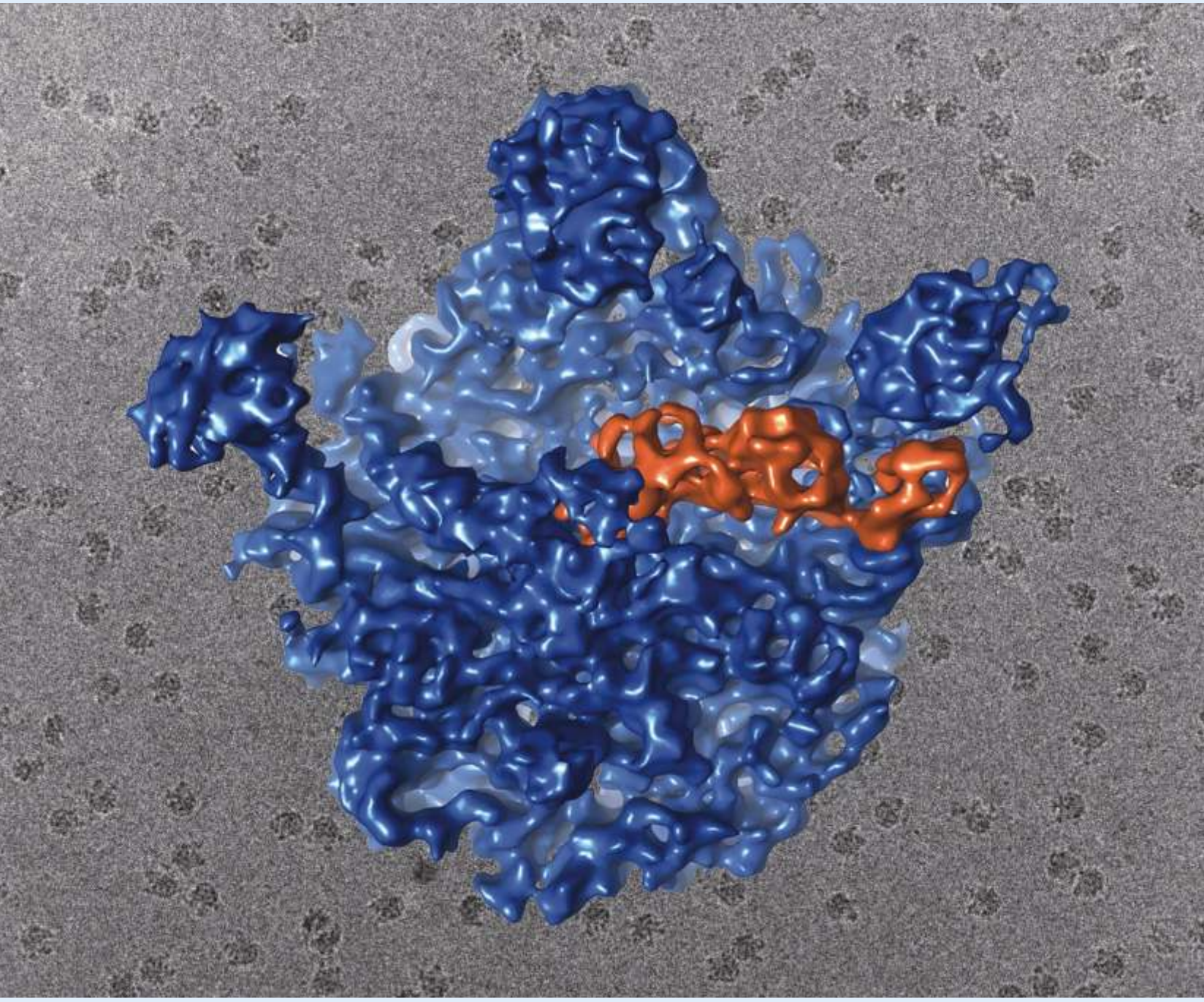
CSIR-IICB

सी.एस.आई.आर – भारतीय रासायनिक जीवविज्ञान संस्थान

CSIR-Indian Institute of Chemical Biology



वार्षिक प्रतिवेदन

Annual Report 2018-19

Front cover picture courtesy: Dr. Jayati Sengupta

Surface representation of cryo-electron microscopy generated density map of the universally conserved GTPase HflX (in presence of **Nonhydrolyzable** ATP and GTP analogs)-bound 50S ribosomal subunit (blue), with HflX colored orange.

Ref: J Cell Biol. 2018 Jul 2;217(7):2519-2529.

वार्षिक प्रतिवेदन
Annual Report 2018-19

Jadavpur Campus

Salt Lake Campus

सी.एस.आई.आर - भारतीय रासायनिक जीवविज्ञान संस्थान
४, राजा एस. सी. मल्लिक रोड, यादवपुर, कोलकाता - ७०० ०३२, भारत
CSIR - INDIAN INSTITUTE OF CHEMICAL BIOLOGY
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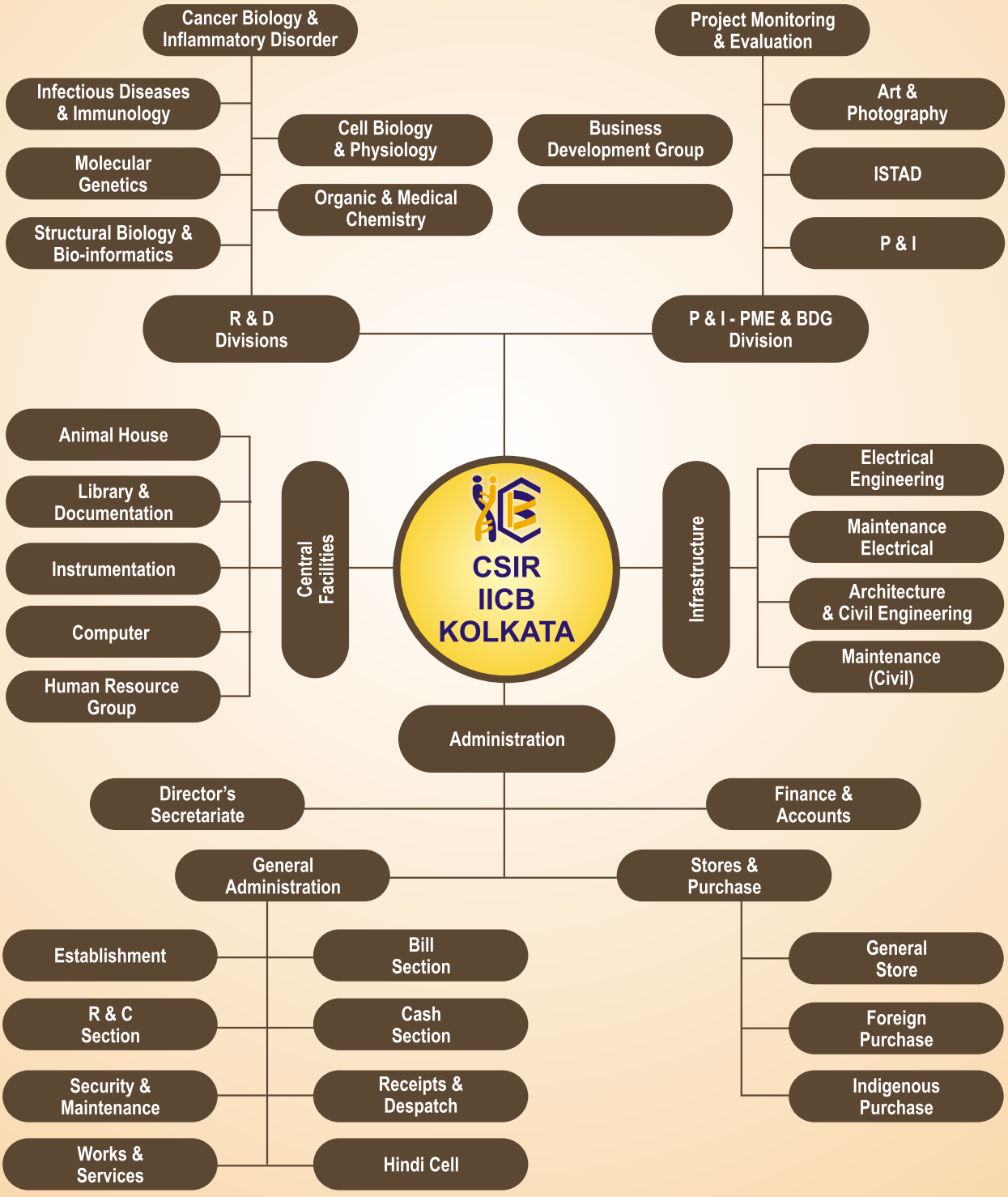
Cancer Biology & Inflammatory Disorder
Infectious Diseases & Immunology
Molecular Genetics
Structural Biology & Bio-informatics
Cell Biology & Physiology
Organic & Medical Chemistry
R & D Divisions
Project Monitoring & Evaluation
Art & Photography
ISTAD
P & I
P & I - PME & BDG Division
Business Development Group
Animal House
Library & Documentation
Instrumentation
Computer
Human Resource Group
Central Facilities
CSIR IICB KOLKATA
Infrastructure
Electrical Engineering
Maintenance Electrical
Architecture & Civil Engineering
Maintenance (Civil)
Administration
Director's Secretariate
Finance & Accounts
General Administration
Stores & Purchase
Establishment
R & C Section
Security & Maintenance
Works & Services
Bill Section
Cash Section
Receipts & Despatch
Hindi Cell
General Store
Foreign Purchase
Indigenous Purchase

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Director's Report

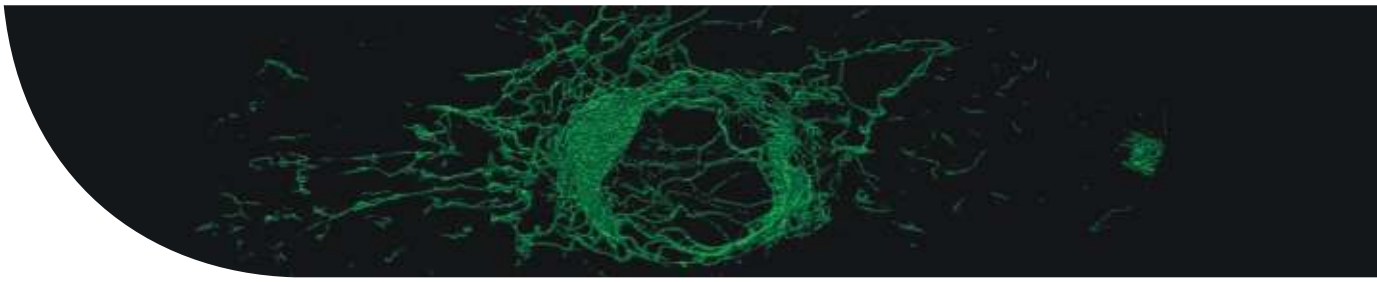
Prof. Samit Chattopadhyay
CSIR-IICB, Kolkata

I am delighted to publish the Annual Report of CSIR-IICB for the period of 2018-19. This Annual Report portrays a brief understanding of the overall activities of the institute in terms of its science and scientists. This Annual Report would also provide information about the administrative and service divisions of the institute and outline the infrastructure, assets and other aspects of scientific and academic managements.

The journey of Indian Institute of Chemical Biology (IICB) began in the year 1935 as Indian Institute of Medical Research, with a vision of solving the most pressing healthcare problems in our country. It is currently a constituent laboratory of the CSIR engaged in cutting edged research and development of therapies and diagnostic strategies of human diseases under the Healthcare theme of CSIR. It's my privilege to take this opportunity to reflect on our progress during this year in general and to envision the contribution towards the scientific future of our nation to be specific.

The strength of CSIR-IICB comes from the presence of a group of chemists and biologists, and hence the progress of the institute also depends on both groups of researchers. Like preceding years the institute continued its growth through quality research on diseases of national importance and biological problems of global interests, employing sophisticated state-of-the-art technology in keeping abreast with the rapid and unprecedented momentum that life science research has gained global attractions over the last few decades. In order to strengthen the basic research and to attain translational objectives, a second campus, a quadric storey building was constructed at Salt Lake, Kolkata which is operational. The unit is named CSIR-IICB Translational Research Unit of Excellence (TRUE). This new unit has objective for research facilitation by establishing advanced technological platforms, establishing a Biomedical Incubation Center for MSMEs, startup companies and translating discoveries made by CSIR-IICB. In addition to its strong basic research capabilities, the institute is now aiming towards the translation of indigenous innovations to affordable technology for societal benefits of the common man.

Six research divisions manage the research and development activities of CSIR-IICB. In the 'Cancer Biology and Inflammatory Disorder' division, the scientists conduct research studies on a range of cancers including lung, brain, oral, breast, pancreatic and leukemia to name a few. In the 'Cell Biology and Physiology' division, the researchers investigate subcellular organelles and intracellular signaling events under normal and diseased states. The institute has a strong 'Infectious Diseases and Immunology' division, which conducts detailed investigations on a number of infectious diseases of national importance, including leishmania, cholera and malaria to mention a few. The faculty members of 'Molecular Genetics' division, aim to understand the molecular genetic basis of human diseases prevalent in Indian population. The institute houses a strong 'Organic and Medicinal Chemistry' division, in which the members develop synthetic strategies and synthesize new, generic and nature inspired molecules targeting different communicable and non-communicable human diseases. The scientists in the 'Structural Biology and Bioinformatics' division uses cutting edge structural biology, biophysics and computational biology tools to develop structural and mechanistic details biological macromolecules with implications in multiple human disease conditions.



Our scientific productivity has been reflected in 210 publications, which are published during 2018 in prestigious international journals. These journals include the Journal of Biological Chemistry, ACS Biochemistry, Journal of Immunology, FASEB Journal, Trends in Immunology, Cell Reports, Nucleic Acid Research and Journal of Cell Biology etc. Reputed international journals including Organic Letters, ACS Chemical Neuroscience and Experimental Hematogy published cover pages in 2018 based on scientific contributions of CSIR-IICB. The contributions of CSIR-IICB scientists have been reflected in 16 books and book/chapters, which were published during 2018 solely. CSIR-IICB scientists bagged a number of prestigious awards and fellowships in 2018, which included National Bioscience Award (Dr. Dipyaman Ganguly); Fellowship of the National Academy of Sciences (Dr. Arun Bandyopadhyay) and the Fellowship of the West Bengal Academy of Sciences and Technology (Drs. Chinmay Chowdhury and Surajit Ghosh). The year 2018 saw a major push towards the upgradation of the Central Instrumental Facility of the institute by virtue of its purchase of two new instruments, a FCS and a X-ray diffraction system. In addition to institutional research funds, IICB scientists have also been successful in obtaining numerous peer-reviewed competitive grants from various national and international agencies. IICB scientists and students also organize and participate in national and international scientific symposiums and conferences along with several out-reach programs. Our graduate students are amongst the best in the country and their training involves proper coursework, along with work seminars to showcase their exercises. All these initiatives will enhance the commitment of IICB in supporting the scientific community and society, along with the development of public-private partnership and human resource development.

As a leading institute in research, our focus has been to provide 'Affordable Healthcare through Modern Science'. We have offered substantial attention in developing drugs from our indigenous and natural resources of native Indian plants. I am indeed happy to note that the stride for progress has continued unabated towards excellence and in the last few years we have taken major steps to translate its research results into products for societal benefit. The institute is doing well in terms of technology transfer. Drugs like 'Asmon' and 'Prostalyn' developed by us from Indian medicinal plants are now marketed.

CSIR-IICB has always remained as a centre of choice for promising researchers with aspiration to work in biological and chemical fields. I extend my warm gratitude to all the staff members of our Institute for their sincere activity and cooperation in sustaining the growth and maintaining the reputation of CSIR-IICB. CSIR-IICB will continue to focus on important questions relevant to human health with a view to developing a better understanding of physiological processes and potentially answers to several burning biological questions.

Cancer Biology & Inflammatory Disorder Division

Members :

Dr. Snehasikta Swarnakar (Head), Prof. Samit Chattopadhyay, Dr. Mrinal K Ghosh, Dr. Malini Sen, Dr. Dipyaman Ganguly, Dr. Amitava Sengupta, Dr. Shilpak Chatterjee, Dr. Siddik Sarkar, Dr. Amit K. Srivastava, Dr. Smrutisanjuta Behera, Dr. Krishna Das Saha, Dr. Shila E. Besra

The division is focusing on the mechanisms of several inflammatory diseases and cancers including gastric, brain, lung, ovarian and oral cancers and leukemia. The major interest lies on developing basic knowledge by utilizing cutting edge-approaches e.g. transcriptomic, genomic, metabolomic, proteomic and bio-informatics. The other important area encompasses discovery of new therapeutics using natural products and target-based synthetic peptides against biomolecules associated in cancer development. In addition, studies are on novel therapeutics and combinatorial approach to effectively kill both differentiated and dedifferentiated cancer cells. Besides, the combinatorial biomarkers in quantifying prognosis of breast and ovarian cancer are area of interest. Divisional research articles on cancer and inflammation biology received huge appreciation by vast scientific community of the world. In brief our research areas are as follows:
To detect matrix metalloproteinases (MMPs) mainly MMP-9,-7,-13 gene polymorphism and susceptibility for gastric cancer risk; the role of growth factors and proteases during severity of endometriosis and its protection by restoring the protease/aniprotease balance; novel flavonoid from natural sources as inhibitor of MMP9 activity and consequently use them as anti gastric ulcer agent. To study the cellular homeostasis via transcriptional regulation of matrix binding protein namely SMAR1 in cancer; the role of Wnt signaling in immune response, infection, inflammation and Wnt-Induced Signaling Proten-3 (WISP3) in sustenance of the musculoskeletal system; the redox balance in chondrocytes and regulation of mitochondrial functions and implication of small compounds to treat inflammatory bowel diseases by balancing Th17 and Treg population.

To understand the importance of innate immune cells particularly dendritic cells, in sterile context of inflammation including autoimmunities, metabolic syndrome and cancer. To discover a critical pathogenetic event in obesity associated metaflammation and insulin resistance and to identify the role of a tumor cell derived metabolite in intratumoral immunosuppression. To discover novel small molecule antagonists of toll-like receptor 9, in a number of sterile autoreactive clinical contexts; how metabolic pathways engage in diverse transcriptional programme and fate of lymphocytes in inflammatory diseases and anti-tumor immunity; the metabolic checkpoints in response to microenvironmental cues that instruct T cells to engage a discrete metabolic state and distinctive functionality.
To investigate the therapy resistance mechanisms in ovarian and lung cancer especially: Role of error-prone translesion DNA synthesis (TLS) in chemotherapeutic drug-induced mutagenesis and chemoresistance development; influence of miRNAs in the maintenance of cancer stem cells (CSCs) population; role of CSCs plasticity in therapy resistance; discover the link between DNA repair and chemoresistance; anti-cancer screening of small molecules/natural compounds that can sensitize the CSC population to chemotherapeutic drug treatment. Meta analyses of RNASeq (transcriptomics) data using R/RStudio/Bioconductor packages including machine learning algorithms that reveal, cell differentiation, proliferation/ quiescence and transmembrane receptor signaling pathways in intratumor heterogeneity, therapy resistance and cancer relapse in ovarian and breast cancer. To study the role of 'malefactor quiescent cancer initiator cells' to understand evade therapy and intra-tumor heterogeneity in breast and ovarian cancer using 3D tumor-spheroid, organoid and in-vivo mouse models. To study on cell-autonomous and non-cell-autonomous molecular determinants that regulate hematopoietic stem cells (HSC) self-renewal, differentiation and interaction with hematopoietic microenvironment; underpinnings of dysregulated nucleosome remodeling, intra-cellular heterogeneity in human myelodysplasia and acute myeloid leukemia.

To design stable, cost-effective and non-immunogenic nano particles having controlled release efficacy in disease model and to study the pharmacodynamics and pharmacokinetics of nanoparticles. Prepare, green synthesized metal nanoparticles, glucose capped gold nanoparticles, magnetite polymeric nanocomposites and folic acid tagged mesoporous nano particle conjugated with anticancer agents. To study the association of EGFR and Wnt/β-catenin signaling during initiation and progression of brain cancer. Open up the combinatorial therapeutic approach for killing cancer cells via (a) Wnt/β-catenin, EGFR, NF-kB and ER pathways (b) 'CK2-PML-FoxO3a' and 'CK2-PP2A-Stat3' axis in prostate cancer and glioma (c) RNA helicase, p68 inhibitor in cancer therapy. (d) post-translational regulation of oncogenes and tumor suppressors (pRB and p53) by E3 ligase CHIP and deubiquitinase HAUSP.

Dr. Snehasikta Swarnakar

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MATRIX METALLOPROTEASES (MMPS) ARE KEY PLAYER IN ENDOMETRIOSIS AND GASTRIC ULCERAION

Participants

SRF : Nilanjana Deb, Anuradha Pandit, Yasmin Begam, Preety Choudhary, Project SRF

JRF : Sudipta Mallick, Abhishek Chatterjee,
RA : Dr. Vineet Kumar Mishra
SERB-NPDF : Dr. Tapasi Roy and Anirban Manna, Sr. Technician (2)

BACKGROUND:

We study the pathogenesis of gastric ulcer, gastric cancer, endometriosis and ovarian cancer. We address different causative factors and their mechanism of actions behind their pathogenesis. MMP9 mediated pathway for gastric ulceration has been established for our research. Endometriosis, which is characterized by the deposition and growth of endometrial tissues outside the uterine cavity, poses a major risk factor for infertility and ovarian cancer. The mechanism of endometriosis development is poorly understood. My laboratory is interested in understanding the role of matrix metalloproteinases (MMPs), a group of zinc containing calcium dependent endopeptidases, which are involved in the degradation of different extra-cellular matrix proteins in disease progression. Previous studies from my laboratory have identified altered expression of few matrix metalloproteinases in endometriosis and gastric ulcer. In addition to promoting cellular migration and invasion, certain MMPs are involved in other cellular responses e.g. apoptosis, angiogenesis. The association of MMP promoter polymorphism and hormonal regulation driving endometriosis are currently under progression.

AIMS AND OBJECTIVES:

- To understand the specific role of MMPs in the pathogenesis of endometriosis and gastric ulcer. To study the hormonal regulation of endometriosis and crosstalk with MMPs.
- To understand the association of MMP promoter polymorphism with the progression of endometriosis.
- Screening and identification of natural compounds as novel MMP inhibitors as anti-inflammatory or anti-ulcerative agents.

WORK ACHIEVED:

Investigating the role of MMP13 and oxytocin in endometriosis disease progression

Although altered expression of few matrix metalloproteases including MMP-2, -3, -7 has been documented, however, the involvement of MMP13 has not been reported. We found the association of -77 A/G polymorphism on MMP13 activity as well as endometriosis risk in eastern Indian case-control cohorts. 390 individuals were genotyped for MMP13 -77A/G by PCR-RFLP while expression and activity was checked. A significant correlation of MMP13 -77 AG genotype ($p<0.05$, OR-1.7) as well as AG+AA ($p<0.05$, OR-1.6) in comparison to GG genotype was found with endometriosis progression. In addition, individuals with A allele showed significantly higher expression of MMP-13 as compared to GG carriers in both serum and endometriosis tissue (Fig. 1A-C). Work is in progress with more individuals to validate the functional polymorphism of MMP13 -77 A/G and disease susceptibility.

Endometriosis is an estrogen dependent disease thus hormonal deregulation is said to be the most plausible cause. Oxytocin receptor (OTR) is upregulated by estrogen and an altered expression of OTR has been identified in previous studies in the diseased condition. However, the relation between oxytocin and MMPs is not been identified so far. Herein in vitro studies using human endothelial cells showed that treatment with oxytocin increases cell proliferation rate. Results also showed that oxytocin facilitates endometriosis progression by increasing active MMP2 activity especially its active form. Furthermore, a downregulation of active MMP7 has been pronounced, which is involved in the invasiveness of ovarian endometriosis, thereby showing a dual nature of oxytocin in endometriosis. In addition, we also found a positive correlation of oxytocin with autophagic marker ATG5 and Beclin1 **(Fig. 1D-E).**

Melatonin protects against forced swim stress-induced gastric ulceration

Gastric Ulcer was induced in BALB/C mice through physical stress by means of forced swim stress for 4 hours at 22+/-2°C. Free melatonin (12 mg/kg b.w.) was administered orally 1hr prior to swim stress to evaluate the gastro protective efficacy. Gastric lesions in the fundic mucosa were scored and the ulcer index was quantified (Table 1). In comparison to the control group, mice subjected to forced swim stress showed severe gastric lesions.

Visible gastric hemorrhagic lesions in the fundic stomach were decreased significantly in melatonin (12 mg/kg b.w.), neem fruit and leaf pre-treated mice (Table 1), omeprazole was used as positive control. Histological inspection of the tissue indicated that forced swim stress caused exfoliation of the gastric epithelial cells along with disruption of the mucosal layer of stomach compared with that of control (Fig. 2A). The extent of the gastric mucosal injury was evaluated from the percentage of mucosal injury, which comprised hemorrhage and disruption of gastric epithelial cells. Pre-treatment with melatonin rescued gastric damage and restored the intact epithelial layer as well as continuous mucosal and submucosal layers.

Table 1:

Gastro protective effect of melatonin, omez and neem	
Sample	**Ulcer Index**
Control	**0**
Stress	**55.49**
Stress + Melatonin	**7.25**
Stress + Omez	**1.5**
Stress + Neem leaf	**10.2**
Stress + Neem bark	**15.9**
Stress + Neem fruit	**8.53**
Stress + Neem seed	**12.9**

Melatonin reduces proMMP-3 activity in stress-induced gastric ulcer

MMP-3 activities were assessed from the experimental gastric tissues. To compare the activity of MMP-3 equal amounts of gastric tissue extracts from different mice group were subjected to casein zymography. The densitometric analysis of zymographic bands shows that stress increased MMP-3 activity in the gastric tissues significantly (Fig. 2B) while prior treatment with melatonin decreased its activity to ~37 fold. Besides, stress induced ulcer model in rat was developed and the effect of Omeprazole was studied. Omeprazole helps in suppressing DNA damage as observed in Fig. 2C.

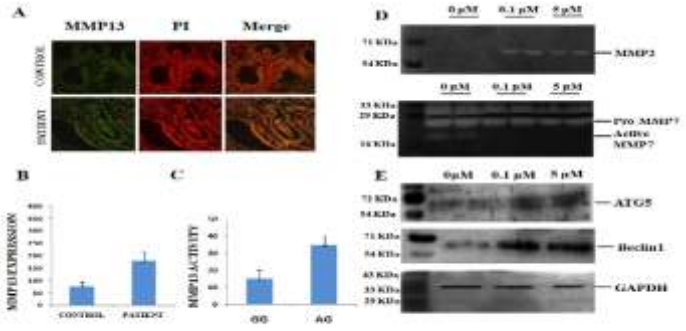


Figure 1

Fig. 1. (A) *Immunofluorescence staining of endometriotic tissues, (B, C) MMP13 activity in control, patient and GG/AG genotypes, respectively, (D) When oxytocin is added in endocervical epithelial cells (End1/E6E7) active MMP-2 activity is increased while active MMP-7 activity is greatly reduced, (E) Oxytocin treatment induces autophagy marker ATG5 and Beclin1 in End1/E6E7 cells.*

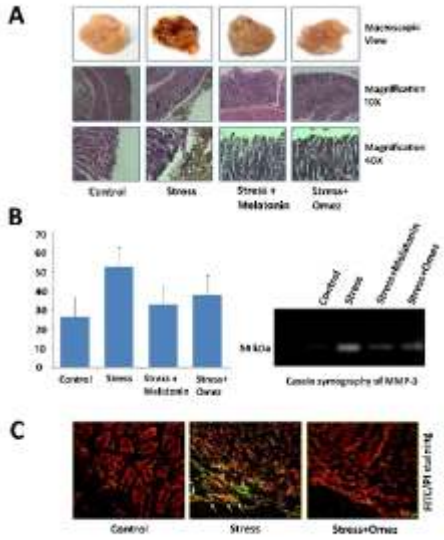


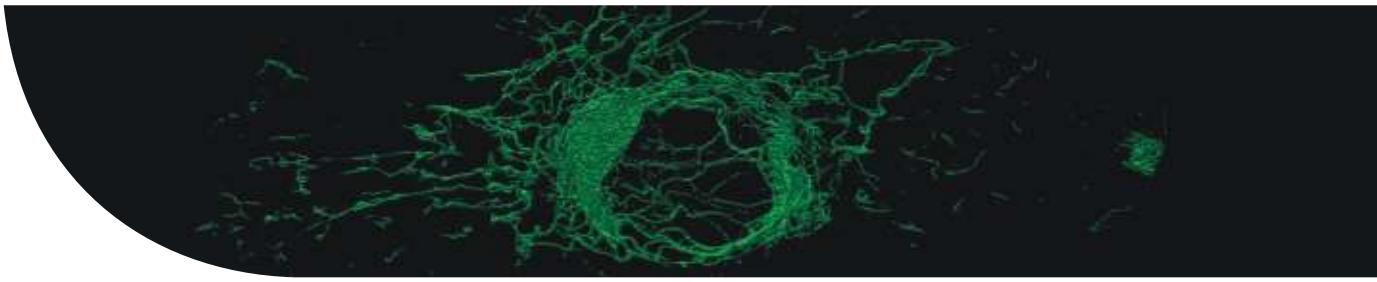
Figure 2

Fig. 2. (A) *Gastro-protective action of nano-melatonin against forced swim stress induced gastric ulceration. Macroscopic image of gastric tissues of control, stress, and melatonin pre-treated mice (n=4). Hematoxylin and eosin staining for stomach tissue sections of control, stress, melatonin pre-treated mice. (B) Casein zymography of gastric tissues from control, stress and melatonin pre-treated mice developed quantified and evaluated in histogram. (C) TUNEL staining of gastric mucosal sections of rat, merging of PI-stained nuclei (red) and FITC stained (green). White arrows indicate DNA fragmentation co-localized in the nuclei of ulcerated tissues.*

FUTURE RESEARCH PLANS:

Identification of a biomarker and development of a prognostic kit using MMP13/MMP7 as a tool for the early detection of endometriosis.

Study the crosstalk between MMPs and oxytocin to find a specific target to abrogate MMP activity against endometriosis disease progression.



Specific inhibition of specific MMPs by small molecules is our challenging task to halt gastric inflammation.

PUBLICATIONS:

Pandit, A., Begum, Y., Chatterjee, Kasturi., and Swarnakar, S. (2018) Hormonal regulation of endometriosis and clinical significance. **IJBB** 55, 351-360.

Chatterjee, K., Jana, S., Choudhary, P., and Swarnakar, S. (2018) Triumph and tumult of matrix metalloproteinases and their crosstalk with eicosanoids in cancer. **Cancer Metastasis** Rev. 37, 279-288.

Pramanik, S. K., Pal, U., Choudhary, P., Singh, H., Reiter, R. J., Ethirajan, A., Swarnakar, S., and Das, A. (2019) Stimuli-responsive nanocapsules for the spatiotemporal release of melatonin: Protection against gastric inflammation. **ACS Appl. Bio Mater.** DOI: 10.1021/acsabm.9b00236

Subramanian, L., Maghajothi, S., Singh, M., Kesh, K., Ananthamohan, K., Sharma, S., Khullar, M., Victor, S.M., Swarnakar, S., Asthana, S., Mullasari, A.S., and Mahapatra, N.R. (2019) A common tag nucleotide variant in MMP7 promoter increases risk for hypertension via enhanced interactions with CREB transcription factor. **BioRxiv**. DOI: https://doi.org/10.1101/568774.

BOOK CHAPTERS:

Nilanjana Deb, Sudipta Mallick, A Jaiswal, Anirban Manna, U Mabalirajan and **Snehasikta Swarnakar** (2018) Role of matrix metalloproteinase and oxidants in lung diseases. Oxidative stress in lung diseases. Vol. 2 Springer Nature Singapore.

AWARDS / HONOURS / MEMBERSHIPS:

Students:

Nilanjana Deb

Best oral paper presentation at the National conference "Present Scenario, Challenges & Future Perspective of Drug Discovery & Smart Delivery System Development" at Asansol.

Anuradha Pandit

Best poster award in International Congress on Endometriosis in 2019 at Jaipur.

EXTRAMURAL FUNDING:

Title: Mechanistic evalution of anti-cancer property against in vitro and in vivo cancer models with the active constituents of the bark of Diospyros melanoxylon.
Start year: April, 2016 ; **End year:** March, 2019
Funding agency: ICMR, India

Title: Role of Matrix Metalloproteinases and heat shock proteins in stress-induced gastric cell damage: Effect of antioxidant thereon.
Start year: May, 2015 ; **End year:** May, 2018
Funding agency: LSRB-DRDO, India
CONFERENCES / WORKSHOPS : 11 Nos.

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB:

Guha Research Conference (GRC)
Start Date: November 30, 2018 ; **End Date:** December 04, 2018
Year: 2018
Venue: Santiniketan, West Bengal, India

INVITED TALKS:

Specific role of matrix metalloprotease7 for malignancy in endometriosis; Invited lecture; 87h Annual meeting of IABS, Sher-Kasmir Univ, Kasmir, April 20-22, 2018.

MMP-2 and -7 are associated to angiogenesis and EMT during endometriosis; Invited lecture; Angiogenesis Meet, Kolapur, Pune, October, 2019.

EGFR-mediated MMP-7 upregulation in ovarian endometriosis; Invited lecture; Guha Research Conference (GRC), Santiniketan, West Bengal, India, November 30 December 04, 2018.

Striking a balance among MMPs in gastric and ovarian cancer; Invited lecture; Research Council Meet, CSIR-IICB (Saltlake campus), March 2018.

Importance of Science Awareness in modern day for healthy life; Guest lecture; Annual day celebration, Satish Chandra Memorial School, Nadia, January 12, 2019.

Specific signalling by specific metalloprotease(s) during endometriosis; Invited lecture; 8th Annual meeting of IABS, NIIST, Kerala, February 25-27, 2019.

Do Matrix metalloprotease Matter? Invited lecture; International Congress on Endometriosis, Jaipur, India, March 8-10, 2019.

Genetic Polymorphism of MMPs and Risk of Gastric Cancer; Invited lecture; Trends in Modern biology, Visva-Bharati, Santiniketan, India, March 23-24, 2019.

Anti-inflammatory mechanism of a novel flavonoid from neem leaf; Guest lecture; National Conference on drug discovery at Gupta College, Asansol, April 06, 2019.

