for "Establishment of National Biological Data Centre in India".

Dr. Deepti Jain

1. Invited talk titled "Transcription Regulation of flagellar gene network in Pseudomonas aeruginosa" at BIOSPARKS-2019 held at Jawaharlal Nehru University, New Delhi from 15-16th March, 2019.
2. Nominated to attend the Bio-Care Conclave on the occasion of Women's Day held at NIPGR, New Delhi from 8th-9th March, 2019.
3. Invited talk titled "Inhibition of gene expression as a strategy to prevent biofilm formation in Pseudomonas aeruginosa" at the International Conference on Structure Assisted Discovery of Novel Therapeutics held at RCB from February 12-16, 2019.
4. Invited talk at the NII Alumni meet held at NII, New Delhi on September 30th, 2018.
5. Attended the Protein Society Meeting held at the International Centre for Genetic Engineering and Biotechnology August 25th, 2018.
6. Invited talk titled "Transcription Regulation of flagellar gene network in Pseudomonas aeruginosa" and chaired a session at the Transcription Assembly meeting at the Centre for DNA Fingerprinting and Diagnostics, Hyderabad, 25th-27th July, 2018.
7. Organizing member of the International Conference on Structure Assisted Development of Novel therapeutics, 12-16 February 2019.
8. Nominated to attend the India International Science Festival and the Women Scientist Entrepreneur Conclave organized by DBT held from October 5th-8th, 2018 at Lucknow.
9. Faculty In charge for the "Open Day" organized at RCB on 24th September, 2018 under the banner of India International Science Festival.

Dr. Vengadesan Krishnan

1. Invited talk on 'Structural basis of sortase-mediated pilus assembly via expose-ligate-seal mechanism' at Pondicherry University on December 20, 2018.
2. Visited Elettra-Sincrotrone Trieste, Italy during 18-21 February, 2019 under DST-Elettra partnership programme.

3. Attended 35th DeLCON Steering & Negotiation Committee Meeting for subscription of e-Resources held at ICGEB, New Delhi, on December 3, 2018.
4. Participated in the three day workshop on Federated Identity and Access Management (INFED - Off Campus Access to E-Resources using Shibboleth) held at INFLIBNET Centre, Gandhinagar during October 15 - 17, 2018.
5. Visited MX beamlines at European Synchrotron Radiation Facility (ESRF), France during September 26-29, 2018 under DBT-ESRF partnership programme.
6. Involved in organizing Regional Training Workshop on "Developing Effective and Inclusive Science, Technology and Innovation Policies" held at Regional Centre for Biotechnology, Faridabad, during March 6-8, 2019.
7. Co-organized "Advanced Workshop on Molecular Docking and Virtual Screening" at Regional Centre for Biotechnology, Faridabad on February 2, 2019.
8. Co-organized international conference on "Structure Assisted discovery of novel therapeutics" held at Regional Centre for Biotechnology (RCB), Faridabad during February 13-16, 2019.
9. Organized user awareness & training workshop on "How to use Science Direct for research" at Regional Centre for Biotechnology, Faridabad on November 30, 2018 with Elsevier.

Dr. Prem S. Kaushal

1. Invited talk titled 'The cryo- electron microscopy (cryo-EM) structure of the group II intron' at the 'EMSI International Conference XXXVII Annual Meeting' organized by EMSI, at Mayfair Convention Centre, Bhubaneswar during 16-17 July, 2018.

Prof. Prasenjit Guchhait

1. Invited talk titled "Platelet cytokine promote Dengue and Japanese encephalitis infection" at the International Conference of Emerging Research in Biosciences, Bilaspur, October 28-30, 2018.
2. Invited talk titled "Platelet factor promotes replication and rapid propagation of Dengue and Japanese encephalitis viruses during infections" at the 87th Annual Conference of the Society of Biological Chemists India, Manipal, November 24-27, 2018.

Dr. Tushar Kanti Maiti

1. Invited talk titled 'Proteostasis mechanism and its implication in Parkinson's Disease' at the NCR Biotech Cluster Seminar Series 'Neuroscience Research: Current Trends and Future Scope' organized by National Brain Research Centre, Manesar on 10th October 2018.
2. Invited talk titled 'Protein redox modification and its implication in neuro-degenerative diseases' at the '10th Annual Meeting of Proteomics Society, India (PSI) & International Conference on Proteomics for Cell Biology and Molecular Medicine' organized by National Centre for Cell Science, Pune during 12-14th December 2018.
3. Invited talk titled 'Clinical proteomics: From discovery to biomarker identification' at the 'RCB Mass Spectrometry & Proteomics Workshop' organized by Regional Centre for Biotechnology, Faridabad during 17-20th December 2018.
4. Invited talk titled 'DJ-1 inhibits primary and secondary nucleation through adhesive surface and remodels mature α-synuclein fibrils to toxic conformations' at the '7th International Conference on Molecular Signaling ICMS-2019' organized by Department of Zoology, Savitribai Phule Pune University and National Centre for Cell Science, Pune during 23-25th January 2019.
5. Invited talk titled 'Atomic Force Microscopy and its Applications in Biology' at the '2nd RCB Bioimaging School' organized by Regional Centre for Biotechnology during 25-30th March 2019.

Dr. Sam J. Mathew

1. Visited the Department of Human Genetics, University of Utah, USA, as part of the "work outside the host institution" scheme of the Wellcome Trust-DBT India Alliance Intermediate Fellowship awarded for the project, "The role of developmental myosin heavy chains in skeletal muscle development, regeneration, homeostasis and disease", from 22 December 2018 - 14 January 2019.
2. Organized the 2nd RCB Bioimaging School at RCB from March 25-30, 2019.
3. Invited talk "Model systems to study development, regeneration and disease", at CMS College, Kottayam, Kerala on March 19, 2019.

Dr. Geetanjali Chawla

1. Attended and presented poster showcasing the research and academic programs of Regional Centre for Biotechnology at the 4th India International Science Festival (IISF) organized by the Ministry of Science and Technology, Ministry of Earth Sciences in association with Vijnana Bharati at Indira Gandhi Pratishthan, Lucknow, October 5-8th, 2018.
2. Invited talk titled 'MicroRNA pathways in aging and dietary restriction' at the 'International Conference on Genome Architecture and Cell Fate Regulation' organized by University of Hyderabad, December 3-6th, 2018.

Dr. Pinky Kain

1. Invited talk on "Understanding taste and its modulation using Drosophila melanogaster asa model system" at the Buck Institute of Aging, Novato, USA, October 5, 2018.
2. Mentoring students at Freedom English Academy (FEA), India, since 2018.

Prof. Sudhanshu Vrati

1. Invited Valedictory lecture on 2nd November 2018 to the participants of the 2nd Refresher Course in Life Sciences & Biotechnology and the 111th Orientation Programme being organized by UGC-HRDC, Jawaharlal Nehru University, New Delhi.
2. Invited Plenary Lecture on "Mosquito-borne viral infections in India: Development of novel vaccine candidates" at the 14th international conference on "Vectors and vector-borne diseases" on 10th January 2019 at Bhubaneswar.
3. Invited talk on "Development of a rotavirus vaccine: The India Story" on 15th March 2019 in the faculty development program (FDP) on "Agriculture, Health and Society" organized by Hansraj College, New Delhi.
4. Chaired a session at the Symposium on "Emerging Trends in Biological Sciences for Societal Development" held during 18th – 19th March, 2019 ILS, Bhubaneswar.
5. Visited USA as part of the DBT delegation to India-USA Biosecurity Dialogue, Washington, DC during 6-7 September, 2018 and attended Young Investigators meeting, University of Chicago on 9 September, 2018.
6. Visited Grenoble, France to attend the 30th Anniversary of the European Synchrotron Radiation Facility 25-28 November 2018.
7. Visited AIST, Japan to participate in the 6th AIST International Imaging Workshop during 20-23 January 2019 and delivered an invited talk on "Development of novel vaccine candidates and antivirals against Chikungunya virus".

Dr. Chittur V. Srikanth

1. Invited seminar titled 'Tracking the unanticipated routes of Salmonella Typhimurium infection' at the 'NCR Cluster meeting held in NII' on 23rd May 2018.
2. Invited lecture titled 'Understanding the mechanisms of Salmonella Typhimurium infections' held at the ' IMTECH' Chandigarh in international conference on Microbial pathogenesis and new frontiers during 23rd-25th March 2019.

3. Invited lecture titled 'The unexpected joys of traveling the tricky terrains in biotechnology research' held at the 'Maitreyi College, Delhi University' in national conference Trends in Life Sciences and Biotechnology, held during 19th-20th February 2019.
4. Seminar at the International Symposium on Infectious Disease Biology held at RCB and Jamia Hamdard during 12-14th November 2018.
5. Organizing Secretary of International Symposium on Infectious Disease Biology held at RCB, Faridabad and Jamia Hamdard, Delhi between 12-14th November 2018.

Dr. Manjula Kalia

1. Invited Speaker for 6th Molecular Virology Meeting at School of Bioscience, IIT Kharagpur, 28 February- 2 March 2019. "Japanese encephalitis virus deploys lineage-specific entry portals for infection in mammalian cells".
2. Visit to the laboratory of Dr. Sebastien Lacroix-Desmazes, INSERM, Paris, France in capacity of joint CEFIPRA project "Host-virus interactions and antibody therapy for Japanese encephalitis" 9-16 December 2018.
3. Co-organizer and Invited speaker: "International Symposium on Infectious Diseases" 12-14 November 2018, Organized by Regional Centre for Biotechnology, Faridabad & Jamia Hamdard, New Delhi. "Interactions between host Autophagy machinery and Japanese encephalitis virus: Implications for Pathogenesis".
4. Co-organizer: Immunocon 2018 "Immunotherapy and Advances in Immunology" 1-3 November 2018, Translational Health Science & Technology Institute, Faridabad, India.
5. Co-organizer 2nd RCB Bioimaging School, RCB, 25-30 March 2019.

Dr. Arup Banerjee

1. Invited talk titled "Role of microRNAs in the pathogenesis of Japanese Encephalitis virus infection" at the 6th Molecular Virology Meeting organized by IIT Kharagpur, West Bengal, from Feb 28-March 2, 2019.
2. Invited talk titled "Understanding viral pathogenesis using System Biology approach" at THSTI-IVI Joint Symposium organized by the International Vaccine Institute, Seoul, the Republic of Korea from November 22, 2018.
3. Invited talk titled "Transcriptomic insights into Dengue pathogenesis" at the International Symposium on Infectious Diseases organized by Regional Centre for Biotechnology, Faridabad and Jamia Hamdard from 12th-14th November 2018.

Dr. Avinash Bajaj

1. Invited talk at "Towards Simulating Cell Membranes: Closer to Reality" TSCM2019 held on February 6, 2019 at Heidelberg Institute of Theoretical Sciences, Heidelberg, Germany.
2. Invited talk at symposium entitled "From Genes to Network: Recent trends in Cell Signaling" held during December 14-15, 2018 at Amity University, Haryana.
3. Invited talk at DST supported special workshop in Nano Science and Technology for Schedule Tribes students/ researchers/ teachers held during December 3-8, 2018 at INST, Mohali.
4. Invited talk at Fall Meeting of the Korean Society of Biomaterials held during October 18-19, 2018 at Pangyo, Republic of Korea.
5. Invited talk at International Conference on Environmental Health Sciences held during October 14-17, 2018 at Yeosu, Republic of Korea.