Prof. Samit Chattopadhyay

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Understanding the novel functions of chromatin remodeling protein, SMAR1

Participants

Aftab Alam, RA
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Shruti Joshi, CSIR-SRF
Sonal Patel, CSIR-SRF
Apoorva Parulekar, UGC-SRF
Arpankumar Choksi, CSIR-SRF
Priyanka, DBT-SRF
Richa Pant, NCCS-SRF
Vibhuti Kumar Shah, DBT-SRF
Tanaya Roychowdhury, UGC-SRF

Collaborator(s)

Dr. Amitava Das, NCL, Pune
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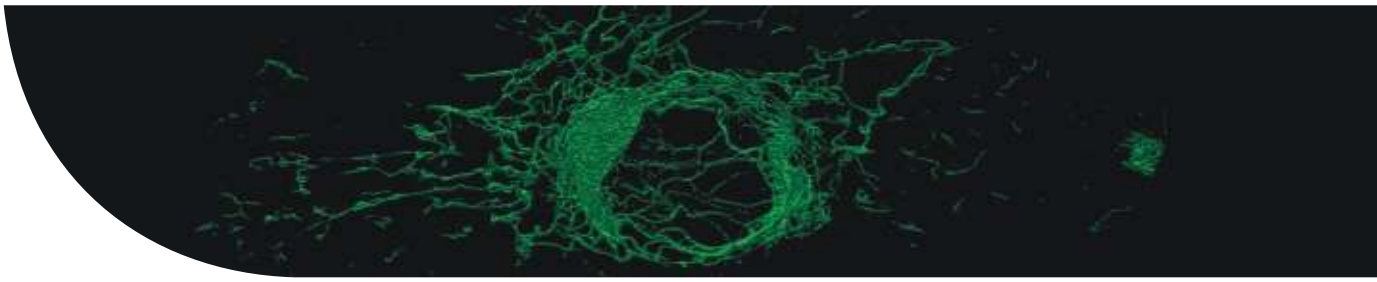
Dr. Saumitra Das, IISc, Bengaluru
Dr. Subhrangshu Chatterjee, Bose Institute, Kolkata
Dr. Ramanamurthy Bopanna, NCCS
Dr. Manas K Santra, NCCS
Dr. Pankaj Poddar, CSIR-NCL, Pune
Dr. Parasuraman Jaishankar, IICB, Kolkata

Background

The interphase nucleus is characterized by the presence of nuclear matrix, which provides basic shape and structural integrity to the nucleus. It mainly comprises of nucleic acids and proteins as the interacting partners and is important for various cellular processes like replication, transcription, splicing, DNA damage repair and recombination. Amongst different factors involved in compaction and tethering of chromatin to nuclear proteins, Scaffold/Matrix binding proteins (MARBPs) play a central role. SMAR1 (Scaffold/Matrix Attachment Region binding protein 1) is one such nuclear matrix-binding protein identified from double positive mouse thymocytes (Chattopadhyay et al., 2000, Genomics). SMAR1 is a known chromatin modifier, which recruits HDAC1/mSin3a repressor complex to cyclin D1 promoter and thereby inhibiting its transcription (Rampalli et al., 2005, Mol Cell Biol). Interestingly, SMAR1 is also reported to interact with p53 and play a decisive role between cell cycle arrest and apoptosis (Sinha et al., 2010, EMBO J). SMAR1 is also known to be a stress response protein, wherein it regulates the acetylation status of Ku70 by interacting with HDAC6 (Chaudhary et al., 2014, Cell Death and Disease). Additionally, SMAR1 was reported to negatively regulate alternative splicing by modulating the acetylation status of Sam68 by recruiting HDAC6 (Nakka et al., 2015, PNAS). ChIP-seq analysis suggested that SMAR1 binds and regulate miR-371-373 which is an important miRNA cluster involved in cancer and metastasis (Mathai et. al., 2016, Scientific Reports). We have also reported that SMAR1 governs the switch between effector T cells and regulatory T cells by allowing the commitment of T cells to Th2 lineage and suppressing the Th1 and Th17 lineage commitment. (Mirlekar et.al., 2015, Mucosal Immunology; Mirlekar et. al., 2017, Frontiers in Immunology). It has also been observed that with the progression in grades of breast carcinoma, there is a drastic reduction in levels of SMAR1 (Singh et al., 2007, PLoS One). Recently we reported that in higher grades of colorectal cancers, reactivation of Wnt/β-Catenin results in proteasomal degradation of SMAR1 through D boxes (Taye et. al., 2018, Oncotarget). The proteosomal machinery that is involved in degradation of SMAR1 involves CDC20, which is an E3 Ubiquitin Ligase that mediates this degradation. (Paul et. al., 2017, Cell Death and Disease). Recently, ChIP-Seq data of 14 S/MAR binding proteins were analyzed and the binding site coordinates of these proteins were used to prepare a non-redundant S/MAR dataset of human genome. Along with co-ordinate (location) details of S/MARs, the dataset also revealed details of S/MAR features, namely, length, inter-SMAR length (the chromatin loop size), nucleotide repeats, motif abundance, chromosomal distribution and genomic context. S/MARs identified in this study and their subsequent analysis also suggests that these elements act as hotspots for integration of retroviruses. Therefore, these data will help toward better understanding of genome functioning and designing effective anti-viral therapeutics (Narwade et al., 2019, Nucleic Acids Res.). To facilitate user friendly browsing and retrieval of the data obtained in this study, a web interface, MARome (http://bioinfo.net.in/MARome), has been developed.

Work Achieved

Regulation of antigen processing and presentation by SMAR1 and its implication in tumorigenesis:



Cancer cells evade immune surveillance by down-regulating antigen processing machinery affecting the major histocompatibility complex (MHC) I pathway. Proteins with chaperone activity like calnexin and calreticulin play a pivotal role in MHC I pathway. SMAR1 is a nuclear matrix protein having repressor function and targets a set of specific genes in response to various physiological and environmental conditions. Our experiments confirmed that SMAR1 regulates calnexin gene expression. Immunoprecipitation experiments confirmed interaction between MHC I and calnexin. Flow cytometry analysis revealed that SMAR1 overexpression increases MHC1 expression in cancer. We already had shown that SMAR1 suppresses calnexin expression through HDAC1. Wang et al (2013) reported that p53 regulates MHC1 in cancer and infection by up regulating ERAP1 (ER aminopeptidase1). Our lab had already established the fact that SMAR1 stabilizes p53, so we checked the correlation between SMAR1 and ERAP1 to further strengthen our results. We found that SMAR1 stabilizes p53 and in turn increases ERAP1 expression. Thus, our results led us to predict two tier regulation of MHC I by SMAR1 in both p53 dependent and independent manner (Alam et. al., 2019)

Role of SMAR1 in repression of hTERT and inhibition of cancer stem cell trait in colorectal cancer (Manuscript to communicate)

Telomerase re-activation is one of the hall marks of cancer cells. More than 85% of solid tumors exhibit indefinite proliferation of cells due to reactivation of this enzyme. Telomerase is an RNA-dependent DNA polymerase and is responsible for maintaining the length of the telomeres in actively dividing cancer cells. The reactivation of this enzyme imparts the immortal phenotype that is so typical of a cancer cell. Telomerase is a holo-enzyme, containing a protein moiety and RNA. The catalytic subunit is the hTERT (human Telomerase Reverse Transcriptase) and the RNA entity is hTR (human Telomeric RNA). Reports suggest that only the hTERT is enough to cause reactivation of telomerase in any primary cell. Higher grades of cancer exhibit elevated expression of hTERT and this gives a cancer cell an advantage of replicative immortality. We show that SMAR1 negatively regulates the transcription of hTERT. SMAR1 recruits the HDAC1/mSin3a co-repressor complex at the hTERT promoter and alters the histone marks to bring about repression of hTERT by deacetylating the histones.

Along with imparting indefinite proliferative potential to a cancer cell, hTERT performs several other non-canonical functions which are crucial in successful tumor progression. One such function of hTERT is maintaining the stem cell population in the tumor. We find that SMAR1 acts as a negative regulator of cancer stem cell trait. CD133high cells exhibit lower levels of SMAR1 as compared to the CD133low cells. Also SMAR1 knock down enhances the CD133+ population in colorectal cancer cells. Moreover, knock down of SMAR1 leads to enhanced potential for colonosphere formation. We also find that SMAR1 knock down makes the colorectal cancer cells resistant to anoikis. We thus propose SMAR1 as a novel transcriptional repressor of hTERT and thus the cancer stem cell phenotype. We also propose the use of isothiocynate derivative, SCS-OCL-381, as a SMAR1 stabilizing compound. We find that SCS-OCL-381, stabilizes SMAR1 protein expression and in turn brings about transcriptional repression of hTERT.

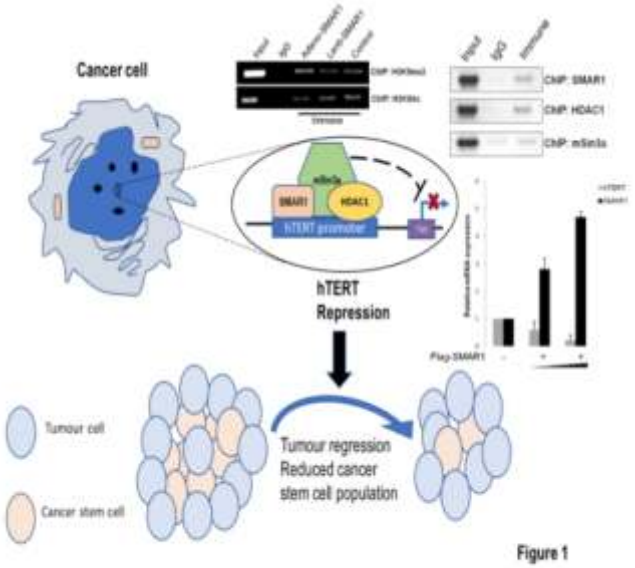
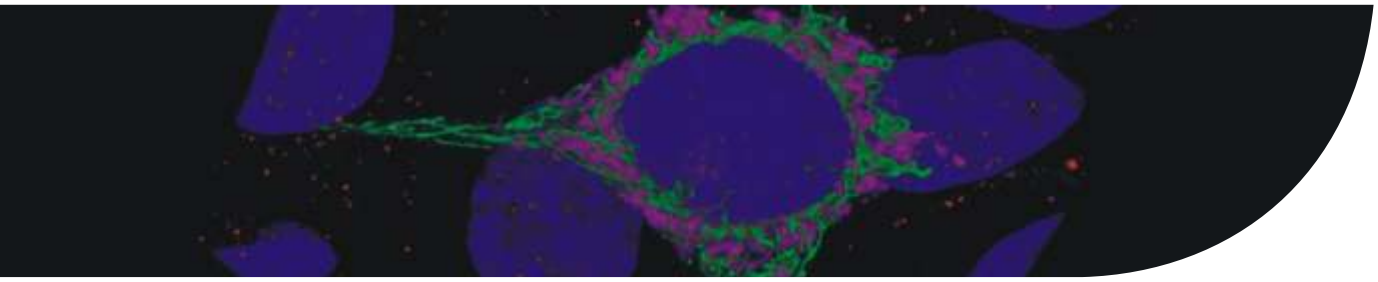
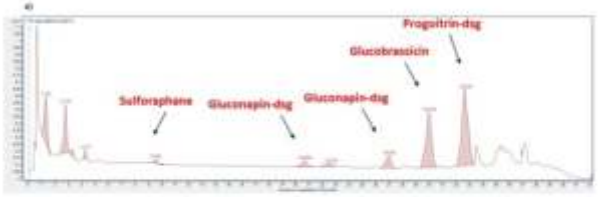


Figure 1: Proposed model. SMAR1 recruits HDAC1/mSin3a co-repressor complex onto the hTERT promoter and brings about epigenetic repression of hTERT expression. This leads to inhibition of cancer stem cell trait in colorectal cancer cells.





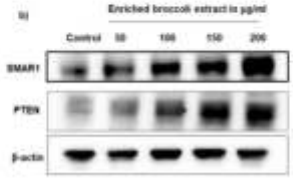


Figure 2

Figure 2: Enriched broccoli extract is effective at stabilizing SMAR1 and PTEN. (a) TIC of enriched broccoli Aqueous extract (b) Effect of extract on oral cancer cells show SMAR1 and PTEN stabilization.

Ongoing research studies:

Surfing the SMAR1 regulatory network in oral cancer (Tanaya Roychowdhury)

Oral cancer ranks amongst the top three in India. Although it is easily detectable and symptoms occur earlier, patients present at a late stage. The overall disease specific mortality rate is 49%. In India it is of significant public health interest due to its high occurrence and expensive treatment regimen. Loss of tumour suppressor genes is one of the keys to cancer development. For example, p53 is either deleted or there is a gain of function mutation in it which confers the cells with increased survival potential. SMAR1 is a matrix attachment region (MAR) binding protein which acts in concert with p53 to suppress tumour formation. We checked for SMAR1 levels in both primary tissues and cell lines using western blot, real time and IHC to confirm downregulation. Scratch wound assay, colony formation assay and sphere formation assay in OSCC cell lines clearly indicated tumour suppressive role of SMAR1. We next developed oral cancer model in Balb/c and found SMAR1 to be downregulated. Thus, SMAR1 stabilization is an attractive therapeutic avenue. Cruciferous family of vegetables act as a good source of anti-cancer compounds. A recent study by Pier Paolo Pandolfi's team published in the prestigious journal Science has clearly highlighted the role of Indole 3 carbinol, a natural compound found in broccoli, in stabilizing PTEN by inhibiting E3-ubiquitin ligase WWP1 in prostate cancer. Sulforaphane is another natural compound found in ample amounts in cruciferous family that has anti-cancer properties. Interestingly, sulforaphane stabilizes SMAR1. These findings led us to formulate an enriched broccoli extract having cancer preventive properties. We have tested our extract on oral cancer cells for its efficacy to stabilize SMAR1 and PTEN. Indeed, we found the aqueous extract to stabilize both the tumour suppressors. We have fed animals with this extract and found all the protective bioactive compounds in blood (Figure 3a & 3b). We are in the process of validating its efficacy in oral cancer mouse model. For detailed understanding of SMAR1 regulated pathways we sent samples for transcriptomics analysis. Data suggests SMAR1 down regulates several key pathways like PI3K-AKT, MAPK, Ras, calcium signaling etc. in oral cancer. Interestingly we found some important oncogenic long non-coding RNAs to be down regulated by SMAR1.

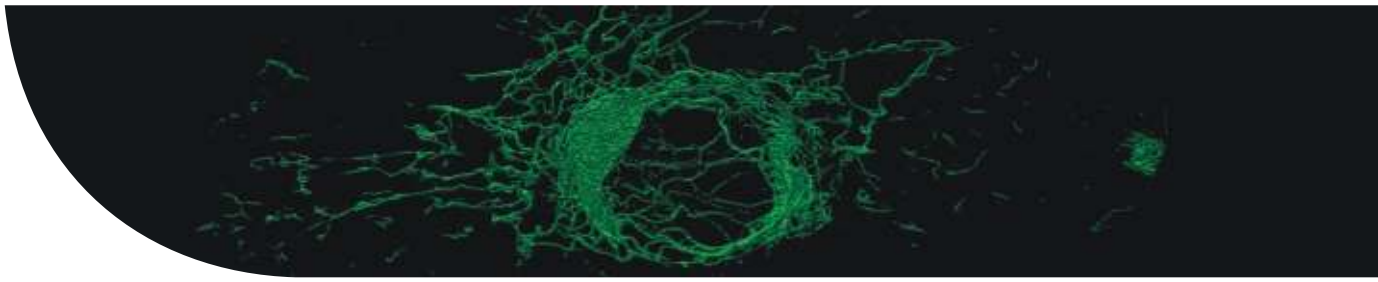
Other research studies:

- Role of SMAR1 in tumor cell metabolism via regulation of PKM alternative splicing (Arpan Choksi)

Cancer cells utilize more glucose and produce more lactate independent of oxygen availability. This phenomenon is known as aerobic glycolysis or Warburg effect. Cancer cells achieve this by upregulating the embryonic isoform of pyruvate kinase enzyme; PKM2. SMAR1 being a tumor suppressor reduces rate of glycolysis and promotes mitochondrial biogenesis. Our Study reveals SMAR1 regulates PKM alternative splicing by interacting with hnRNP A1, hnRNP A2 and PTB in an RNA dependent manner. Moreover, upon treatment with Tubastatin A there is higher expression of PKM2 over PKM1. This suggests that SMAR1 mediated regulation of PKM alternative splicing might be HDAC6-dependent. Therapeutic strategies targeting tumor metabolism and stabilization of SMAR1 expression might prove to be an effective approach to eradicate cancer.

- To decipher the role of SMAR1 in adipogenesis: Its implication in obesity-related cancer (Richa Pant)

Adipogenesis involves the formation of adipocytes from precursor fibroblast cells in a highly orchestrated programme of gene expression. PPARγ is the critical transcription factor in adipogenesis and deregulation of this process may lead to



disproportionate fat deposition which is a major cause of obesity and associated diseases worldwide. Since SMAR1 is reported to repress the expression of different transcription factors and its expression is also reported to be low in high weight gainers as compared to low weight gainers (GEO database), we investigated the potential role of SMAR1 in adipogenesis. SMAR1 expression change during differentiation in 3T3-L1 cell line is validated both at transcript and protein level by real time PCR and immunoblotting respectively. SMAR1 was found to be degraded during adipogenesis by proteasome mediated pathway. Adenovirus mediated overexpression and sh-RNA mediated knockdown of SMAR1 in 3T3-L1 cell line showed a change in expression of PPARγ. Moreover, binding of SMAR1 along with HDAC1 and mSin3a on PPARγ promoter has been confirmed by Chromatin Immunoprecipitation. All together, these results indicate the involvement of SMAR1 in adipogenesis via regulation of PPARγ, the detailed molecular mechanism for the same might be interesting to decode.

- To gain mechanistic insights into LPS-regulated cancer progression: Fine-tuning of tumor suppressor SMAR1 (Priyanka)

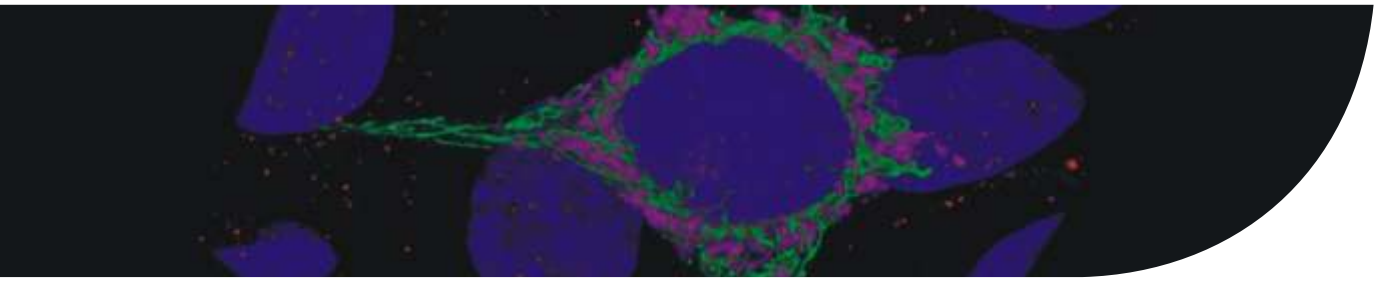
Bacterial extracts are being used for the treatment of cancer from more than a century. The most cited case is that by the physician and surgeon William B. Coley, who observed that many of his patients with various forms of cancer had their tumors regress when they were infected with bacterial pathogens. It was later discovered that LPS was the “haemorrhage producing fraction” of Coley's toxin that accounted for its anti-tumor effect. In this study we observed an increase in the expression of tumor suppressor SMAR1 on LPS treatment in a concentration dependent manner. LPS injection in tumor bearing mice also resulted in tumor regression. So, it can be speculated that LPS mediated activation of TLR pathway in cancer could modulate the expression of tumor suppressor SMAR1 and hence, regulates the tumor progression.

- Studies on chromatin remodeling protein SMAR1 in CD4+ memory Tcell differentiation (Vibhuti Kumar Shah)

Memory T cell subsets differentiation initiates after antigen clearance from host and remain dormant for several months. Tm can quickly/promptly evoke the effector function, high cytokine production and increased response with reduced Ag presentation. The differentiation into its subset i.e. central and effector memory; are governed by Tbet and Eomes which provides poised effector function and cellular longevity, respectively. In this study we show that after immunization, the SMAR1 deficient mice show increased population of effector memory, unlike wild type mice which had more of central memory. In absence of SMAR1, the transcript expression was increased in both the memory subsets. The chromatin remodelling of eomes promoter, in presence/ absence of Notch1, relates to the increased transcript of Eomes in SMAR1 deficient memory subset. Treatment with activator and inhibitor of Notch1 shows the competitive binding of SMAR1 and Notch1 on eomes promoter, thus regulating eomes expression. These findings provide evidence that SMAR1 has a central role in differentiation of memory T cell which could be strategized for treatment of chronic diseases and tumor immunotherapy.

PUBLICATIONS

1. SMAR1 favors immunosurveillance of cancer cells by modulating calnexin and MHC I expression. Alam A, Taye N, Patel S, Thube M, Mullick J, Shah VK, Pant R, Roychowdhury T, Banerjee N, Chatterjee S, Bhattacharya R, Roy R, Mukhopadhyay A, Mogare D, Chattopadhyay S. Neoplasia. 2019 Aug 15;21(10):945-962. doi: 10.1016/j.neo.2019.07.002.
2. Mapping of scaffold/matrix attachment regions in human genome: a data mining exercise. Narwade N, Patel S, Alam A, Chattopadhyay S, Mittal S, Kulkarni A. Nucleic Acids Res. 2019 Jul 2. pii: gkz562. doi: 10.1093/nar/gkz562.
3. Site-specific amino acid substitution in dodecameric peptides determines thestability and unfolding of c-MYC quadruplex promoting apoptosis in cancer cells. Sengupta P, Banerjee N, Roychowdhury T, Dutta A, Chattopadhyay S, Chatterjee S. Nucleic Acids Res. 2018 Nov 2; 46 (19):9932-9950. Doi:10.1093/nar/gky824.
4. Retention of Anticancer Activity of Curcumin after Conjugation with Fluorescent Gold Quantum Clusters: An in Vitro and in Vivo Xenograft Study. Khandelwal P., Alam A., Choksi A., Chattopadhyay S., Poddar P., ACS Omega, 2018, 3 (5), pp 47764785
5. SMAR1 inhibits Wnt/β-catenin signaling and prevents colorectal cancer progression. Taye N., Alam A., Ghorai S., Chatterji D., Parulekar A., Mogare D., Singh S., Sengupta P., Chatterjee S., Bhat M., Santra M., Salunkhe P., Finston S., Chattopadhyay S., Oncotarget, 2018, 9(30):21322-21336.



6. Carbon nanospheres mediated nuclear delivery of SMAR1 protein (DNA binding domain) controls breast tumor in mice model. (Lond). Bhagat PN, Jadhav SH, Chattopadhyay S, Paknikar KM. Nanomedicine, 2018, 13(4):353-372.

7. G-Quadruplex surveillance in BCL-2 gene: a promising therapeutic intervention in cancer treatment. Sengupta P., Chattopadhyay S., Chatterjee S., Drug Discovery Today. 2018, 22(8):1165-1186.

Book Chapters / Invited Reviews

Patel S., Choksi A., Pant R., Alam A., Chattopadhyay S. (2018) Nutritional Programming of Metabolic Syndrome: Role of Nutrients in Shaping the Epigenetics. In: Patel V., Preedy V. (eds) Handbook of Nutrition, Diet, and Epigenetics. Springer, Cham

EXTRAMURAL FUNDING

Samit Chattopadhyay

Metabolic stress induced epigenetic changes in the transcriptional regulator gene SMAR1. 2017-2020 (DBT, India).

Role of Nuclear Matrix Protein SMAR1 as Regulator of Suppressor T cell in Inflammatory Bowel Disease (IBD). 2017-2020 (DBT, India).

Tumor suppressor SMAR1 regulates transcription of β-catenin and protect from metastatic colon cancer. 2016-2019 (DST, India).
Multi-dimensional research to enable systems medicine: acceleration using a Cluster Approach (Systems Medicine Cluster: SyMeC). 2017-2021.

J.C. Bose fellowship. DST-SERB. 2017-2019.

AWARDS / HONOURS

Samit Chattopadhyay
Took over the additional charge of director CSIR- North East Institute of Science and Technology (NEIST), Jorhat from Dr D Ramaiah, former director, CSIR-NEIST on June 30, 2018.

Convener, Sectional Committee, Indian National Science Academy (INSA) (2017 onwards)

Founder Director of Translational Research Unit of Excellence (TRUE), Salt Lake, Kolkata, 2016.

TALKS DELIEVERED

Samit Chattopadhyay

Tumor suppressor SMAR1 and its role in cancer stem cells; 20th transcription assembly meeting, Centre for DNA fingerprinting and diagnostics (CDFD), Hyderabad, India, 26 July 2018

To be or not to be: Recent perspectives on transformation of a cancer; Dr. J N Boruah Memorial Lecture, Agricultural University, Jorhat, India, 30 Aug 2018

Regulation of MHC-I presentation in cancer cells: Possible role of tumor suppressor SMAR1; invited lecture; XLII All India Cell Biology Conference & 2nd International Conference on Trend in Cell and molecular biology, BITS Pilani, KK Birla Goa Campus, Goa, India, 22 December 2018

Recent Perspectives and future goal in doing science in India; Young investigator meet, Guwahati, India, 6-10 March 2019

Chromatin remodeling protein: Transcription factor that functions as an important tumor suppressor; Symposium on emerging trends in biological sciences research, invited speaker, Institute of Life Sciences (ILS), Bhubaneswar, India, 19 March 2019.

Ph. D. Awardee :

Ph. D. Students :	**Date**
1. Aftab Alam	18th June 2018
2. Aritra Das	18th June 2018
3. Sonal Patel	30th October 2018
4. Shruti Joshi	6th February 2019

Dr. Mrinal Kanti Ghosh

mrinal.res@gmail.com

Mechanistic elucidation of signaling crosstalks involved in oncogenesis and development of novel targeted nanodelivery systems for therapeutic intervention of cancer

Participants

Dr. Sibani Sarkar (WoS, DHR, ICMR)

SRF : Neerajana Datta, Veenita Khare, Gouranga Saha, Satadeepa Kal, Dipankar Chakraborty, Bhaskar Basu, Shaheda Tabassum, Rajni Shaw

JRF : Shrabastee Chakraborty, Partha Mohanta, Sunny Kumar, Shubhajit Karmakar

Mr. Sourav Dey (Lab Manager)

Collaborator(s)

Name of collaborator outside CSIR-IICB

Dr. Sandip Chatterjee
Park Clinic, Kolkata

Dr. Uttara Chatterjee
Park Clinic & IPGMER, Kolkata

Dr. Suresh Bajoria
RTIICS, NH, Kolkata

Background

Oncogenesis ("onco", the Latin word for "tumor" and "genesis" meaning "beginning") is an elaborate and complex process by which normal cells turn into cancerous cells. It involves a multitude of genetic and cellular level changes, bringing forth regulation & crosstalks amidst various signalling pathways, which ultimately lead to cancer. Cellular signalling pathways get perturbed, when triggered by mutations or when molecular players defy normal genetics. This leads to undue cellular proliferation, resisting cell death, induced angiogenesis and metastasis, all of which are hallmarks of cancer.

There is a need for properly understanding the signalling mechanics and complex cellular pathways as well as the crosstalk between them so that suitable molecular targets involved in oncogenesis can be identified. Subsequently, it would pave way for further translational research in the arena of cancer therapeutics. Recent advances in the field of translational research has led to development of various novel targeted delivery approaches such as peptide-targeted drug delivery or nanoformulations or combination therapy in order to overcome the hurdles in the therapeutic pathway to curb oncogenesis.

Thus, it is imperative to focus upon the proper balance of basic and translational research in order to achieve significant clinical outcome in the field of cancer therapeutics.

Aims and Objectives

To identify novel molecular targets leading to oncogenesis under different types of cancer scenario.

To investigate the involvement of different signaling pathways such as Wnt, NF-κB and EGFR signaling as well as their crosstalk leading to oncogenesis.

To gain mechanistic insights into the role and regulation of key molecular players such as p68, RelA, CHIP, HAUSP, MGMT, PML and PTEN towards the process of curbing oncogenesis.

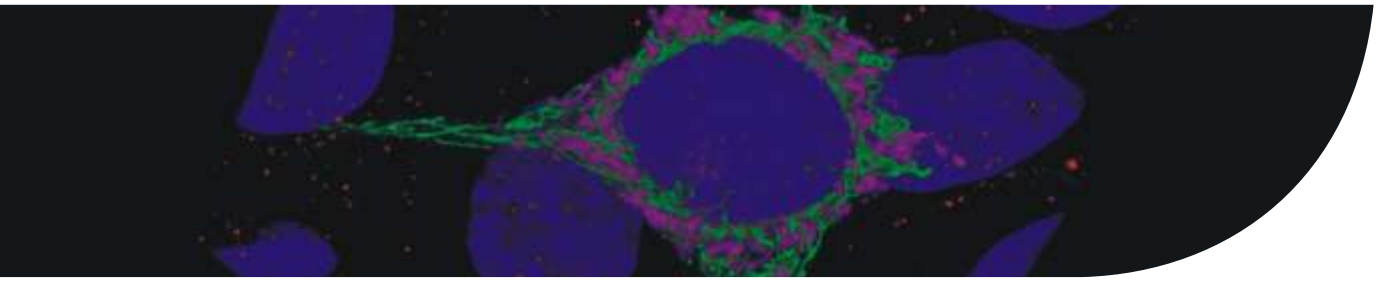
To develop novel targeted drug delivery methods such as peptide based or exosome mediated drug delivery or through various nanoformulations or combinational approach for therapeutic purpose.

Work Achieved

RNA helicase p68 deploys β-catenin in regulating RelA/p65 gene expression: implications in colon cancer

High prevalence of colorectal cancer (CRC) requires proper and thorough understanding of the molecular mechanism underlying its initiation and progression. Chronic inflammation plays a significant role in development of CRC, a key mediator of which are components of NF-κB signaling.

RelA/p65 a crucial member of NF-κB signaling pathway plays diverse role in mediating oncogenesis. RNA helicase p68 apart from being a vital player of RNA metabolism acts as a transcriptional coactivator of several oncogenic transcription factors including β-catenin and is also highly implicated in cancer progression. In our study, we reported for the first time a novel



mechanism of alliance between p68 and β-catenin in regulating the expression of RelA and stimulating the NF-κB signaling axis towards driving colon carcinogenesis.

Our findings report that p68, β-catenin and RelA proteins were found to bear strong positive correlation in normal and colon carcinoma patient samples. Moreover, upon increasing p68 and β-catenin expression both at the mRNA as well as at the protein levels, there was a similar and significant increase of RelA mRNA and protein expression. p68, β-catenin and Wnt3a overexpression elevated RelA promoter activity. Conversely, p68 and β-catenin knockdown diminished RelA promoter activity and led to reduced RelA mRNA and protein expression. p68 was perceived to occupy RelA promoter with β-catenin at the TCF4/LEF (TBE) sites thereby potentiating RelA transcription. p68 and β-catenin complex positively

modulated the expression of important NF-κB target genes, which was further corroborated by our findings in clinical samples. Tumors generated in mice colorectal allograft model, stably expressing p68 further reinforced our in vitro findings.
Thus, our findings report novel mechanistic regulation of RelA through p68 mediated deployment of β-catenin and further elaborates upon the signaling crosstalk between Wnt and NF-κB pathways leading to CRC. Our study unravelled novel modes of p68-mediated colon carcinogenesis, marking it a potential target for therapy.

Future Research Plans

To focus upon translational research via anti-cancer drug discovery from natural products and designing target based synthetic peptides for therapeutic purposes.

Developing peptide based therapeutic approaches and further investigation of targeted drug delivery systems such as nanoparticle or exosome-based approaches for curbing tumorigenesis.

To further into the mechanistic insights involved in the regulation of key molecular players such as p68, HAUSP, CHIP and PTEN for combating cancer.

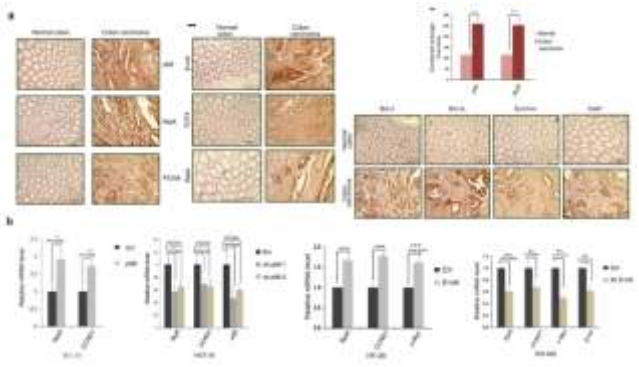


Fig. 1: (a)Representative images depicting immunohistochemical (IHC) staining of p68, RelA, β-catenin, target genes, TCF4 and PCNA conducted in tissue sections derived from human normal colon and colon carcinoma samples (b) mRNA levels of RelA is regulated by p68 and β-catenin under over-expressed and knockdown conditions.

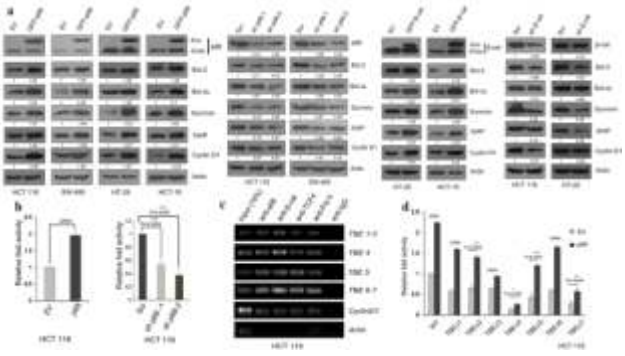


Fig. 2: (a) Protein expression levels of RelA is regulated by p68 and β-catenin under over-expressed and knockdown conditions (b) p68 transcriptionally regulates RelA gene expression through its occupancy at the TBE sites of the RelA promoter depicted by luciferase assay (c) Chromatin Immunoprecipitation assay demonstrating that p68, β-catenin and TCF4 bind to the promoter region of RelA in vivo (d) Luciferase assays using mutant RelA promoters depicted that the deletion of TCF-4 binding sites (TBEs) markedly reduced the RelA promoter activity.

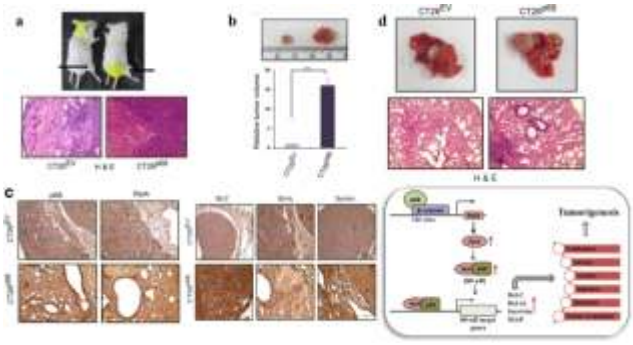


Fig. 3: (a) p68 overexpression in mice colorectal allograft model leads to enhanced primary tumor growth and corresponding H&E-stained images of the respective tumor sections (b) Representative images of the generated primary tumors (c) Representative images depicting IHC staining conducted in lung metastatic nodules containing tumor tissue sections. (d) Representative images of lungs with metastatic nodules, the corresponding H&E-stained images and schematic representation, depicting p68 coactivation of β-catenin in upregulation of RelA transcriptional activity.

PUBLICATIONS

Khare V, Tabassum S, Chatterjee U, Chatterjee S and Ghosh MK* (2019). RNA helicase p68 deploys β-catenin in regulating RelA/p65 gene expression: Implications in Colon cancer. J Expt. & Clinic Can Res. 38(330): 1-19. {IF=6.2}

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Sarkar S, Chakraborty D, Bhowmik A and Ghosh MK* (2019). Cerebral ischemic stroke: cellular fate and therapeutic opportunities. Frontiers in Bioscience, Landmark 24: 435-450. {IF=2.5}

Bhattacharya S, Chakraborty D, Basu M and Ghosh MK* (2018). Emerging insights into HAUSP (USP7) in physiology, cancer and other diseases. Signal Transduction & Targeted Therapy 3(17) 1-12. {IF=5.873}

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Paul I, Basu M and Ghosh MK* (2018). CHIP (Carboxy Terminus of HSC70 Interacting Protein). Encyclopedia of Signaling Molecules, 2nd Edition, 1083-91.

Basu B, Bhattacharya S, Saha G and Ghosh MK* (2018). USP7 (Ubiquitin Specific Protease 7). Encyclopedia of Signaling Molecules, 2nd Edition, 5848-54.

EXTRAMURAL FUNDING

A Novel Nanotechnology based Approach of Glioma Therapy by Targeting HAUSP -MDM2 axis in combination with Temozolomide. 2019 2022: DST-SERB, India. Total cost: ~Rs.40 Lakhs (Ongoing).

Development of a combinatorial nanovehicles assisted therapeutic system for the efficient treatment of glioma. 2018 2021: DST-Nano Mission, India. Total cost: ~Rs.42.0 Lakhs (Ongoing).

Glucocorticoid Receptor-Assisted Drug Sensitization (GRADS) in colorectal cancer therapy: Nano-therapeutic strategy towards repurposing of anti-cancer drugs. 2018 2021: DST-SERB Total cost: Rs.30.67 Lakhs (Ongoing).

CONFERENCES / WORKSHOPS 6

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

INVITED TALKS BY CSIR-IICB FACULTY

Human health and cancer: A difficult journey for clinicians and basic scientists. Annual Meeting and Mini-Symposium. Indian Association for Cancer Research (IACR)-West Bengal Chapter, Sept 14, 2018.

Emerging modalities to improve cancer outcomes. 14th Indo-Australian Biotechnology Conference, ACTREC, Tata Memorial Centre, Navi Mumbai, 22-23 October 2018.

INVITED SESSION CHAIRPERSON

SINP School on Epigenetics. SINP, Kolkata, September 27, 2018.

- Role of the chromatin associated factor Nucleolin in oncogenesis- by Dr. Philippe Bouvet
- Histone H2A isoforms: Whether important in defining a cellular phenotype- by Dr. Sanjay Gupta

Dr. Malini Sen
msen@iicb.res.in

Role of Wnt Signaling in Host Pathogen Interaction and Immune Response
Functional Analysis of Cell Communication Network-Factor 6 (CCN6) in Relation to Progressive Pseudo Rheumatoid Dysplasia (PPRD)

Participants

Dr. Archya Sengupta, RA
SRF : Mr. Suborno Jati, Mr. Deepesh K. Padhan, Ms. Tresa Rani Sarraf

JRF : Ms. Shreyasi Maity, Ms. Ananya Ganguly, Mr. Soham Sengupta

Mr. Indrajit Sikder, Lab Assistant

Collaborator(s)
Dr. Victor Nizet
University of California -San Diego, CA, USA

Dr. Sushil K. Mahata
University of California San Diego, VA Medical Center, CA, USA

Background & Work Achieved:

Wnt Signaling in Host Pathogen Interaction and Immune Response: Wnt signaling was discovered as an important component of embryogenesis and tissue patterning (Cadigan and Nusse 1997). Wnts comprise a large family of secreted glycoproteins, which bind to transmembrane receptors termed Frizzled and ROR/RYK to give rise to complex signaling pathways important for cell physiology (Dijksterhuis, Petersen, and Schulte 2014; Green, Nusse, and van Amerongen 2014; Corrigan et al. 2009, 2). We previously demonstrated that Wnt5A, a member of the Wnt family is responsible for sustaining immune response by macrophages (Naskar et al. 2014). This finding is corroborated by our current preliminary observations of the role of Wnt5A in antigen presentation. Very recently we have reported that Wnt5A signaling promotes resistance to infection by both Leishmania donovani and bacterial pathogens (Chakraborty et al. 2017; Jati et al. 2018).

Functional Analysis of CCN6 in Relation to PPRD: CCN6 codes for a 354 amino acid multimodular protein that is expressed by most cells of mesenchymal origin. CCN6 mutations have been linked to PPRD, a musculoskeletal disorder characterized by muscle wasting, cartilage loss, joint stiffness, immobility and morbidity (Hurvitz et al. 1999; Chouery et al. 2017). Yet, the molecular details of CCN6 function and PPRD pathogenesis remain unclear. We previously demonstrated that CCN6 regulates IGF1 function and chondrocyte hypertrophy (Repudi, Patra, and Sen 2013). Later we were able to show that CCN6 localizes to mitochondria controlling mitochondrial function (Patra et al. 2016, 6). This attribute of CCN6 is being validated in relation to PPRD, using zebrafish colony, which we recently set up.

Future Research Plan:

We plan to evaluate the potential of Wnt signaling in regulating host resistance vs. susceptibility to microbial infections in molecular detail. We also plan to dissect the function of CCN6 in relation to mitochondria so that the pathogenesis of PPRD and mitochondrial disorders can be unraveled.

Reference:

Cadigan, K. M., and R. Nusse. 1997. “Wnt Signaling: A Common Theme in Animal Development.” Genes & Development 11 (24): 32863305.

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Chouery, Eliane, Sandra Corbani, Jaleleddine Dahmen, Leila Zouari, Moez Gribaa, Nadia Leban, Jemni Ben Chibani, et al. 2017. “Progressive Pseudorheumatoid Dysplasia in North and West Africa: Clinical Description in Ten Patients with Mutations of WISP3.” Egyptian Journal of Medical Human Genetics 18 (3): 299303. Https://doi.org/10.1016/j.ejmhg.2016.11.004.

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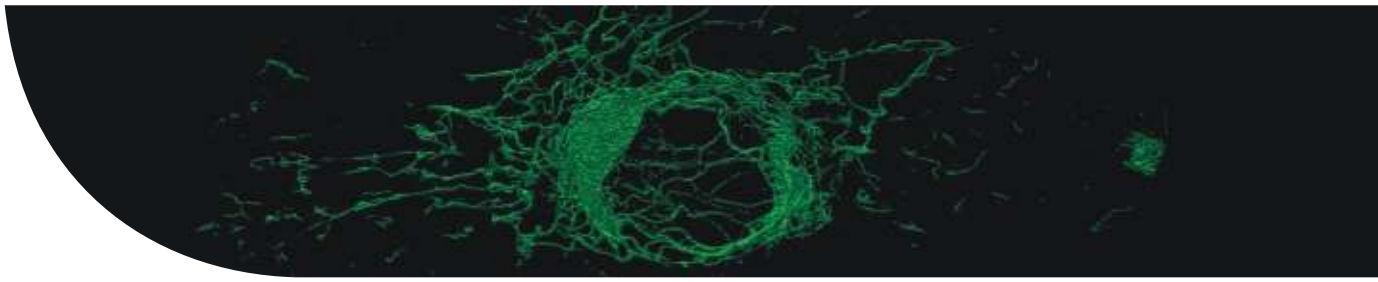

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Patra, Milan, Sushil K Mahata, Deepesh K Padhan, and Malini Sen. 2016. "CCN6 Regulates Mitochondrial Function." J Cell Sci 129 (14): 28412851.

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PUBLICATIONS (2018-2019)

Jati, S., Kundu, S., Chakraborty, A., Mahata, S. K., Nizet, V., Sen, M. (2018). Wnt5a signaling Promotes Defense against Bacterial Pathogens by activating a host autophagy circuit. Frontiers in Immunology, 9, 679

Book Chapters

Jati, Suborno, and Malini Sen. "Wnt Signaling Regulates Macrophage Mediated Immune Response to Pathogens." In Macrophage at the Crossroads of Innate and Adaptive Immunity. IntechOpen, 2019.

Chakraborty, Arijit , Maity, Shreyasi and Malini Sen
"Wnt5A Signaling Antagonites *L. Donoraui* infection:. Leishmaniasis - from Basic Research to the Field IntecHOpen, 2019

Ph.D. Dgree Awarded

Arijit Chakraborty

AWARDS

Students

Suborno Jati
Certificate of Appreciation from CSIR-Indian Institute of Chemical Biology for achieving excellence in research work during the year 2017-2018.

EXTRAMURAL FUNDING

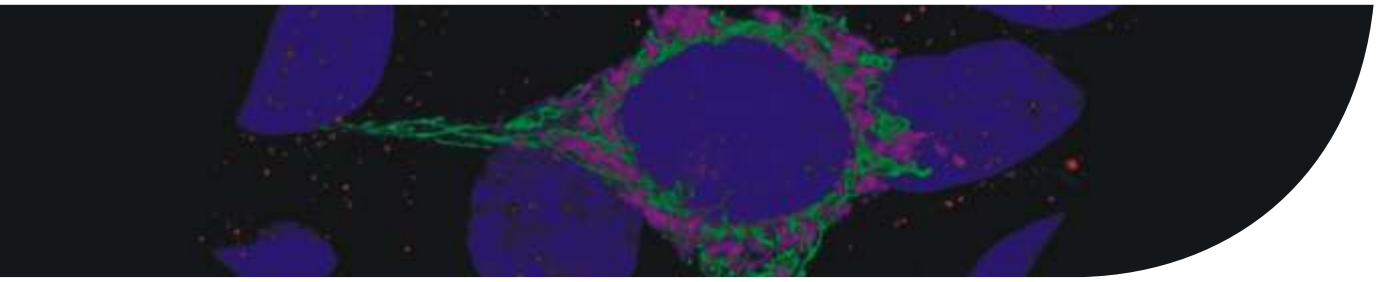
Malini Sen

Role of Wnt5A signaling in bacterial infection. 2018-2021 (DBT, India)
Evaluating WISP3 (Wnt Induced Secreted Protein 3) and promoting societal benefit in the context of PPRD (Progressive Pseudo Rheumatoid Dysplasia), a debilitating genetic disorder. 2018-2021. DBT, India

Potential of Wnt5A signaling in promoting host defence against L. Donovani infection. 2018-2021. ICMR, India

INVITED TALK

Malini Sen
Wnt5A Signaling in Macrophages Restricts Leishmania donovani Infection; Leishmaniasis 2018, Caparica, Portugal, October 2018



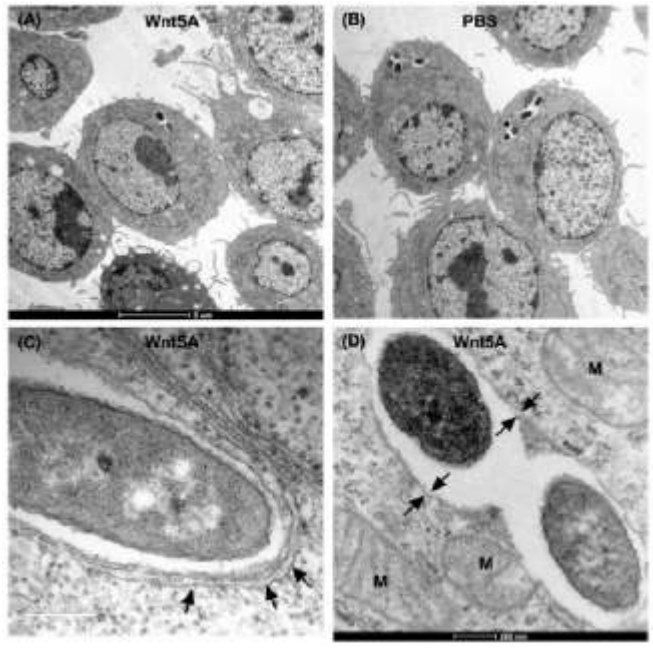


Figure 1 :
Electron microscopy demonstrating Wnt5A-induced autophagosome like moieties and bacterial killing after Pseudomonas aeruginosa (PA) infection. Lesser number of bacteria present in Wnt5A-treated cells compared to PBS-treated cells (A,B). Arrows point to double membrane or multilamellar structures encapsulating bacteria in Wnt5A-treated macrophages (CD). M represents mitochondria.

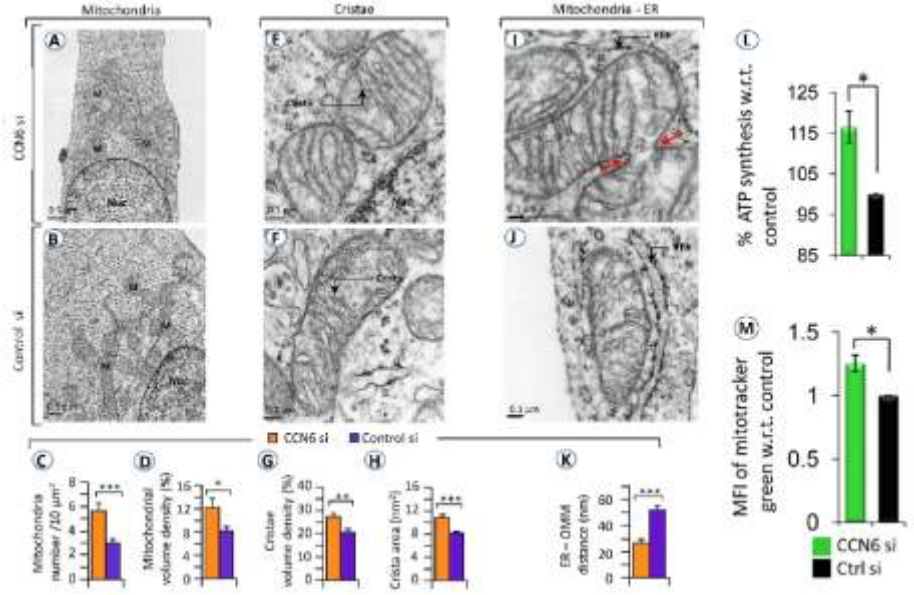


Figure 2
Electron microscopy data showing mitochondrial morphology and ERmitochondria juxtaposition in CCN6-knockdown vs control cells. (A)-(D) low magnification (2500×) EM showing comparison of mitochondrial number and mitochondrial volume density by morphometric analyses in CCN6 knockdown vs control set (n=25). (E)-(H) high magnification (15,000×) images of mitochondria showing increased cristae volume density and crista area (morphometric analyses taking n=100)). (I)-(K) high magnification (15,000×) EM of mitochondria and rough endoplasmic reticulum (RER) showing the distance between mitochondria and ER. Morphometric analyses (n=25) revealed closer association of mitochondria and ER in CCN6si cells than in control set. (L) ATP synthesis within isolated mitochondria of CCN6-knockdown cells is higher than the control, as measured by using a luminometer and an ATP determination kit (n=4). (M) Flow cytometric analysis of MitoTracker green fluorescence demonstrating mitochondrial mass in CCN6-knockdown C-28/I2 cells with respect to control (n=3). MFI: mean fluorescence intensity. n represents the number of independent experiments. Data are represented as mean±s.e.m.; *P<0.05, **P<0.01; ***P<0.001

Dr. Dipyaman Ganguly

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Dendritic cell biology at the crossroads of autoimmunity, cancer and protective immunity

Participants

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Oindrila Rahaman, UGC-SRF
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Chinky Shiu Chen Liu, CSIR-JRF
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Ranit D'Rozario, UGC-JRF

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Background

The basic premise for immune algorithm is distinguishing self from nonself. This is achieved by different modules of host immune system. The 'innate' immune system recognizes the nonself based on predominantly nonself-associated molecular patterns (PAMPs), while the 'adaptive' immune axis adapts to the nonself molecular determinants. These two work together toward an effective immune response. An effective immune response to an invading pathogen (nonself) leads to protective immunity and a defective response leads to overt infection. On the other hand, an unintended response to the self-entities leads to autoimmune disorders, while a misjudged tolerance to the altered self contributes to tumorigenesis. Our research broadly concentrates on role of innate immune axis in the crossroads of infection, autoimmunity and cancer. Dendritic cells (DCs) are the innate cells with most of the decision-making responsibilities for an ensuing immune response or tolerance. We try to decipher the governing principles of self-nonself discrimination by the germline-encoded invariant pattern recognition receptors (PRRs) expressed by DCs and how they work in a given clinical context.

Aims and Objectives

There are three major aspects that we explore:

- Innate immune regulation and molecular mechanisms of dendritic cell function
- Role of innate immune deregulation in autoreactive inflammation
- Deciphering the role and modulation of dendritic cells in tumor microenvironment

Work Achieved

1. Discovery of a hitherto unknown regulatory mechanism in human plasmacytoid dendritic cells driven by endocannabinoids.
   Rahaman O et al., J Immunol, 2019.
2. Development of novel small molecule antagonists for toll-like receptor 9, a promising therapeutic target in systemic autoimmune diseases as they inhibit activation of plasmacytoid dendritic cell activation and type I IFN induction. Pharmacokinetic, toxicity and ADME studies are ongoing and preliminary results identified promising lead molecules.
   Paul B et al., Eur J Med Chem, 2018.
   Patent Appli CSIR Ref No. 0034NF2017, 2017. Patent Application No. Patent WO2017163264A1.

Future Research Plans

We plan to further investigate the role of plasmacytoid dendritic cell in contexts of sterile inflammation, perform preclinical

validation of the novel TLR9 antagonists in diabetes and systemic lupus. A program on molecular characterization of innate immune events in terms of mechanotransduction and endocannabinoids signaling are also ongoing.

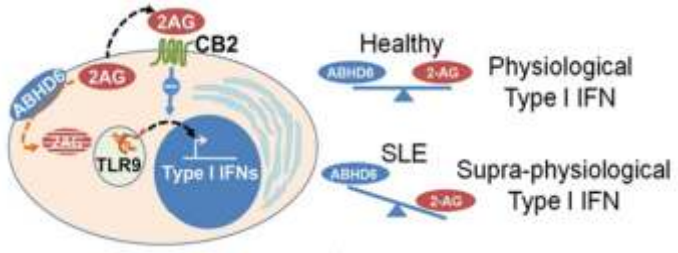


Fig 1. Mechanistic model of the endocannabinoid driven rheostat mechanism for human plasmacytoid dendritic cells. (Rahaman O et al., J Immunol, 2019)

PUBLICATIONS

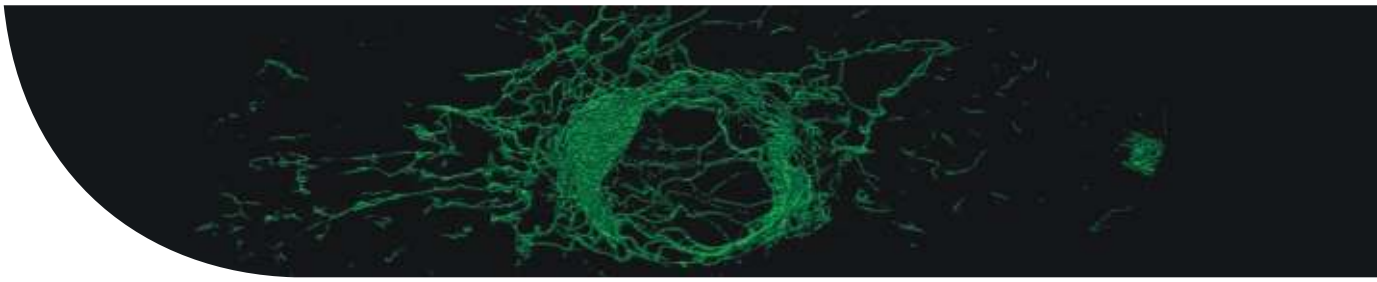
1. Liu CSC, Ganguly D. Mechanical Cues for T Cell Activation: Role of Piezo1 Mechanosensors. Critical Reviews in Immunology 2019. Epub. DOI: 10.1615/CritRevImmunol.2019029595
2. Rahaman O, Bhattacharya R, Liu CSC, Raychaudhuri D, Ghosh AR, Bandopadhyay P, Pal S, Goswami RP, Sircar G, Ghosh P, Ganguly D. Cutting Edge: Dysregulated endocannabinoid-rheostat for plasmacytoid dendritic cell activation in a systemic lupus endophenotype. Journal of Immunology, 2019 Mar 15;202(6):1674-1679.
3. Paul B, Rahaman O, Roy S, Pal S, Satish S, Mukherjee A, Ghosh AR, Raychaudhuri D, Bhattacharya R, Goon S, Ganguly D#, Talukdar A#. Activity-guided development of potent and selective toll-like receptor 9 antagonists. European Journal of Medicinal Chemistry. 2018 Nov 5;159:187-205.

AWARDS / HONOURS / MEMBERSHIPS

2017/18- National Bioscience Award
2019- CDRI Award for Excellence in Drug Research
2017- Member, Executive Committee, Indian Immunology Society

EXTRAMURAL FUNDING

No.	Title	Funded by	PI/Co-PI	Amount (Lakh INR)	Brief description
1	Probing endosomal toll - like receptor 9 biology using novel small Molecule antagonists	SERB	Co-PI	32.0 (3 yrs, 2015-2018)	Gaining structural insight into TLR9 antagonism using small molecules and development of novel small molecule antagonists of toll -like receptor 9 (Roy et al, *Eur J Med Chem*, 2017; 2 Patents)
2	Role of type I interferons in cerebral malaria	DBT	PI	54.0 (3 yrs, 2016-2019)	Deciphering the role of type I IFNs in protective immunity in a preclinical model of cerebral malaria, to understand pDC biology at the crossroads of autoimmunity and protective immunity
3	Exploring therapeutic efficacy of novel toll -like receptor 9 antagonists in type 2 diabetes	SERB	PI	50.0 (2 yrs, 2017-2019)	Pharmacokinetics, toxicity and preclinical efficacy of novel small molecule TLR9 antagonists in preclinical model of diet - induced obesity
4	Indo-Australia Collaboratve Research on Neglected Tropical Disease	DBT	Co-PI	140.0 (3 years, 2017-2020)	Development of novel small molecule antileishmanial compounds
5	Swarnajayanti Fellowship grant	DST	PI	200.0 (5 years, 2018 - 2023)	Mechanistic exploration of the pathogenetic role of type I interferons in metabolic syndrome and preclinical validation of therapeutic targeting



CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

International Symposium on Frontiers in Development & Molecular Medicine, March 1-3, 2019, at Biswa Bangla Convention Center, Kolata, India.

TALKS BY CSIR-IICB FACULTY

August, 2018 : Annual Conference of Society for Inflammation Research, Bangalore, India.

September, 2018 : Indian Institute of Science, Bangalore, India.

November, 2018 : 45th Annual Conference of Indian Immunology Society, THSTI, Faridabad, India.

November, 2018 : National Institute of Immunology, New Delhi, India.

February, 2019 : Molecular Immunology Forum, Hyderabad, India.

March, 2019 : International Symposium on Frontiers in Development and Mol. Medicine, Kolkata, India.

April, 2019 : DBT-NIAID Vaccine Adjuvant Development Collaborative Workshop, National Institute of Immunology, New Delhi.

Dr. Amitava Sengupta

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Epigenetic regulation of hematopoiesis & human acute myeloid leukemia pathobiology

Participants

UGC-SRF: Mayukh Biswas, Sayan Chakraborty
CSIR-SRF: Shankha Subhra Chatterjee, Sayantani Sinha

Liberalis Debraj Boila, CSIR-SRF, SPM Fellow

Shalini Dasgupta, Trainee, KIIT, Bhubaneswar
Palash Kumar Seal, Trainee, Dept. Biochemistry, Univ Calcutta

National Collaborator(s)

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Dr. Rajib De, NRS Medical College & Hospital, Kolkata
Dr. Prantar Chakrabarti, NRS Medical College & Hospital, Kolkata
Dr. Dipty Jain, Govt. Medical College, Nagpur
Dr. Ariandam Talukdar, CSIR-IICB, Kolkata
Dr. Punit Prasad, ILS, Bhubaneswar
Dr. Sanjay Kumar, Centre for Stem Cell Research, Vellore
Dr. Debojyoti Chakraborty, CSIR-IGIB, New Delhi
Dr. Siddhartha Roy, Bose Institute, Kolkata

Background

Stem cells possess two fundamental properties; self-renewal and differentiation. Bone marrow-resident adult **hematopoietic stem cells** (HSC) respond to physiological stimuli and regenerate hematopoiesis. Dysregulated self-renewal and arrest in differentiation of HSC and progenitors induce leukemic transformation.

Physiological aging is associated with the onset of chronic and lifestyle diseases including cancer. **Hematopoietic aging** is characterized by clonal expansion of myeloid-biased hematopoietic stem cells/ progenitors and by increased risk of development of myeloid leukemia. Although the majority of patients with **acute myeloid leukemia** (AML) initially respond to chemotherapy, many of them subsequently relapse, and the mechanistic basis for **AML persistence** following chemotherapy remains poorly understood.

In our laboratory at IICB we have been trying to test the hypothesis that epigenetic dysregulation within hematopoietic compartment is involved in hematopoietic aging and causes AML pathogenesis. We are particularly interested at understanding the cell-autonomous and non-cell-autonomous molecular determinants that regulate HSC self-renewal, differentiation and interaction with hematopoietic microenvironment or niche.

In addition, from a translational perspective HSCs draw attention because of their potential use in stem cell and gene therapy. Presently we are engaged in **CSIR MMP** on Sickle Cell Anemia towards targeted gene editing to foster pre/clinical translation for **autologous cell therapy**.

Our overreaching aim is identification of altered and unique **epigenetic fingerprints** in human myeloid leukemia, and characterization of epigenetic **vulnerabilities** in AML.

Aims and Objectives

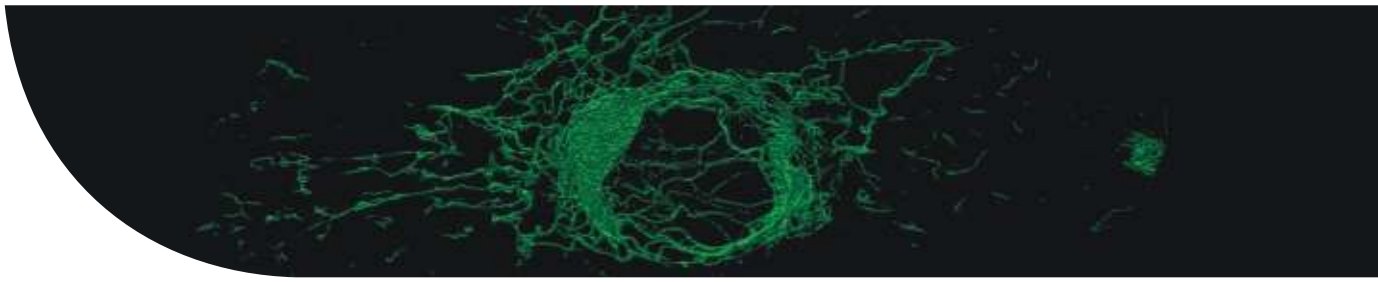
Investigate **epigenetic regulation** of myeloid leukemia pathophysiology
Determine **cell-autonomous** mechanisms of hematopoietic stem/progenitor transformation
Elucidate **microenvironment regulation** in hematopoiesis

Work Achieved

Cancer genome sequencing studies have focused on identifying oncogenic mutations. However, mutational profiling alone may not always help dissect underlying epigenetic dependencies in tumorigenesis. Nucleosome remodeling and deacetylase (NuRD) is an ATP-dependent chromatin remodeling complex that regulates transcriptional architecture and is involved in cell fate commitment.

We demonstrate that loss of MBD3, an important NuRD scaffold, in human primary AML cells associates with leukemic NuRD. Interestingly, CHD4, an intact ATPase subunit of leukemic NuRD, co-immunoprecipitates and participates with H3K27me3/2-demethylase KDM6A to induce expression of atypical guanine nucleotide exchange factors, dedicator of cytokinesis (DOCK) 5 and 8 (DOCK5/8), promoting Rac GTPase signaling.

Mechanistically, MBD3 deficiency caused loss of histone deacytelase 1 occupancy with a corresponding increase in KDM6A, CBP, and H3K27ac on DOCK5/8 loci, leading to derepression of gene expression. Importantly, TCGA AML cohort



reveals that DOCK5/8 levels are correlated with MBD3 and KDM6A, and DOCK5/8 expression is significantly increased in patients who are MBD3low and KDM6Ahigh with a poor survival. In addition, pharmacological inhibition of DOCK signaling selectively attenuates AML cell survival. Because MBD3 and KDM6A have been implicated in metastasis, our results may suggest a general phenomenon in tumorigenesis.

Collectively, these findings provide evidence for MBD3-deficient NuRD in leukemia pathobiology and inform a novel epistasis between NuRD and KDM6A toward maintenance of oncogenic gene expression in AML.

Future Research Plans

Future research would be directed to functionally dissect contributions of chromatin remodelers and epigenetic modifying-enzymes in HSPC transformation in **myeloid leukemia.** We also propose to investigate molecular underpinnngs of **mesenchymal stroma-HSC crosstalk in hematopoiesis and bone marrow failure**.
In addition, following the mandate of CSIR MMP on Sickle Cell Anemia we would perform targeted genome engineering for applications in **autologous gene/cell therapy**.

PUBLICATIONS

- Biswas M,1 Chatterjee SS,1 Boila LD, Chakraborty S, Banerjee D, Sengupta A*. MBD3/NuRD loss participates with KDM6A program to promote DOCK5/8 expression and Rac GTPase activation in human acute myeloid leukemia. FASEB J 2019: 33, 5268-5286.
- Saha S, Murmu KC, Biswas M, Chakraborty S, Basu J, Kolapalli SP, Chauhan S, Sengupta A, Prasad P. Transcriptomic analysis identifies RNA binding proteins as putative regulators of myelopoiesis and leukemia. Front Oncology 2019, in press.

AWARDS/HONOURS/MEMBERSHIPS

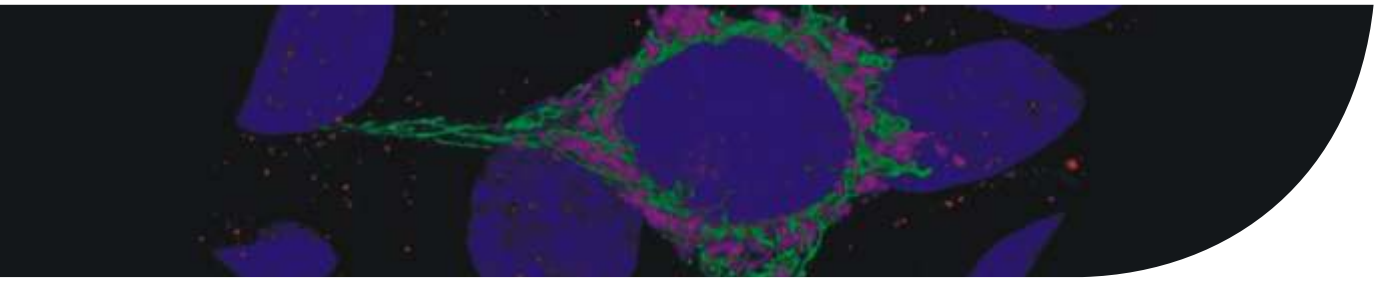
2019 ICMR-DHR International Fellowship for Indian Biomedical Scientists
2019 Keystone Symposia Global Health Travel Award
2018 International Society for Experimental Hematology Travel Award, CA, USA (Shankha Subhra Chatterjee)
2018 DBT-CTEP Travel Award, International Society for Stem Cell Research, Melbourne, Australia (Liberalis Debraj Boila)
2018 Cold Spring Harbor Asia Travel Award, Chromatin, Epigenetics & Transcription, Suzhou, China (Sayantani Sinha)

EXTRAMURAL FUNDING

- Deciphering Epigenetic Dysregulation in Hematopoietic Stem Cell Transformation in Human Myelogenous Leukemia, PI, 2017-20, DBT, Govt. of India.
- Targeted hematopoietic stem cell engineering for Sickle Cell Anemia therapy, PI & Nodal Sct., 2017-20, CSIR Sickle Cell Anemia Mission, Govt. of India.

CONFERENCES/WORKSHOPS

2019 Organiser, International Symposium on Frontiers in Development & Molecular Medicine: Models to Insights (FDMM), March 1-3, Biswa Bangla Convention Center, Kolkata
2019 Biswas M,1 Chatterjee SS,1 Boila LD, Chakraborty S, Banerjee D, Sengupta A*. MBD3/NuRD loss participates with KDM6A program to promote DOCK5/8 expression and Rac GTPase activation in human acute myeloid leukemia. FDMM, Kolkata.
2019 Chatterjee SS,1 Biswas M,1 Boila LD, Banerjee D, Sengupta A*. SMARCB1 deficiency integrates epigenetic signals to oncogenic gene expression program maintenance in human AML. FDMM, Kolkata.
2019 Boila LD, Chatterjee SS, Biswas M, Banerjee D, Sengupta A*. H3K27 and H3K9 histone lysine demethylases are involved in human HSPC aging and myeloid leukemia. FDMM, Kolkata.
2019 Sinha S, Chatterjee SS, Biswas M, Kumar S, Sengupta A*. BAF regulation in mesenchymal stromal fate determination and hematopoiesis. FDMM, Kolkata.
2019 Chakraborty S, Biswas M, Chatterjee SS, Sengupta A*. Epigenetic insights into mesenchymal stromal inflammation. FDMM, Kolkata.
2019 Saha S, Murmu KC, Basu J, Sengupta S, Biswas M, Sengupta A, Prasad P. Global gene expression profiling of RNA binding proteins in myeloid differentiation and leukemia. FDMM.
2018 Biswas M,1 Chatterjee SS,1 Boila LD, Chakraborty S, Sinha S, Banerjee D, Sengupta A*. UTX and MBD3 epistasis



regulates Rac GTPase activation and sensitizes human acute myeloid leukemia cells to DOCK inhibition. Blood 132, 3880.

2018 Chatterjee SS,1 Biswas M,1 Sengupta A*. Transcriptional cooperativity between SWI/SNF and NuRD chromatin remodelers in acute myeloid leukemia. International Society for Experimental Hematology (ISEH), CA, USA (ISEH Travel Award).

2018 Boila LD, Sinha S, Chatterjee SS, Banerjee D, Sengupta A*. H3K27 and H3K9 histone lysine demethylases are involved in human HSPC aging and myeloid leukemia. International Society for Stem Cell Research (ISSCR), Melbourne, Australia (DBT-CTEP Travel Award).

2018 Sinha S, Sengupta A*. SWI/SNF regulates osteogenic differentiation potential of mesenchymal stromal cells. Cold Spring Harbor Asia (CSHA) Conference on Chromatin, Epigenetics & Transcription, Suzhou, China. (CSHA Travel Award).

TALKS BY CSIR-IICB FACULTY

2019 From AML epigenetics to precision medicine. Cancer Research Conference, JNM Hospital, Kalyani.

2019 Epigenetic hallmarks of human leukemia. Vellore Institute of Technology, Vellore.

2019 CRISPR/Cas-guided gene editing in hematopoietic stem/progenitor cells. Workshop on recent advances in CRISPR-Cas9 genome editing, CSIR-IICB, Kolkata.

2019 Collate & Collaborate: Investigator's Perspective-Panel discussion, Regional Young Investigator's Meeting, Presidency University, Kolkata.

2019 Epigenetic plasticity in human acute myeloid leukemia pathobiology. International Symposium on Frontiers in Development & Molecular Medicine: Models to Insights (FDMM), Kolkata. India.

2018 Epigenetic insights in human acute myeloid leukemia pathobiology. One-day Conference on Translational Bioinformatics, Bose Institute, Kolkata. India.

2018 Dregulated nucleosome remodeling in human acute myeloid leukemia. International Conference on Genome Architecture & Cell Fate Regulation (GACFR), University of Hyderabad, Telengana, India.

2018 Epigenetic derangements in human myeloid leukemia. Tata Medical Center, Kolkata.

2018 SWI/SNF: A bona fide player in cell-autonomous and non-autonomous regulation of hematopoiesis. 7th International Meeting of Chromosome and Chromatin Biology, JNCASR, Bangalore, India.

2018 Chromatin remodeler plasticity in human AML. International Meeting on Cancer Biology- Still a Challenge in 21st Century & SINP School on Epigenetics, Saha Institute of Nuclear Physics, Kolkata, India.

2018 Epigenetic regulation in aged hematopoiesis and human leukemia pathogenesis. Indian Academy of Sciences, Bangalore, India.

2018 Decoding molecular epigenetic fingerprints in hematopoiesis & MDS/AML pathobiology. 6th Molecular Pathology Workshop, Tata Medical Center, Kolkata, India.

2018 Hematological vistas of immunology. World Immunology Day, CSIR-IICB, Kolkata.

Dr. Shilpak Chatterjee

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Mechanistic exploration of the role of S1PR1 in regulating the functional fate of tumor infiltrating CD8 T cells

Participants

JRF : Anwesha Kar, Ishita Sarkar, Snehanshu Chowdhury, Debashree Basak

Collaborator(s)

Dr. Dipyaman Ganguly
Dr. Sandip Paul
Dr. Saikat Chakrabarti

Collaborator(s) from outside IICB
Dr. Asima Mukhopadhyay
Tata Medical Center, Kolkata

Background

Immunotherapy of cancer is emerging as a powerful weapon in the oncological armamentarium. In past few years considerable efforts have been made to harness the cytotoxic potential of the CD8 T cells to eradicate cancer. Yet, elimination of established tumor is impeded due to the dysfunctionality of the T cells at the tumor site. Therefore, there is an unmet need to understand the intricate cellular mechanisms driving the functional impairment of T cells in cancer in order to devise therapeutic strategies to improve their responsiveness for immunotherapeutic intervention.