Dr. Sivaram V. S. Mylavarapu

1. Invited talk titled "Intercellular Transport through Tunneling Nanotubes: Mechanisms of Formation and Function" delivered at the All India Institute of Medical Sciences, New Delhi on March 15, 2019.
2. Invited talk titled 'Mechanisms of Tunneling Nanotube Formation" delivered at the 11th annual conference BioEpoch 2019 of the School of Biotechnology, Jawaharlal Nehru University, New Delhi on March 14, 2019.

Dr. Saikat Bhattacharjee

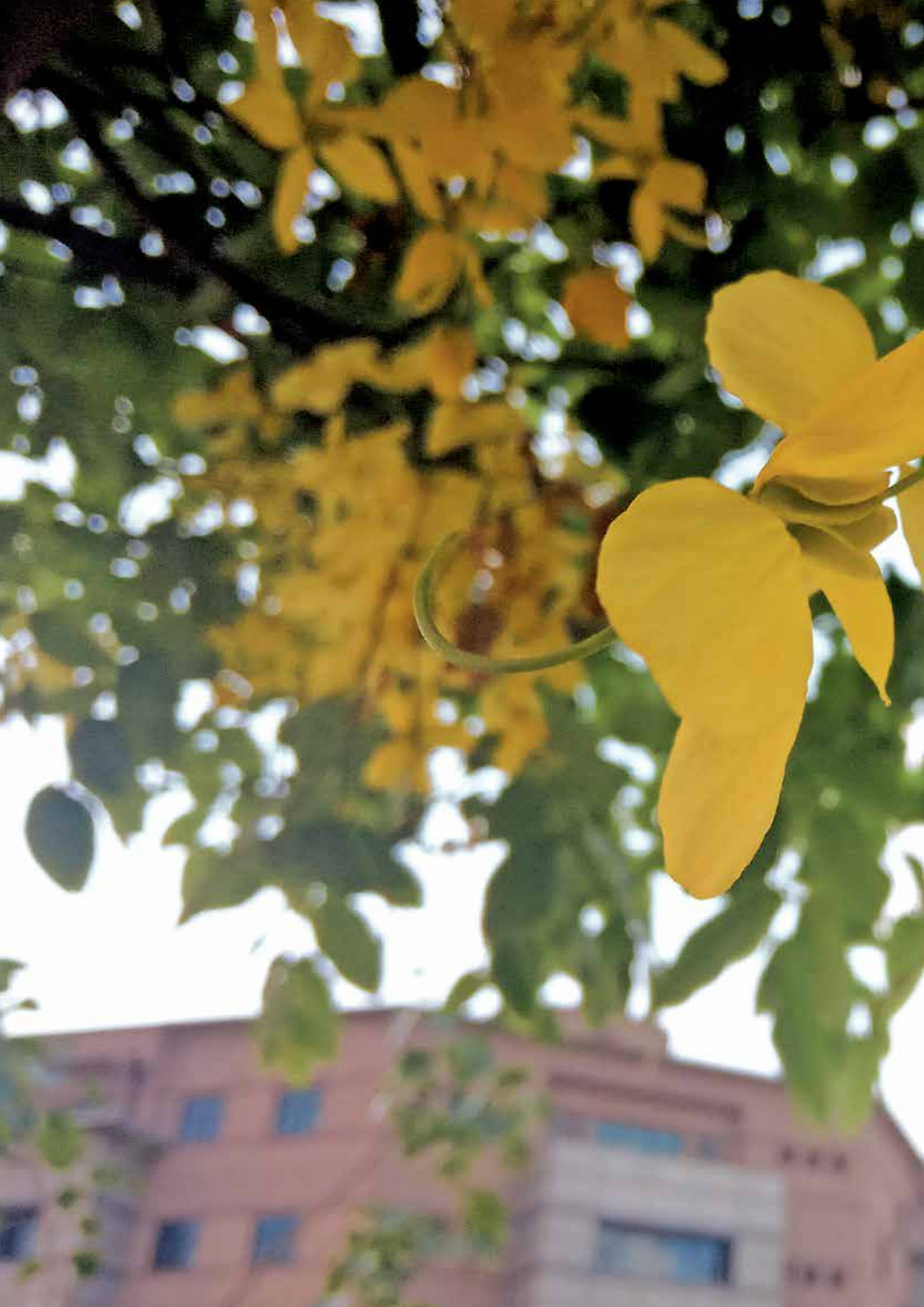
1. Invited Seminar presentation titled 'Defense moderation by Inositol phosphates: Balancing the imbalance' at Molecular Intricacies of Plant-Associated Microorganisms (MIPAM) Meeting, held at NIPGR, New Delhi (Feb 1 - 3, 2019).

Dr. Divya Chandran

1. Attended and co-organized the 2nd RCB Bioimaging School, RCB, March 25-30, 2019.
2. Attended the DBT-BioCARe conclave: Women Scientists Achieving Great Heights, NIPGR, 8-9 March, 2019.
3. Invited lecture on "Effectoromics-based identification of novel pea powdery mildew pathogenicity determinants" at the Molecular intricacies of Plant-Microbe Interactions conference, NIPGR, February 1-3, 2019.
4. Showcased RCB's research, training and education-related activities at the Mega Science, Technology & Industry Expo, India International Science Festival (IISF), Lucknow, October 5-7, 2018.

Dr. Ambadas B. Rode

1. Invited talk entitled "Targeting and Tuning Conformational Equilibria in Non-Coding RNAs: A Promising Approach for Biomedical Applications at 6th World Congress on Nano-medical Sciences–ISNSCON-2018" during 7-10th January 2019, Vigyan Bhawan, New Delhi.
2. Selected as one of the few participants to attend and present a poster entitled "tRNAs modulates oncogenes expression by shifting the hairpin-G-quadruplex conformational equilibrium" in RNA at 11th Young Investigators Meeting during 6-10th March 2019, Guwahati.



EXTRAMURAL ACTIVITIES & NETWORKING

ESRF Access Program

Regional Centre for Biotechnology (RCB) and European Synchrotron Radiation Facility (ESRF) have entered into an agreement concerning the medium-term use of synchrotron for non-propriety research for the benefit of the Indian scientific community as a whole, and notably the structural biology research groups. The program provides access to Indian investigators to high intensity macromolecular crystallography, small angle X-ray scattering experimental stations and the Cryo-Electron Microscopy Facility located in ESRF.

Since the start of this arrangement, more than 75 researchers from 25 different institutes from all over India have obtained X-ray diffraction, small angle X-ray scattering and Electron Microscopy data for different macromolecules and macromolecular assemblies. At present, the data collected at ESRF has resulted in more than 50 publications. Researchers from the following research establishments have visited ESRF: Institute of Microbial Technology (Chandigarh), Jawaharlal Nehru University (New Delhi), Institute of Life Sciences (Bhubaneswar), Institute of Stem Cell & Regenerative Medicine (Bangalore), All India Institute of Medical Sciences (New Delhi), Indian Institute of Science (Bangalore), Poornaprajna Institute of Scientific Research (Bangalore), Regional Centre for Biotechnology (Faridabad), Indian Institute of Science Education & Research-Pune, Indian Institute of Technology-Delhi, Indian Institute of Technology- Roorkee, National Centre for Cell Sciences (Pune), Indian Institute of Science Education & Research-Thiruvananthapuram, Central Drug Research Institute (Lucknow), Saha Institute of Nuclear Physics (Kolkata), National Institute of Mental Health & Neurosciences (Bangalore), CSIR-Institute of Genomics & Integrative Biology (New Delhi), CSIR-Central Leather Research Institute (Chennai), University of Madras (Chennai), International Centre for Genetic Engineering and Biotechnology (New Delhi), Indian Institute of Technology-Bombay, National Institute of Science Education & Research (Bhubaneswar), Translational Health Sciences & Technology Institute (Faridabad), National Chemical Laboratory (Pune), and Indian Institute of Technology-Kharagpur. The access to ESRF has helped Indian scientists to obtain data that will aid formulation of innovative solutions to problems faced by the nation in public health, agriculture and environmental issues.

Academic Programs with GlaxoSmithKline

RCB has started interdisciplinary doctoral programs in the area of Biostatistics and Bioinformatics through collaboration with the global pharmaceutical giant GlaxoSmithKline (GSK). The program is subject to RCB statutes, ordinances and regulations. Since RCB's current strength lies mostly in the area of Life Sciences and Biotech Sciences, these interdisciplinary programs are being conducted in partnership with other institutions by creating a virtual faculty pool. The MOU for the program was signed in the year 2018. Two students have registered so far for the program. The students are being paid an attractive scholarship/ fellowship of Rs. 45,000/- during their tenure as JRF for two years followed by Rs. 50,000/- for the next three years.

Association with AIST, Japan

The Department of Biotechnology (DBT), through the Regional Centre for Biotechnology (RCB), and the National Institute of Advanced Industrial Science & Technology (AIST), through its Biomedical Research Institute (BRI), Japan had entered into a partnership for capacity building initiatives in bio-imaging and biotechnology in the year 2014. This initiative facilitates enhancement of career opportunities for scientists and researchers working in biomedical, clinical, and related areas of biotechnology, complementing the existing bilateral research cooperation between the Govt. of India and the Govt. of Japan.

A DBT-AIST joint lab (DAILAB) for advanced research training in bio-imaging and biotechnology, including high end in vivo and in vitro imaging, has been established at RCB. The DAILAB facilitates joint research collaborations engaging Indian and Japanese scientists and support selected Indian researchers for training in specialized areas of bio-imaging and biotechnology, both in Japan and in India. The DAILAB at RCB has been set up for training and research in advanced imaging, with in vivo imaging, high end confocal, fluorescent, and bright field imaging, as well as cell culture capabilities. Workshops with a focus on imaging related technologies and symposia have been conducted as part of the DAILAB in AIST Japan and at RCB, bringing together experts and students for theoretical and hands on imaging sessions, taking advantage of the facilities and expertise available as part of this initiative.

This collaboration provides an opportunity for both the institutions in capacity building, training and research collaborations, and will benefit young scientists not only in India and Japan but also from other UNESCO member countries in the Asia-Pacific and SAARC regions. Indeed, through the current initiatives, RCB, an institution engaged in broad-based multidisciplinary training, education and research is poised for broadening its horizons and will facilitate bridging science and knowledge dissemination for the betterment of mankind.

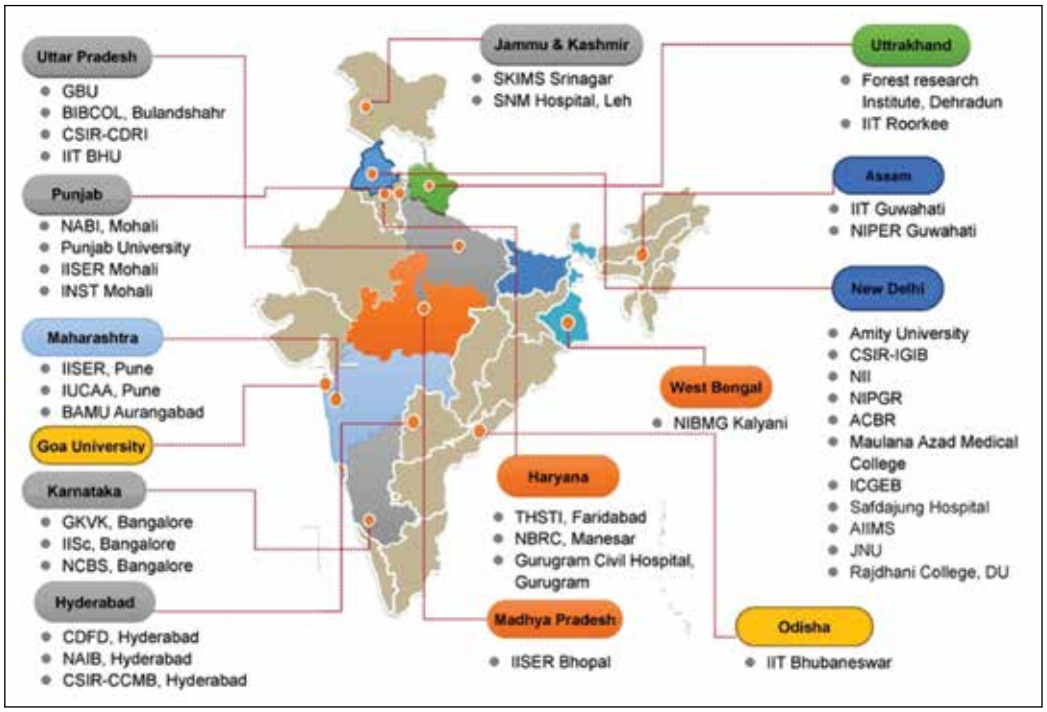
Collaborators of Faculty Members

Besides the structured collaborations as described above, RCB scientists collaborate with a number of scientists across the various institutions. These are listed below.