Sphingosine-1-phosphate receptor 1 (S1PR1) signaling has been shown to regulate diverse cellular processes and plays a pivotal role in T cell trafficking and differentiation. S1PR1 can activate various signaling pathways of which persistent activation of STAT3 and Akt have been reported in multiple cell types present at the tumor site. Compelling evidences suggest that although transient activation of STAT3 and Akt in T cells regulate distinct functional phenotype, persistent activation has been shown to be associated with the dysfunctional state of T cells at the tumor site. Recent study by Scharping et al revealed that mitochondrial insufficiency of tumor infiltrating CD8 T cells, a metabolic hallmark of T cell unresponsiveness, could be in part due to the sustained activation of Akt which repressed PGC1, an important transcription factor for mitochondrial biogenesis. Moreover, activation of Akt has also shown to dampen the anti-tumor response of T cells by repressing Foxo family transcription factors which regulates the expression of key memory associated genes (TCF7, Bcl6 and -catenin), prerequisite for eliciting durable anti-tumor T cells response. Similar to Akt, activation of STAT3 in tumor infiltrating CD8 T cells has been shown to dampen their anti-tumor response. It is reported that sustained activation of STAT3 in CD8 T cells not only restrains their abundance at the tumor site but also attenuates the expression of cytotoxic genes. However, it remains to be elucidated which T cell specific sensory mechanisms that in response to the tumor microenvironmental cues activate and sustained these signaling pathways leading to the dysfunctionality of CD8 T cells at the tumor site. Our preliminary study suggests that tumor derived CD8 T cells with characteristic features of functional exhaustion had elevated expression of S1PR1. Previously it has been reported that S1PR1 signaling has a profound effect on the accumulation of Treg in the tumor milieu. However, the precise role of S1PR1 on CD8 T cells at the tumor site has not been explored. Therefore, the proposed study aims to understand whether the expression of S1PR1 on tumor infiltrating CD8 T cells act as a negative regulator to blunt the anti-tumor response of T cells and whether it can be used as a drugable target to improve the efficacy of immunotherapy of cancer.

Aims and Objectives

- Determine the precise role of S1PR1 mediated signalling cascades in regulating the effector function of CD8 T cells at the tumor site.
- Elucidate the role of S1PR1 in regulating the metabolic fitness of CD8 T cells at the tumor site.
- Determine the therapeutic potential of targeting S1PR1 to improve the anti-tumor potential of CD8 T cells.
- Evaluate the combinatorial approach of targeting S1PR1 along with anti-PD1 to improve the efficacy of the anti-PD1 therapy.

Work Achieved

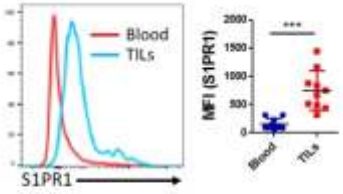
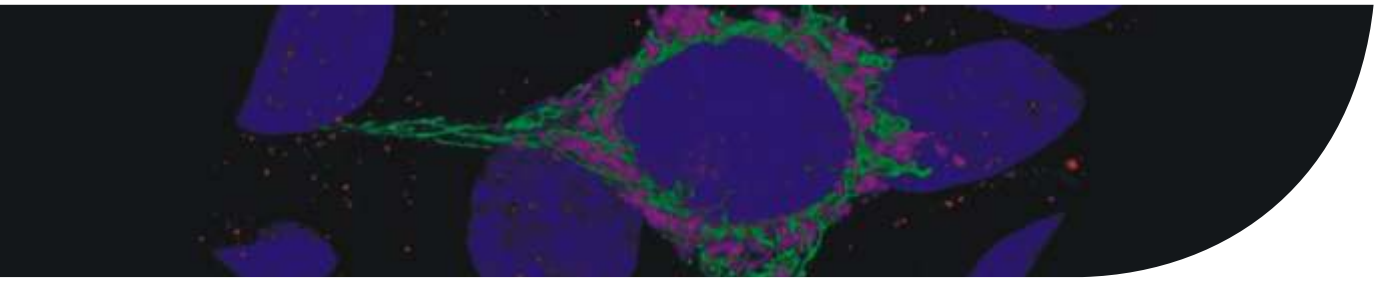


Figure 1. CD8 T cells from OSCC tumor site exhibit increased cell surface expression of S1PR1. (A) Flow cytometry analysis of the expression of S1PR1 on CD8 T cells from either OSCC tumor site or peripheral blood of a patient with OSCC. Adjacent scatter plot represents the cumulative data of mean fluorescence intensity (MFI) of S1PR1 expression on CD8 T cells from 10 patients (n=10) with OSCC. ***p<0.005

Oral squamous cell carcinoma (OSCC) tumor derived CD8 T cells exhibit increased cell surface expression of S1PR1. Given that tumor infiltrating Treg exhibit high cell surface



expression of S1PR1 [23], which regulates their abundance at the tumor site, we sought to determine the expression status of S1PR1 on CD8 T cell present at the tumor site. For this purpose, we analyzed paired tumor and peripheral blood derived CD8 T cells from ten (n=10) OSCC patients. Flow cytometry analysis revealed that CD8+ TILs derived from the OSCC tumor site exhibited increased cell surface expression of S1PR1 as compared to T cells from PBMC of same patient (Fig 1).

CD8 T cells obtained from the OSCC tumor site are functionally exhausted. We next wanted compare the functionality of CD8 T cells either isolated from the tumor site (having high expression of S1PR1) or from peripheral blood (low expression of S1PR1). For this purpose, cells were activated in vitro for 4h and production of various intracellular cytokines were measured. Flow cytometry analysis revealed that frequency of CD8 T cells expressing IFN-γ was approximately 3-fold downregulated in tumor derived T cells as compared to PBMC. Similarly, percentage of CD8 T cells expressing granzyme B (GZMB) and TNF-α was approximately 4-fold and 3-fold downregulated respectively in tumor derived CD8 T cells as compared to PBMC (Fig 2A &2B). Together these data suggest that tumor derived T cells with high expression of S1PR1 are intrinsically impaired to exhibit effector function.

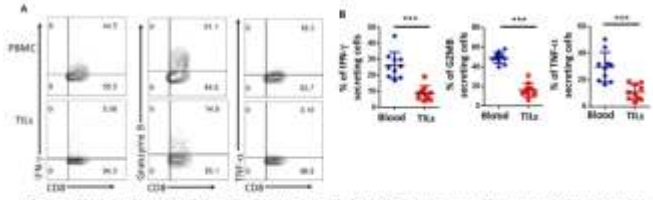


Figure 2. CD8 T cells from OSCC tumor site are functionally impaired. CD8 T cells from either OSCC tumor site or peripheral blood were stimulated with PMA and ionomycin in presence of golgi block for 4h and intracellular cytokines were assessed using flow cytometry. (A) Dot plot represents frequency of cells secreting either IFN-γ or GZMB or TNF-α from a paired sample (tumor tissue and blood from same patient) of a patient with OSCC. (B) scatter plots represent cumulative data with statistical analysis of percentage of cells secreting each cytokine from 10 patients (n=10) with OSCC. ***p<0.005

Future Research Plans

1. Determine the role of S1PR1 in regulating the CD8 T cell functionality in the tumor microenvironment.
2. Determine the therapeutic potential of targeting S1PR1 on TILs to improve the anti-tumor T cells.

PUBLICATIONS (2018-2019):

1. Chakraborty P*, Chatterjee S*, Kesarwani P*, Thyagarajan K, Iamsawat S, Dalheim A, Nguyen H, Selvam SP, Nasarre P, Scurti G, Hardiman G, Maulik N, Ball L, Gangaraju V, Rubinstein MP, Klauber-DeMore N, Hill EG, Ogretmen B, Yu XZ, Nishimura MI, Mehrotra S. Thioredoxin-1 improves the immunometabolic phenotype of antitumor T cells. J Biol Chem, 2019, 294(23): 9198-9212.

2. Chatterjee S*, Chakraborty P*, Daenthanasanmak A, Iamsawat S, Andrejeva G, Luevano LA, Wolf M, Baliga U, Krieg C, Beeson CC, Mehrotra M, Hill EG, Rathmell JC, Yu XZ, Kraft AS, Mehrotra S. Targeting PIM Kinase with PD1 inhibition Improves Immunotherapeutic Anti- Tumor T Cell Response. Clinical Cancer Research, 2019, 25(3): 1036-1049

3. Wilson KR, Kang IH, Baliga U, Xiong Y, Chatterjee S, Moore E, Parthiban B, Thyagarajan K, Borke JL, Mehrotra S, Kirkwood KL, LaRue AC, Ogawa M, Mehrotra M. Hematopoietic Stem Cells as a Novel Source of Dental Tissue Cells. Sci Rep, 2018, 8(1): 8026

4. Daenthanasanmak A, Wu Y, Iamsawat S, Nguyen HD, Bastian D, Zhang M, Sofi MH, Chatterjee S, Hill EG, Mehrotra S, Kraft AS, Yu XZ. PIM-2 protein kinase negatively regulates T cell responses in transplantation and tumor immunity. J Clin Invest, 2018, 128(7): 2787-2801.

5. Chatterjee S, Daenthanasanmak A, Chakraborty P, Wyatt MW, Dhar P, Selvam SP, Fu J, Zhang J, Nguyen H, Kang I, Toth K, Al-Homrani M, Husain M, Beeson G, Ball L, Helke K, Husain S, Garrett-Mayer E, Hardiman G, Mehrotra M, Nishimura MI, Beeson CC, Bupp MG, Wu J, Ogretmen B, Paulos CM, Rathmell J, Yu XZ, Mehrotra S. CD38-NAD+Axis Regulates Immunotherapeutic Anti-Tumor T Cell Response. Cell Metabolism. 2018, 27(1): 85-100

(* equal first authorship)

AWARDS / HONOURS / MEMBERSHIPS

Wellcome Trust-DBT India Alliance Intermediate Fellowship

EXTRAMURAL FUNDING

Role of endoplasmic reticulum (ER) stress induced UPR signaling in regulating the metabolic fitness and functionality of CD8+ T cells in cancer. Start year: 2020, End year: 2024; Agency: India Alliance DBT Wellcome.

CONFERENCES / WORKSHOPS

Number of abstract India: 1

Dr. Siddik Sarkar

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Biomarker Identication and Therapeutics Targeting Cancer Cell Heterogeneity and Therapy Resistanace in Ovarian Cancer

Participants

JRF : Sourabrata Chakraborty, Riddhi Pal, Debleena Basu

Collaborator(s)

Dr. Mahitosh Mandal, IIT Kharagpur, Kharagpur, WB, IND
Dr. Amit K. Srivastava, CSIR-IICB, Kolkata, WB, IND

Background

Genetic or molecular changes accumulate over time and transform the normal stem, progenitor or even the differentiated cells into cancer stem/initiator cells (CSCs/CICs) that eventually give rise to heterogeneous tumor. Heterogeneity in terms of histopathology and molecular classifications is observed in ovarian cancer, and to add further complexities, intra-tumor heterogeneity is observed between the tumor cells co-existing in the same tumor. Thus, it is anticipated that there will be differential responses to chemotherapeutic regimens in the ovarian cancer patients and also within the cells of the same ovarian cancer patients. Currently debulking surgery along with carboplatin (platinum derived drugs) is used as first-line treatment in ovarian cancer, and as expected there are non-responders (recurrence time <6 months) and responders (recurrence time >6 months) group. The differential gene expression between the two groups helped in the identification of biomarkers/novel molecules and the key signaling pathways involved in chemo-resistance. The proliferation/ quiescence, cell differentiation and transmembrane receptor signaling pathways were involved in tumor heterogeneity, therapy resistance and cancer relapse in ovarian cancer. This provides us the indication of the involvement of quiescent cancer cells in the development of cancer heterogeneity and chemo-resistance.

Thus, identification of quiescent cancer stem cells and molecules and signaling pathways involved in transformation of fast proliferating cells into quiescence stem cells is pivotal. Subsequently targeting the heterogeneous tumor consisting of both fast proliferating matured differentiated as well as the quiescent undifferentiated cancer cells is important for overcoming chemo-resistance and relapse in ovarian cancer.

Aims and Objectives:

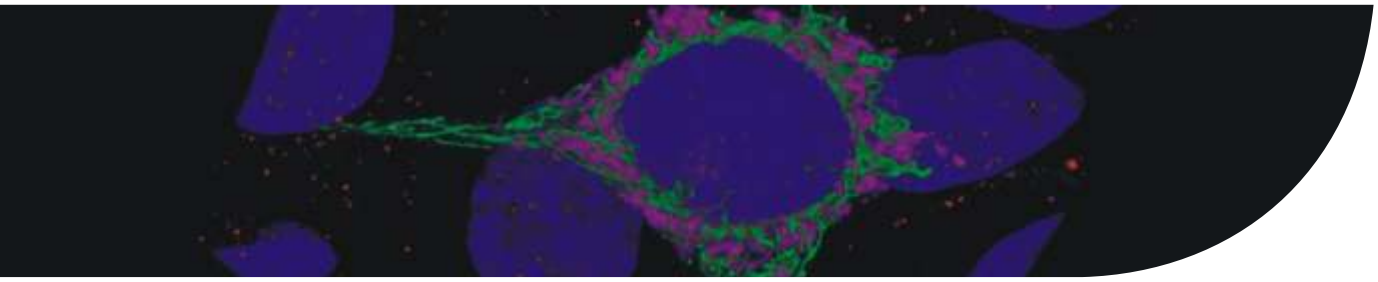
Broadly the research of our laboratory is focused on Biomarker identication and therapeutics targeting cancer cell heterogeneity and therapy resistance in ovarian cancer with various sub-aims/objectives:

I. Identification of cancer quiescent cell populations and associated quiescence biomarkers in the tumor
II. Assay development and diagnostics
III. Molecular targeted therapy for cancer targeting both fast proliferating and quiescent therapy resistant cancer stem cells

Work Achieved

The drug response or follow up data of serous ovarian cancer patients (n=223) were downloaded from TCGA portal (https://portal.gdc.cancer.gov/). The enrolled patients are further divided into recurrent (tumor recurrence during the follow up time or with in 5 years) and non-recurrent (no evidence of recurrence during the follow up time or in 5 years). They are further classified as sensitive (drug free interval duration > 6 months) or resistant (drug free interval <6 months) to platinum drugs based on drug free interval. Thus, the groups are classified based on two factors (recurrence and sensitivity). The number of patients in each group is shown in Fig. 1A.

The RNASeq (transcriptomics) ovarian cancer data was analyzed using R/RStudio/Bioconductor packages (edgeR, limma). The differential gene expression between the groups are shown in Fig. 1B. There are in total of 340 (112 upregulated and 228 down regulated) genes that showed differential expression in Nonresponders (Recurrent cancer with drug free interval < 6 months) respect to (w.r.t) complete responders (Non recurrent cancer with drug free interval > 6 months). Venn Diagram was plotted to show the genes that are exlusively expressed in Non responders (Fig. 1C). It was observed that the molecules are enriched in negative regulation of cell cycle (p-value 2.2E-05) and cell dedifferentiation pathways (p-value 2.3E-04). Thus, there is a strong evidence showing the interconnection of non-responders (chemo-resistance to platinum derived drugs) and negative regulation of cell cycle or genes responsible for quiescence state of the cells. The differentiation in during genes are downregulated in non-responders wrt to complete responders further providing the evidences of dedifferntiated cells/ cancer initiator cells in the development of chemoresistance.



The cancer quiescent cells were isolated based on dye retaining properties as shown in Fig. 2A and B. By using the 3D microspheroid culture sytem, we have noticed the role of quiescent cancer as the initiator cells for the formation of tumorsphere. The involvement of cancer quiescence will be further expanded in numerous ovarian cancer cells and in primary ovarian cancer tissue.

Future Research Plans

The quiescent cells will be sorted and studied for microspheroid formation (enriched stem cells) will be expanded in numerous cell lines.and the chemoresistance properties will be investigated. RNASeq analyses will be performed in the quiescent cells to identify the markers responsible for quiescence. Further, the scRNASeq analyses will be performed in clonal populations of cells originated from single cell (sc) of quieccence cancer cells to study cancer plasticity and heterogeneity.

Figures legends

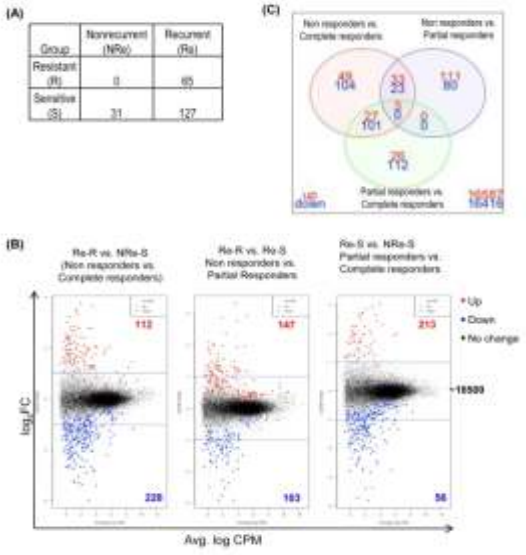


Fig. 1: Cancer quiescence and its involvement in dedifferentiation pathways and chemoresistance: The ovarian cancer follow-up data was downloaded and divided into subgroups based on the properties of recurrence and drug sensitivity; A. The differential expression was analyzed using R and associated Bioconductor packages. The genes showing fold difference of 1.5 and and false discovery rate (FDR) ≤ 0.05 that are differentially expressed between the groups were shown; B. Venn diagram showing the exclusively or mutually inclusive genes expressed between the groups; C.

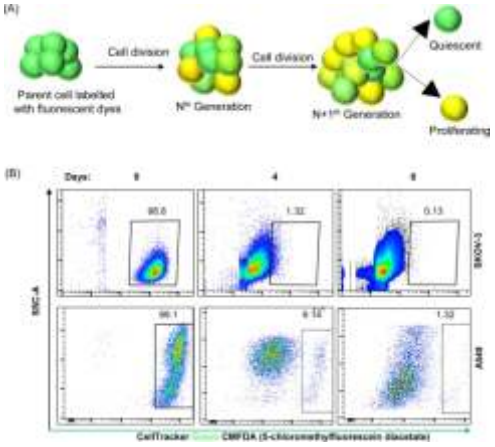


Fig. 2: Identification and isolation of cancer quiescent cell using dye dilution approach: Experimental design showing uniform labeling of cells with green fluorescent cell tracker dye and using the dye dilution approach to isolate the dye retaining cancer quiescent cells and the fast proliferating (faded dye) cancer cells; A. The ovarian cancer cell SKOV-3 and lung cancer cell line A549 were used and using the dye dilution approach, the cancer quiescent cells (~1 % of the mixed populations) were isolated using FACS; B.

PUBLICATIONS

Sarkar, S., Malekshah, OM., Nomani, A., Patel, N., Hatefi, A. (2018). A novel chemotherapeutic protocol for peritoneal metastasis and inhibition of relapse in drug resistant ovarian cancer. Cancer Medicine 7, 3630-3641

Kumar, BNP., Puvvada, N., Rajput, S., Sarkar, S., Mahto, MK., Yallapu, MM., Pathak, A., Emdad, L., Das, SK., Reis, RL., Kundu, SC., Fisher, PB., Mandal, M. (2018). Targeting of EGFR, VEGFR2, and Akt by Engineered Dual Drug Encapsulated Mesoporous Silica-Gold Nanoclusters Sensitizes Tamoxifen-Resistant Breast Cancer. Molecular pharmaceutics 15, 2698-2713.

CONFERENCES / WORKSHOPS : 1

INVITED TALKS BY CSIR-IICB FACULTY

SIDDIK SARKAR

Title: Hands on state-of-the-art multicolour Flowcytometry workshop for basic and clinical Applications

Invited talk

Venue: Regional Medical Research Centre (RMRC), North East Region.

City: Dibrugarh, Country: INDIA, Month Year: July 2018.

Dr. Amit Kumar Srivastava

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Understanding the role of translesion DNA synthesis in chemoresistance of lung adenocarcinoma

Participants

RA : Dr. Priyanka Saha

JRF : Devendra Shukla, Tanima Mandal, Ayesha Noor

Collaborator(s)

Name of collaborator outside CSIR-IICB

Dr. Rakesh Pathak, IISER, Berhampur
Dr. Sanjay Kumar, IISER Tripuati
Prof. Qi-En Wang, The Ohio State University, USA

Name of collaborator within CSIR-IICB
Dr. Deepak Kumar
Dr. Siddik Sarkar

Background

Lung cancer is the leading cause of cancer related death among both men and women worldwide. The most distressing aspects of lung cancer are acquired drug resistance and tumor relaspe, which are recently believed to be caused by cancer stem cells (CSCs). Therefore, understanding the molecular mechanisms leading to metastasis and chemoresistance is important for the development of next generation effective treatment for lung carcinoma. Translesion DNA synthesis (TLS), a DNA damage tolerance mechanism is mediated by specific DNA polymerases, which are able to replicate across certain types of damaged sites in template DNA with the help of monoubiquitylated PCNA (ub-PCNA). A large body of research shows that TLS polymerases do not have proofreading activities and may lead to accumulation of mutations that drive carcinogenesis. Therefore, cancer cells may employ the TLS pathway to bypass the DNA damage site, and thus is believed to develop chemo/radio resistance. Based on these scientific premises, we hypothesize that enhanced error-prone translesion DNA synthesis (TLS) plays a crucial role in drug resistivity of lung adenocarcinoma. Herein, we propose to identify the TLS polymerases and underneath molecular mechanisms which leads to drug resistance of lung adenocarcinoma. Additionally, we plan to screen small molecules/natural products that can inhibit the TLS polymerases activities to prevent the emergence of chemoresistance. The proposed study is very important for healthcare because it seeks to identify molecular targets whose inhibition will facilitate enhanced cell death by chemotherapeutic drugs.

Aims and Objectives

We proposed four specific aims to explore mechanisms through which TLS polymerases lead to chemoresistance in lung CSCs. Our main goal is to discover new drug targets in lung CSCs to help eliminate CSC population, and ultimately prevent development of acquired chemoresistance.

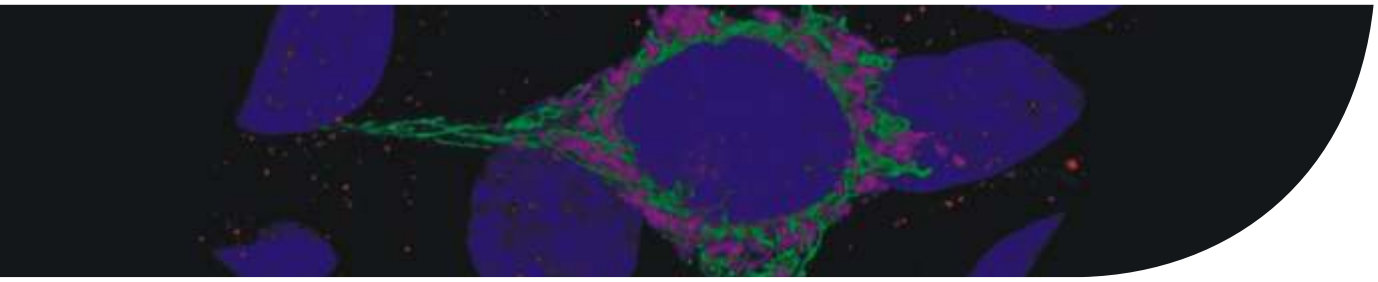
1. To determine the levels of TLS polymerases and ub-PCNA in lung CSCs
2. To determine the functional role of TLS polymerases in lung CSCs
3. To identify the miRNAs regulating TLS polymerases activities
4. Screening of small molecules/natural products that can inhibit TLS polymerases activities

Work Achieved

A large body of research has shown that CD133+ cells could be considered as cancer stem-like cells in lung cancer. We have isolated and characterized the cancer stem-like cells (CD133+) from human lung cancer cell line A549 (Fig 1). We isolated CD133+ and CD133- cells either using Fluorescence-Activated Cell Sorting (FACS) or magnetic beads (Miltenyi Biotech). CD133+ cells were cultured in ultra-Low attachment plates in serum-free DMEM/F12 medium supplemented with serum replacement, EGF, bFGF and insulin. CD133- cells were grown in RPMI 1640 medium supplemented with 10% FBS. To characterize the CD133+ cells, expression of various stem cell markers (Nanog, Oct-4 and Sox-2) was analyzed by Real Time-PCR. We observed enhanced expression of stem cell markers in CD133+ cells as compared to adherent CD133- cells. Further, we found that CD133+ cells exhibited a markedly reduced level of reactive oxygen species (ROS) compared to their corresponding CD133- cells. These findings suggest that CD133+ cells have CSCs like properties.

Future Research Plans

- To study the regulation of TLS in lung CSCs.
- Deciphering the role of miRNAs in maintenance of CSCs.
- Role of CSCs plasticity in therapy resistance



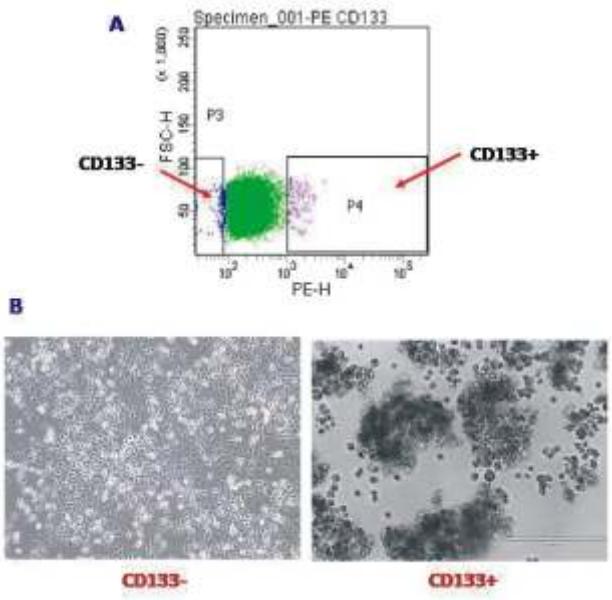


Fig. 1: Isolation and culture of CD133- and CD133+ cells. (A) CD133- and CD133+ cells were sorted from A549 cells using FACS. (B) Photographs of CD133+ and CD133- cells.

PUBLICATIONS

Srivastava, AK*., Banerjee, A*., Cui, T., Han, C., Cai, S., Liu, L., Wu, D., Cui, R., Li, Z., Zhang, X., Xie, G., Selvendiran, K., Patnaik, S., Karpf, AR., Liu, J., Cohn, DE., Wang, QE. (2019). Inhibition of miR-328-3p impairs cancer stem cell function and prevents metastasis in ovarian cancer. Cancer Research. **79(9)**, 2314-2326 (*equal contribution).

Cui, T*., Srivastava, AK*., Han, C., Wani, N., Liu, L., Gao, Z., Qu, M., Zou, N., Zhang, X., Yi, P., Yu, J., Bell, E., Yang, SM., Maloney, D., Zheng, Y., Wani, A., Wu, D., and Wang, Qi-en.(2018). DDB2 represses ovarian cancer cell dedifferentiation by suppressing ALDH1A1. Cell death and disease. **9(5)**, 561 (*equal contribution).

Book Chapters

Devendra Shukla, Tanima Mandal, Ayesha Noor, Deepak Kumar, Sanjay Kumar and Amit Kumar Srivastava (2019). Tumor suppressive proteases revisited: role in inhibiting tumor progression and metastasis. Cancer-Leading Proteases: Structures, Functions, and Inhibition. Elsevier Inc.(Academic Press), Wyman Street, Waltham, MA 02451, USA. (In press)

AWARDS

Early career research award (SERB-DST) 2018.

EXTRAMURAL FUNDING

Ramalingaswami Fellowship, D.O. No. BT/HRD/35/02/2006, 19/04/2018 to 18/04/2013. (DBT, India).

Early career research award. 3 years, 2018 (SERB-DST, India).

Bio-assay guided isolation of anti-cancer compounds from Pterocarpus santalinus and assessment of cytotoxicity, pharmacokinetics and detailed nolecular mechanisms. 2 years, 2019 (National Biodiversity Authority, India)

CONFERENCES / WORKSHOPS

1

Dr. Smrutisanjita Behera

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Analysis of sphingolipid mediated calcium signaling in plants

Participants

Mouli Nahar, Project Assistant

Background

Sphingolipids are integral part of membranes. They mediate several cellular processes both in plants and animals. However, unlike in animals far less is known about the function of sphingolipids in plants. The studies in animals suggest that individual spingolipids have specific cell biological functions. Additionally, it is also evident that altering the level of a single sphingolipid in the cell results in a metabolic ripple effect. Such alteration disturbs multiple physiological processes. To understand how they evoke such pleiotropic effect, understanding the function of individual spingolipid is important. At cellular level sphingolipids have different target sites. The nucleus, the endoplasmic reticulum, mitochondria and lysosomes are known targets of sphingolipid in animals. In plants phytosphingosine is an important sphingolipid. It is involved in PCD in Arabidopsis via Ca2+ and ROS pathway. However its mode of action is still unclear. Moreover, other possible functions of phytosphingosine in plant cells are still unexplored. Detail investigation of the mode of action of phytosphingosine and its role in modulating PCD by Ca2+ and ROS will provide us important information about this signaling sphingolipid.

Apart from understanding the function of phytosphingosine, similar approach can be adapted for the investigation of role of other sphingolipids. Ceramide synthase catalyses the production of ceramide from Phytosphingosine. Very-long-acyl-chain sphingolipids are produced from ceramide. Very-long-acyl-chain sphingolipids enhance the translocation of auxin transporter PIN1 to the plasma membrane (Markham et al. 2011). Phytoshingosine can also be phosphorylated to phytosphingosine-1-phosphate by the enzyme sphingosine kinase. Phytosphingosine-1-phosphate is known to interfere with ABA signaling in Arabidopsis. SPHK1-oe plants are more sensitive to ABA mediated guard cell closure and inhibition of seed germination (Coursol et al. 2005; Worrall et al. 2008). Further extension of the project can uncover the modulation of ABA and Auxin mediated processes by sphingolipids like phytosphingosine, phytosphingosine-1-phosphate, ceramides and very-long-acyl-chain sphingolipids.

Aims and Objectives

Investigation of the modulation of ROS and Calcium signaling in PCD by phytosphingosine

Investigation of modulation of phytohormons like Auxin, Cytokinine by phytosphingosine

Investigate the role of phytosphingosine in plant cell growth and plant cell death

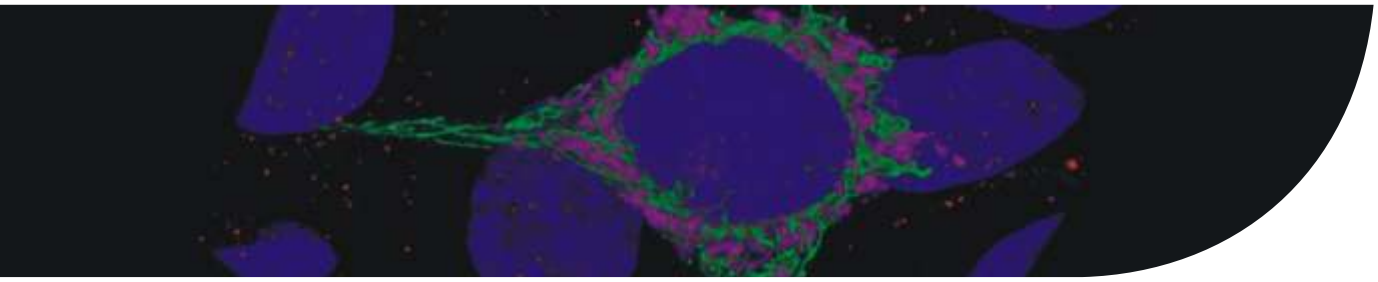
Work Achieved

First of all we have established that phytosphingosine induces cell death in Arabidopsis seedlings. By performing Hoechst staining we observed a clear nuclear staining in Arabidopsis seedlings treated with phytosphingosine. Using transgenic Arabidopsis plants expressing the Ca2+ indicator YC3.6 we have observed phytosphingosine induced calcium signals in the nuclei of root cells of Arabidopsis.

We have also observed that phytosphingosine treatment disrupts the actin cytoskeleton organization in Arabidopsis root cells.

Arabidopsis seedlings grown in plates containing phytosphingosine, shows reduced growth as compare to control plants. In order to investigate the possible reason, we have used transgening Arabodopsis lines that express the Auxin reporter DR5:GFP, or the cytokinine reporter tcs:GFP. In control plants a clear GFP signals were observed in the root tip cells, suggesting higher concentration of auxin and cytokinine in the root tip cells. However, in the phytosphingosine treated seedlings, the GFP signal was not present at the root tip cells. This finding indicates that phytosphingosine interferes with the growth hormone auxin and cytokinine which results in the retardation in growth.

In order to get detail insight of effect of phytosphingosine, we have carried out a transcriptomic analysis by NGS method. We have treated eight day old Arabidopsis seedlings with 10 micro molar Phytosphingosine for 1 hour. Interestingly, we have found distinct groups of gene families which were up regulated in the Phytosphingosine treated samples. Calmodulin like 37, calmodulin 9, Calcium-dependent lipid-binding (CaLB domain) family protein, cyclic nucleotide gated channel 19 and several Calmoduline like proteins together with some calcium channels were found to be up-regulated after phytosphingosine treatment.



Additionally, many of the disease resistance protein (TIR-NBS-LRR class), MAPKs and WRKY transcription factors were up regulated in phytosphingosine treated samples. This finding hints towards the involvement of phytosphingosine in plant defense response.

Future Research Plans

Investigation of modulation of phytohormons like Auxin, Cytokinine by phytosphingosine would be done by hormonal profiling.

Figures

Fig. 1: A) Proposed functions of plant sphingolipids, B) Role of plant sphingolipids, phytosphingosine in plants, i) Model showing possible mode of action of sphingolipids in plants, ii) Effect of phytosphingosine on plant growth, iii) Nuclear Ca2+ signals generated by phytosphingosine in transgenic Arabidopsis root cells expressing nuclear localized Ca2+ indicator YC3.6, iv) Cell death induction by phytosphingosine shown by Hoechst staining.

Fig. 2: Insert legend / key here

Fig. 3: Insert legend / key here

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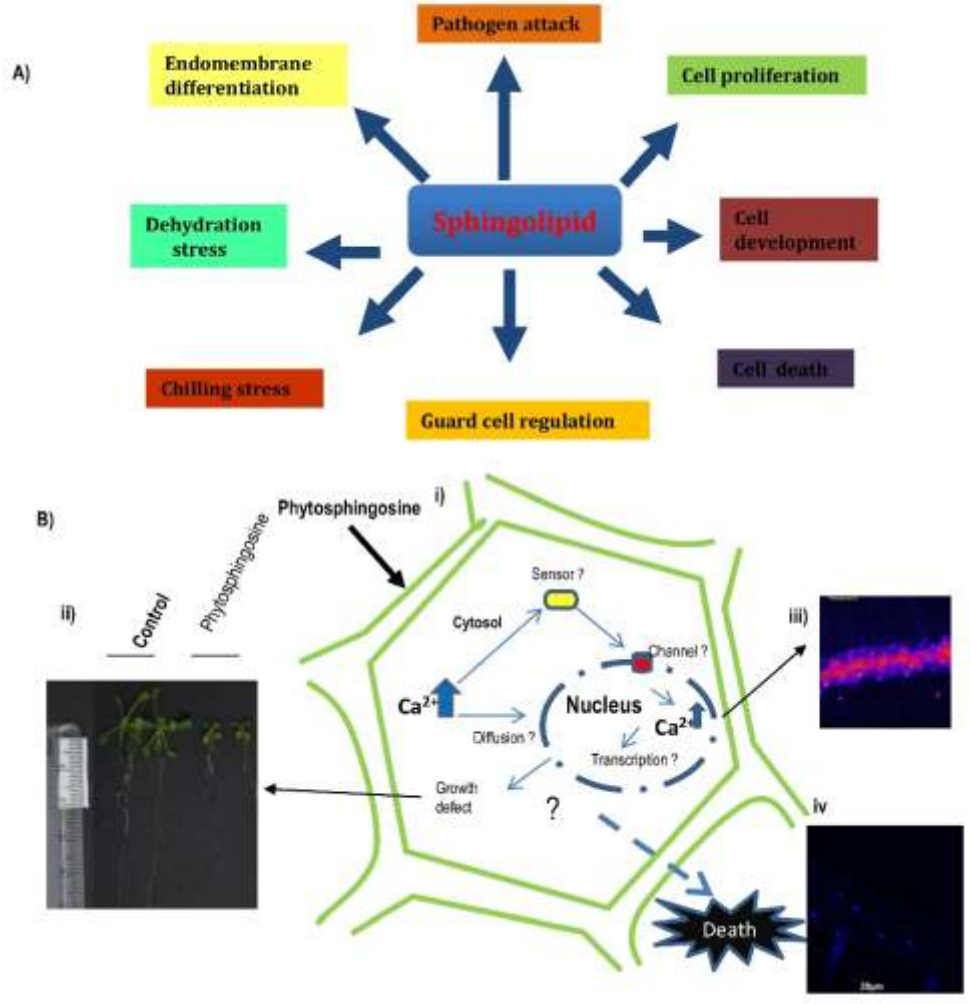
PUBLICATIONS

Behera S, Zhaolong X, Luoni L, Bonza MC, Doccula FG, De Michelisa MI, Morrisd RJ, Schwarzländere M, Costa A. (2018). Cellular Ca2+ signals generate defined pH signatures in plants. Plant Cell 30(11) 2704-2719



Dr. Krishna Das Saha

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Folic acid-conjugated magnetic mesoporous silica nanoparticles loaded with quercetin for improved delivery against colon cancer.