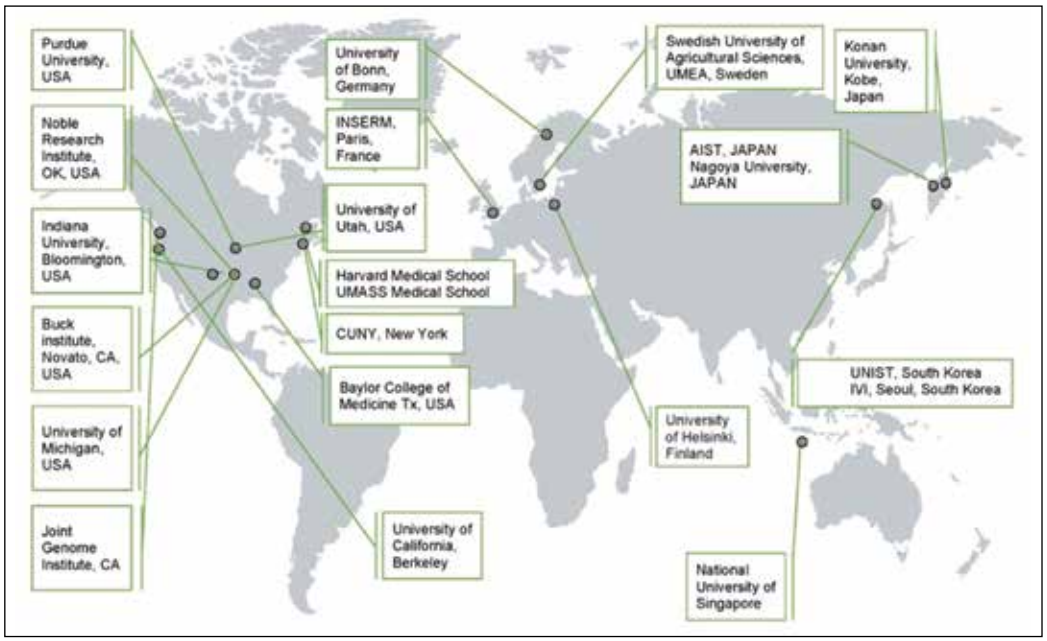
	RCB Principal Invistigator	Collaborators
1	Prof. Sudhanshu Vrati	Dr. Renu Wadhawa (AIST, Japan) Dr. Sanjay Batra (CDRI, Lucknow) Dr. USN Murthy (NIPER, Guwahati)
2	Dr. Deepak T. Nair	Prof. Sudhanshu Vrati & Dr. Deepti Jain (RCB) Prof. D. N Rao (Department of Biochemistry, IISc, Banglore) Dr. Dinakar M. Salunke (ICGEB, New Delhi) Prof. Ajit Kembhavi (IUCAA, Pune)
3	Dr. Avinash Bajaj	Dr. Sagar Sengupta and Dr. Arnab Mukhopadhyay (NII, New Delhi) Dr. Ujjaini Dasgupta (Amity University, Manesar) Dr. Aasheesh Srivastava (IISER Bhopal) Dr. Lipi Thukral (Institute of Genomics and Integrative Biology, New Delhi) Prof. Ja-Hyoung Ryu (UNIST, South Korea)

4	Dr. Chittur Srikanth	Prof. Vineet Ahuja (AIIMS New Delhi), Dr Amit Awasthi (THSTI, Faridabad), Prof. Linda Kenny (National University of Singapore), Prof. Bobby Cherayil (Harvard Medical School, USA) and Dr. Ana Maldonado Contreas (Umass Medical School, USA) Dr. Nitin Chaudhary (IIT Guwahati), Dr Rekha Puria (GBU, UP), Dr Richa Arya (ACBR, New Delhi) and Dr. Girish Ratnaparkhi (IISER, Pune)
5	Dr. Vengadesan Krishnan	Prof. Airi Palva (University of Helsinki, Finland)
6	Dr. Tushar Kanti Maiti	Dr. Shinjini Bhatnagar (THSTI, Faridabad) Dr. Dinakar M Salunke (ICGEB, New Delhi) Professor Partha P Majumder and Dr. Arindam Maitra (NIBMG), Kalyani) GARBH-Ini Cohort Study Site (Gurugram Civil Hospital, Gurugram) GARBH-Ini Cohort Study Site (Safdarjung Hospital, New Delhi) Dr. Siddarth Ramji (Maulana Azad Medical College, New Delhi)
7	Dr. Deepti Jain	Dr. Gopaljee Jha (NIPGR, New Delhi) Dr. Divya Chandran (RCB), Prof. Sudhanshu Vrati (RCB), Prof. Deepak Nair (RCB) and Dr. Sanjay Batra (CDRI, Lucknow)
8	Dr. Manjula Kalia	Dr. Sebastien Lacroix-Desmazes (INSERM, France) and Dr. Nimesh Gupta (NII, New Delhi)
9	Dr. Arup Banerjee	Dr. Julia Lynch (IVI, South Korea) Mr. Chandra B Benjwal (BIBCOL, Bulandshahar) Dr. Shaheen Akhtar Ansari (BIBCOL, Bulandshahar) Dr. Anirban Basu (NBRC, Manesar) and Dr. Sujata Mohanty (AIIMS, New Delhi)
10	Dr. Sam Mathew	Prof. Gabrielle Kardon (University of Utah, USA) Dr. Dimple Notani (NCBS, Bangalore)
11	Dr. Divya Chandran	Dr. Mary Wildermuth and Dr. Shauna Somerville (University of California Berkeley and Joint Genome Institute, California) Dr. Deepti Jain (RCB) Dr. Atul Goel (CDRI, Lucknow) Dr. Yashwant Kumar (THSTI, Faridabad)
12	Dr. Saikat Bhattacharjee	Prof. Gabriel Schaaf (University of Bonn, Germany) Dr. K. Vengadesan (RCB)
13	Dr. Nidhi Adlakha	Prof. Rakesh Bhatnagar, Dr. Charanpreet Kaur (JNU, New Delhi) Dr. Kinshuk Raj Srivastava (RCB)
14	Dr. Ambadas B. Rode	Prof. Sheshnath Bhosale (Goa University) Dr. Pradip Salunke (Panjab University, Chandigarh) Dr. Gyan Prasad Modi (IIT BHU, Varanasi) Dr. Bhabatosh Das (THSTI, Faridabad) Dr.Sunil Tekale (Dr. Babasaheb Ambedkar Marathwada University, Aurangabad) Dr. NaoKi Sugimoto (FIBER, Konan University, Japan)
15	Dr. Rajender K. Motiani	Dr. Rajesh S Gokhale (NII, New Delhi) Dr. Sridhar Sivasubbu and Dr. Vivek Natarajan (IGIB, New Delhi)
16	Dr. Ramu S. Vemanna	Prof. Udayakumar M, Dr. Sheshshayee MS, Dr. Prasanna Kumar M (University Agricultural Sciences, Bangalore) Dr. Patrick Zao (Noble Research Institute, USA) Dr. Maneesh Bandari (Forest Research Institute, Dehradun) Dr. Kiran Mysore, Noble Research Institute, OK, US
17	Dr. Kinshuk Raj Srivastava	Prof. David Sherman and Prof. Brandon Rotolo (University of Michigan, USA) Dr. Pawan Rai (University of Delhi, New Delhi) and Dr. Krishna Kishore Inampudi (AIIMS, New Delhi) Dr. Nidhi Adhlakha and Dr. Prashant Pawar (RCB)
18	Dr. Prashant M. Pawar	Dr. Clint Chappel (Purdue University, USA) Dr. Ewa J Mellerowicz (Umea Plant Science Centre, Sweden)
19	Dr. Geetanjali Chawla	Dr. Nicholas S. Sokol and Dr. Jason Tennessen, Prof. Pankaj Kapahi (Buck Institute, USA) Dr. Monika Garg (NABI, Mohali)
20	Dr. Sivaram Mylavarapu	Dr. Mahak Sharma (IISER, Mohali) Dr. Megha Kumar (CSIR-CCMB ,Hyderabad) Dr. Jayanta Bhattacharya (THSTI-IAVI, Faridabad) Dr. Chetana Sachidanandan (CSIR-IGIB, New Delhi) Dr. Anjana Saxena (CUNY, New York), Dr. Subba Rao Gangisetty (IISc, Bengaluru)

National Collaborations



International Collaborations



Extramural Funding

Investigator	Project	Funding Agency	Grant Amount (Rs.)	Duration
Dr. Deepak T. Nair	The role of DNA Polymerase IV in ROS mediated lethality: Structure and Mechanism	Department of Biotechnology	15 lakh	2016-2020
Dr. Deepak T. Nair	Mechanism of mutagenic & translesion DNA synthesis by a mycobacterial Y-family DNA polymerase	Science & Engineering Research Board	59.34 lakh	2017-2020
Dr. Deepak T. Nair	"Does variation occur in the dinB gene during stress adaptation?"	Department of Biotechnology	58.86 lakh	2018-2021
Dr. Deepak T. Nair	Molecular Interactions critical for DNA Mismatch Repair	Science & Engineering Research Board	24.91 lakh	2018-2021
Dr. Deepak T. Nair	Access to Macromolecular Crystallography Beamlines of ESRF, France	Department of Biotechnology	1749.41 lakh	2017-2020
Dr. Deepti Jain	Insights into the signal transduction mechanism of GraXSR regulon required for antibiotic resistance in Staphyloccocus aureu	Science & Engineering Research Board	43.8 lakh	2019-2020
Dr. Deepti Jain	Structure and mechanism of FleQ, master regulator of transcription of flagellar and biofilm genes in Pseudomonas aeruginosa	Department of Biotechnology	68.0 Lakh	2018-2021
Dr. Deepti Jain	Establishing the mechanism of action of Bg_9562, the broad spectrum antifungal protein	NCR Biotech Science Cluster	10 Lakh	2019-2020
Dr. Vengadesan Krishnan	Structural studies on pilus proteins from Lactobacillus ruminis	Department of Biotechnology	44.5 lakh	2018-2020
Dr. Vengadesan Krishnan	Investigating Functional Role of Polyketide Modifying Enzymes in Mycobacterial Biology	Science & Engineering Research Board	8.1 lakh	2019-2022
Dr. Prem S. Kaushal	Understanding the translation strategies adopted by Mycobacterium tuberculosis during dormancy	Science & Engineering Research Board	46.33 lakh	2019-2022
Dr. Prasenjit Guchhait	Understanding the distinct developmental and functional properties of the neonatal immune system and their clinical consequences in the neonatal period	Department of Biotechnology	183.1 lakh	2014-2019
Dr. Prasenjit Guchhait	Mechanism of rapid propagation of dengue virus during infection	Department of Biotechnology	100.1 lakhs	2018-2021
Dr. Prasenjit Guchhait	Role of platelet activation in the development of systemic inflammations in patients with type-2 diabetes	Department of Biotechnology	761.1 lakh	2019-2022
Dr. Prasenjit Guchhait	Consultancy	RythRx Therapeutics, LLC	USD 10000	2017-2019
Dr. Tushar Kanti Maiti	Inter-institutional programme for Maternal, Neonatal and Infant Sciences: a translational approach to studying PTB	Department of Biotechnology	6.13 Cr	2014-2019
Dr. Tushar Kanti Maiti	A "bench to bedside" model for clinical and translational science between academic research institutes and hospitals focused on fetal growth restriction and preterm birth	Department of Biotechnology	23.12 Lakh	2017-2021
Dr. Sam J. Mathew	The role of developmental myosin heavy chains in skeletal muscle development, regeneration, homeostasis and disease	Wellcome Trust-DBT IndiaAlliance Intermediate Fellowship	352 lakh	2014-2020