Participants

Research Associate: Dr. Krishnendu Manna (AYUSH-NMPB)
NPDF fellow: Dr.Niladri Mukhejee
Project fellow: Mr. Snehasis Mishra (UGC DAE)
Project fellow: Ms. Saswati Banerjee (DBT-Project)
SRF: Ms. Tanushree Das (CSIR)
SRF: Ms. Sayoni Nag (UGC)
JRF: Ms. Saheli Roy (ICMR)
JRF: Ms. Moumita Saha (DST-Inspire)
JRF: Ms. Sanchaita Mandal (DBT-Project)

Collaborator(s)

Name of collaborator outside CSIR-IICB

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Dr. Mijanur Rahaman, CU, Kolkata
Dr. Chittaranjan Sinha, Jadavpur University , Kolkata
Dr. Joydev Dinda, Utkal University, Odisha
Dr. Utpal Dey, Tripura University
Dr. Rajkumar Duary, Tezpur University, Assam

Dr. R. K. Pal
National Research Center on Pomegranate, Solapur, Maharashtra

Name of collaborator within CSIR-IICB
Dr. Arindam Talukdar

Dr. Biswadip Banerji
Dr. Krishnananda Chattopadhaya

Background:

Effectiveness of cancer therapy depends on the ability of the therapeutic to eradicate the tumour without or with affecting minimum number of healthy cells. Development of cancer-specific drugs or delivery systems can preferentially localise existing agents to the tumour site and can solve these problems of conventional anticancer drugs by allowing targeted delivery. Common mesoporous silica nanoparticles (MSN) SBA-15 and MCM-41 have large surface area of the pores which allows these particles to be filled with a drug. Release profile of drugs can be altered by modulating pore diameter of the MSN. Also, these particles are taken up by the biological cells through endocytosis and some cancer cells engulf more of the particles than healthy cells. Solubility and bioavalibility of the insoluble or poorly soluble drugs is also increased when entrapped with such MSN. The folate receptor (FR) is a recognised biomarker for tumour cells due to its overexpression on a large number of tumours. Cancer specific target molecules such as folic acid (FA) can be readily attached through amide reactions with the outer surface of SBA-15. As PH adjacent to cancer cell is acidic, PH responsive MSN designing will give additional therapeutic advantages.

Again, theranostics nanoparticles (NPs) contain diagnostic and therapeutic functions in one integrated system, enabling diagnosis, therapy, and monitoring of therapeutic response at the same time. For diagnostic function, inclusion of non-invasive imaging modalities, among which nano-imaging through magnetic resonance imaging (MRI) has the potential to detect and diagnose cancer.

Among anticancer and cancer preventing drugs, flavonoids are the most studied ones. The natural flavonoid, quercetin inhibits the release of P-glycoprotein, a drug efflux pump over expressed in many cancer cells. Quercetin also inhibits the protein tyrosine kinases (PTKs) responsible for cell proliferation and differentiation is over expressed in cancer cells.

Our study has been directed at multi-functional nanoparticles, combining tumour targeting, tumour therapy and tumour imaging in an all-in-one system, providing a useful multi-modal approach in the battle against cancer.

Objectives:

- Designing of a mesophorous silica nanoparticle (SBA-15)
- Functionalization of SBA-15 with folic acid (FA)
- Loading of quercetin (QN) in SBA-15 functionalized with folic acid (FA)
- Embedding of acid labile magnetite ferroso-ferric oxide (IO) with the FA-functionalized QN-loaded mono disperse SBA-15 (FA-IO-SBA-15-QN)
- Evaluation of anticancer activity of the nanocomposites, FA-IO-SBA-15-QN both In vitro and In vivo against colon carcinoma

Work achieved:

Designing of nanoparticle: Figure 1 shows the schematic presentation of preparation of nanoconjugates.

Characterization of nanoconjugate: SBA-15, FA-SBA-15, and FA-IO-SBA-15-QN were prepared and characterized by FTIR (Figure 2A) and XRD (Figure 2B). Additional transmittance peaks were observed in FA-IO-SBA-15-QN due to the presence of Fe3O4 at the surface of functionalized SBA-15 (Figure 2A). The small angle powder XRD patterns of four materials, i.e., calcined SBA-15, SBA-Cl, FA-SBA-15, and FA-IO-SBA-15-QN are shown in Figure 2B. Pure SBA-15 material displayed three characteristic diffraction peaks at 2θ region (0.91, 1.58, and 1.82) for three distinctive planes (100) strong, (110) weak and (200) weak, respectively which suggested the presence of the ordered 2D-hexagonal mesoporous structure. In Figure 2C, the N2 adsorption/desorption isotherms of FA-IO-SBA-15-QN at 77 K was observed. Pore size distribution plot was estimated from this sorption isotherm using the NLDFT model (Figure 2D), and it displayed trimodal peak pores of 3.2, 5.0 and 7.6 nm.

Cytotoxicity of nanoconjugate: Cytotoxic activity of native QN as well as of different components of FA-IO-SBA-15-QN, including Folic Acid (FA), Iron Oxide (Fe3O4), mesoporous silica nanoparticle (SBA-15) was studied in colorectal carcinoma cells (HCT 116). Cytotoxicity of nanoconjugate was about 3-4 times higher than free quercetin (Figure 3A).

Contrasting property of FA-IO-SBA-15-QN In vitro and in vivo : The contrast effect of the FA-IO-SBA-15-QN was assessed by measuring transverse (T2) relaxation times of dispersed nanostructures under the MRI equipment (3.0 T). As evident in Figure 3B, The T2-weight MR signals were significantly enhanced with the dose-dependent increase of FA-IO-SBA-15-QN in HCT 116 cells. Contrastingly, there was no MR signal when HEK-293 cells were treated with FA-IO-SBA-15-QN, suggesting the pH-sensitive contrasting property of nanomaterial.

A tumor-bearing murine model was developed using subcutaneous injection of CT-26 cells and tumour suppressive role of FA-IO-SBA-15-QN over native QN was examined. Administration of FA-IO-SBA-15-QN (15 mg/kg) on CT-26 tumor-bearing supressed tumor growth with higher efficacy than free QN.

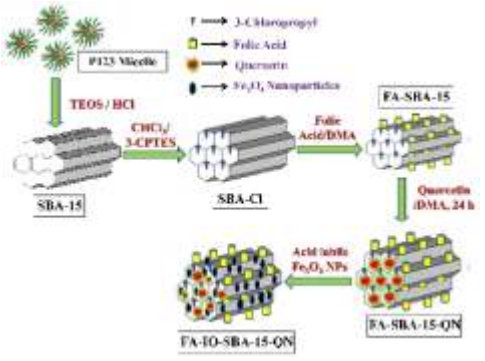


Figure 1: Schematic representation of FA-IO-SBA-15-QN synthesis

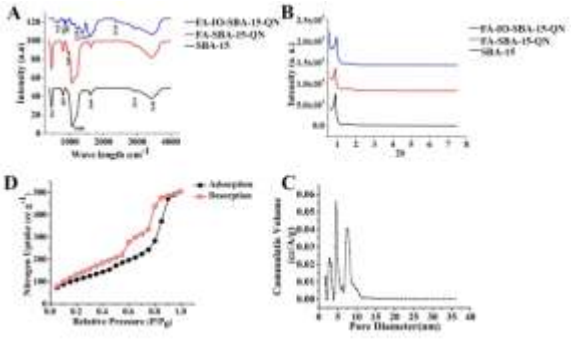


Figure 2: Line graph representing (A) FTIR spectra, (B) XRD pattern, (C) N2 adsorption and desorption isotherms, and (D) relative pore diameter of SBA-15, FA-SBA-15QN, and FA-IO-SBA-15-QN

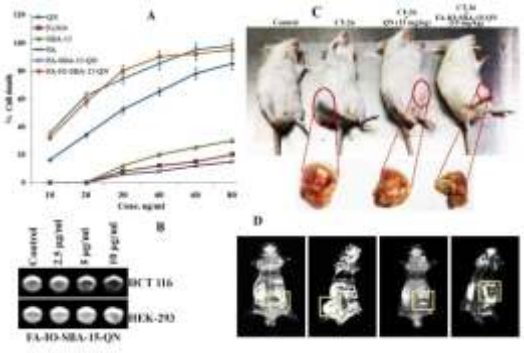
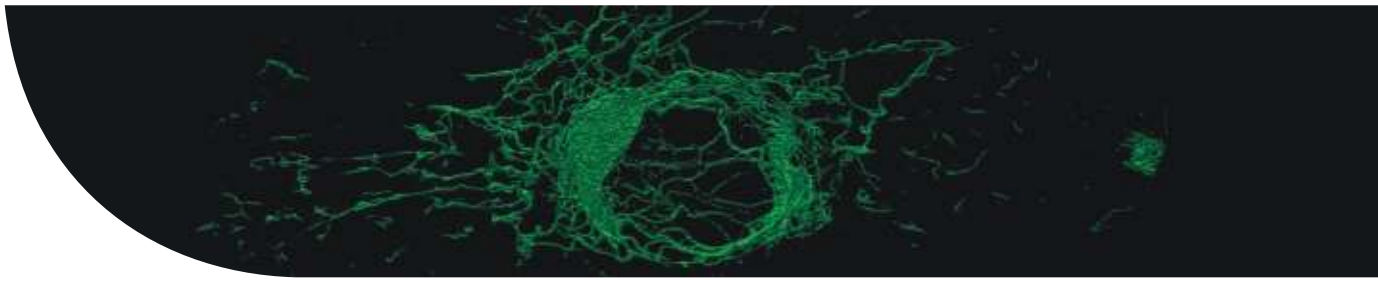


Figure 3: (A) Study on cytotoxic potential of different concentration of QN, Fe3O4, SBA-15, FA-SBA-15QN, and FA-IO-SBA-15-QN. (B)) In vitro T2 weight MRI images of HCT 116 and HEK-293 cells after the treatment of FA-IO-SBA-15-QN (C) Experimental animals showing tumor growth inhibitory activity of QN and FA-IO-SBA-15-QN (D) In vivo T2 weight MRI images of CT-26 tumor-bearing mice.



Future Research Plans:

Designing of multi-functional and multi-targeted nanoparticles for improved delivery of anticancer drugs.

Publications:

Programmed supramolecular nanoassemblies: enhanced serum stability and cell specific triggered release of anti-cancer drug S. Mondal, M. Saha, M. Ghosh, S. Santra, M. A. Khan, K. Das Saha and M. R. Molla, Nanoscale Adv., 2019, DOI: 10.1039/C9NA00052F.

Tannic acid-stabilized gold nano-particles are superior to native tannic acid in inducing ROSdependent mitochondrial apoptosis in colorectal carcinoma cells via the p53/AKT axis. S Nag, K Manna and K Das Saha. RSC Adv.: 2019; 9, 8025

Amelioration of diabetic nephropathy using pomegranate peel extract stabilized gold nanoparticles: Assessment of NF-κB and Nrf2 signaling system. K Manna, S Mishra, M Saha, S Mahapatra, C Saha, G Yenge, N Gaikwad, R Pal, D Oulkar, K Banerjee, K Das Saha. International Journal of Nanomedicine. 2019: 4, 1753-1757

Efficient Detection of Early Events of α-Synuclein Aggregation Using a Cysteine Specific Hybrid Scaffold. Chatterjee S, Ghosh S, Mishra S, Das Saha K, Banerji B, Chattopadhyay K. Biochemistry. 2019. 58(8):1109-1119.

Bromelain with peroxidase from pineapple are more potent to target leukemia growth inhibition - A comparison with only bromelain. R Debnath, N Chatterjee, S Das, S Mishra, S Das, K Das Saha, D Ghosh, and D Maiti. Toxicology in Vitro (2.9); 2019, 24-32

Synthesis of Triazole-Substituted Quinazoline Hybrids for Anticancer Activity and a Lead Compound as the EGFR Blocker and ROS Inducer Agent. B Banerji, K Chandrasekhar, K Sreenath, S Roy, S Nag and K Das Saha, ACS Omega; 2018, 3, 16134−16142

Highly selective and sensitive recognition of Zn(II) by a novel coumarinyl scaffold following spectrofluorometric technique and its application in living cells. S Dey , R Purkait, C Patra , M Saha, S Mondal, K Das Saha and C Sinha, New Journal of Chemistry (3.277); 2018, 42, 16297-16306

A new triazine based π-conjugated mesoporous 2D covalent organic framework: its in vitro anticancer activities. SK Das, S Mishra, K Manna, U Kayal, S Mahapatra, KD Saha, S Dalapati, G. P. Das, A.A. Mostafa and Asim Bhaumik, Chemical Communications. 2018. (6.29); 54 (81), 11475-11478

Isoelectronic Pt (ii)and Au (iii)N-heterocyclic carbene complexes: a structural and biological comparison. B K Rana, S Mishra, D Sarkar, T K Mondal, S K Seth, V Bertolasi, K Das Saha, C.W. Bielawski, A. A. Isab and Joydev Dinda, New Journal of Chemistry (3.277), 2018, 42, 10704

Use of rhodamine-allyl Schiff base in chemodosimetric processes for total palladium estimation and application in live cell imaging. A K Bhanja, S Mishra, K Kar, K Naskar, S Maity, K Das Saha and C Sinha, New Journal of Chemistry (3.277); 2018, 42, 17351

EXTRAMURAL FUNDING

Assessment of Virgin Pomegranate Seed Oil and its Encapsulated Form on the Management of Obesity and Associated Inflammation: A Molecular Approach (just approved for 3 years) DST-SERB, India

Synthesis and characterization of different chrysin derivatives followed by screening of anti-obesogenic activity, anti-diabetogenic activity in vitro: assessment of in vivo activity with the lead compounds. (approved for 3 years) . DBT-NER, India.

Utilization of promegranate for development of functional medical ingredients. Start date:29-12-2016 (3 years). NMPB-AYUSH, India

Designing bioactive peptides from whey liquid waste of the dairy industry: Functionality and health benefit in Obesity, Obesity associated disorders with exploration of molecular mechanism. Start date- 02.01.2017 (3 years). DBT- NER, India.

Dr Shila Elizabeth Besra

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Natural Compound Loaded Nanostructured Lipid Carriers: Characteristics and Anti- Cancer Activities in Cancer Cells.

Participants

SRF : Samrat Chakraborty, Nilanjana Deb
JRF : Kanika Kisku

Collaborator(s)

Name of collaborator outside CSIR-IICB
Dr. Santanu Basu
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Prof. Biswajit Mukherjee & Prof. Tarun Jha
Jadavpur University, Kolkata.

Dr. Ashok Kumar Patanaik & Dr. Sougato Banerjee
B.I.T. Mesra, Ranchi.

Prof Kalyan Kumar Sen & Mr. Rana Datta
G.C.T.S., Asansol.

Name of collaborator within CSIR-IICB
Dr. Snehasikta Swarnakar
Cancer Biology & Inflammatory Disorder Division.

Dr. P. Jaishankar & Dr Chinmay Chowddhury
Organic & Medicinal Chemistry Division.

Background

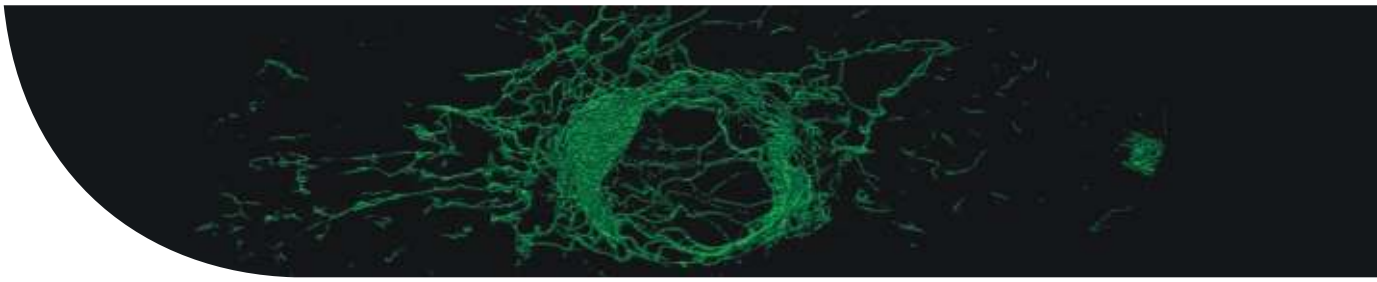
Gastrointestinal tract (GIT) cancer involves malignancy in esophagus, stomach, bowel, rectum, liver, and pancreas. 'Oral chemotherapy', a major leap forward, has become Chemotherapy at Home that radically has upgraded the clinical practices of chemotherapy and immensel improved the overall quality of patient life. It is now possible to orally administer decent number of anticancer drugs, avoiding the possible complications and adverse after-effects of surgical interventions. Besides, it can encounter several typical issues like poor stability and low solubility and/or bioavailability, the major drawbacks in their inability to penetrate the mucosal barrier, disrupting drug absorption in the GI tract. Thus oral chemotherapy, as novel and attractive it may seem, continues to be a major challenge when it comes to formulations. Nanoparticle based drug delivery systems can orally deliver cancer therapeutic molecules. NLCs are superior for GI targeting via passive mechanisms for its better tolerance, low leakage, controlled drug release, higher oral bioavailability, large-scale production, less toxicity Oral drug delivery using NLCs are preferred as they have distribution on a larger surface area, better stability, enhanced protection of incorporated drugs, improvement in consistency of plasma level, sustained release, modest decrease in bioavailability and site-specific targeting, etc. However, the great challenge in developing efficient nano-carrier for oral administration is to overcome the absorption barrier of intestinal mucosa, consisting of intestinal epithelial cells as well as the mucus layer. Anticancer herbal medicines like orcinol glucoside (OG) with high safety margins have novel pharmacotherapeutic leads in cancer treatment that include diverse beneficial biological and pharmacological activities, treatment of GI degenerative disease, immunomodulatory activity, antioxidant, antidepressant, adaptogenic activities neuroprotectiveactivity, etc. This study reports, for the first time, physicochemical characterization and biological activity of OG, together with its cytotoxic activities against different GI tract cancer cell lines including hepatoma cell lines. Toxicity of free OG had also been checked against various normal cell lines.

Aims and Objective:

- Formulation of Orcinol glucoside (OG) - loaded nanostructured lipid carrier (NLC), coated with polyethylene glycol-25/55-stearate (PEG-25/55-SA).
- In vitro cytotoxicity evaluation of OG loaded NLC against gastrointestinal tract (GIT), colon and hepatoma carcinoma cell lines.

Work Achieved

It is being expected that the PEGylated formulations would possess the sustainability in withstanding the adverse physiological extremities like the most significant metabolic activities and phase I / II enzymatic activities in the intestines. NLCs were prepared using tristearin, oleic acid and PEG-25/55-stearate by hot homogenization-ultrasonic dispersion; characterized by DLS, TEM, SEM, AFM, entrapment efficiency



and drug loading capacity studies. NLC diameter ranged from 160 to 230 nm with negative zeta potential of −8 to −20 mV. TEM/SEM and AFM studies suggest spherical and smooth surface morphologies (Fig. 1 & 2). Differential scanning calorimetry studies reveal the loss of crystallinity when OG was incorporated into the NLC. NLCs showed initial burst release, followed by sustained release of OG. PEG-NLC exhibited superior anticancer activity against GIT and also in hepatoma cancer cell lines (Fig. 3). This is the first report demonstrating a practical approach for possible oral delivery of OG in GIT and targeting hepatoma cancer, warranting further in vivo studies for superior management of GIT cancer.

Future Research Plans

- To establish the anti-cancer activity in Glioma and hepatocellular carcinoma cell lines along with identifying the active constituents plant source.
- To establish the potential PLGA nanoparticle encapsulating the anticancer compound in-vitro as well as in-vivo.
- To establish the potential of different natural compounds as immunostimulating and as anticancer.

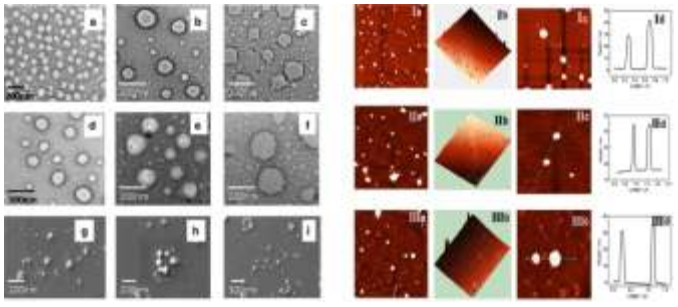


Fig. 1A & 1B: Figure 1A shows TEM (a-f) and SEM (g-i) images of (A and G) TS+OA, (B and H) TS+PEG-25-SA+OA and (C, I) TS+PEG-55-SA+OA NLC respectively. D, E and F are the corresponding OG loaded formulations. Figure 1B shows AFM images of (I) TS+OA (II) TS+PEG-25-SA+OA and (III) TS+PEG-55-SA+OA NLC formulations. (a) two-dimensional images, (b) three dimensional images and (c) and (d) section analyses.

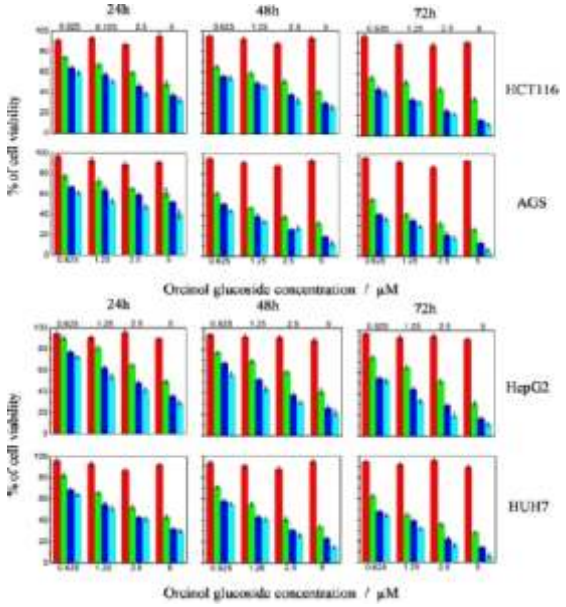


Fig. 2: In vitro cytotoxicity activity of representative PEG coated bare NLC (—) and orcinol glucoside loaded with different NLCs: TS+OA (—); TS+PEG-25-SA+OA (—) and TS+PEG-55-SA+OA (—) on the viability of HCT116, AGS, HepG2 and Huh-7 cell lines.

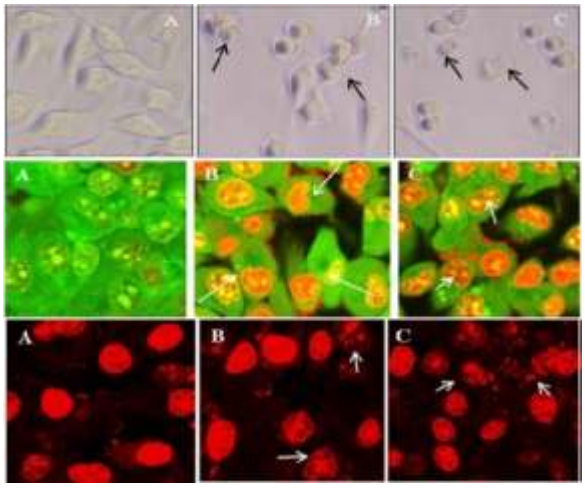
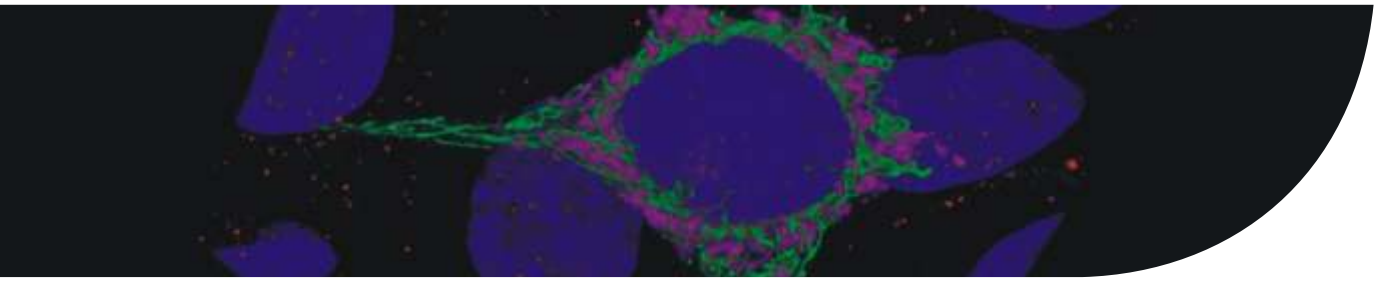


Fig. 3: Light, Fluorescence and Confocal microscopic images of B16F10 melanoma cells post- treatment with 5-FU and ELA. Control cells marked (A) show intact cell membrane integrity. (B) and (C) represent cells treated with IC50 dose of ELA and 5-FU exhibiting cell shrinkage, membrane disintegration, nuclear fragmentation and chromatin condensation indicating the generation of apoptotic bodies.



PUBLICATIONS

Nahak, P., Gajbhiye, R.L., Karmakar, G., Guha, P., Roy, B., Besra, S.E., Bikov, A.G., Akentiev, A.V., Noskov, B.A., Nag, K., Jaisankar, P., Panda, A.K. (2018) Orcinol Glucoside Loaded Polymer - Lipid Hybrid Nanostructured Lipid Carriers: Potential Cytotoxic Agents against Gastric, Colon and Hepatoma Carcinoma Cell Lines. Journal of Pharmaceutical Research, 35: 198.

Deb, N., Hansda, A., Dutta, S., Pattanaik, A., Besra, S.E. (2018) Lawsonia alba leaves induce apoptosis and cell cycle arrest in B16F10 melanoma cells. International Journal of Pharmacy and Pharmaceutical Science, 10:96-101.

Invited Reviews

Reviewed paper for the Journal, IJPPS on 23-05-2018. The manuscript entitled "A prospective analysis on the pattern, laboratory variations and management of acute poisoning in a teritiary care hospital." http://innovareacademics.in/journals/index.php/ijpps

Reviewed paper for the Journal, Letters in Drug Design & Discovery, on 24.04.2018. "Design, preparation and evaluation of novel cholinesterase inhibitors as anti-alzheimer's disease". http://benthamscience.com/journals/letters-in-drug-design-and-discovery.

Awards & Honours

Student's

Name- Miss Nilanjana Deb

Award- Best oral paper presentation entitled "Diospyros Melanoxylon Bark Extract Inhibits Leukemic Cell Growth Through Mitochondrial-Mediated Apoptosis and MMP Regulation" at the National conference "Present Scenario, Challenges & Future Perspective of Drug Discovery & Smart Delivery System Development" on 06.04.2019. Organised by Gupta College of Technological Sciences, Ashram More, Asansol- 713301.

Name- Mr. Vishal Sharma

Award- Best poster presentation entitled "Effect of tea on human embryonic kidney cells (HEK293T) and murine macrophage cell lines (RAW264.7)" at the National conference "Present Scenario, Challenges & Future Perspective of Drug Discovery & Smart Delivery System Development" on 06.04.2019. Organised by Gupta College of Technological Sciences, Ashram More, Asansol- 713301.

Extramural Funding:

Dr. Shila Elizabeth Besra

DBT- BIOTECH RISE PROGRAM 2016-2017, West Bengal, India.

Starting Date-03.04.2017
Ending Date - 05.02.2019

Cell Biology & Physiology Division

Members :

Dr. Arun Bandyopadhyay (Head), Dr. Sib Sankar Roy, Dr. Rupasri Ain, Dr. Subhas Biswas, Dr. Partha Chakravarti, Dr. Mabalirajan, Dr. Prem Tripathy, Dr. Joy Chakraborty

This division deals with systems and cell biology with a focused interest in understanding normal physiology and disease in human patients, preclinical animal models and cellular systems. These investigations further incorporate molecular events at the subcellular organelles, intracellular signalling and the regulation of gene expression. The research endeavours also have strong translational focus towards development of novel druggable targets, diagnostics and therapeutic leads. Major interests are in the area of neurological diseases, reproductive physiology, cardiovascular disease, metabolic diseases and lung diseases.

Dr. Arun Bandyopadhyay

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Understanding the role of peroxisome proliferator activated receptor a (PPAR á) in mitochondrial impairment and hypertrophy in cardiomyocytes

Participants

PA : Dipak Kar

SRF : Dibyanti Mukherjee, Ritu Kumari,

Background:

Highly efficient cellular adaptive mechanisms to external stimuli provide enormous biochemical plasticity which allows normal physiological process to continue up to a certain limit. When the limit of such biochemical plasticity is reached, a pathological situation arises which might be initiated at the molecular level and ultimately summed up in the form of disease phenotypes. In cardiovascular system, pathological conditions such as hypertension, ischemia, valve disease etc. induce myocyte hypertrophy which is characterized by increase in cell size accompanied by transcriptional remodeling and bioenergetic remodeling. Cardiomyocyte hypertrophy is an excellent example of such adaptive changes which ultimately transforms into maladaptive stage in the event of chronic stress. The external mechanical stress to the cardiomyocytes which influences biochemical signaling eventually may jeopardize intracellular organelles. In cardiomyocytes, mitochondrion is one of such targets of chronic stress in which bioenergetics imbalance and dysfunction are very prominent.

Peroxisome proliferator activated receptors (PPARs) belong to the nuclear receptor super family and play significant role in cardiac energetics and cardiac metabolism. Although all three PPARs play essential roles in fatty acid metabolism, PPARα is the principle transcription factor in the fatty acid oxidation in tissues with high fatty acid oxidation rates such as heart, skeletal muscle, liver, kidney etc. and play important role in cardiac energetics. Several synthetic ligands are available in the market which can act as PPAR activators e.g. fibrates like bezafibrate, fenofibrate, clofibrate etc. can activate PPARα whereas TZDs (e.g. rosiglitazone, pioglitazone etc.) can activate PPARγ. It is well known that several important genes in fatty acid oxidation are downregulated and expressions of PPARs like PPARα are also reduced during cardiac hypertrophy. Although PPARα signaling is known to be associated with hypertrophic growth of cardiomyocytes, the molecular mechanism of mitochondrial impairment via this pathway in hypertrophy remains unknown.

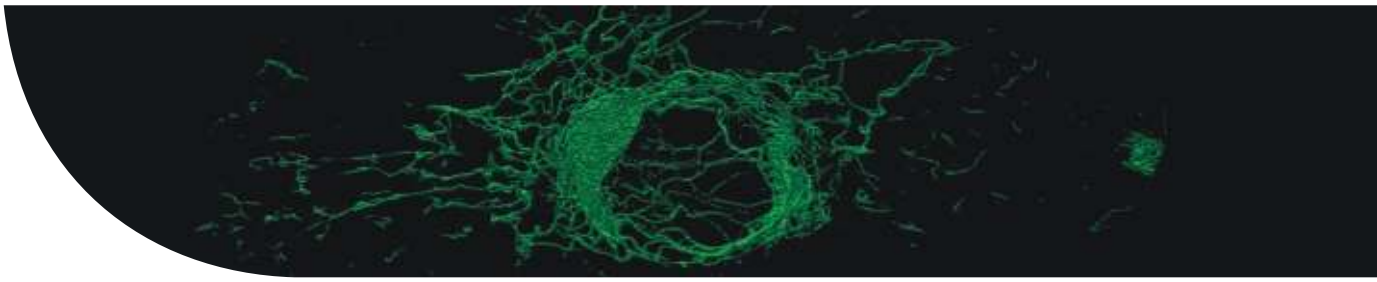
Aims and Objective: The objective of this study was investigation of the causative role of PPARα signaling and understanding the mechanism of mitochondrial dysfunction in cardiomyocytes.

Work Achieved : Hypertrophy of the H9c2(2-1) cardiomyocytes was induced by adrenergic agonist, phenylephrine (PE) and structural as well as functional remodeling of the mitochondria were evaluated using PPARα agonist, fenofibrate. Co-treatment of H9C2 cells with PE and fenofibrate restricted increase in cell size and expression of markers genes such as atrial-natriuretic peptide (ANP), brain-natriuretic peptide (BNP) and β-myosin heavy chain (β-MHC) compared to those with PE alone. Fenofibrate prevented PE-induced down regulation of PPARα-target genes like CPT-I and MCAD. Mitochondrial trans-membrane potential (Δψm) and motility were reduced by PE which were significantly checked by fenofibrate. Increase in both ROS production and calcium level in PE-treated cells were ameliorated by fenofibrate. Mitochondrial activity and ATP generation were reduced by PE which were rescued by fenofibrate. Fenofibrate also prevented PE-induced down regulation of mitochondrial genes like VDAC-I and COX-IV. Expression of several miRNAs were altered in hypertrophic cardiomyocytes which were restored when co-treated with fenofibrate. miR28 was found to target 3- untranslated region of VDAC-I. Overall, the results demonstrate that PPARα signaling is critically involved in mitochondrial dysfunction in hypertrophic cardiomyocytes in which miR28 plays a pivotal role.

Future Research: Understanding regulation of PGC1 in mitochondrial biogenesis in cardiomyocytes

PUBLICATIONS

Kar, D. and ***Bandyopadhyay A***. Targeting Peroxisome Proliferator Activated Receptor α (PPAR α) for the Prevention of Mitochondrial Impairment and Hypertrophy in Cardiomyocytes. (2018) Cell Phyiol.Biochem **49**, 245-259.



CONFERENCES / WORKSHOPS
3

INVITED TALKS BY CSIR-IICB FACULTY

Arun Bandyopadhyay

Title : Proteomic Analysis Reveals Dysregulated Cholesterol Transport in Subjects with Acute Coronary Syndrome.
Invited Talk
NCCS, Pune
Proteomics Society of India Annual Meeting, December 13, 2018.

Arun Bandyopadhyay

Title Dysregulated Signaling in Cholesterol Transport in Acute Coronary Syndrome
Invited Talk
NCCS, Pune
7th International Conference on Molecular Signaling, January 23, 2019
Invited Talk
NCCS, Pune
Proteomics Society of India Annual Meeting, December 13, 2018.