Dr. Sam Mathew	The Role of MET-CBL signaling in Rhabdomyosarcoma	Department of Biotechnology	24 lakh	2015-2019
Dr. Masum Saini (Fellowship supervisor Dr. Sam J. Mathew)	Role of Sprouty2 as a modulator of Met signaling during mammalian skeletal muscle development, regeneration and disease	Wellcome Trust-DBT IndiaAlliance Early Career Fellowship	167 lakh	2018-2022
Dr. Sam Mathew	The Role of Transducin-like Enhancer of Split 3 (TLE3) in Regulating Myogenesis	Science & Engineering Research Board	64 lakh	2017-2020
Dr. Geetanjali Chawla	Post-transcriptional regulators of aging and dietary restriction	Wellcome Trust-DBT IndiaAlliance Intermediate Fellowship	359 lakh	2018-2022
Dr. Pinky Kain	Understanding taste and its modulation using Drosophila as a model system	Wellcome Trust-DBT IndiaAlliance Intermediate Fellowship	3.5 Crores	2016-2021
Dr. Sudhanshu Vrati	DBT-AIST International Center for Translational and Environmental Research (DAICENTER)	Department of Biotechnology	144.90 lakhs	2018-2021
Dr. C. V. Srikanth	Investigations into structural organization and curvature-dependent membrane binding of alpha-synuclein	Department of Biotechnology	17.2 lakh	2017-2020
Dr. C. V. Srikanth	Studies on epigenetic alterations during Salmonella infection and their long-term implications	Science & Engineering Research Board	48 lakh	2017-2020
Dr. Manjula Kalia	Host-Virus Interactions and Antibody Therapy for Japanese Encephalitis	Indo-French Centre for the Promotion of Advanced Research	68.14 lakhs	2015-2019
Dr. Manjula Kalia	Interactions between Japanese Encephalitis virus and host autophagy pathway: Implications for pathogenesis	Science & Engineering Research Board	58.40 lakh	2016-2019
Dr. Manjula Kalia	Pharmacological Modulation of Autophagy as a Potential Therapeutic for Japanese encephalitis	Department of Biotechnology	81.20 lakh	2019-2022
Dr. Arup Banerjee	Understanding the therapeutic role of adult stem cell-derived exosome in combating virus-induced neurodegenerative disease	Department of Biotechnology	29.418 lakh	2018-2021
Dr. Arup Banerjee	Investigating the molecular modulatorsof microglial activation and their effect on JEV pathogenesis	Science & Engineering Research Board	41.12 lakh	2018-2021
Dr. Avinash Bajaj	Engineering of membrane targeting molecular probes for diagnosis of mycobacterial infections	Science & Engineering Research Board	50.446 lakh	2019-2022
Dr. Avinash Bajaj	Combating topical and medical device related multidrug resistant fungal infection using molecularly engineered antifungal hydrogels	Department of Biotechnology	92.39 lakh	2019-2022
Dr. Avinash Bajaj	Spatiotemporal targeting of multiple pathway using engineered polymer gatekeepers in porous nanomaterials for cancer combination therapy	Science & Engineering Research Board	60.768 lakh	2018-2021
Dr. Avinash Bajaj	Temporal targeting of siRNA therapeutics to the gastrointestinal tract (GIT) using chimeric nanogels	Department of Biotechnology	84.308 lakh	2017-2020
Dr. Avinash Bajaj	Development of biocompatible surfaces for ESKAPE pathogens	Department of Biotechnology	41.268 lakh	2017-2020

Dr. Avinash Bajaj	Molecular engineering of low molecular weight injectable hydrogels with sustained drug release for cancer therapy	Department of Biotechnology	42.6 lakh	2016-2019
Dr. Avinash Bajaj	Engineering of self-assembled lipidated nanoparticles for cancer combination therapy	Science & Engineering Research Board	47.6652 lakh	2016-2019
Dr. Avinash Bajaj	Investigating the role of BLM helicase as a global tumor suppressor: understanding its regulatory loops and using the knowledge for therapeutic and clinical applications in cancer biology	Department of Biotechnology	29.436 lakh	2015-2020
Dr. Sivaram V S Mylavarapu	Prolyl Isomerization of Dynein Light Intermediate Chains as a Regulatory Driver for Mitosis	Science & Engineering Research Board	22 lakhs	2018-2021
Dr. Pushpa Kumari (fellowship supervisor Dr. Sivaram V S Mylavarapu)	Understanding the Role of Exocyst Complex in Cell Division and Development in Caenorhabditis elegans	Wellcome Trust-DBT IndiaAlliance Early Career Fellowship	144.93 lakh	2014-2020
Dr. Saikat Bhattacharjee	Investing a key regulatory defense assembly and pathogen effectorinduced perturbations duing innate immune signaling of plants	Department of Biotechnology	92.016 lakh	2018-2020
Dr. Saikat Bhattacharjee	The identification and characterization of defense signaling pathways primed by sea6energy products	Sea6energy PVT. LTD, Bengaluru	7.2 lakh	2018-2019
Dr. Divya Chandran	Deriving gene regulatory networks mediating legume host-powdery mildew pathogen cross-talk during compatible and incompatible interactions	Department of Biotechnology	43.16 lakh	2016-2019
Dr. Divya Chandran	Identification of novel regulators and nodes of response mediating powdery mildew sporulation on legumes	Science & Engineering Research Board	39.11 lakh	2017-2020
Dr. Naini Burman (fellowship supervisor Dr. Divya Chandran)	Functional characterization of HY5 homolog in rice	Department of Science and Technology	7 lakh	2018-2023
Dr. Ramu S Vemanna	Identification and functional characterization of genes involved in protein translation, degradation and develop inhibitors to understand bacterial pathogenicity in rice	Science & Engineering Research Board	89 lakh	2017-2022
Dr. Ramu S Vemanna	Disruption of genome integrity to create genetic variability by editing (using CRISPR-CAS9) the genes associated with DNA mismatch repair and characterization of their relevance in crop improvement	Department of Biotechnology	70.168 lakh	2017-2020
Dr. Ambadas B. Rode	Rationally targeting and tuning riboswitch mediated gene regulation for therapeutic and biotechnological applications	Department of Biotechnology	88 lakh	2018-2023
Dr. Nidhi Adlakha	Identification and characterization of a novel inducer system for efficient decomposition of plant biomass	Department of Science and Technology	35 lakh	2015-2020

RESEARCH & INNOVATION INFRASTRUCTURE

BSC BioNEST Bio-Incubator

The BSC BioNEST Bio-Incubator (BBB) has been established to foster innovation, research & entrepreneurial activities in biotechnology related areas. The mission of BBB is to stimulate the establishment & growth of biotechnology start-up companies. By fulfilling the mission, BBB contributes towards enhancing the economic health of the region. The Bio-Incubator at the NCR Biotech Science Cluster (BSC) is funded by BIRAC under the BioNEST (Bioincubators Nurturing Entrepreneurship for Scaling Technologies) scheme. The BBB is managed and operated by Regional Centre for Biotechnology. With the objective of fostering Indian biotech innovation and entrepreneurship, it aims to help start-ups, nurture their innovative ideas and develop globally competitive products and technologies. It helps emerging companies gain access to mentors, training program, shared space, professional assistance, capital and other services that will move them on to the fast track to success. BBB is also facilitating networking sessions on company formation, IP consultancy, potential source of capital in addition to providing access to domain experts in the field of science and technology. The BBB is primarily focused on life sciences, biopharma, bio-med-tech and its allied areas for incubation.

The 35,000-square feet covered area at BBB consists of labs of different denominations for incubation. It offers shared lab benches as well as independent cubicles to incubates to choose as per their requirement. Two common instrument labs (Central Instrumentation Facility) have been set up that house basic to high-end equipment to support the start-ups in addition to instrument workshop. The incubator also provides adequate space for conducting meetings, video conferencing, and seminars. Incubatees have access to the Advance Technology Platform Centre (ATPC), which houses the state-of-the-art instrumentation facility and pool of expert scientists. Selection process for incubation has been kept simple with affordable facility usage charges.

The facility was opened in November 2018 & after its grand start has attracted many entrepreneurs. Currently, BBB is incubating 2 companies which are working on different domains in Healthcare sector. BBB provides an ideal entrepreneurial ecosystem with latest infrastructure, pool of mentors and supportive staff. The BBB facility is operated & managed by seasoned and skilled professionals with rich corporate experience. The team act as a support system for all start up at various stages of their development ranging from IP support, strategic business development, coaching & mentoring the young start up for growth opportunities, fund raising & collaboration opportunity. The BBB is running several Start-up strategic programme to boost entrepreneurship in the National Capital Region. The main programme include Talks on entrepreneurship under program IDEA (Ignite & Develop Entrepreneurial Aptitude). BBB after its successful operational start has conducted many events / workshop and aims to do so in near future to nurture entrepreneurial spirit. Provided below is the list of start-ups operating from the BBB.

The BBB benefits a wide range of stakeholders in BSC and beyond. Key stakeholders

S. No.	Name of the Incubatee	Individual or a Company	Area of Work
1	NextGen InVitro Diagnostics (P) Ltd.	Company	Diagnostic
2	QbD Biosciences Pvt Ltd.	Company	Life Science

include incubatee companies/entrepreneurs and their employees, the community at large, and educational institutions. Companies/individuals that incubate at BBB enjoy this unique infrastructure and technical support as they have an easy start in having affordable office space, access to shared equipment, meeting facilities and on-site business and technical assistance. BBB invites all young start-ups & innovators to come forward and experience the unique start up ecosystem of the facility and convert their dream into reality.

Technology Advancement Unit

The Indo-Swiss Collaboration in Biotechnology (ISCB) is a bilateral research and development programme, jointly funded and steered by the Swiss Agency for Development & Cooperation (SDC) and Department of Biotechnology (DBT) which was initiated as New ISCB programme in October 1997. The mandate of ISCB is to develop products and biotechnological processes which can be used or applied for the benefit of the rural communities in India and to build capacities of Indian Institutes and promote partnerships between Institutes as well as private companies of the two countries. SDC has established Project Monitoring Unit (PMU) in Switzerland to facilitate and monitor the projects carried out under ISCB. SDC has taken the decision to end their support to ISCB & phase out the partnership to foster capacity building in a final 2-year phase (Phase V (16) until October 2019. DBT has also sanctioned the project "Establishment of Technology Advancement Unit (TAU)" on 9.9.2014 for 5 years at a total cost of Rs. 219.76 Lakhs (revised to Rs. 219.88 Lakhs in January 2017) at the Regional Centre for Biotechnology (RCB) as an adjunct to the Project Management Unit (PMU) of SDC with the following objectives:

1) Create a conducive environment for product development and technology advancement & transfer as facilitator, advisor, and supporter for the project partners of the ISCB programme through the facilitation of access to new skills and expertise.
2) Implementation of all activities of ISCB in extension and adoption by farmers.
3) Coordination of networking among stakeholder groups along the whole value chain.
4) Lead in monitoring at the project/network level along the whole value chain.
5) Build-up public awareness of ISCB activities and in general life sciences and biotechnology.
6) Coordination and organization of capacity building of ISCB partners.
7) Provide support service to DBT in dealing with ISCB project funds.
8) Provide support to the PMU of SDC in planning, reporting, and monitoring of ISCB.

Technologies transferred

Following technologies were developed under ISCB phase III and transferred to different private and public partners:

1. Chickpeas resistant against pest insect pod borer using (Cry1Ac) developed by AAU (Jorhat)-Indian partner & University of Basel- Swiss partner. It was transferred to private partner, Sungro (Delhi) & Public partners Punjab Agricultural University (Ludhiana) and Indian Institute of Pulse Research (Kanpur) under Non Exclusive License Agreement and Material Transfer Agreement.
2. Chickpeas resistant against pest insect pod borer using (Cry2Aa) developed by AAU (Jorhat)-Indian partner & University of Basel- Swiss partner. It was transferred to private partner,Sungro (Delhi) & Public partner, Punjab Agricultural University (Ludhiana) under Non Exclusive License Agreement and Material Transfer Agreement.
3. Chickpeas resistant against pest insect aphid using (ASAL) developed by Bose Institute -

Indian partner and University of Basel- Swiss partner. It was transferred to private Indian partners Sungro (Delhi) and Bioseed (Hyderabad) under Non Exclusive License agreement.

4. Biofertilizer technology to improve yield and quality of wheat and rice developed by IIT (Delhi); GB PUAT (Pantnagar); TERI, (Delhi)- Indian partners and FiBL (Frick); University of Basel; University of Neuchâte- Swiss partners. It was transferred to private Indian partner: NFCL (Hyderabad) under Non-Exclusive License Agreement.

Ongoing ISCB Phase V Research projects

The following 4 network projects sanctioned by DBT, are under implementation in Phase V of ISCB (continued from Phase IV) under Indo-Swiss Collaboration in Biotechnology which will end by October 2019:

1. Biofertilization and Bioirrigation for sustainable mixed cropping of pigeon pea and finger millet (BIOFI) Network with goal of development of sustainable pigeon pea & finger millet intercropping systems based on the selection of responsive cultivars and the validated process of biofertilizers & bioirrigations. Project will completed by October 2019.
2. Indo Swiss Cassava Network with goal of development of virus and white fly resistance in Cassava varieties. The duration of the project further extended for 6 months from 19.10.2018 to 31.03.2019 with no cost.
3. Ragi Network with goal to develop nutritionally superior and climate resilient Ragi, facilitate effective integration of Ragi into the national nutritionally Genetic enhancement & bioavailability – Finger millet (Ragi). Project will be completed by October 2019.
4. Pigeon Pea Network with goal of improvement of Pigeon pea for plant type, pod borer resistance, and moisture stress tolerance. Project will be completed by October 2019.

TAU has assisted DBT in facilitating financial release and review of progress reports of network projects. TAU also facilitated project partners and the participating institutions in NBA Notification, Biological Material Transfer (to and from India to Switzerland), IP Management and Capacity building.

The ISCB Symposium 2018 was held during 3-4 December 2018 at the National Academy for Agricultural Sciences (NASC) Complex in New Delhi, India. TAU co- ordinated the symposium with PMU of SDC. The main objective of the Symposium was to highlight the achievements of the ISCB program to an international audience, supplemented with presentations of selected national and international speakers outside project partners. It was attended by around hundred participants form both the Indian and Swiss side, representing researchers in biotechnology, socio-economics, as well as representatives of the public sector.

Biosafety Support Unit

Biosafety Support unit (BSU) is established by Department of Biotechnology, Government of India as a part of the reforms to strengthen biosafety regulatory system in partnership with Regional Centre for Biotechnology (RCB). BSU scientists have been trained with specialization in various scientific disciplines, falling into two major biotechnology areas i.e. Agri-Biotech and Bio-Pharma. The Major activities undertaken by BSU during the year 2018-19 include:

- Provided assistance to RCGM/GEAC (Statutory bodies established under Rules 1989 of EPA 1986) in the scrutiny of all the applications received for conducting research in biotechnology, product development and monitoring field requirements, compliance of the approved protocols/procedures to be followed at the time of field trials (Event selection, BRL-I and BRL-II) and preclinical toxicology (PCT) data and other regulatory compliances.

- Assisted the RCGM secretariat in developing revised guidelines and protocols for generating biosafety data to address the challenges raised by the emerging new areas of Biotechnology such as Genome Editing.
- BSU team is also fulfilling the training needs of the personnel engaged in Biosafety regulations and developing e-learning modules for IBSCs and other stakeholders working in the regulatory science.
- BSU is fully engaged in providing a communication platform for scientific community and other stakeholders through Indian Biosafety Knowledge Portal, an online portal for all transaction and submission and tracking of applications.
- BSU provided all necessary services to Review Committee on Genetic Manipulation (RCGM) and assisted RCGM secretariat in organizing scheduled meetings of the RCGM, various sub-committees and monitoring teams, etc.

Major accomplishments of BSU

1. RCGM/GEAC Related Activities**:** BSU evaluated applications submitted to Review Committee on Genetic Manipulation (RCGM) for consideration in RCGM meetings (165th to 173rd Meetings) during year 2018-19 and extended its support towards conducting the meetings of RCGM by preparing Agenda notes and draft recommendations. Further, in-depth desk review was carried out for each of the application/reports submitted by the applicants on confined field trials (CFTs) and pre-clinical trials (PCT). Similarly, applications for import/export/ transfer/receive, and information items in the field of agriculture and pharma were also assessed. Further BSU continued its full support to GEAC by providing Risk assessment and risk management plan (RARMP) documents for each application considered in the GEAC meetings during the year 2018-19. Agriculture Group has drafted and submitted 10 RARMP documents for Agri-Biotechnology related applications. Agriculture group also assessed 46 Import/Export/Transfer/Receive applications, 32 applications for new genes/ events and 156 Research & Development information applications. Bio-Pharma Group has drafted and submitted 8 RARMP documents for Bio-Pharma related applications. Bio-Pharma Group assessed 200 Import/ Export/ Transfer/ Receive applications, 59 Pre-clinical toxicity (C3/ C5) applications and 509 Research &Development information applications during the 2018-19.
2. Check-list of Bio-pharma applications: BSU assisted DBT in preparing "Checklist for information required in the Applications/ reports on Pre-Clinical Toxicity study of Similar Biologics" which was notified by DBT on 31.08.2018 and made available at DBT website (http://www.dbtindia.nic.in/wp-content/uploads/checklist.pdf) to help the stakeholders with information required during the filling of C3 and C5 bio-pharma applications.
3. Draft General Principles, Regulatory Framework, and Data Requirements for Biosafety Assessment of Genome Edited Organisms and policy towards promotion and responsible use of genome editing research and applications in agriculture, healthcare, livestock and industry: BSU assisted (i) The Apex committee under the chairmanship of Dr K Veluthambi and 3 sub-committees constituted for preparation of draft document on the regulatory framework and data requirement for Genome edited organisms/products and (ii) Advisory Committee constituted under the Chairmanship of Dr G Padmanaban for preparing draft policy document on Genome editing. The Draft regulatory framework and Data requirement document is under the consideration of RCGM and the draft national policy document is under preparation.
4. Launch of Indian Biosafety Knowledge Portal (IBKP): BSU Scientists facilitated RCGM secretariat for the development of IBKP, more specifically in revising all application formats, undertaken multi-user functionality testing, supported during backend conversion from oracle to MS-sql. Further, BSU assisted and coordinated with NIC team during Security clearances.
5. Revision and updation of Biosafety Protocols and Guidelines: BSU has undertaken a major activity of revision/ updation of various guidelines related to biosafety of

recombinant DNA research. The "Regulations and guidelines on biosafety of recombinant DNA research and Biocontainment 2017" released by Prof. K. VijayRaghavan, Secretary, Department of Biotechnology (DBT), have been notified on 1st April 2018. The BSU assisted different working groups in preparing following draft guidelines that are under RCGM consideration: 1. Guidelines on assessment of GE micro-organisms, 2. Guidelines on Stacked GM plants/ genes.

6. On behalf of RCGM secretariat, BSU support to Food Safety and Standards Authority of India (FSSAI) scientific panel on GM food BSU supported FSSAI Scientific panel on GM food for preparing the following documents: Principles of risk assessment for GM food including formats of the application forms; GM food labelling policy; establishing notified GM food testing laboratories in India. Further BSU also assisted in preparation of draft Gazette notification for GM food assessment, labelling and detection. Additionally, a draft document was prepared for assessment of processing aids for FSSAI and extended support in assessment of the applications received for inclusion of enzymes in the positive list.
7. Other activities
    i. BSU has extended support to the Sub-Committees constituted for formulating Biosafety guidelines on (a) conduct and monitoring Confined Research Trials (CRTs) on genetically engineered (GE) Mosquitoes and(b) GE silk worm. BSU also prepared (a) Concept note on MEA meeting on 'Inter-ministerial meeting to discuss India's position on the UN resolution concerning the role of S&T in international security & disarmament'; (b) Input on Australia Group's survey for India's view on regulating publications of items pertaining to AG group common control list; (c) Comment on 'Inter-Ministerial coordination meeting agenda prepared by MEA to prepare for the Biological and Toxin Weapons Convention (BWC) 2018 Meeting of States Parties.
    ii. As per the RCGM requirement, BSU staff participated in various monitoring committees (CCC)that ensure compliance during confined field trials/ facility evaluation etc.
    iii. Supported RCGM/GEAC for drafting affidavits/ replies for various Supreme Court cases and parliamentary questions.
8. Training and Capacity Building:
    a. BSU scientists attended following conferences:
        1. Three BSU scientists attended biosafety training program sponsored under USDA Cochran fellowship in December, 2018;
        2. Workshop on "CRISPR/Cas mediated genome editing: applications, tools, and experimental design" UDSC, New Delhi.
    b. BSU in association with TERI trained delegation Biosafety regulators from different African countries (as part of the Biotechnology and biosafety study tour to India for African Nationals) on 'Food/Feed & Environmental Risk Assessment.

Training workshop conducted by BSU for African Officials - February 2019

9. Presentations made by BSU: BSU staff gave invited talks or posters in various international and regional forums such as:
    a. SynBioBeta 2018 Conference during October 1-4 in California, USA.
    b. Sixth Indo-US biosecurity dialogue held on 21-22 Feb 2019 Hyderabad, India.

c. Presentation onRegulating GM and genome edited products at XIV Agriculture Science Congress, Innovations for Agricultural Transformation, India, 20-23 February 2019.

d. Presentation on "Regulating New Breeding Technologies in Agriculture" for mini symposium on "The impact of New plant breeding technologies in Agriculture" in September 2018.