Dr. Sib Sankar Roy

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Understanding the molecular mechanism and pathophysiology of metabolic disorders; focusing on cancer and obesity-linked insulin resistance

Participants

SRF : Eshani Karmakar, Parash Prasad, Sampurna Ghosh, Priti Chatterjee, Prasenjit Das

JRF: Shreya Bandyopadhyay, Deepshikha Ghosh, Sekh Eashayan Tanbir, Suman Pakhira, Koushik Sarkar, Bhaswati Banerjee, RA

Collaborator(s)

Name of collaborator outside CSIR-IICB, Institute's name, City- if in India / Country- if outside India

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Dr. Susanta Roychoudhury
Saroj Gupta Center for Cancer Research and Institute, Kolkata
Prof Urmi Chatterjee, University of Calcutta, Kolkata
Prof Arindam Banerjee, IACS, Kolkata
Dr. Ashima Mukherjee
Chittaranjan National Cancer Institute, Kolkata
Dr. Jhuma Ganguly
Indian Institute of Engineering Science and Technology, Howrah

Name of collaborator withinCSIR-IICB

1. Dr. Saikat Chakraborty

Background

Metabolic disorders have emerged as an immensely complicated area of research demanding greater insights and better understanding. Sedentary lifestyle and food habits are the leading factors resulting in the rise of metabolic problems globally. Apart from the well-characterized metabolic disorders, cancer has been identified as complex one in recent years. Most of the times, the cancer cases are associated with either late diagnosis or with inadequate/inefficient therapeutic interventions, which further deteriorate the problems. Lack of early diagnosis alongside chemoresistance and further recurrence are the major obstructions being faced in this domain, around the world. In this context, ovarian pathology entails the extensive and major complex problems in recent years and ovarian cancer becomes the most lethal type of cancers among all the gynecological malignancies. The terrifying high lethality associated with ovarian cancer is owing to its late diagnosis due to nearly asymptomatic early phases followed by metastasis into the peritoneal cavity. High heterogeneity in the cells of tumours makes the therapy more complicated. In addition, therapy resistance and recurrence become pertinent issues in ovarian cancer patients. Therefore, a clear understanding of the underlying mechanism of the disease initiation and progression would provide an alley for the development of future therapeutic strategies. Thereby, our lab intends to study the disease progression in different model systems, which in the long run might provide some clues to the possible drug targets.

Aims and Objectives word limit 100-150

- To interpret the onco-metabolite and growth factor-mediated signaling network governing the EMT and invasion in ovarian cancer cells. Development of metabolic modulators for therapeutic usage.
- Preparing Bio Bank of ovarian cancer patients samples to make a large cohort to clinically validate our findings. Exploring molecular pathways underlying the stemness/ chemoresistance in ovarian cancer cells.
- Deciphering protein-protein interactions in transcriptional regulation and subsequent bio-energetic adaptations in cancer cells. Growth Factor-mediated alternative splicing of receptors contributing to metastatic potential and metabolic shift in cancer cells.
- To establish the significance of retinoid signaling in ovarian cancer and unravel the relevant therapeutic targets associated with obesity-induced insulin resistance.
- Development of early diagnostic markers and therapeutic leads against ovarian cancer for design and synthesis of anti-cancer small molecules in future (in collaboration with Chemists).

Work Achieved

Growth factors play major role in oncogenesis. One of the mechanisms through which FGF induces the mesenchymal switch in tumour cells has been delineated (J Cell Biochem, 2018). FGF9 treatment on the ovarian cancer cells upregulates proto-oncogene ETS1, which directly binds to the promoters of

VEGFA/VEGFR2 resulting in aerobic glycolysis and subsequent invasiveness. FGF2, however, works by binding to its receptor FGFR2, which occurs in two splice-isoforms FGFR2IIIb (epithelial) and FGFR2IIIc (mesenchymal). Interestingly, FGF2 was found to control the expression of the splice-isoforms of its own receptors, thereby contributing to the cancer progression.

Alteration in signaling pathways in cancer cells can impart chemoresistance/stemness, providing a major survival advantage. We successfully showed how Smad and non-Smad pathways downstream of TGFβ, contribute to the formation of stem population, which carried stemness markers like CD44 alongside lineage-specific markers (CD31, CD45 etc.; J Cell Biochem, 2018). This study not only shows the acquisition of stemness properties but also provides a hint on how stem population gives rise to heterogeneity. Our continuing work on metabolic reprogramming in tumour cells gives rise to the newly identified oncometabolites that could be potential early diagnostic markers. The tumour-specific expressions of a few receptors for such oncometabolites have been identified, which are potent therapeutic targets. Strategies are going on to inhibit these receptors.

Retinoic acid (RA) metabolism is linked with obesity and we showed that de-regulated retinol metabolism causing hepatic fibrosis, where Sirt1 activity has been associated with. Further, Saroglitazar, a dual PPARα/γ agonist with mostly PPARα activity, showed an overall improvement in NASH (Liver Int. 2018). The link between obesity and colorectal cancer (CRC) has been a research focus. Reduction of RA synthesis enhanced the invasiveness of colon cancer cells by changing the bio-energetic status suggesting RA-metabolic pathway modulators could possibly act as therapeutic agents for CRC.

Future Research Plans word limit 100

Cancer cells develop altered bio-energetic pathways producing different types of 'onco-metabolites', contributing to cancer progression. Glutamine and onco-metabolites (Lactate, Lysophosphatidic acid, LPA, etc.) contribute greatly to cancer pathophysiology. Research at our laboratory has been focused on identifying proteins regulating metabolite production/flux, owing to their immense therapeutic value. Further research is being conducted to understand the mitochondrial dynamics associated with the gain of stemness properties. Parallel studies are also directed towards the understanding the mechanisms involved in the overall metabolic shift of the cancer cells, with particular emphasis on understanding the role of certain transcription factors like Pitx2 and Ets1 in ovarian cancer progression.

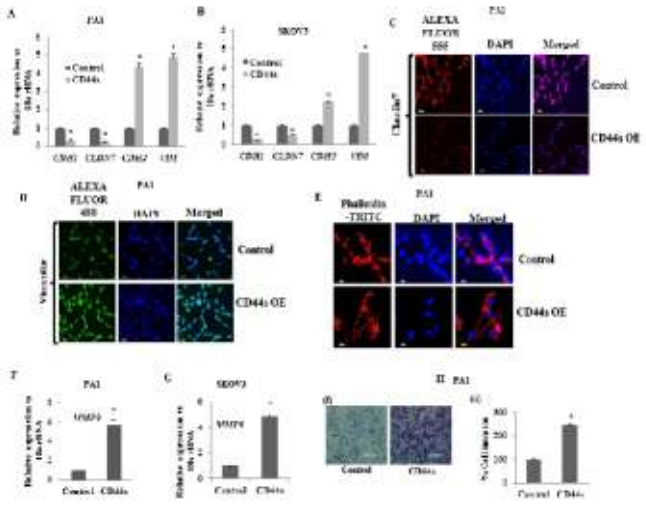
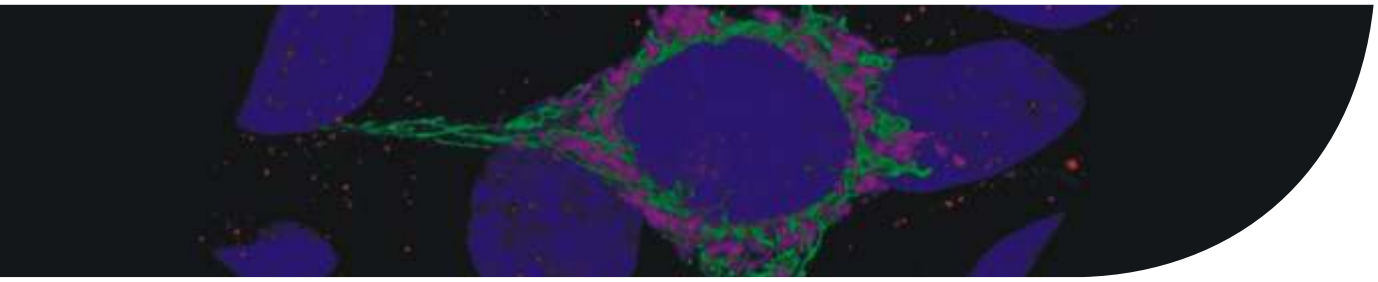


Fig. 1: CD44s isoform regulates EMT/invasion of OC cells: Relative mRNA expression of CDH1, CLDN7, CDH2 and VIM in CD44s-overexpressed PA1 (A) and SKOV3 (B) cells monitored by Q-PCR. Subcellular localization of Claudin7 (C) and Vimentin (D) was examined by IF confocal microscopy in CD44s-overexpressed PA1 cells. DAPI-stained nuclei are represented in the middle panel and the right panel shows their merged image. The images were taken at the same exposure time. Scale bar=10μm. (E) Phalloidin staining of CD44s-transfected PA1 cells to monitor actin rearrangement by confocal microscopy. Scale bar=10μm. (F-G) The mRNA expression of MMP9 was examined in PA1 (F) and SKOV3 (G) cells upon CD44s-overexpression. (H) Matrigel transwell assay was performed to monitor cell invasion in similarly transfected PA1 cells. Three independent fields for each well was used for cell counting and the representative images are shown (i) and plotted (ii) with error bars (* $p < 0.05$).



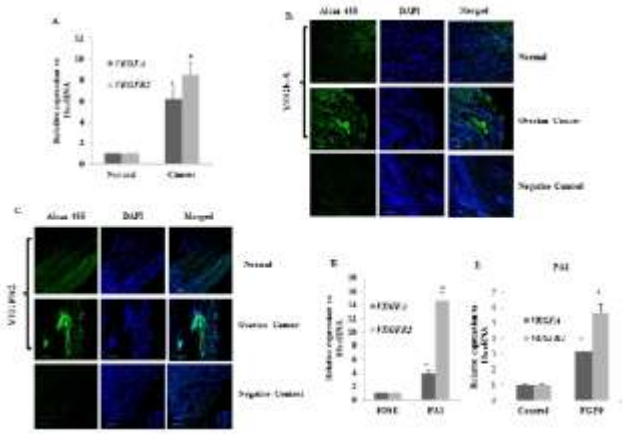


Fig2: FGF9-dependant regulation of VEGFA and VEGFR2: (A)RNA isolated from the tissue samples obtained from normal and OC patients to check the expression levels of VEGFA and VEGFR2 by Q-PCR. (N=10). The protein levels and localization of VEGF-A (B) and VEGFR2 (C) examined by IHC in human ovarian tissue sections with anti-VEGF-A and VEGFR2 antibodies followed by Alexa Flour-488 (green)-conjugated secondary antibodies. DAPI-stained nuclei are represented in the middle panel and the right panel shows their merged image. In negative control, only secondary antibody and DAPI were used. Scale bar-100 µm. (N=20). (D) mRNA levels of VEGFA/VEGFR2 compared between IOSE and PA1 cells by Q-PCR. (E) RNA isolated from FGF9-treated PA1 cells and the expression profile of VEGFA/VEGFR2 was monitored by Q-PCR. Relative gene expression is calculated and represented as 'fold' change in the Y-axis (mean+SEM). The statistical analysis is done as mentioned earlier (*p < 0.05).

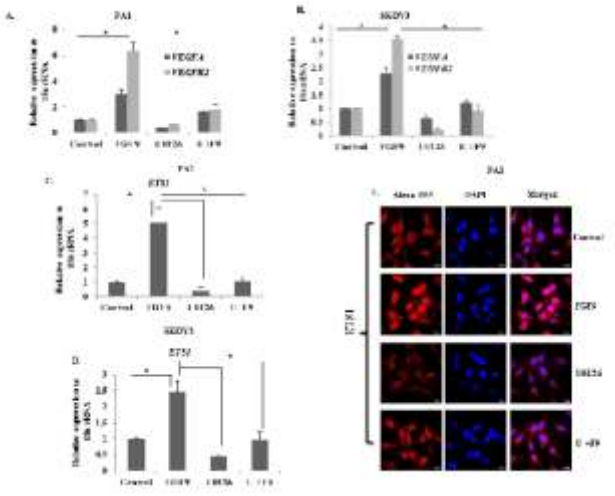


Fig3: FGF9-mediated regulation of VEGF/VEGFR2 expression and subsequent cell invasion involves ERK-signaling pathway: RNA isolated from PA1 (A) and SKOV3 (B) cells treated with FGF9 alone or in presence of U0126 (U + F9) and the expression profile of VEGFA/VEGFR2 was checked by Q-PCR. ETS1 mRNA levels were monitored in both PA1 (C) SKOV3 (D) cells in the same way. (E) The expression and sub-cellular localization of ETS1 observed by immunofluorescence confocal microscopy using anti-ETS1 antibody followed by Alexa Flour-555 (red) conjugated secondary antibody. DAPI-stained nuclei are represented in the middle panel and the right panel shows their merged image (*p < 0.05).

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Tulika Mitra, Parash Prasad, Pritha Mukherjee, Susri Ray Chaudhuri, Urmi Chatterji and Sib Sankar Roy* (2018) Stemness and chemoresistance are imparted to the OC cells through TGFβ1 driven EMT. J Cell Biochem; 119(7):5775-5787.

Bhattacharya R, Mitra T, Chaudhuri SR, Roy SS* (2018) Mesenchymal splice isoform of CD44 (CD44s) promotes EMT/invasion and imparts stem-like properties to ovarian cancer cells. J Cell Biochem. 119(4):3373-3383.4

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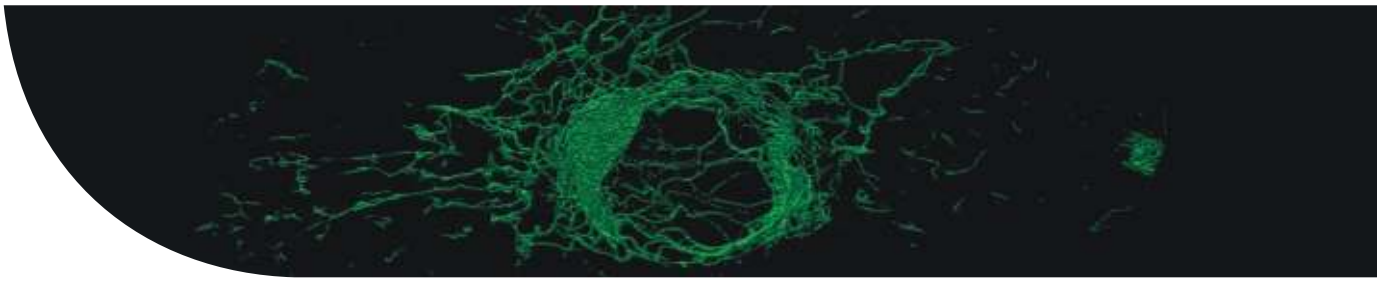
Jain MR, Giri SR, Bhoi B, Trivedi C, Rath A, Rathod R, Ranvir R, Kadam S, Patel H, Swain P, Roy SS, Das N, Karmakar E, Wahli W, Patel PR (2018). Dual PPARα/γ Agonist Saroglitazar Improves Liver Histopathology and Biochemistry in Experimental NASH Models. Liver Int. 38(6):1084-1094.



Nandi I, Chall S, Chowdhury S, Mitra T, Roy SS, Chattopadhyay K. (2018) Protein Fibril-Templated Biomimetic Synthesis of Highly Fluorescent Gold Nanoclusters and Their Applications in Cysteine Sensing. ACS Omega. 3(7):7703-7714.

Banerjee S, Chowdhury S, Mitra T, Sanyal D, Roy SS, Chattopadhyay K (2018). The role of intestinal fatty acid-binding proteins in protecting cells for fatty acid induced impairment of mitochondrial dynamics and apoptosis. Cell Physiol Biochem. 51(4):1658-1678.

CONFERENCES / WORKSHOPS
8

Award :

Received ISCA - Platinum Jubilee Award in 2019, confered by Indian Science Congress Association.

INVITED TALKS BY CSIR-IICB FACULTY

Roy SS
Growth factor-mediated signalling events and tumour progression; Invited, Two days' Workshop cum National Seminar on "Trends in modern biology: Techniques and applications" organized by National Institute of Pharmaceutical Education and Research, Kolkata and Department of Zoology, Visva-Bharati, Santiniketan, India, March 2019.

Roy SS
Alternative splicing of growth factor receptor gene and tumour progression; Invited,7th International Conference on Molecular Signaling (ICMS-2019), NCCS, Pune and Pune University and Society for Molecular Signaling, India, January 2019.

Roy SS
Alternative splicing of growth factor receptor gene regulating EMT/Invasion in tumour cells; CMBC-2019; "National Conference on Cellular and Molecular Basis of Cancer: Molecules to Mechanisms", Dept of Biotechnology, Pune University, February 2019.
Roy SS, Ray U, Roychowdhury S, Ghosh S, Ghosh D, Chatterjee BP

Cancer Metabolism and Metabolic Modulator, 106th Indian Science Congress, LPU, Jalandhar, January 2019.

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Regulation of molecular and cellular rendezvous of trophoblast, endothelial and vascular smooth muscle cells at the feto-maternal interface.

Participants

Madhurima Paul, DBT-RA
Sarmita Jana, CSIR-RA
Sarbani Saha, Project-RA
CSIR-SRF : Trishita Basak, Debdyuti Nandi, Sonali Das

CSIR-JRF : Rumela Bose

Collaborator(s)

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Background

Placental morphogenesis is a key developmental event that governs the most vulnerable period of human life. Central to this process is differentiation of trophoblast stem (TS) cells into various lineages of trophoblast cells that execute an array of molecular events essential for normal growth of the embryo in utero. Trophoblast cells, the parenchymal cells of the placenta, form the backbone of the gestational conduit that is essential for viviparity. These important cells produce hormones and cytokines that redirect the activities of the maternal environment and they possess transport machinery that facilitates the delivery of nutrients to the fetus. Disruptions in trophoblast development can lead to early pregnancy loss, intrauterine growth retardation, and tumorigenesis. These represent serious health problems whose etiologies are not sufficiently understood. Therefore, understanding the molecular regulation of trophoblast development is pivotal to combat pregnancy associated disorders.

During development, specialized populations of trophoblast cells from the placenta invade the uterine blood vessels, replace endothelial cells and acquire endothelial cell phenotype. This hallmark event is termed as “trophoblast-vasculogenic mimicry”. This 'trophoblastic vascular colonization' is an effective mechanism for removing maternal vasomotor control and dramatically augmenting the delivery of maternal resources to the placenta. Associated with the 'trophoblastic vascular colonization' are phenotypic changes in vascular smooth muscle cells (VSMCs) surrounding the uterine mesometrial arteries. Mechanisms underlying the control of VSMC phenotype are not well understood.

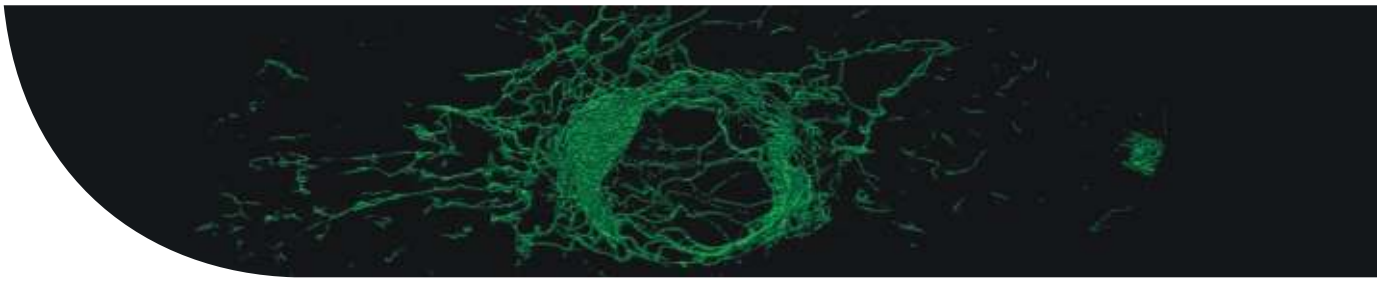
The focus of our work is on deciphering the molecular players, cellular signaling events involved in the trophoblast stem cell self renewal, and differentiation leading to formation of a functional placenta. We are in particular interested in how the early trophoblast niche is regulated by miRNAs, transcription factors and specific cellular signaling events to ensure normal development. We also investigate how trophoblast derived factors modulate VSMC to impart phenotypic changes required for normal progression of pregnancy. We use the tools and concepts of molecular biology, cell and developmental biology, genetics, microscopy to further our understanding of trophoblast stem cell differentiation, angiogenesis and placental development.

Aims and Objectives

There are three major aspects that we explore:
Molecular regulation of trophoblast cell self-renewal, differentiation and function.
Regulation of vascular smooth muscle de-differentaition in utero.
Decidual cell morphogenesis during development.

Work Achieved:

- We demonstrated that there exists intrinsic cellular factors that oppose the systemic regulation and fine tune the local milieu to protect from disease condition, such as intra-uterine growth restriction (Scientific reports, 2018)
- We identified a regulatory intra-cellular adaptor molecule that drives trophoblast stem cell differentiation to giant cell trajectory (Stem Cell Research, 2018)
- We unravelled the mechanism of trophoblast directed de-differentiation of vascular smooth muscle cells at the maternal-fetal interface (Nandy and Ain, 2019).
- We identified two miRNA clusters that form regulatory



network with CDX2 and cell cycle regulators, which equipoise trophoblast stem cell self renewal and regulation of differentiation (Saha and Ain, 2019).

Ongoing and Future Research:

We are currently working on a) the role Hippo signaling in trophoblast development, b) molecular regulation of trophoblast-vasculogenic mimicry, c) mitochondrial metabolism in trophoblast differentiation. In addition, two post-docs in the lab are working on a) molecular regulation of cardiac hypertrophy and b) role of NOSTRIN in epithelial mesenchymal transition during colorectal carcinogenesis.

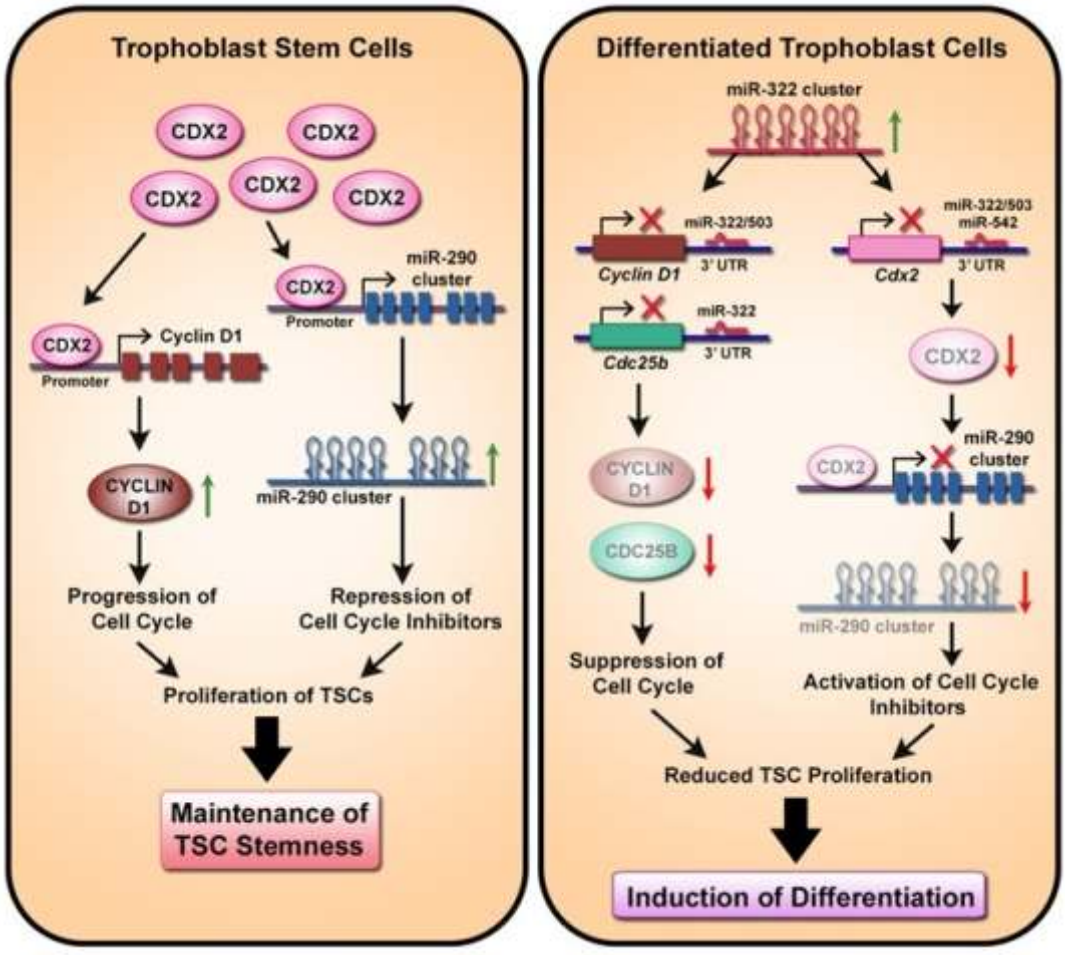
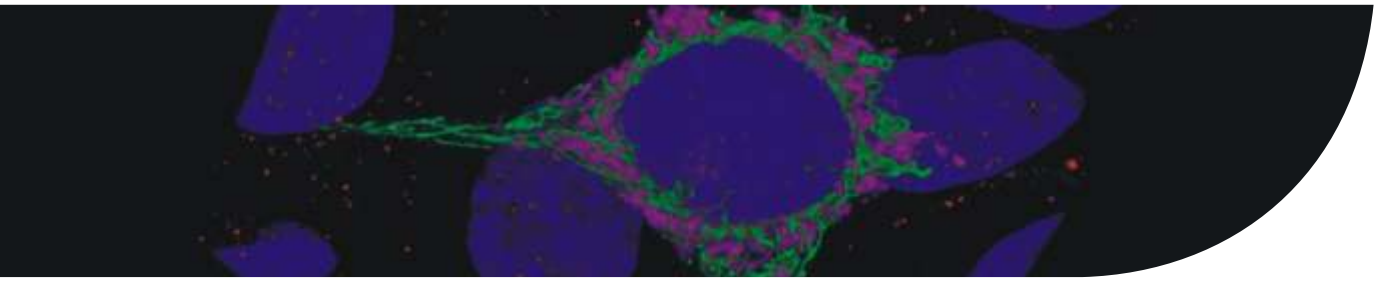


Fig 1: Schematic representation of the regulatory network of CDX2, cell cycle regulators and miRNA clusters in TS cells and differentiated trophoblast cells. CDX2 is abundant in TS cells. It transactivates the miR-290 cluster and CYCLIN D1 by binding to their promoter regions. Subsequently, the miR-290 cluster members suppress the cell cycle inhibitors (CKIs), while CYCLIN D1 promotes the proliferation of TS cells and thus collectively, maintain the stemness. Upon differentiation the miR-322 cluster is up regulated leading to suppression of CDX2 expression. Depletion of CDX2 leads to down regulation of miR-290 cluster and consequent up regulation of CKIs. Members of the miR-322 cluster also down regulate the CYCLIN D1 and CDC25B levels to abolish the G1/S transition and suppress the proliferation of TS cells and thus induce TS cell differentiation. (Saha and Ain, 2019)



PUBLICATIONS

1) Basak T and **Ain R** (2019) Long non-coding RNAs in placental development and disease. Non-coding RNA Investigation. 3:(14): 1-46.
2) Chakraborty S and **Ain R** (2018) NOSTRIN: A novel modulator of trophoblast giant cell differentiation. Stem Cell Research. 31:135-146.
3) Chakraborty S, Islam S, Saha S and **Ain R** (2018) Dexamethasone-induced Intra-Uterine Growth Restriction impacts NOSTRIN and its downstream effector genes in the rat mesometrial uterus. Scientific Reports. DOI: 10.1038/s41598-018-26590-3.
4) Bose R and **Ain R** (2018) Regulation of transcription by Circular RNAs. In "Circular RNAs: Biogenesis and Functions", Springer Nature Publishers, Book Series: **Advances in Experimental Medicine and Biology**.

AWARDS / HONOURS / MEMBERSHIPS

2017- Member, American Society of Biochemistry and Molecular Biology
Life member, Indian Society for Study of Reproduction and Fertility
Life member, International Federation of Placenta Association

EXTRAMURAL FUNDING

No.	Title	Funded by	PI/Co-PI	Amount (Lakh INR)	Brief description
1	Regulation of trophoblast-vasculogenic mimicry	DBT	PI	40.068 (3 yrs, 2017-2020)	Identification of trophoblast intrinsic factor and signaling pathways involved in trophoblast-vascular transformation.
2	Cellular Prion: A novel regulator of decidual cell function at the maternal-fetal interface	ICMR	PI	61.59 (3 yrs, 2019-2022)	Elucidation of function of cellular Prion in morphogenesis of decidua
3	Molecular regulation of spiral-artery remodeling	DBT	PI	64.90 (3 yrs, 2019-2022)	Studies on invasive trophoblast cell mediated de-differentiation of vascular smooth muscle cells surrounding uterine spiral arteries.

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Understanding molecular basis of neurodegeneration in models of Parkinson's disease

Participants

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JRF: Soumita Goswami

Collaborator(s)

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Krishnananda Chattopadhyay
Structural Biology and Bioinformatics division

Indubhushan Deb, Biswajit Banerjee, R Natarajan, Ranjan Jana
Organic and Medicinal Chemistry division

Background

Parkinson's disease (PD) is the most common neurodegenerative movement disorder resulting from the selective loss of dopaminergic neurons in the substantial nigra pars compacta (SNpc) region of midbrain. The loss of dopaminergic neurons in SNpc region results in loss of dopaminergic innervations to the striatum. The various cellular pathways such as protein misfolding and aggregation, disruption of autophagic catabolism, oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress have been implicated in death of these specific dopaminergic neurons. PD is mostly idiopathic, albeit few genes are identified as sole cause for familial form of the disease. The defining cause of sporadic PD is still a mystery.

BH3 (BCL-2 homology domain 3)-only proteins of the BCL-2 family such as PUMA (p53 upregulated modulator of apoptosis) along with other proteins of the family such as Bim, Bmf co-operate in inducing neuron death in response to cellular stress. PUMA is known to be a target of p53 and it executes cell death in response to p53 activation. It has also been shown that PUMA can be regulated by p53 independent manner. We have previously shown that Puma is trancriptionaly regulated by FoxO3a (Forkhead box O3a) in addition to p53.

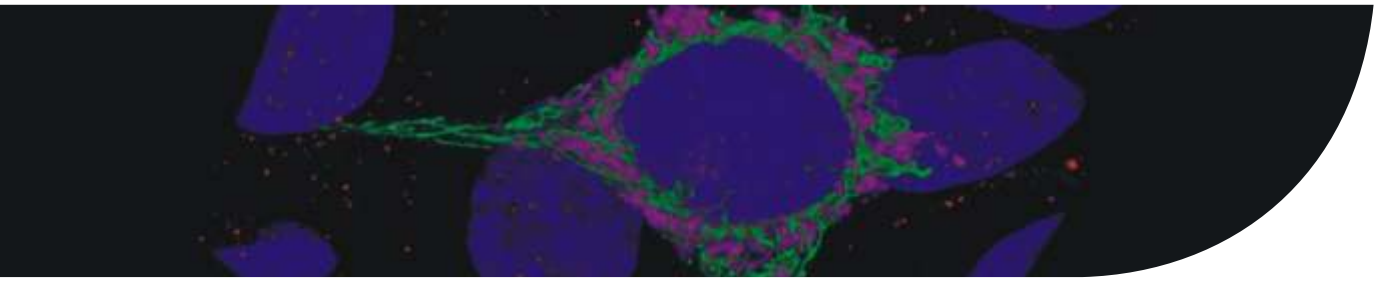
FoxO's activity is regulated by a complex array of post-transcriptional modifications which controls its subcellular localization and transcriptional activity. Recently, we have shown that upon Aβ exposure, Akt mediated phosphorylation of FoxO3a is diminished with simultaneous increase in its phosphorylation at ser207 by mammalian sterile 20-like kinase 1(MST1) and arginine methylation by protein arginine methyltransferase1 (PRMT1). These post-translational modifications lead to nuclear translocation of FoxO3a. The pro-apoptotic proteins Bim and PUMA are the transcriptional targets of FoxO3a and mediators of neuron death in response to Aβ. However, whether FoxO3a is activated in PD and mediates neuron death via Puma is yet to be investigated.

Aims and Objectives

To investigate the role of PUMA in neuronal death in models of PD.
To determine the post-translation modifications of FoxO3a in PD.
To understand the transcriptional regulation of puma by FoxO3a in PD.
To check the role chromatin remodeler in transcriptional regulation of puma by FoxO3a.

Work Achieved

Although great progress has been made in understanding the pathogenesis of PD, a therapy that halts the disease progression or cures the disease is still overdue. Current treatment mainly



targets dopamine metabolism to supply more dopamine. However, it becomes toxic at later stages. Therefore, a complementary therapy that blocks the death of dopaminergic neurons might be beneficial. Hence, deeper understanding of mechanism of dopaminergic neurons death in relevant models of PD is quintessential. In this study, we found that FoxO3a undergoes multiple post-translational modifications which render its nuclear localization in dopaminergic neuronal cells in response to 6-OHDA, a PD mimetic. The nuclear redistribution of FoxO3a is significantly increased in dopaminergic neurons of 6-OHDA infused rat brains as well. Moreover, FoxO3a is required for dopaminergic neurodegeneration in response to 6-OHDA as RNAi mediated silencing of FoxO3a protects these cells from 6-OHDA toxicity. In a search of the downstream targets we identified Puma as a direct target of FoxO3a. By knocking down FoxO3a we could successfully block the upregulation of the pro-apoptotic protein Puma in this model. Recently, it has been reported that chromatin remodeler SWI/SNF binds to FOXO and activates transcription. We found that BAF57, a subclass of SWI/SNF is upregulated and play a necessary role in neuron death induced by 6-OHDA. Moreover, it is required for induction of Puma by FoxO3a in this cellular model of PD.

We propose a cascade for 6-OHDA induced neuronal death (Fig. 3): in healthy cells, transcription factor FoxO3a is localized in cytosol as an inactive complex bound with 14-3-3 protein. 6-OHDA, a PD mimetic, treatment leads to a number of post translational modifications of FoxO3a which in turn causes its nuclear translocation. In nucleus, FoxO3a in association with BAF57 (a crucial member of chromatin remodeler SWI/SNF complex) binds with the FoxO binding site on Puma promoter. This binding results in increased PUMA expression and neuronal cell death.