Advanced Technology Platform Centre

Advanced Technology Platform Centre (ATPC) is a Department of Biotechnology (DBT), Government of India-funded platform that provides a medium for innovative researchers to turn their scientific ideas into reality. It is a part of the NCR Biotech Science Cluster situated at Faridabad (NCR Delhi). Its primary goal is to accelerate innovations in Science & Technology and plug a huge gap in the innovation pipeline that has previously attenuated the ability of Indian researchers to realize their true potential. It is laced with state-of-the-art research facilities, specialized personnel and world-class infrastructure. With an intent to make a significant contribution to the global research pool, ATPC is ever vigilant towards generating reproducible and reliable data, complying with international research standards. The centre is ambitiously generating deliverables addressing the issues in public health, agriculture and skill development sectors. ATPC has six facilities with advanced technology platforms in the field of Protein Purification and Molecular Interactions; Mass Spectrometry; Flow Cytometry; Genomics; Optical Microscopy and Electron Microscopy. Details of these are provided below.

1. **Protein Purification and Molecular Interactions Platform**: This facility aims at aiding researchers in upscaling protein production with the help of fermenters followed by downstream purification using state-of-the-art facilities. Interactions amongst biomolecules can be studied with the help of latest available technologies like BioLayer Interferometry and MicroScale Thermophoresis. This platform facility is currently providing

the following services.

a. Expression screening of the protein-of-interest by sub- cloning its gene into vectors with different tags.

b. Over-production of recombinant proteins in 7-litre and 14-litre fermenters (Eppendorf 7L, 14L).

c. Protein purification by affinity chromatography and size-exclusion chromatography using AKTA Prime and AKTA pure FPLC systems (GE Healthcare).

d. Molecular interaction studies using BioLayer Interferometry (Pall ForteBio) and MicroScale Thermophoresis (Nanotemper Tech.)

2. **Mass Spectrometry Facility:** The Mass Spectrometry Facility offers a comprehensive suite of modern instrumentation for the separation, identification and quantitation of a wide range of

molecules. At present, the facility maintains three mass spectrometry instruments – Triple TOF 5600 plus, MALDI TOF/TOF 5800, QTRAP 6500 PLUS, Flexar HPLC. The facility currently provides services for:

a. Identification and quantification of known and unknown Proteins/ Peptides / metabolites using data-dependent (DDA) and data independent (DIA) analysis,
b. PTM analysis,
c. Labelled (iTRAQ, SILAC etc.) and label-free quantitative proteomics, and
d. Basic, cation exchange fractionation of proteins using HPLC.

3. **Flow Cytometry Facility:** FACS Facility is providing services for cell counting, cell sorting, biomarker detection, protein engineering, and multiparametric analysis of the physical and/or chemical characteristics of cells, and is routinely used for the diagnosis of health disorders, and other advanced fields of basic research, clinical practice and clinical trials. The Facility is equipped with the following instruments:
   a. FACSVerse (Beckton Dickinson)
   b. Accuri C6 (Becton Dickinson)
   c. InfluxTM Cell Sorter (Beckton Dickinson)
   d. Gallios (Beckman Coulter)

4. **Genomics Facility:** Genomics Facility aids researchers in the field of molecular marker analysis, gene expression analysis and determination of copy number variations using ABI 3500 Genetic Analyzer and Droplet Digital PCR (ddPCR) (Bio-Rad). ABI 3500 Genetic Analyzer is a fluorescence based 8-capillary, Sanger sequencing based instrument with an integrated software for instrument control, data collection, quality control, base-calling and size-calling of samples. ddPCR provides simultaneous clonal amplification and fluorescence-based quantification of nucleic acids in a contained environment of distinct water-in-oil droplets, providing absolute, precise and reliable quantification. The facility provides following services:
   a. A wide range of services in the field of microbial sequencing, targeted DNA sequencing, epigenetic analysis, pathogen analysis, genetic disease research, SNP analysis and

biomarker analysis are being provided with ABI 3500 Genetic Analyzer.

b. Determination of rare DNA target detection, determination of copy number variations and measurement of gene expression levels are studied using Droplet Digital PCR (ddPCR).

5. **Optical Microscopy Facility:** At present the facility hosts three state-of-the-art instruments–

   a. High Content Imaging System (Molecular Devices, Model: ImageXpress Microconfocal): It is an integrated cellular quantitative imaging and analysis system designed for rapid and automated screening of fluorescently labelled fixed and live cells in microplates, and slides. The system also provides environmental control for live cell imaging, move fluids to and from cells for compound addition.

   b. Super Resolution Microscope (Carl Zeiss, Model Elyra PS1)

   c. Laser Scanning Confocal Microscope (Carl Zeiss, Model: LSM 880): These two instruments image fluorescently labelled live and fixed cells, animal tissues and microbial samples. The system is equipped with high quantum-efficiency detectors which are helpful in acquiring images even in very low signal.

The resolution achieved by different modules of super-resolution microscope are:

   a. Super Resolution Structured Illumination Microscopy (SR SIM): a resolution up to 120 nm

   b. Total Internal Reflection Fluorescence Microscope (TIRF): resolution between 50-100 nm

   c. Photo Activable Localization Microscopy (PALM): resolution up to 10 nm

   d. Stochastic Optical Reconstruction Microscopy (STORM): resolution up to 10nm

6. **Electron Microscopy Facility:** The Electron Microscopy Facility is one of the pioneer facilities in North India that houses Cryo-Electron Microscope: JEM2200FS with 200kV field emission gun, in-column energy filter (Omega filter) and highly sensitive Gatan K2 summit direct detection camera. The facility also houses Transmission Electron Microscope (TEM): JEM1400 FLASH (120kV) by JEOL and VolumeScope Scanning Electron Microscope (SEM) by FEI with serial block-face imaging solution. A wide range of applications are being provided by this facility in the field of life sciences and material sciences giving intricate details of specimen morphology, structure and composition. The Facility provides services for–

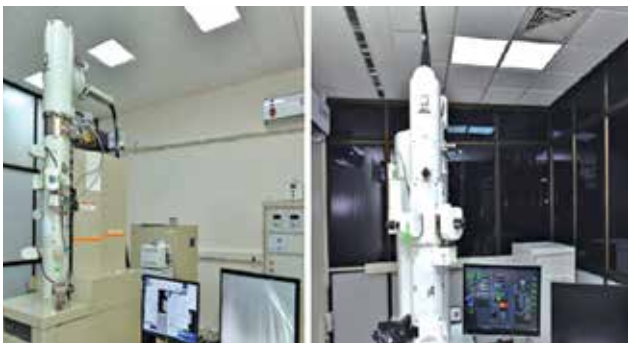
a. High contrast TEM imaging of biological specimens (including macro-molecular materials, tissue sections and viruses etc.) and material science samples (polymeric and metallic nanoparticles etc.) from the low magnification (min. mag. 10X) to the high magnification (max. mag. 1.2 MX) with resolution up to 0.38 nm by JEM 1400 Flash.

b. Cryo-imaging using minimum dose exposure: zero loss imaging; energy filters and tomography by JEM2200FS.

c. Surface topology of samples with excellent z-resolution using serial block face imaging in LoVac and LoVac mode VolumeScope SEM.

Other Major Research Infrastructure Facilities

Macromolecular Crystallography



This facility has an automated nanodispenser for crystallization experiments, vibration free crystallization incubator, UV and light microscopes, two X-ray generators (Sealed tube & Metal jet) with optics, detectors and cryostreams.

Nuclear Magnetic Resonance (NMR) Spectrometer

The NMR Bruker AscendTM 400 MHz Spectrometer is intended for rapid acquisition of routine 1D and 2D NMR experiments. This Spectrometer is perfectly equipped to tackle a wide variety of research problems and is mainly dedicated to chemistry studies. The AscendTM magnet incorporates the key technologies of the UltraShieldTM Plus magnets. The Bruker AscendTM 400 MHz is equipped with a 5 mm BBFOPLUS probe with 2H "lock" channel and z gradient. The spectrometer is also equipped with a control temperature unit prepared to work at temperatures ranging from -50 °C to +50 °C.

High Performance Computing Cluster & IT Infrastructure

A high performance computing cluster with 8 nodes and a total of 128 processors is available for research in computational biology. The Information and Communication facilities at RCB are continuously evolving with state-of-the-art facilities. All the computers at RCB are provided with the latest updated software and hardware. Internet, printing and scanning facilities are also available throughout the network. An impressive array of information technologies and resources have been deployed with a harmonious blend of old and new, notable among these are:

Computing Facilities

Desktops/ Laptops, multifunction printers have been provided to the staff with internet connectivity. There are about 150+ client machines with windows 8.2 & 10, Red Hat Linux and Mac OS X. There is a common Personal Computer in each lab for students to access various

commercial off-the-shelf software such as Adobe Premium & Standard Suite 6, Systat 13, Sigma Plot, PyMol, Turnitin, Endnote x6/x8/x9, and Corel Draw Graphics Suite x6 for preparing manuscripts, various reports and presentations. Quick heal Seqrite end point security total edition 7.4 has been implemented as protection from viruses, adware, spyware etc. Biometric Attendance System (BAS) has also been enabled for the staff, to register attendance by simply presenting his/her biometric (finger print). In addition, online resources are available for scholars for research, case studies and for preparation of their projects.

Internet Connectivity

RCB has 1 Gbps shared internet leased line from National Knowledge Network offering high speed Internet connectivity in the campus, through the campus LAN. Additionally, a 50 Mbps RF connectivity has been provisioned from an alternate service provider as a backup. RCB's network infrastructure comprises about 1000 metres of fibre, with a 10 G backbone, 95+ wireless access points, and 35+ switches that provide on-campus wired connectivity. The RCB has implemented a security policy to ensure the highest levels of network health and security. The Centre has been functioning in conformity with the guidelines of the Government of India with regard to guidelines on IPV6 implementation and has also been an active participant in the Government initiatives of the "Digital India Campaign". The campus is fully covered by Wi-Fi through 95+ wireless access points. Wi-Fi access is provided to internal users by media access control (MAC) address authentication and to visitors by separate guest accounts. The Campus Network is protected using Fortigate 500D - where Unified Threat Management as a primary network gateway defense solution has been implemented with traditional firewall built into an all-inclusive security product able to perform multiple security functions: network firewalling, network intrusion detection/prevention (IDS/IPS), gateway antivirus (AV), gateway anti-spam, content filtering, load balancing, data loss prevention, and on-appliance reporting.

E-mail and Website

The e-mail system at RCB, offers a user-friendly web based e-mail allowing users to access mails, both from inside the campus and outside. A very competent & experienced IT service support team has been put in place and the Centre is also in the process of developing & implementing a highly attractive, user-friendly and dynamic web-site. Basic information about the institute, academic research, infrastructure, people, news and announcements is being regularly updated on the website.

Telephone Connectivity

The Campus has a PRI connectivity from Bharat Sanchar Nigam Limited and a distribution of about 200+ extensions for ease of communication within the campus and connecting with the outside world.

Audio Visual and Video Conferencing Facility

Auditorium, conference and seminar halls are equipped with a hi-tech sound and projection system, digital podium and Internet connectivity. These facilities are actively used for regular seminar series, colloquia and distinguished lectures, hands- on workshops and symposiums/ conferences. In addition, projection facility has been setup in class rooms and discussion rooms for regular teaching, lab meetings and scientific discussions. RCB has an Internet-based Video Conferencing Facility setup in the Seminar Hall comprising of Polycom HDX 7000 system. This facility is used for holding virtual seminars or conferences. Classrooms, meeting rooms and conference halls are furnished with the latest digital technology i.e. digital podium, LCD projection system with audio/ video facility and video conferencing systems in the Institute.

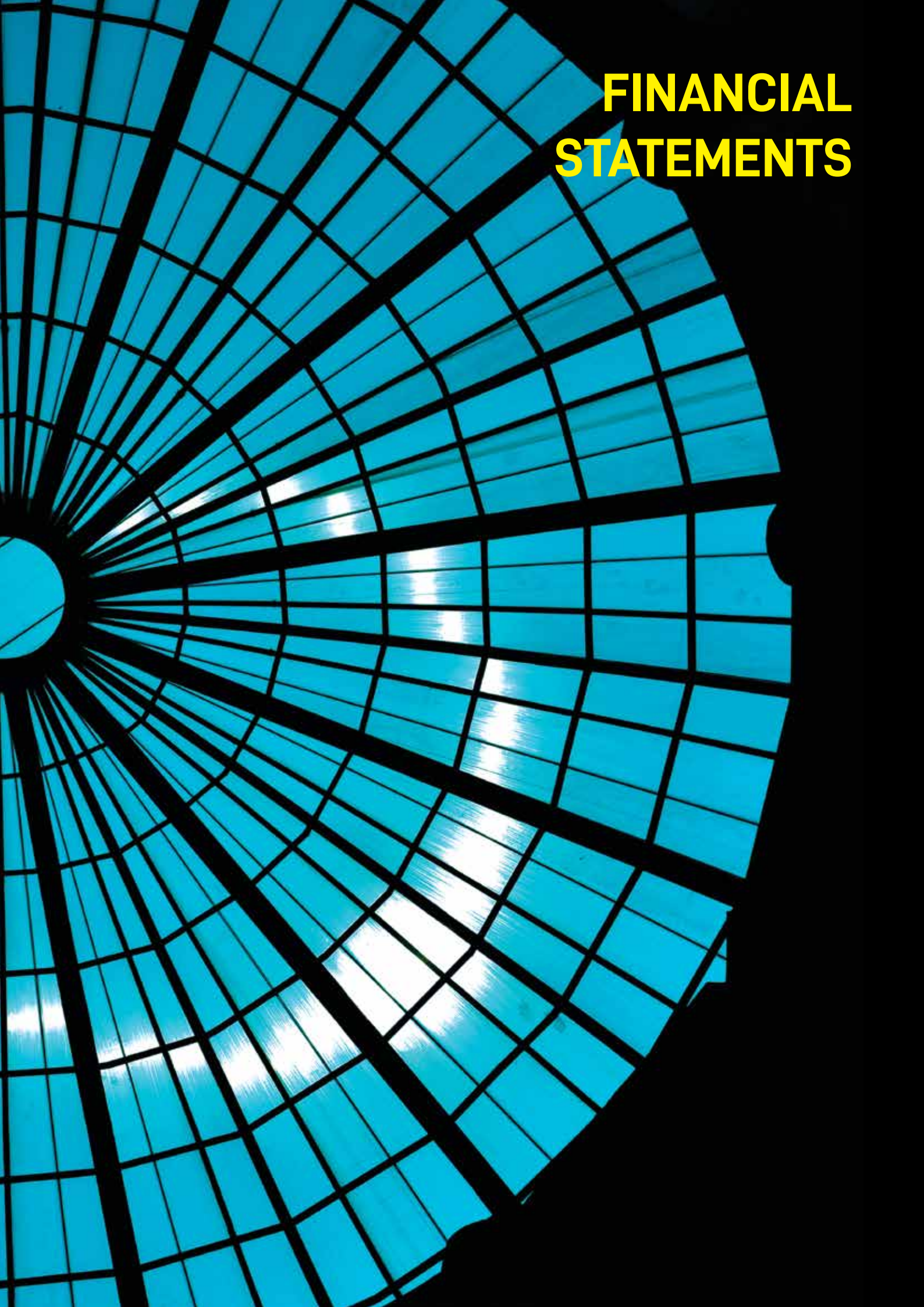
Office Automation

RCB is moving towards adapting a paperless work environment in which the use of paper is eliminated or greatly reduced. This is done by converting documents and other papers into digital form and development of various online applications (services or facilities) through the intranet portal named eRCB. All the faculty and students have access to this customised online software package being used for administrative applications. In continuation of paperless work environment using office automation, IT has to implement the ERP System in the upcoming year. This system will provide paperless centralised automation mechanism to complete any task faster with the better traceability & reporting. This system will have centralized cover of all the major activities for five sections i.e. Finance, HR, Purchase, Academics & General Administration.

Office of Connectivity

Office of Connectivity is mainly the coordination office for the NCR Biotech Science Cluster and is responsible to establish a governance structure for the management of common facilities. It was proposed to create an innovative and efficient management structure, so that the advantage of having different institutions co-located in a cluster, with their respective competencies can be nurtured through systematic sharing of knowledge and resources. Office of Connectivity is working towards integrating the partner institutions of the cluster to focus on seamless connectivity for accomplishing best results in accelerated technology absorption by implementing strategic networks and scaling up of the innovative technology initiatives by facilitating coordination, collaboration and sharing of efforts within the Cluster setting for various key projects. An Office of Connectivity has been set up and recruitments on key positions have been done to oversee the implementation of Phase-II works of the NCR Biotech Science Cluster, Faridabad. This office is also acting as a hub for integration of the future infrastructural requirements of the partner institutions and has been able to draft a master plan for development of the Zone- II (in 85 acres of land) of the NCR Biotech Science Cluster. In the very first year of establishment, this office has been able to achieve the following milestones:

1. Phase-II works of the NCR BSC has been awarded to M/s UCEPL during November 2018 and RCC structure of Phase-II Buildings have been almost completed.
2. Master plan for Zone-II of the NCR BSC has been prepared in coordination with the partner institutions and has been approved by the Building Committee.
3. Capitalization of Phase-I Buildings of the NCR BSC was quite complex considering pooling of funds by partner institutions for multiple buildings and has been completed.
4. Optimum layout for creating the biocontainment system in Biosafety Level-3 Facility has been finalized and NIT is ready to be floated.



FINANCIAL STATEMENTS

REGIONAL CENTRE FOR BIOTECHNOLOGY,FARIDABAD
BALANCE SHEET AS AT 31ST MARCH, 2019

Amount (In Rs.)

LIABILITIES	Schedule	31.03.2019	31.03.2018
Corpus / Capital Fund	1	567,200,541	158,946,572
Reserves and Surplus	2	9,303,113	415,012
Earmarked/Endowment Funds	3	-	-
Secured Loans and Borrowings	4	-	-
Unsecured Loans and Borrowings	5	-	-
Deferred Credit Liabilities	6	-	-
Current Liabilities and Provisions	7	1,489,084,474	611,393,319
BIOTECH SCIENCE CLUSTER (BSC)			2,288,971,991
TOTAL		**2,065,588,128**	**3,059,726,894**
ASSETS			
Fixed Assets	8	556,533,012	143,210,252
Investment From Earmarked/Endowment Funds	9	-	-
Investment-Others	10	521,817,706	257,597,100
Current Assets, Loans, Advances etc.	11	297,719,145	554,855,187
BIOTECH SCIENCE CLUSTER (BSC)	8		
a. Capital Work in Progress		689,518,265	1,986,973,829
b. Advance to BSC Construction		-	106,243,350
c. Funds in short term deposits		-	3,400,000
d. Accrued interest & TDS		-	7,447,176
Miscellaneous Expenditure		-	
(to the extent not written off or adjusted)			
TOTAL		**2,065,588,128**	**3,059,726,894**
SIGNIFICANT ACCOUNTING POLICIES AND NOTES ON ACCOUNTS	24		
CONTINGENT LIABILITIES	25		

Schedules 1 to 25 form an integral parts of Accounts

(REETESH AGGARWAL) INTERNAL AUDITOR

(C.B.YADAV) ADMINISTRATIVE OFFICER (F)

(DR. DEEPIKA BHASKAR) REGISTRAR

डॉ. दीपिका भास्कर, रजिस्ट्रार
Dr. Deepika Bhaskar, Registrar
क्षेत्रीय जैवप्रौद्योगिकी केंद्र
Regional Centre for Biotechnology
फरीदाबाद, हरियाणा / Faridabad, Haryana

(Dr. SUDHANSHU VRATI) EXECUTIVE DIRECTOR

प्रो. सुधांशु व्रती / Prof. Sudhanshu Vrati
कार्यपालक निदेशक / Executive Director
क्षेत्रीय जैवप्रौद्योगिकी केंद्र / Regional Centre for Biotechnology
फरीदाबाद - 121 001 (हरियाणा), भारत/Faridabad - 121 001 (Haryana), India

REGIONAL CENTRE FOR BIOTECHNOLOGY,FARIDABAD

INCOME AND EXPENDITURE ACCOUNT FOR THE YEAR ENDED 31st MARCH, 2019

Amount (In Rs.)

INCOME	Schedule	31.03.2019	31.03.2018
Income from Sales/ Services	12	7,563,715	-
Grants/Subsides	13	235,270,777	200,748,262
Fees/Subscriptions	14	2,809,111	6,062,801
Income from Investments	15	-	-
Income from Royalty, Publication etc.	16	-	-
Interest Earned	17	-	4,507,343
Other Income	18	4,196,271	796,720
Increase/(Decrease) in stock of Finished goods and works in progress	19	-	-
Deferred Income-Fixed Assets		46,668,435	57,653,664
TOTAL (A)		**296,508,309**	**269,768,790**
EXPENDITURE			
Establishment Expenses	20	67,872,066	103,415,910
Other Administrative Expenses etc.	21	168,579,707	108,699,216
Expenditure on Grants , Subsidies etc.	22	-	-
Interest	23	-	-
Depreciation (Net Total at the year-end-corresponding to Schedule 8)		46,668,435	57,653,664
Prior period Adjustment A/c (ANN-A)		-	-
TOTAL(B)		**283,120,208**	**269,768,790**
Balance being excess of Income Over Expenditure (A-B)		**13,388,101**	**-**
Transfer to special Reserve(Specify each)			-
Transfer to /from General Reserve			-
BALANCE BEING SURPLUS /DEFICIT CARRIED TO CORPUS/CAPITAL FUND		**13,388,101**	**-**
SIGNIFICANT ACCOUNTING POLICIES AND NOTES ON ACCOUNTS	24		
CONTINGENT LIABILITIES	25		

Schedules 1 to 25 form an integral parts of Accounts

(REETESH AGGARWAL)
INTERNAL AUDITOR

(C.B.YADAV)
ADMINISTRATIVE OFFICER (F)

(DR. DEEPIKA BHASKAR)
REGISTRAR

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(Dr. SUDHANSHU VRATI)
EXECUTIVE DIRECTOR

प्रो. सुधांशु व्रती / Prof. Sudhanshu Vrati
कार्यपालक निदेशक / Executive Director
क्षेत्रीय जैवप्रौद्योगिकी केंद्र / Regional Centre for Biotechnology
फरीदाबाद - 121 001 (हरियाणा), भारत/Faridabad - 121 001 (Haryana), India

Schedule 24: Accounting Policies and Notes Forming Parts of the Balance Sheet and Income & Expenditure Account for the Year Ended at 31st March, 2019.