Future Research Plans

- Understanding the role of age dependent DNA damage in endoplasmic stress, dysfunction of mitochondria and their implication in metabolism of Aβ and hyperphosphorylation of tau protein.
- To study the kinetics and role of secretion profile of astrocytes, displayed through a plethora of cytokines, on neuronal health and related changes in both cellular and animal models of Alzheimer's disease.
- Studying astrocyte subtypes, their secretory profiles and role in disease pathogenesis.
- Identifying regulators of autophagy flux during neurodegeneration.
- Bioassay guided isolation of potential phytopharmaceutical leads against Alzheimer's disease.
- Detection of disease specific signatures for Alzheimer's disease in clinical samples.
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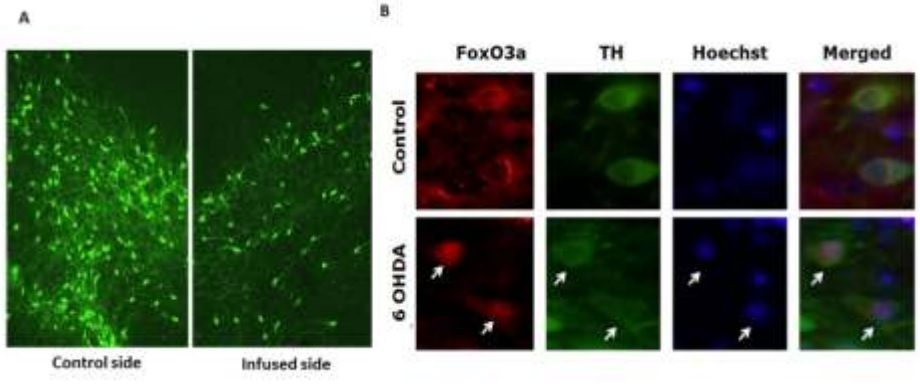
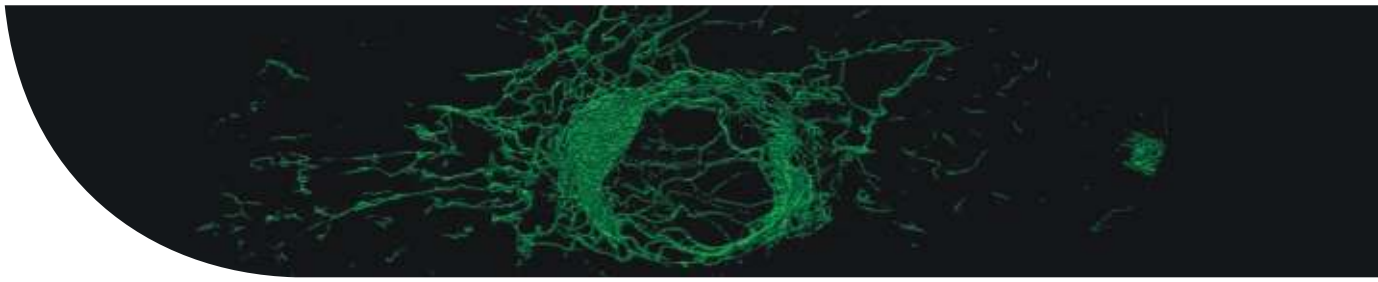


Figure 1: FoxO3a translocates from cytosol to nucleus in response to 6-OHDA in vivo.
A. The rats were infused with PBS (indicated as control) or 6-OHDA in the MFB. The animals were sacrificed after 14 days and the brain slices were immunostained with TH for DA neurons (shown in green). Result shows a marked reduction of green TH positive DA cells in infused side compared to control side. B. The brain slices were co-immunostained with TH for DA neurons (shown in green) and FoxO3a (shown in red). The nuclei were stained with Hoechst. The arrow indicates nuclear translocation of FoxO3a in DA neurons from SNpc of 6-OHDA infused rat brains. Images were taken under 40X objective. Representative images with similar result from 4 brain slices from 3 different animals in each group are shown here.



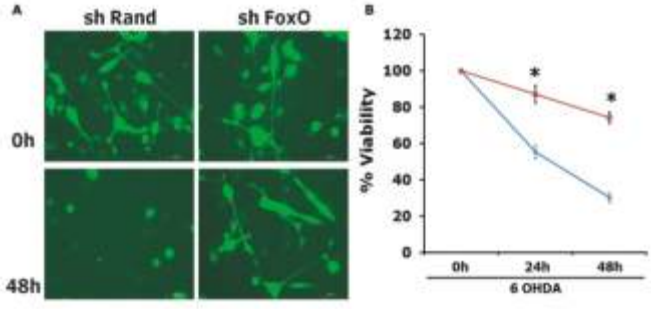


Figure 2: siRNA mediated knockdown of FoxO protects neuronal PC12 cells following 6-OHDA treatment.
A. Neuronal PC12 cells were transfected with shRAND or shFoxO. 48h post transfection cells were treated with 6-OHDA. Green live cells were counted under fluorescence microscope at indicated times. Representative micrograph images of shRAND or shFoxO transfected cells at 0h and 48h of 6-OHDA post-treatment. B.Graphical representation of percentage of viable shRand and shFoxO transfected cells following 6-OHDA treatment. Data represented as mean ± S.E.M. n = 6. Asterisks denote statistically significant difference with control, * p<0.05.

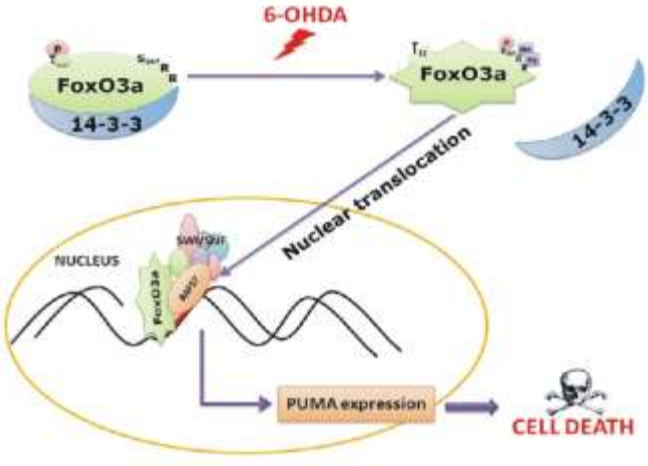


Figure 3: A schematic showing the cascade for 6-OHDA induced neuronal death.

PUBLICATIONS

Akhter, R., Saleem, S, Saha, A. and Biswas, S C (2018). The pro-apoptotic protein Bmf co-operates with Bim and Puma in neuron death induced by β-amyloid or NGF deprivation. Mol Cell Neurosci 88:249-257.

Saleem. S, Saha. A, Akhter. R and Biswas, S C (2018). Cooperation of BH3-only proteins in killing neurons. Biomed Res Clin Prac. 3(2): 1-3.

Book Chapters / Invited Reviews

Sanphui P., Saha, A. and Biswas, S C (2019). RNAi mediated silencing of FoxO factors. Methods in Molecular Biology 1890:131-140.

EXTRAMURAL FUNDING

Subhas Biswas
Alzheimer's disease: identification of common targets regulating both apoptosis and autophagy during neurodegeneration. 2018 2021. (DST, India).

Alzheimer's disease: is age-related subtle DNA damage the trigger of the sporadic Alzheimer's disease? 2019 2022. (DST, India)

Research and development work for value addition of the product "Medha Plus". 2018 2019. (Parker Robinson Pvt Ltd., India)

CONFERENCES / WORKSHOPS

Number of Abstracts in National/International Conference: 13
Number of Abstracts in International (Overseas) Conference: 4

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

NeuroUpdate; Nov 24, 2018; IICB, Kolkata

INVITED TALK

Alzheimer's disease: pathogenesis and therapeutic strategies; the 3rd J.J. Ghosh Memorial lecture organized by India Acdemy of Neurosciences Kolkata chapter, 30th Aug, 2018, Kolkata.

Dr. Partha Chakrabarti

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Ubiquitin Proteasomal System in the pathogenesis of Non-alcoholic fatty liver disease (NAFLD)

Participants

SRF : Sougata Niyogi, Debajyoti Das,

JRF : Jit Sarkar, Saheli Chowdhury, Pratiti Mandal, Ankita Sarkar, Tanusree Das,

Collaborator(s)

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Gastroenterology and Hepatology, Institute of Postgraguate Medical Education and Research, Kolkata

Dr. Sujoy Ghosh
Endocrinology, Institute of Postgraguate Medical Education and Research, Kolkata

Dr. Om Tantia
ILS hospital, Kolkata

Dr. Subhransu Chatterjee
Bose Institute, Kolkata

Name of collaborator within CSIR-IICB
Dr. Arindam Talukdar
Dr. Sandip Paul
Dr. Dipyaman Ganguly
Dr. Sanjay Dutta

Background

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver diseases encompassing hepatic steatosis, nonalcoholic steatohepatitis (NASH) and cirrhosis and is increasingly recognized as the leading cause of liver dysfunction. The pathological hallmarks of NASH are steatosis, inflammation, hepatocyte death and fibrosis. Progressive fibrosis leads to irreversible damage to liver parenchyma and end stage liver disease. No specific therapeutic are available for NASH and understanding of molecular mechanisms are thereby of utmost importance.

Over the years we have identified deregulation of **Ubiquitin Proteasomal System** (UPS) as one major cellular event in pathogenesis of NAFLD. Ubiquitination is a post translational modification wherein ubiquitin is added to a target protein. The process is mediated in three consecutive steps by three different enzymes. The first step consists of ATP-dependent activation of ubiquitin by E1-ubiquitin activating enzyme followed by transfer of ubiquitin from E1 to the active site cysteine of E2 via trans thioesterification reaction. The final step is carried out by E3 ubiquitin ligases which catalyses the formation of an isopeptide bond between lysine of the target protein and C-terminal glycine of ubiquitin. Multiple ubiquitin residues can thereafter be added to the first residue yielding a polyubiquitin chain. Once a protein is ubiquitinated, it is usually targeted for degradation by the 26S proteasome.

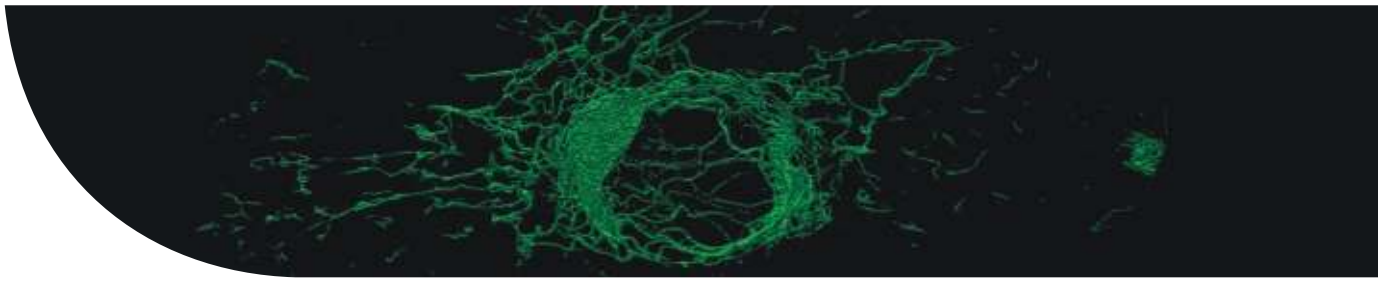
We have identified an E3 ligase COP1 responsible for the hepatic lipid turnover by degrading adipose triglyceride lipase (ATGL). We have moreover identified pigment epithelium-derived factor (PEDF) as the physiological cue for COP1 mediated ATGL degradation in cellular nucleus.

Aims and Objectives

- Identifying the impact of proteotoxicity and proteasomal activity in NAFLD and NASH
- Impact of PEDF on hepatocyte lipid metabolism and fatty liver disease

Work Achieved

- **Proteotoxic stress in increased in NAFLD**. We stumbled upon a very intriguing observation wherein we found that the ubiquitination of proteins increased drastically in mice fed high fat diet (HFD) for 3 months (a preclinical NAFLD/NASH model) (Fig1). The total ubiquitylated proteins were increased as shown by immunohistochemistry (IHC) and Western blotting (Fig1). These data suggest that proteotoxic stress is associated with NAFLD.
- **PEDF controls hepatic lipid metabolism via ATGL-COP1 axis**. Adipose triglyceride lipase (ATGL) plays a compelling role in hepatic lipid turnover and in the pathophysiology of non-alcoholic fatty liver disease. Hepatic ATGL is post-transcriptionally regulated by E3 ubiquitin ligase constitutive photomorphogenic1 (COP1) through polyubiquitylation and proteasomal degradation. However the physiological cue for



COP1-mediated hepatocellular degradation of ATGL remained unknown. Here we checked for the role of pigment epithelium-derived factor (PEDF), a moonlighting hepatokine and the so-called ligand of ATGL for its stability in hepatocytes. We show that PEDF diminishes ATGL protein stability by promoting its proteasomal degradation in COP1-dependent manner. Despite being a secretory glycoprotein, PEDF is also sequestered in the nuclear compartment so as COP1. Interestingly, PEDF enhances nuclear import of predominantly cytosolic ATGL protein for its subsequent proteasomal degradation in the nucleus (Fig 2, lower panels). PEDF also controls cell autonomous hepatocyte lipid accumulation and mobilization through COP1-ATGL axis (Fig 2, upper panels), thereby unraveling a novel pathway for hepatic lipid metabolism (Fig 3).

Future Research Plans

- Unraveling of molecular mechanism of proteotoxic hepatic injury in NAFLD
- Identification of specific DUB as novel therapeutic target in NAFLD/NASH
- Delineating role of PEDF on sterile hepatic inflammation in NASH

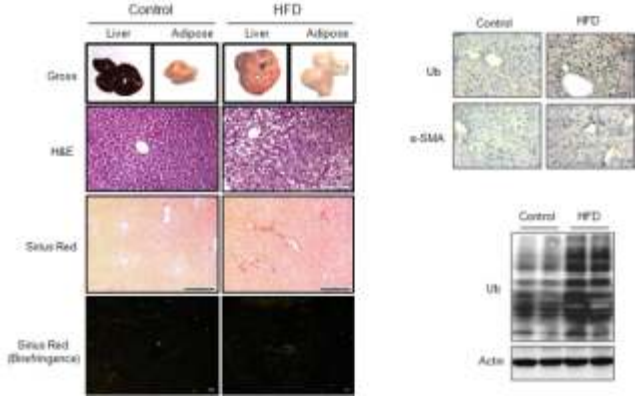


Fig. 1: Increased ubiquitylation in livers of NAFLD/NASH mice. High fat diet (HFD) induced NAFLD model (upper left) having increased ubiquitin levels shown by IHC (upper right) and Western blot (lower right).

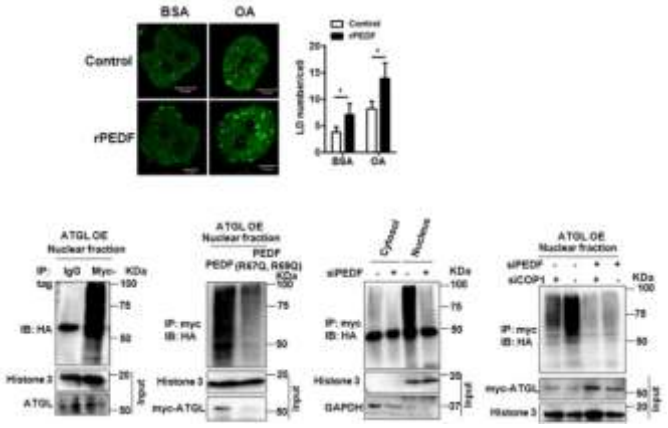


Fig. 2: PEDF treatment increases lipid content in primary murine hepatocytes (upper panel). Ubiquitylation of ATGL is compartmentalized to the nuclear fraction and abrogated by either knockdown of PEDF or COP1 (lower panels)

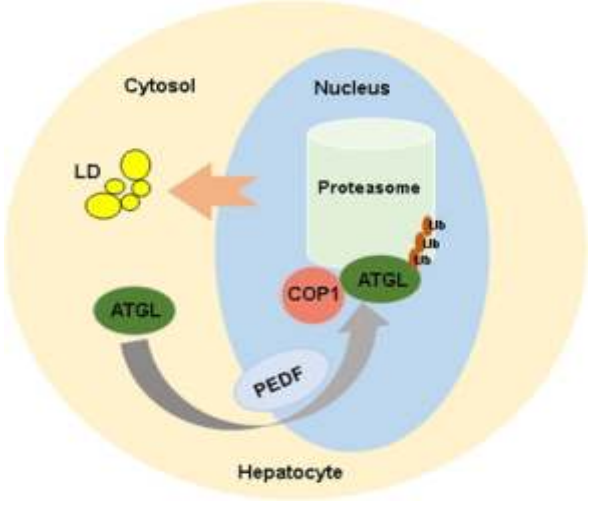
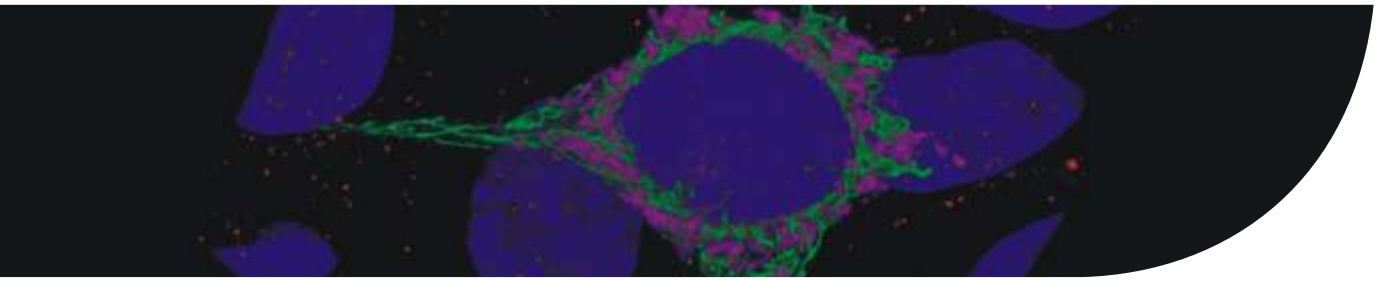


Fig. 3: Schematic for the novel hepatic lipid turnover pathway; PEDF helps nuclear entry and COP1-mediated proteasomal degradation of ATGL thus tempers the intracellular lipid content in hepatocyte.



PUBLICATIONS

- Niyogi, S., Ghosh, M., Adak, M., Chakrabarti, P. (2019) PEDF Promotes Nuclear Degradation of ATGL through COP1. Biochem Biophy Res Commun **512**, 806-811
- Banerjee, I., De, M., Dey, G., Bharti, R., Chattopadhyay, S., Ali, N., Chakrabarti, P., Reis, RL., Kundu, SC., Mandal, M. (2019) A peptide-modified solid lipid nanoparticle formulation of paclitaxel modulates immunity and outperforms dacarbazine in a murine melanoma model. Biomater Sci **26**, 1161-1178
- Palit, S., Mukherjee, S., Niyogi, S., Banerjee, A., Patra, D., Chakraborty, A., Chakrabarti, S., Chakrabarti, P., Dutta, S. (2018) Quinoline-glycomimetic conjugates reducing lipogenesis and lipid accumulation in hepatocytes. ChemBiochem (Accepted)
- Adak, M., Das, D., Niyogi, S., Challa, N., Ray, D., Chakrabarti, P. (2018) Inflammasome activation in Kupffer cells confers a protective response in nonalcoholic steatohepatitis through pigment epitheliumderived factor expression. FASEB J. (Accepted)
- Khan, MW., Layden, BT., Chakrabarti, P. (2018) Inhibition of mTOR complexes protects cancer cells from glutamine starvation induced cell death by restoring Akt stability. Biochim Biophys Acta (BBA) **17**, 2040-2052 (selected for BBA collection on 'Programmed Cell Death' 2018)

Book Chapters / Invited Reviews

- Nargis, T., and Chakrabarti, P. (2018) Significance of circulatory DPP4 activity in metabolic diseases. *IUBMB Life* **70**, 112-119.

AWARDS / HONOURS / MEMBERSHIPS

Faculty

Scientist's Name : Partha Chakrabarti

Memberships

- **Member,** SERB Programme Advisory Committee on Health Science (PAC-HS) (2018-19).
- **Member,** DBT Task Force on Metabolic Diseases & Autoimmune Disorders (2018)

EXTRAMURAL FUNDING

Name : Partha Chakrabarti

- Elucidation of Roles of Inflammatory Mediators in Pancreatic β Cell and hepatocyte dysfunction in Type 2 Diabetes. 2017-20. (ICMR, India)
- A yearlong prospective study on the role of incretin pathway in obesity and glycemia control in patients undergoing bariatric surgery. 2016-19. (West Bengal DBT, India)
- Non-alcoholic fatty liver disease (NASH). 2018-20. (CSIR, India)
- Sterioselective total synthesis of marine macrocyclic lactone biselyngbyaside and its variants and their biological activities. (DST-SERB, India)

INVITED TALKS BY CSIR-IICB FACULTY

Name Surname: Partha Chakrabarti

- Exploring the Hepatic Niche in Metabolic Disorder; Invited talk; Indian Academy of Biomedical Sciences, February 2019, CSIR-NIIST, Thiruvananthapuram, India
- A Search for the Indian 'Thin-Fat' Diabetes; Invited talk; One day symposium, School of Biological Science, Indian Association for Cultivation of Sciences, 20nd Feb, 2019
- Exploring the Hepatic Niche in Metabolic Disorder. Invited talk; Frontiers in Development and Molecular Medicine (FDMM), Kolkata, March 2019
- Unraveling Lipid Turnover in Nonalcoholic Fatty Liver Disease (NAFLD). 6th International Conference on Molecular Signaling (ICMS) 2018, University of Hyderabad.
- Preclinical Models for Fatty Liver Disease. Invited talk; Symposium at Indian Institute of Liver and Digestive Sciences (IILDS), Sonarpur, West Bengal, 2018
- Identification of PEDF-ATGL-COP1 Axis in Fatty Liver Disease; Invited talk; Young Investigators Meet (YIM) 2018, Thiruvananthapuram

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Role of RXR gamma in steroid resistant asthma and COPD

Participants

SRF : Ashish Jaiswal

JRF : Joytri Dutta, Sabita Singh, Archita Ray, Anupama Mukherjee

Collaborator(s)

Name of collaborators outside CSIR-IICB

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Dr Anurag Agrawal, CSIR-IGIB, Delhi

Background and origin of the research plan

Lung diseases are amongst the top three threats to public health globally (see http://www.thelancet.com/themed/global-burden-of-disease). The glucocorticoids (GCs) are commonly prescribed medicines to fight against various diseases including asthma and COPD. However, 5-20% of asthma patients and almost every COPD patient do not respond to glucocorticoids. This non-responsiveness is the major reason why COPD and steroid resistant asthma are responsible for the major burden of entire lung diseases. The treatment of steroid insensitive/resistant patients is really a big challenge for clinicians who use either very high dose GCs or secondary immunosuppressants and both strategies lead to worser side effects. Thus, two crucial things are needed in this area: a) identification of factors responsible for steroid insensitivity and b) discovery of safer steroid sensitizing agents that would help us to use GCs in effective and safer way. One common denominator for both the diseases (Steroid insensitive asthma and COPD) is airway neutrophilia. Though the exact etiologies for airway neutrophilia are not known, it is strongly suggested that environmental pollutants are the reasons for airway neutrophilia. However, the detailed studies are not available.

Origin of hypothesis

As the mechanims for the steroid resistance are not completely known, we wanted to dissect in a thorough manner towards developing steroid sensitizing agents so that we can use low concentrations of steroids in a safer way and thus improve the sensitivity along with the reduction in the adverse effects upon long use. To understand the mechanisms, we have used our own lab findings along with the literature knowledge. We have initiated steps to design the experiments to further dissect the novel mechanisms for steroid resistant asthma and COPD. As we found the clinical correlation of increased asthma severity with lower expression of RXR-gamma, a nuclear receptor, we hypothesized that RXR-gamma may improve steroid sensitivity in asthmatic and COPD condition.

Aims and Objectives

1. To determine the status of RXR gamma in steroid resistant asthma and COPD
2. Mechanistic understanding behind the steroid sensitive property of RXR gamma

Work Achieved

a) We found RXR/RAR (Retinoid X receptor/Retinoic acid receptor) binding site in first intron of GR gene that contains promoter like features

b) **RXR-γ is found to regulate the expression of glucocorticoid receptor** by binding to GR gene [CHIP assay, and oligo pull down assay and enhancer assays].

c) Opposite correlation between GRα and RXRγ was found in PBMCs of asthmatic patients. These indicate the possibility of modulating GRα and thus steroid sensitivity by altering RXRγ levels.

d) Inhaled corticosteroid use lead to increased **Glucocorticoid receptor beta** expression in asthmatics.

e) RXR-γ siRNA administered naïve mice had not only showed the features of steroid insensitive asthma features but these mice also had elastin fragmentation both in lung arterial wall and lung parenchyma with increased neutrophils in lung parenchyma (data not shown). These indicate that

neutrophils are common denominator for both steroid insensitive asthma and COPD.

f) **The levels of RXR-γ are reduced in lungs of human COPD patients** and **asthmatic** patients.

g) DHA is found to be reduced in COPD and asthma patients compared to controls. The reduction was more prominent in steroid insensitive asthmatics compared to sensitive asthmatics. However, there was no deficiency of Vitamin A in asthmatics.

h) The ligand of RXR, **DHA (docosahexaenoic acid) which is also a nutritional supplement, improved the steroid sensitivity** in steroid resistant **asthma** mice model at **12.5mg/kg as it reduced the inflammation and airway hyper responsiveness though vitamin A could not reduce the inflammation and Airway hyper responsiveness.**

i) The entire mechanistic understanding behind the steroid sensitive property of RXR gamma has been shown in Figure 1 as a scheme diagram.

Future Plans:

1. DHA supplementation along with inhaled budesonide in 40 steroid insensitive/resistant asthmatics in 40 patients
2. To correlate the ex vivo steroid insensitivity with clinical steroid insensitivity in steroid resistant asthma and COPD patients
3. Beneficial role of DHA in cigarette smoke exposed/Smar-1 siRNA induced spontaneous emphysematous mice

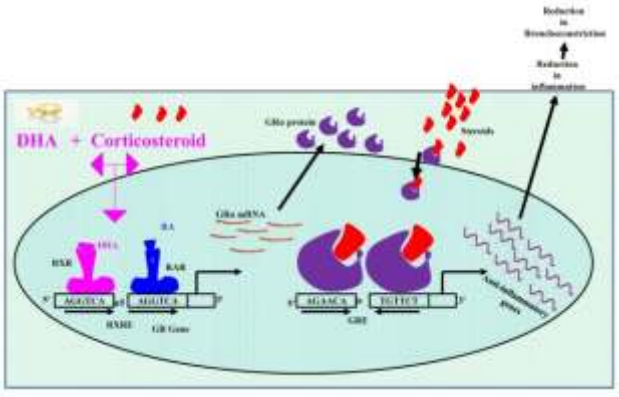

Figure 1. Possible mechanisms of Rxr-γ mediated steroid resistance and improvement of steroid sensitivity by Docosahexaenoic acid (DHA), a known RXR ligand. The present study hypothesizes and provides evidence for the fact that in steroid sensitive asthma, RXRγ heterodimerizes with RAR to bind to rexinoid receptor element (RXRE) present on intron 1 of glucocorticoid receptor (GR) gene and regulates the expression of GRα. When activated by corticosteroids, it homodimerizes and binds to glucocorticoid receptor element (GRE) present on various pro-inflammatory cytokines and anti-inflammatory cytokines genes and reduces the inflammation. However, in steroid insensitive condition, when RXRγ levels are low, the regulation on GRα is lost and the expression of GRα is reduced. This further leads to loss of regulation of inflammatory cytokine genes expression and tilting the cellular milieu towards pro-inflammatory and hence, causing steroid insensitivity. This steroid insensitivity is alleviated upon upregulation of RXRγ or addition of docosahexaenoic acid (DHA).

PUBLICATIONS in last one year:

1: Khanna K, Chaudhuri R, Aich J, Pattnaik B, Panda L, Prakash YS, **Mabalirajan U**, Ghosh B, Agrawal A. Secretory Inositol Polyphosphate 4-Phosphatase Protects against Airway Inflammation and Remodeling. Am J Respir Cell Mol Biol. 2019 Apr;60(4):399-412.

2: Jain V, Raina S, Gheware AP, Singh R, Rehman R, Negi V, Murray Stewart T, **Mabalirajan U**, Mishra AK, Casero RA Jr, Agrawal A, Ghosh B. Reduction in polyamine catabolism leads to spermine-mediated airway epithelial injury and induces asthma features. Allergy. 2018 Oct;73(10):2033-2045.

3. Nilanjana Deb, Sudipta Mallick, Ashish Jaiswal, Anirban Manna, **Ulaganathan Mabalirajan**, Snehasikta Swarnakar. Role of MMPs and Oxidants in Lung Diseases. Pages 149-170. Book titled Oxidative stress in Lung diseases Volume 1, edited by Sajal Chakraborti et al Springer Book, 2019.

Dr. Prem Prakash Tripathi
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Role of endogenous neuronal progenitors in neurogenesis following neurodegeneration

Participants

JRF: Ms. Jhilik Dey, Ms. Sreyashi Chandra

PA: Mr. Tanjim Alam

Background:

Adult neurogenesis persists constitutively in two regions of the brain, subventricular zone (SVZ) and hippocampal subgranular zone (SGZ). The existence of endogenous progenitor cells raises the possibility of harnessing these populations of cells to replace neuron lost as a result of traumatic brain injuries and neurodegenerative diseases. Recent evidence indicates that neurogenesis is upregulated in SVZ, SGZ, and in pPV in several brain injury models such as ischemia, stroke and seizure. Kainic acid (KA)-induced seizure in hippocampus provides a powerful model for investigating the molecular mechanisms of KA induced neurodegeneration and neurogenesis. These results suggest that endogenous progenitor cells exhibit significant plasticity and are potentially multipotent, indicating that manipulation of endogenous progenitor cells to repopulate neurons lost as a result of injury and disease may be an achievable goal. However, many gaps exist in our knowledge of the normal distribution, cellular dynamics, and migratory behaviour of endogenous progenitors, even in the normal adult brain. Neuronal progenitors actively proliferate and produce new neurons in the adult brain. These studies suggested that neuronal progenitors cells are stimulated to proliferate in the injured brain. We would like to investigate, if endogenous progenitor cells respond to kainic acid (KA) induced brain injury by proliferation, neuroblast generation and migration to injury site.

Aims and Objectives:

1) To determine the distribution of neuronal progenitor cells and dissect their cellular dynamics under basal conditions and KA induced neurodegeneration.
2) Whether newly generated neuroblasts get recruited at damaged site after KA induced neurodegeneration and participate in the brain circuitry.

Work Achieved:

Distribution of SOX2+ progenitor cells was determined within neurogenic niches of adult brain, to document their cellular dynamics under basal conditions. Adult brains were dissected in PBS, fixed overnight in PBS, 4% PFA at 4°C, cryoprotected in PBS, 30% sucrose overnight at 4°C and embedded in cryostat freezing medium. Brains were coronally sectioned in 10 um thick slices and placed serially onto slides. Sections were post fixed for 10' with 4% PFA. For the detection of nuclear antigens an antigen enhancement step was performed by briefly boiling the slides in 10 mM sodium citrate pH 6.0 using a microwave. Sections were incubated in permeabilization/blocking solution (0.2% Triton X--100, 10% goat serum in PBS) for 30 min at RT and incubated with primary antibodies diluted in PBS plus 2.5% goat serum, 0.05% Triton X100 at 4 C overnight. Sections were incubated with the appropriate speciesspecific secondary antibodies conjugated to Alexa568at 1:400 dilution for 2hr at RT, then incubated with DAPI nuclear counterstain, and coverslipped with Fluoromount-G. Sox2 staining at dorsal hippocampal level shows expression of neuronal progenitors population in SGZ and hilus of dentate gyrus. We are additionally investigating various other markers such as Nestin, Tbr2, Dcx and NeuN under basal condition as well as after KA induced neuroegenration.

To access the effect of Kainic acid induced neurodegeneration, we used MTT assay to determine cell viability of SH-SY5Y neuroblastoma cells. Different concentrations of kainic acid (KA) ranging from 1 µM to 100 µM were used to evaluate cell viability after 24hr post treatment. Results proved that kainate exposure induced a reduction of cellular viability in dose-dependent response manner. After 24 h, it was possible to observe a decrease of cell viability in cells exposed to 1 µM kainic acid (87.9±5.1%), to 2.5 µM kainic acid (78±8.1%), 5 µM kainic acid (67.56±4%), 10 µM kainic acid (69.2±2.1%), 25 µMkainic acid (60±2.3%), 50 µM kainic acid (54.8±12%), versus the controls (100±6.2%; Fig. 2).

Future research plan:

1) Valproic Acid-Induced Neurodevelopmental Defects- Valproic acid (VPA), a widely used antiepileptic and mood

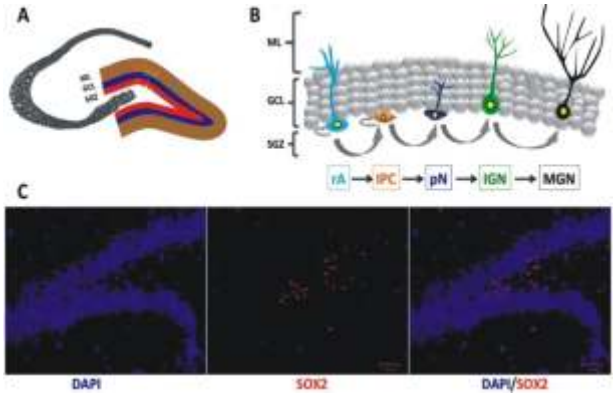

Figure 1- A) Diagramatic representation of Adult hippocampus and various cell layers such as Subgranular zone (SGZ), Granular cell layer (GCL) and Molecular later (ML) in dentate gyrus. **B)** Lineage progression during adult hippocampal neurogenesis. **C)** Adult mice brain at dorsal hippocampal section shows staining of Sox2+ progenitors population in in SGZ and hilus of hippocampus.

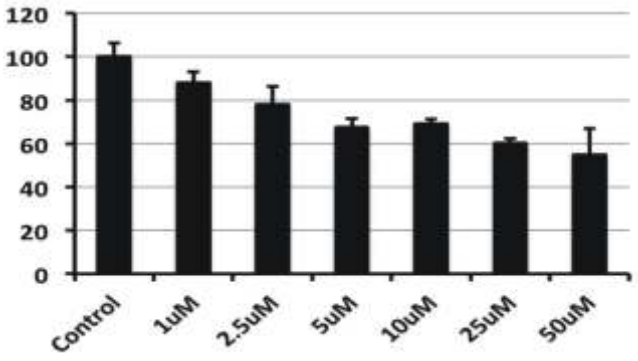

Figure 2- Percentage cell viability calculated by MTT assay in control cells, and in kainate-treated cells. Cells were exposed to kainate 1, 5, 10, 25, and 50 μM for 24 hr. Data are expressed as percentage of controls (100%).

stabilizing drug, causes neurodevelopmental defects including autism spectrum disorder (ASD). Clinical and experimental data have shown the involvement of multiple brain regions such as cerebral cortex, hippocampus and cerebellum in ASD pathophysiology. We propose to first develop a mice model of autism by in utero exposure of VPA and its link to ASD. We will further characterize cell types and subcellular compartments of cerebral cortex, hippocampus and cerebellum throughout stages of mouse brain development.

2) Neuroprotective effects of essential oil against kainic acid induced seizure-Component of essential oil has shown its pharmaceutical characteristics in various diseases, including neurological disorders such as epilepsy. In this study, we will isolate various components of essential oil and will evaluate for their neuroprotective effects against KA-induced epilepsy models in vitro and in vivo.

Publications:

1) **Tripathi PP**, Arami H, Banga I, Gupta J, Gandhi S. (2018) Cell penetrating peptides in preclinical and clinical cancer diagnosis and therapy. Oncotarget. 9(98):37252-37267.

2) Gandhi S, Gupta J, **Tripathi PP** (2019) The Curious Case of Human Hippocampal Neurogenesis. ACS ChemNeurosci. 10(3):1131-1132

Extramural Funding:

Role of endogenous intermediate progenitors in neurogenesis following neurodegeneration. Start year: 2018, End year 2021, Agency: DST, Govt of India

Conferences/Workshops
Number of Abstract, India: 3

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Mechanism of Mitochondrial quality control on progressive neurodegeneration

Participants

CSIR-JRF : Moumita Roy, Rupsha Mondal

UGC-JRF : Chayan Banerjee

Background and origin of the research plan

Though mitochondria are prime source of ATP, they can quickly change from a source of energy to pro death organelles by producing reactive oxygen species (ROS) and releasing components required for apoptosis. In order to prevent build-up of ROS and accumulation of aberrant proteins/organelles, cells employ a defense mechanism to remove dysfunctional mitochondria via autophagy, a process termed as mitophagy. The current literature depicts that mitophagy requires the involvement of both autophagic machineries and ubiquitin proteasome complex. Proteasome localization to depolarized mitochondria as well as degradation of outer mitochondrial membrane (OMM) ubiquitinated proteins and disruption of the mitochondrial membrane are pivotal elements in the orchestration of mitophagy. It was not clear however, how OMM rupture can enable mitophagy until recently, when it was demonstrated that OMM rupture leads to the exposure of Prohibitin 2, which acts as one of the receptors for autophagic machineries to form mitophagic vesicles. However, it is still not clear which / how protein complexes on OMM help to rupture the membrane. Interestingly, during aging, efficiency of both proteasome complex and autophagy goes down. As neurons are high energy demanding cells, hindrance in mitochondrial quality control may contribute to their death. Inside brain, modulation of mitophagy adaptors, in combination with intra region specific inputs may lead to area specific neurodegeneration.