1. The annual accounts have been prepared in the revised format of accrual system of accounting, except for extramural funds and other project grants.
2. Since the RCB Bill has been passed and notified on 1.3.2017 and thereafter the statutes, ordinances and regulations approved during September 2017, the liabilities on account of Gratuity & leave encashment of the Centre has been incorporated in the accounts for FY 2018-19 in accordance with the approved service conditions of the RCB, based on actuarial valuation.
3. a) Recurring Grants have been recognized in the Income & Expenditure account and non-recurring Grants have been shown as part of capital.
   b) Grants for core Funds relatable to depreciable fixed assets are treated as deferred income and recognized in the Income and Expenditure Account on a systematic and rational basis over the useful life of such assets i.e. such grants are allocated to income over the periods and in the proportions in which depreciation is charged (As per Accounting Standard 12). During the year income recognized in respect of such grants amounts to Rs. 4,66,68,435.00
4. a) The depreciation has been provided w.e.f. the date of installation/put to used of fixed assets as per the rates prescribed by Income Tax Act 1961. During the previous year depreciation has been charged at per rate prescribed.
   b) Depreciation has been charged during the year of acquisition and no depreciation is provided during the year of assets sold/discarded. In respect of additions to/deductions from fixed assets during the year, depreciation is considered on Pro-rata basis
5. a) Fixed assets have been created with core grants received from the Department of Biotechnology. No equipment procured out of project funds have yet been capitalized.
   b) Fixed Assets are stated at cost acquisition inclusive of inward freight, duties and taxes and incidental and direct expenses related to acquisition
6. All purchases of chemicals, glassware, consumables, and stationary have been charged to consumption at the time of purchased without working out closing stock at the end of the year.
7. Further all entries relating to purchase of consumable/equipments or other fixed assets in accounts are being passed only at the time of submission of satisfactory inspection/ installation report irrespective of the date of actual receipts of the supplies/equipments.
8. Transactions denominated in foreign currency are accounted at the exchange rate prevailing at the date of transaction.
9. The institute has a policy of incurring expenditure on various projects in accordance with the sanctioned budget under various heads of accounts irrespective of the actual releases during a financial year. Since the actual release of money by the sponsoring agency is subject to various factors, the expenditure on approved heads of accounts is being incurred within the overall sanction of the project.
10. The balances of the previous year have been rearranged as per requirement and shown in Balance Sheet against the relevant heads.
11. Expenses and Overheads incidental to construction of building of institute as well as other buildings in the NCR BSC, as reported by the Project Monitoring Consultant (Engineers India Limited), are added to the capital work in progress to be capitalized along with the building only on submission of final accounts by the PMC. The project is being operated with an agreement which stipulates operation of an Escrow Account by NCR Biotech

Science Cluster. The authorized signatories are Engineers India Ltd. (Project Management Consultant)

12. The Institute has received contribution of Rs. 1406.10 Lakhs (including RCB) from various institutes for the Phase II of the construction of campus at Faridabad. The consolidated details are as under:

Sl. No.	Constituent Partner	Opening Balance as on 1.04.2018	Received during 2018-19	Total receipts on 31.3.2019
1.	THSTI	0.00	450.00	450.00
2.	RCB	0.00	369.00	369.00
3.	NCR-BSC Project	567.00	00.00	567.00
4.	Interest on investment of BSC funds	9.32	20.10	20.10
	Total	**576.32**	**839.10**	**1406.10**

13. The Capital Work in progress booked in the accounts includes the construction of laboratory building of ATPC, Bio-incubator and hostels & faculty housing and common facilities etc. of THSTI, RCB, under Phase I Extension and Phase II. The expenditure under Phase-I was transferred to the respective stakeholders as per their contribution and area wise expenditure.
14. Interest earned on saving bank account and fixed deposits during the financial year 2018-19 of Rs. 199.40 Lakhs has been allocated to the respective on pro-rata basis.

Schedule 25: Contingent Liabilities

1. Purchase orders for consumables worth Rs. 2,68,71,725.00 ordered during 2018-19 are outstanding as on 31.03.2019 which have not been recognized in the books of accounts.
2. Purchase orders for Equipment worth Rs. 2,42,57,161.00 ordered during 2018-19 are outstanding as on 31.03.2019 which have not been recognized in the books of accounts.

(C B Yadav)
Administrative Officer (F&A)

(Dr. Deepika Bhaskar)
Registrar
Dr. Deepika Bhaskar, Registrar
Regional Centre for Biotechnology

(Dr. Sudhanshu Vrati)
Executive Director
Prof. Sudhanshu Vrati
Executive Director
Regional Centre for Biotechnology

Place: Faridabad
Date: 20/06/2019


REGIONAL CENT

INSTITUTIONAL GOVERNANCE

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  Secretary
  Department of Biotechnology
  New Delhi - 110 003
- **Prof. M. Radhakrishna Pillai (Member Ex-officio)**
  Director
  Rajiv Gandhi Centre for Biotechnology
  Thiruvananthapuram - 695 014, Kerala
- **Prof. Saumitra Das (Member Ex-officio)**
  Director
  National Institute of Biomedical Genomics
  Kalyani- 741 251, West Bengal
- **Prof. Gagandeep Kang (Member Ex-officio)**
  Executive Director
  Translational Health Science & Technology Institute
  Faridabad - 121 001
- **Mr. Eric Falt (Member Ex-officio)**
  Director
  UNESCO Delhi Office, New Delhi - 110 021
- **Dr. Y. K. Gupta (Permanent Invitee)**
  Former Professor & Head, Department of Pharmacology
  All India Institute of Medical Sciences
  New Delhi - 110 029
- **Dr. Alka Sharma (Special Invitee)**
  RCB Coordinator
  Scientist-G, Department of Biotechnology
  Govt. of India
  New Delhi
- **Dr. Nitin K. Jain (Member Ex-officio)**
  RCB Nodal Officer
  Scientist-E, Department of Biotechnology
  Govt. of India, New Delhi
- **Prof. Sudhanshu Vrati (Convenor)**
  Executive Director
  Regional Centre for Biotechnology
  Faridabad - 121 001

Programme Advisory Committee (PAC)

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  Former Professor & Head, Department of Pharmacology
  All India Institute of Medical Sciences
  New Delhi 110 029
- **Dr. Debashis Mitra (Member)**
  Director
  Centre for DNA Fingerprinting and Diagnostics
  Hyderabad 500 039
- **Dr. Rashna Bhandari (Member)**
  Staff Scientist
  Centre for DNA Fingerprinting and Diagnostics
  Hyderabad 500 039
- **Dr. Vidita Vaidya (Member)**
  Sr. Scientist
  Tata Institute of Fundamental Research
  Mumbai
- **Dr. Shrikumar Suryanarayan (Member)**
  Chairman
  Sea6 Energy, Bengaluru 560 065
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  Professor & Head, Department of Plant Molecular Biology, University of Delhi, South Campus
  New Delhi 110 021
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  Vice-Chancellor
  Banaras Hindu University, Varanasi 221 005
- **Dr. Joel Sussman (Member)**
  Dept. of Structural Biology
  The Weizmann Institute of Science, Israel
- **Prof. Angelo Azzi (Member)**
  Vascular Biology Laboratory
  Tufts University, USA
- **Prof. R. Venkata Rao (Member)**
  Vice Chancellor
  National Law School of India University
  Bengaluru 560 072
- **Dr. Alka Sharma (Member)**
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  Govt. of India, New Delhi
- **Dr. Nitin K. Jain (Special Invitee)**
  Scientist-E, Department of Biotechnology
  Govt. of India
  New Delhi
- **Prof. Sudhanshu Vrati (Member Secretary)**
  Executive Director
  Regional Centre for Biotechnology, Faridabad 121 001

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  Executive Director
  Regional Centre for Biotechnology
  Faridabad 121 001
- **Deans (Members Ex-officio)**
  Regional Centre for Biotechnology
  Faridabad 121 001
- **Sh. Chandra Prakash Goyal (Member Ex-officio)**
  Joint Secretary (Administration)
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- **Mr. Eric Falt (Member Ex-officio)**
  Director
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  Ministry of Human Resource Development
  Govt. of India, New Delhi 110 066
- **Joint Secretary (Member Ex-officio)**
  UNES Division
  Ministry Of External Affairs
  Govt. of India, New Delhi 110 001
- **Registrar (Permanent Invitee)**
  Regional Centre for Biotechnology
  Faridabad 121 001
- **Finance Officer (Permanent Invitee)**
  Regional Centre for Biotechnology
  Faridabad 121 001
- **Controller of Administration**
  (Member Secretary Ex-officio)
  Regional Centre for Biotechnology
  Faridabad 121 001

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- **Mr. B. Anand (Member Ex-officio)**
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  New Delhi
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  RCB Nodal Officer
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- **Controller of Administration (Member Ex-officio)**
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  Faridabad 121 001
- **Finance Officer (Member Secretary Ex-officio)**
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  Registrar, Regional Centre for Biotechnology
  Faridabad 121 001

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Faculty

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Professor
Dr. Prasenjit Guchhait

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Dr. Avinash Bajaj
Dr. Sivaram V.S. Mylavarapu
Dr. C.V. Srikanth
Dr. Vengadesan Krishnan
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Dr. Nidhi Adlakha
Dr. Prem Singh Kaushal
Dr. Ramu S. Vemanna
Dr. Rajender K. Motiani
Dr. Kinshuk Raj Srivastava

Wellcome Trust DBT IA Intermediate Fellow
Dr. Pinky K. Sharma
Dr. Geetanjali Chawla

DST Inspire Faculty

Dr. Naini Burman
Dr. Prashant M. Pawar

DBT Biocare Awardee
Dr. Kanchan Bhardwaj

Wellcome Trust-DBT IA Early Career Fellow

Dr. Pushpa Kumari
Dr. Masum Saini

Young Investigators

Dr. Siddhi Gupta
Dr. Shivendra Pratap
Dr. Yashika Walia Dhir
Dr. Raghavendra Aminedi

Management

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Executive Director
Prof. Sudhanshu Vrati

Staff Officer to Executive Director
Dr. Nidhi Sharma

Technical Assistant
Mr. Ramesh Chandiramouli

Academics, Administration, Finance and Purchase

Registrar
Dr. Deepika Bhaskar

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Mr. C.B. Yadav

Section Officers
Mr. Rakesh Kumar Yadav
Mr. Sanjeev Kumar Rana
Mr. Sudhir Kumar

Management Assistants
Mr. Chakrawan Singh Chahar
Mr. Sumit Sharma
Mr. Vinod Kumar

Documentation Assistant
Mr. Priyanshu Joshi

Technical

Executive Engineer
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System Administrator
Mr. Naveen Kumar

Technical Officers
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Mr. Deepak Kumar
Mr. Vijay Kumar Jha
Mr. Atin Jaiswal

Technical Assistants
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Mr. Madhava Rao M
Ms. Vishakha Chaudhary
Mr. Nagavara Prasad G
Dr. Shaminder Singh

Consultant (Scientific & Technical)
Dr. Nirpendra Singh

Advanced Technology Platform Centre

Application Scientists
Dr. S. Chandru
Dr. Rashmi Kumariya
Dr. Indu Barwal
Dr. Neha Sharma

Senior Technical Officers
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Mr. Ankit Verma

Technical Officers
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Dr. Richa Mehra
Mr. Subodh Jain
Ms. Priyanka Bhardwaj
Mr. Ghanshyam Sharma

Electronics Engineer
Mr. Rajesh Kumar

Executive Assistants
Mr. Amit Kumar Yadav
Mr. Praveen Kumar
Mr. Navin Kumar Yadav

BSC BioNEST Bio-Incubator

Chief Operations Officer
Ms. Suman Gupta

Intellectual Property Manager
Ms. Malvika Garg

Business Development Manager
Mr. Sudhanshu Shekhar

Technical Assistant
Mr. Anshumouli Bhardwaj

Management Assistant
Ms. Natasha Thapa

Office of Connectivity

Chief Executive Officer
Dr. Feroz Khan Suri

Deputy Manager (Civil)
Mr. Vijay Kumar Arora

Management Assistants
Mr. Yash Pal Singh
Ms. Mahua Das
Mr. Naveen Swaroop


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