Aims and objective:

- Characterization of OMM protein complexes during depolarization.
- Identification of inner mitochondrial membrane proteins (IMM) which communicate with the outer membrane proteins at the initial stages of mitophagy.
- In *vivo* characterization of mitophagy related IMM and OMM protein proximity during aging.

Work achieved so far

We have determined the time points of depolarization induced mitophagy progression in neuronal cell line. We found that OMM rupture starts from 2h onwards whereas mitochondrial mass starts to go down after 4h of CCCP treatment (Fig. 1A). The results were confirmed by visualising mitochondria after HSP60 immunostaining (Fig. 1B,C). We have also determined the mitochondrial membrane rupture point by trypsin digestion assay, which showed that by 4h OMM becomes very porous (Fig. 1D). Thus to catch the protein complex formation at the OMM we treated the cells with CCCP for 2h, for further experimentations. Once we determined the time points we first wanted to monitor if depolarization can alter the OMM morphology just before rupture. Atomic force microscopic images of isolated rat brain mitochondria showed that homogenous distribution of the OMM channels were altered after CCCP treatment, which appeared more in clusters in the later (Fig. 1E). We have also started characterizing the two most abundant mitochondrial channel forming proteins VDAC1 and TOM20 (which are also the targets of proteasome for mitochondrial OMM rupture during mitophagy) in terms of their distribution pattern after depolarization.

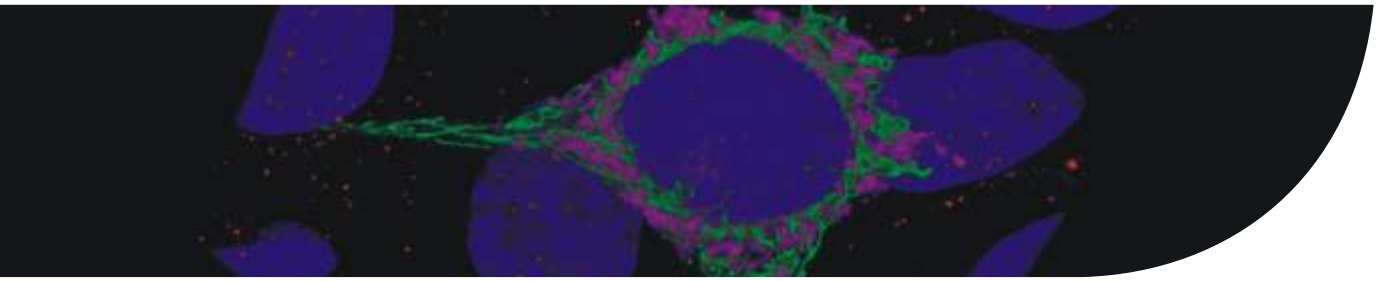
Future research plan

Currently we are characterizing the protein complexes in the OMM and IMM using mass spectrometry. We are also performing immunoprecipitation followed by mass spectrometry to determine the interacting proteins of VDAC1 and TOM20 during formation of different complexes.

Publications

Chakraborty, J., von Stockum, S., Marchesan, E., Caicci, F., Ferrari, V., Rakovic, A., Klein, C., Antonini, A., Bubacco, L., Ziviani, E (2018) USP14 inhibition corrects an in vivo model of impaired mitophagy. EMBO Mol Med, **10**,e9014.

Basso, V., Marchesan, E., Peggion, C., Chakraborty, J., von Stockum, S., Giacomello, M., Ottolini, D., Debattisti, V., Caicci, F.,



Tasca, E., Pegoraro, V., Angelini, C., Antonini, A., Bertol,i A., Brini, M., Zivian,i E (2018) Regulation of Endoplasmic Reticulum-Mitochondria 1 contacts by Parkin via Mfn2. *Pharmacol Res*, **138**:43-56.

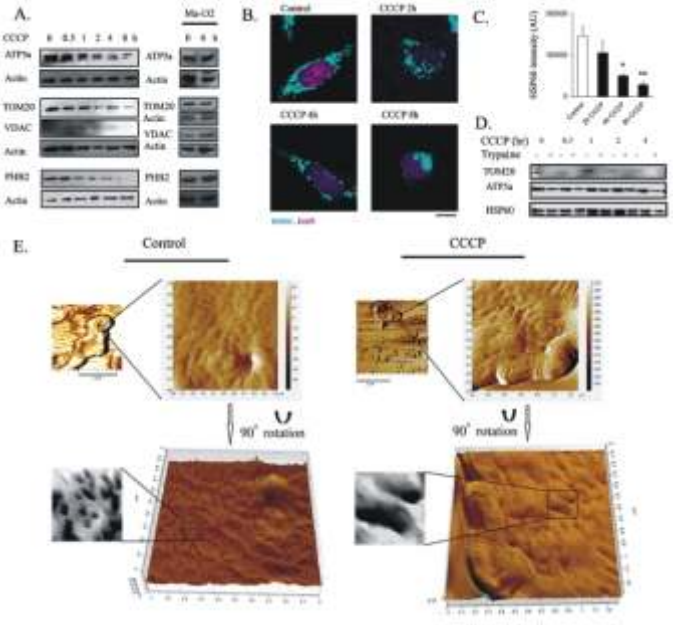
von Stockum, S., Sanchez-Martinez, A., Corrà, S., Chakraborty, J., Marchesan, E., Locatello, L., Da Rè, C., Cusumano, P., Caicci, F., Ferrari, V., Costa, R., Bubacco, L., Rasotto, M., Szabo, I., Whitworth, AJ., Scorrano, L., Ziviani, E (2019) Inhibition of the deubiquitinase USP8 corrects a Drosophila PINK1 model of mitochondria dysfunction. *Life Sci Alliance*, **2**.

Extramural funding

USP14 level in different brain regions: correlation between differential neurodegeneration and mitophagy. Start year: 2018, end year: 2019. Agency: International Society of Neurochemistry.

Mitochondrial clearance in aging brain: therapeutic approach against differential neurodegeneration in Parkinson's disease. Start year: 2018, end year: 2021. Agency: DST-SERB, Govt. of India.

Managing mitochondria from dopamine: halting Parkinson's disease progression. Start year: 2018, end year: 2020. Agency: ICMR, Govt. of India.



A. SH-SY5Y cells were treated with CCCP (10 µM) for 0.5h-8h and level of mentioned mitochondrial markers were monitored by immunoblot. MG-132 was used to confirm the degradation of the respective proteins were dependent on proteasome.

B, C. Fixed cells were immunostained for HSP60 after the mentioned period of CCCP treatment. HSP60 intensity was measured at least from 30 cells. Scale bar- 10 µm.

D. After treatment, permeabilised SH-SY5Y cells were subjected to trypsin digestion and cell lysate was probed for the mentioned proteins employing immunoblotting.

E. Fixed rat brain mitochondria was imaged by atomic force microscopy, scale bar as mentioned.

Infectious Diseases & Immunology Division

Members:
Dr. Rupak K. Bhadra (Head), Dr. Uday Bandyopadhyay, Dr. Subhajit Biswas, Dr. Sujoy K. Das, Dr. Upasana Ray, Dr. Sudipta Das (Ramalingaswami Fellow, DBT) and Dr. Mita Chatterjee Debnath

At the Infectious Diseases and Immunology Division of CSIR-IICB, the faculties and fellows are involved in a wide variety of epidemiological, translational and basic science research related to the prevention and control of cholera and other bacterial diseases, leishmaniasis, malaria, ulcers, gastropathy and viral diseases like dengue, chikungunya, herpes and hepatitis B. Work is also being carried out on development of 99mTc-labelled receptor specific peptides and amino acids and lipid carriers coupled to bioactive pharmacophores (nucleoside analogues and drug loaded nanoparticles) to be used as potential radiopharmaceuticals for scintigraphic diagnosis and therapy.

Work on cholera involves (i) studies on the effect of host interaction on virulence, biofilm formation and antibiotic resistance in Vibrio cholerae, (ii) elucidation of stringent response regulatory circuits in V. cholerae and its role in modulation of various virulence traits like motility, cholera toxin production, HA protease production and biofilm formation. Other gastrointestinal pathogen, Helicobacter pylori has also been studied with special emphasis on host pathogen interaction and assessment of the role of gastric microbiome in determining clinical outcome of H. pylori infection. Malaria and gastropathy work is focussed on (i) characterization of putative proteins from Plasmodium falciparum to identify new antimalarial drug target (ii) development of anti-malarial small molecule therapeutics, exploring molecular mechanism of drug resistance in malaria parasite and unfold novel biochemical pathways (iii) understanding of the molecular mechanism of stress-induced gastric mucosal pro-inflammatory response and gastropathy, (iv) evaluation of the role of macrophage migration inhibitory factor, a pro-inflammatory protein on cell growth and proliferation. Work on leishmaniasis comprises of (i) development of a simple, non-invasive and effective diagnostic approach, (ii) comprehensive assessment of liposome-encapsulated drugs as therapeutic agent as well as designing anti-leishmanial treatment strategies by altering lipid composition of host cell membrane, (iii) studies on the immunobiology of leishmaniasis towards identifying potential vaccine candidates and (iv) functional analysis of antigen presentation and antigen processing in Leishmania infected antigen presenting cells, (v) development of novel antimicrobial agent to prevent bacterial infections and research into advanced antibacterial wound dressings for topical wound care management, especially in relation to control of ESCAPE pathogens, (vi) Recently this Division has got a new impetus in leishmaniasis research following the discovery of a 'triple-pathogen' phenomenon in Kala-azar cases. The research showed the involvement of three pathogens viz. Leishmania donovani, Leptomonas seymouri and Lepsey NLV1 virus in visceral leishmaniasis/kala-azar. Thus current research in leishmaniasis involves revisiting the pathogenesis and management in the light of the role played by a protozoan RNA virus in human patients and exploring avenues towards devising new anti-leishmanial strategies.

Work in virology includes (i) studies on epidemiology of dengue, herpes and hepatitis B virus (HBV) infections, (ii) understanding virus assembly process and exploring novel bio-molecular platforms for designing virus like particles as vaccine candidates for dengue and chikungunya, (iii) elucidation of hepatitis B virus S protein (wild type and mutants) in intracellular morphogenesis and trafficking in hepatocytes and its role in occult HBV infections, (iv) molecular characterization of locally circulating herpesvirus clinical isolates including their sensitivity to anti-virals and (v) dengue virus diagnostics.

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rupakbhadra@iicb.res.in

Molecular mechanisms controlling stringent response and other stresses in Vibrio statics cholerae

Participants

SRF:Dipayan Rakhsit, Quoelee Biswas
Project Assistant: Shib Kumar Sharma
Senior Technical Officer (3):Pratap Koyal

Collaborator(s)
Collaborators outside CSIR-IICB

Dr. Bhabatosh Das,
Translation Health Science and Technology Institute (DBT), Faridabad

Background

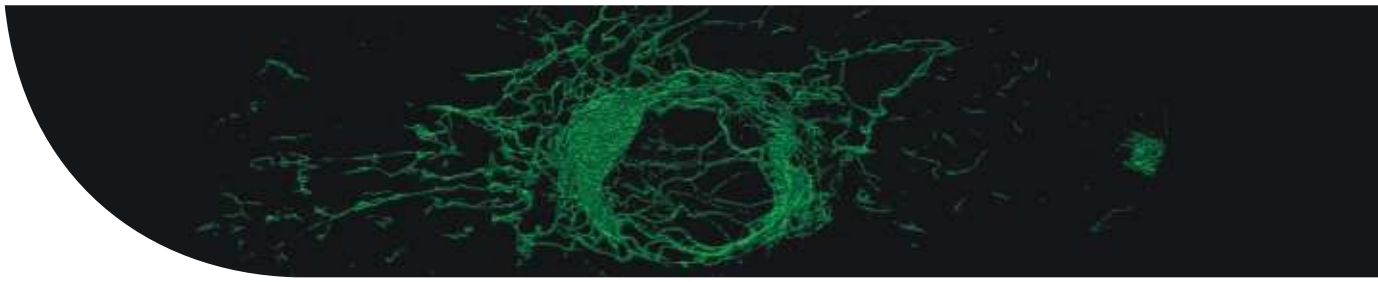
Vibrio cholerae, the cholera pathogen, constantly faces plethora of environmental stresses both under in vitro and in vivo conditions and they have evolved with multiple genetic circuits to combat such situations. We are working on the molecular regulation of nutritional starvation stress in *V. cholerae* as a model system. Nutritional deficiency in bacteria evokes stringent response, which is a global regulatory mechanism controlling various gene regulatory circuits for survival of organisms. Two intracellular small signaling molecules, pppGpp and ppGpp, collectively called (p)ppGpp, efficiently manage the stringent response.We have functionally characterized most of the genes such as *relA, spoT, cgtA, relV, dksA and gppA of V. cholerae,* which are intricately involved in managing the stringent response in *V. cholerae* under amino acid, glucose or fatty acid starvation. Both (p)ppGpp and DksA bind in the secondary channel of the RNA polymerase (RNAP) enzyme and regulates transcription of several genes either positively or negatively so that cells can enter into survival mode as long as the nutritional stress is there. As mentioned, (p)ppGpp needs a 17.5-kDa small protein, called DksA, as an essential co-factor to exert its control over expression of genes. Thus, DksA is an unusual transcription factor which binds with RNAP unlike other transcription factors that bind with DNA. Our study indicates that *V. cholerae* DksA modulates the virulence gene expression in *V. cholerae*. More recent studies support the view that DksA post-transcriptionally controls the expression of cholera toxin (CT) genes, which was not known previously. We are also working on the genesis of new clones of *V. Cholerae* by studying the genetic variation in the CTX locus. In this respect, studies are being carried out on toxigenic non-O1/non-O139 *V. cholerae* strains and regulation of virulence gene expression in these strains. Apart from these studies our group is also interested in investigating the evolution and spread of antimicrobial resistance genes in vibrios.

Aims and Objectives

The major ongoing objective is to elucidate the roles of stringent response pathway genes and regulators in maintaining cellular levels of pppGpp/ppGpp under nutritional starvation stresses and the role of the regulatory protein DksA in fine control of virulence gene expression in *V. cholerae*. Currently we are focusing on functional characterization of the *gppA* gene of the pathogen, the product of which is responsible for the conversion of pppGpp to ppGpp.

Work Achieved

We have already characterized the *relA, spoT and relV* genes of *V. cholerae*, which are responsible for (p)ppGpp synthesis and degradation. In recent years, we are working on the DksA protein, an essential critical regulator of the stringent response pathway of Gram-negative bacteria including *V. cholerae*. We have shown that DksA is critically involved in fine regulation of virulence traits of *V. cholerae*. For example, we found that deletion of the dksA gene of *V. cholerae* leads to down regulation of CT production. Later studies indicated that although CT production is low in *V. cholerae ΔdksA* cells but expression of the genes encoding its regulators, namely, AphA, ToxT and TcpP were found to be high. Furthermore, we have also found that the expression of the *ctxA* gene is also high in *ΔdksA* cells. The enhanced expression of each of these regulators and genes in *ΔdksA* cells may be due to down regulation of the quorum sensing master regulator HapR, a known negative regulator of CT production. However, mutation of the hapR gene in ΔdksAcells did not help in overcoming its defect in CT production suggesting a possible post-transcriptional/translational control of CT production by the DksA regulator of *V. cholerae*. Very recently we have carried out progressive deletion analysis of DksA and showed that the C4-type Zn finger motif present in the C-terminal region of DksA protein is essential for optimal CT production in *V. cholerae* cells. It



may be noted here that this motif has been shown to play important role in DNA/RNA binding, the result of our study indicates a novel complex post-transcriptional regulation of CT expression by *DksA* in V. cholerae. Apart from this, we also found that GppA plays a role in maintaining cellular levels of pppGpp/ppGpp under amino acid starved condition. The current working model on stringent response circuit is shown in Fig. 1.

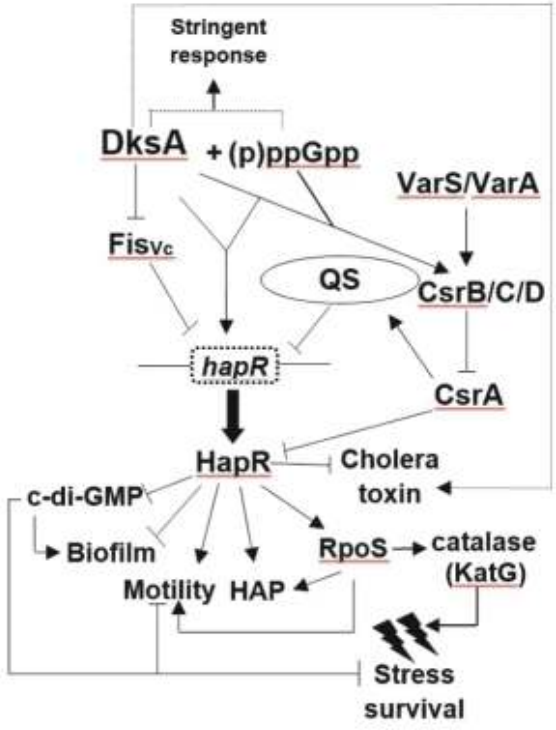


Fig. 1. Working model showing circuitry linking the stringent response regulators DksA and (p)ppGpp in the regulation of expression of virulence and other genes in V. cholerae including haemagglutinin (HAP) and CT production, motility, biofilm formation and stress survival. DksA regulates HAP production through regulation of HapR and RpoS. DksA modulates HapR by regulating the FisVc and CsrB/C/D which are components of the quorum sensing (QS) pathway. Arrow indicates activation and inverted T indicates repression.

Future Research Plans

Further experiments are needed to establish firmly the exact role of the stringent response regulators in controlling virulence gene expression in *V. cholerae*. We are also involved in mutational and functional characterizations of the *V. cholerae gppA* gene, which codes for a phosphohydrolase enzyme and it is needed to convert pppGpp to ppGpp. Apart from this, we will also continue our work on the molecular basis of antibiotic resistance in *V. cholerae* and genetic characterizations of the pathogenicity island genes of V. cholerae non-O1/non-O139 strains including their regulation of expression.

Publications

Basu, P., Bhadra, R. K. (2019) Post-transcriptional regulation of cholera toxin production in *Vibrio cholerae* by the stringent response regulator DksA. Microbiology**165**, 102-112.

Verma, J., Bag, S., Saha, B., Kumar, P., Ghosh, T. S., Dayal, M., Senapati, T., Mehra, S., Dey, P., Desigamani, A., Kumar, D., Rana, P., Kumar, B., Maiti, T. K., Sharma, N. C., Bhadra, R. K., Mutreja, A., Nair, G. B., Ramamurthy, T., Das, B.(2019) Genomic plasticity associated with antimicrobial resistance in Vibrio cholerae. Proc Natl Acad Sci USA**116**, 6226-6231.

EXTRAMURAL FUNDING

Rupak K. Bhadra (PI), Dr. Pijush K. Das (Co-PI)

Targeting deadenilation mediated Kinetoplastidae parasite-specific polycystronic gene regulation for therapeutic intervention
13 May 2016 to 12 May 2019 (Department of Biotechnology, Government of India, India)

CONFERENCES / WORKSHOPS

Number of Abstract submitted and Conference attended
India: 1

Title:Functional characterization of the *gppA* gene of the stringent response regulatory pathway of Vibrio cholerae.
Authors: Dipayan Rakhsit and Rupak K. Bhadra
Name of the Conference: Physicon 2018, 22-24 November, 2018, Serampore College, WB, India.

International: 1
Title: Stringent response regulator DksA modulates intracellular levels of c-di-GMPin *Vibrio cholerae*
Authors: Pallabi Basu and Rupak K. Bhadra
Name of the Conference: United States-Japan Cooperative Medical Sciences Program:53rd Joint Panel Conference on Cholera and other Bacterial Enteric Infections and 21st International Conference on Emerging Infectious Diseases in the Pacific Rim, 26 February to 01st March 2019, Hanoi, Vietnam.

Dr. Uday Bandyopadhyay

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Macrophage migration inhibitory factor activates CD74 NF-κB signalling to control mitochondrial dynamics and cancer cell proliferation

Participants

SRF : Rudranil De, Shubhra J. Saha, Shiladitya Nag

JRF : Subhashis Deasharma, Debanjan Saha, Saikat Pramanik

Collaborator(s)

Susanta Adhikari
Department of Chemistry, University of Calcutta, 92, A. P. C. Road, Kolkata 700 009, West Bengal, India.

Kaushik Biswas
Division of Molecular Medicine, Bose Institute, 93/1, Acharya Prafulla Chandra Road, Kolkata-700 009, West Bengal, India.

Background

Macrophage migration inhibitory factor (MIF) promotes tumor genesis in many forms of colorectal adenomas, intestinal tumors, ovarian cancer, and hepatocellular carcinoma. It is high in serum and epithelial cells of patients suffering from gastric cancer. The link of up-regulated MIF expression in gastrointestinal tract malignancies makes it a biomarker for gastric cancer as well as a probable target in anti-cancer therapies. The role of MIF in carcinogenesis is still not clear, although some critical MIF-mediated pathways including P115, inactivation of p53, and stimulation of angiogenesis have been studied. CD74, the cognate receptor of MIF, activates NF-κB, a key molecular player in cancer and inflammation,. CD74-MIF signaling is suspected to play a significant prognostic role in many malignancies. Mitochondria provide the majority of the energy in cells by synthesizing ATP. As mitochondria are dynamic organelles that continuously undergo fission and fusion and mitochondrial structural integrity plays a critical role in metabolic function. In this study, we propose that MIF, via CD74, regulates mitochondrial stability, which favors cancer cell growth. We also identified the significant role of NF-κB in maintaining the balance of mitochondrial dynamic and physiological integrity to decide cell fate.

Aims and Objectives

- To understand the role of macrophage migration inhibitory factor (MIF) in cancer cell growth and development

Work Achieved

The instrumental role of macrophage migration inhibitory factor (MIF) in cancer cell proliferation is explicit; although which specific roles the cytokine plays to block apoptosis preserving cell growth is still ambiguous. The present study explores different cancer cell lineages (AGS, HepG2, HCT 116 and HeLa) to conclude that silencing of MIF severely deregulates mitochondrial structural dynamics and triggers apoptosis. Apoptosis is evident by flow cytometric analysis, enhanced mitochondrial Bax translocation along with cytochrome c release, down-regulation of Bcl-xL and Bcl-2 as well as up-regulation of Bad, Bax and p53. The data also indicate a concerted down-regulation of Opa1 and Mfn 1 along with a significant mitochondrial translocation and fissogenic phosphorylation of Drp1, cumulatively causing mitochondrial fragmentation upon MIF silencing. Interestingly, MIF silencing has also been found to be associated with decreased NF-κB activation, which in turn increases mitochondrial fission and cell death. In addition, silencing of CD74, the cognate receptor of MIF, remarkably increases mitochondrial fragmentation besides preventing cell proliferation, inducing mitochondrial depolarization and increasing apoptotic cell death. Collectively, the study proposed that MIF, through CD74, constitutively activates NF-κB to control mitochondrial dynamics and stability for promoting carcinogenesis averting apoptosis.

Future Research Plans

To understand the molecular mechanism of MIF-mediated regulation of mitochondrial dynamics, metabolic alteration in cancer cells

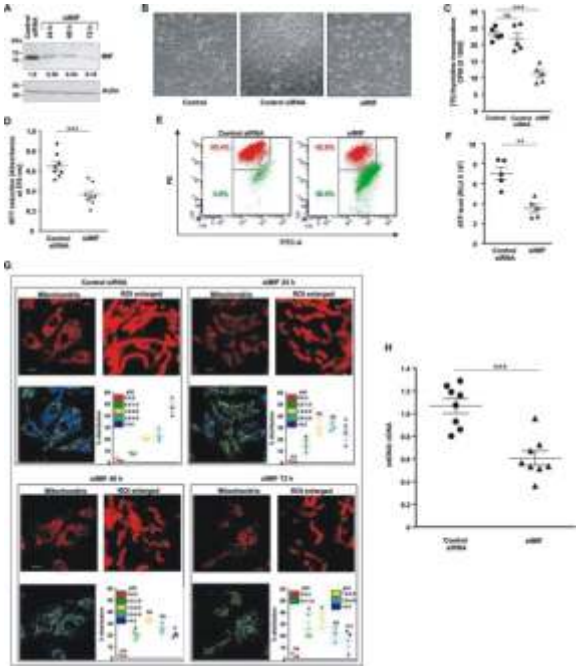


Figure 1. Loss of mitochondrial integrity and increased fission upon MIF down-regulation in AGS cells (De R, et al. J. Biol. Chem 293, 1974019760, 2018)

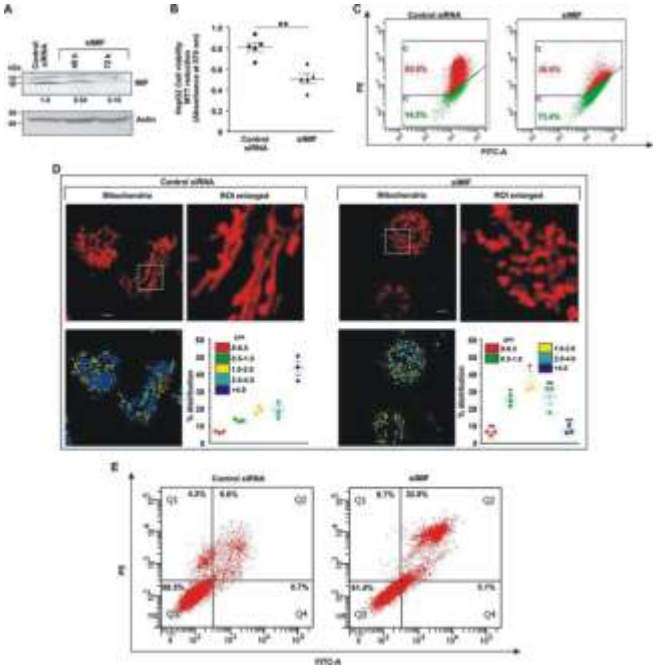


Figure 2. Loss of mitochondrial membrane potential and increaded fission upon MIF down-regulation interfere with HepG2 cell viability. (De R, et al. J. Biol. Chem 293, 1974019760, 2018)

PUBLICATIONS

1. Saha SJ, Siddiqui AA, Pramanik S, Saha D, De R, Mazumder S, Debsharma S, Nag S, Banerjee C, Bandyopadhyay U (2019) Hydrazonophenol, a food vacuole targeted and ferriprotoporphyrin IX-interacting chemotype prevents drug resistant malaria.. ACS Infect Dis. 5, 63-73,

2. De R, Sarkar S, Mazumder S, Debsharma S, Siddiqui AA, Saha SJ, Banerjee C, Nag S, Saha D, Pramanik S, Bandyopadhyay U (2018). Macrophage migration inhibitory factor regulates mitochondrial dynamics and cell growth of human cancer cell lines through CD74-NF-κB signaling. J Biol Chem. ;293:19740-19760

3. Iqbal Mohd S , Siddiqui AA, Banerjee C, Nag S, Mazumder S, De R, Saha S J, Karri S K, Bandyopadhyaya U (2018) Detection of retromer assembly in Plasmodium falciparum by immunosensing coupled to Surface Plasmon Resonance.. BBA - Proteins and Proteomics. 1866, 722-730.

EXTRAMURAL FUNDING

Uday Bandyopadhyay

Grant Title. An insight into the role and regulation of mitochondrial innermembrane uncoupling protein 2 in manipulating host-conducive oxidant-derived macrophage defense mechanism.
2015-2018 (Science and Engineering board, DST, India)

Title: J C Bose Fellowship
2015-2020 (Science and Engineering board, DST, India)

Dr Subhajit Biswas

subhajit.biswas@iicb.res.in

Molecular epidemiology of virus infections in India & elucidating the virus aetio-pathogenesis towards devising strategies of intervention

Participants

SRF : Anisa Ghosh, Subrata Roy
JRF : Ruchi Supekar, Himadri Nath

Tathagata Kayal, Project Assistant

Background

We are looking at the **existence, prevalence & aetio-pathogenesis** of various viral infections in India with special reference to-

1. DNA viruses like **human herpesviruses and hepatitis B virus** (HBV) as well as
2. RNA viruses like **dengue virus** (DENV).
3. We are also investigating whether the elsewhere-reported **Leishmaniaviruses** (LRVs) are also present in **Indian visceral leishmaniasis** (VL)/**kala-azar** cases.

Aims and Objectives

1. Molecular epidemiology of recently circulating dengue virus strains and their correlation to varied disease outcomes in patients; evaluating their detectability by commonly used DENV diagnostic tests like NS1-based ELISAs and DENV-specific RT-PCR assays.
2. Development of easy-to-use point of care system for detection of DENV infections in patient samples.
3. Molecular characterization of locally circulating herpesvirus clinical isolates (eg. herpes simplex virus, human herpesvirus 6 & 7) in terms of growth properties and pathogenesis in cell culture as well as their sensitivity to commonly used antivirals like acyclovir.
4. Study the epidemiology of occult hepatitis B virus infections (OBI) in healthy volunteers as well as patients presenting with otherwise autoimmune skin disorders (eg. pityriasis rosea, psoriasis etc) to see if underlying cryptic HBV infections have any association with externally visible manifestations.
5. Screening of kala-azar samples for the presence of protozoan viruses like LRVs and LepseyNLV1.

Work Achieved

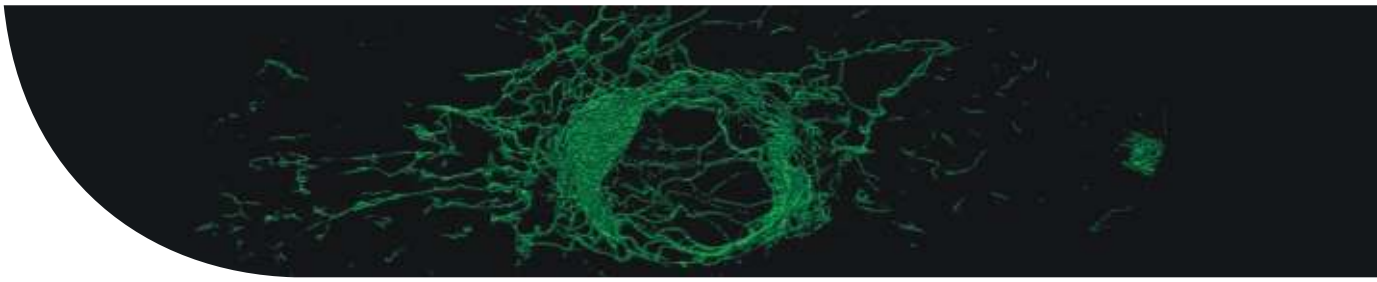
Towards establishing a **platform of Dengue virus (DENV) research at CSIR-IICB**, we evaluated DENV and Zika virus (ZIKV) prevalence in human and vector samples (pilot scale) in Kolkata during 2015-2016, a DENV-endemic city and published our findings in Journal of Medical Microbiology (JMM) in 2018.

In this paper, we have made some seminal discoveries and some scientific recommendations to improve DENV and ZIKV diagnosis. For instance, we have shown that besides adult Aedes mosquitoes, the Aedes larvae are highly infected with DENV (>90%), suggesting transovarial DENV transmission from the infected female to the offspring. This also explains why there is notable surge of DENV infections in the city-dwellers in post-monsoon season in Kolkata.

In the urban settings, with lots of unused sterile water holdings/septic tanks in the ever-increasing construction sites (eg. Salt Lake area), infected eggs and larvae do not face any biological control (unlike in rural areas) which results in increased swarms of infected adult mosquitoes. The latter develop unabated from the infected larvae and spread dengue rapidly in the human host population in the post-monsoon season.

In terms of DENV molecular diagnosis by the standard **Lanciotti** nested PCR, we have shown that scientists who have so far concluded first-round PCR negative samples (no visible band on gel electrophoresis) as DENV-negative, have actually underestimated DENV incidence and prevalence globally. We have conclusively proved that first-round PCR negative samples could come positive on second round final PCR on many instances and we have also provided sequence confirmation of such samples.

We have also checked that all human and vector samples we had studied were ZIKV-negative in Kolkata during 2015-16. We have also made a significant finding that one internationally-used set of ZIKV diagnostic PCR primers unfortunately cross-react with DENV serotype 1 and produce false-positive bands of expected size on the gel. We have proved this cross-reactivity by sequencing the band and showing that it is actually DENV-1 for three separate isolates. The flavivirus research community has been alerted to this problem through our recent publication in the JMM.



Future Research Plans

Research work has been initiated for a highly competitive and multi-institutional **CSIR-Mission Mode Project** entitled "Nano-Biosensors and Microfluidics for Healthcare". This MMP will enable us to do research and development of the much coveted "**Label free, affordable and easy-to-use point of care system for detection of Dengue virus infections in patient sample."**

Being the sole virologist in this multi-institutional MMP, I am serving as the key expert in designing the dengue virus probes (eg. serotype-specific/ pan-dengue etc). I am extending my hands-on expertise to the team carrying out day-to-day experiments towards developing the proof-of-concept for the molecular probe-based dengue diagnostics, which once standardized will form the basis for fabrication into devices. In a nut-shell, as the only virologist in the entire MMP team, I am executing all aspects that involve handling and testing of dengue virus samples.

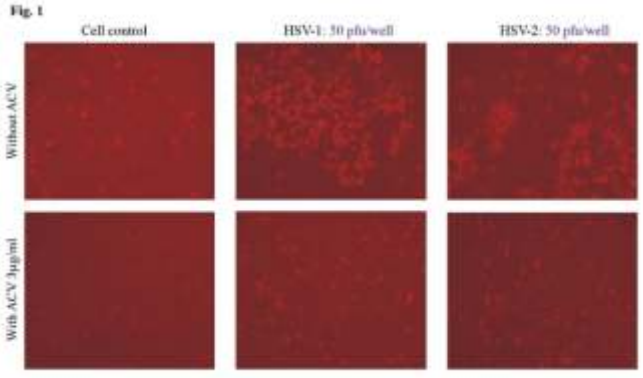


Fig. 1: Herpes simplex virus (HSV) infection in Vero cell culture, with or without Acyclovir (ACV) treatment: Cytopathic effect (plaques) at 48h post-infection. Pfu: plaque forming unit

PUBLICATIONS

Sukla, S., Ghosh, A., Saha, R., De, A., Adhya, S., and Biswas, S* (2018). In-depth molecular analysis of a small cohort of human and Aedes mosquito (adults and larvae) samples from
Kolkata revealed absence of Zika but high prevalence of dengue virus.
Journal of Medical Microbiology, 67, 1109-19.

EXTRAMURAL FUNDING

Dr Subhajit Biswas

Characterization of herpesviruses in clinical samples from Kolkata in terms of their growth kinetics and sensitivity to available antivirals. 2018-2021 (**Higher Education, S & T & Bio-Technology**, Government of West Bengal).

CONFERENCES / WORKSHOPS

Subhajit Biswas

INVITED talk entitled **"Occult hepatitis B virus infections; Novel RNA virus in Indian Kala-azar samples; Rampant Dengue outbreaks in Kolkata: Towards unraveling host-parasite encounter and interactions"** at the **Frontiers in Biotechnology, Chapter III,** National Seminar, organized by the **Department of Biotechnology, St. Xavier's College** (Autonomous), Kolkata, on 12th October, 2018.

INVITED talk as a Lead Speaker entitled **"New lights on aetiology and epidemiology of Indian Leishmaniasis"** at the **19th Indian Veterinary Congress & XXVI Annual Conference of IAAVR,** National Symposium on *'Innovative Progress in Animal Health and Production for Safe and Secured Food under **One Health Perspective**'* held at **West Bengal University of Animal & Fishery Sciences**, Kolkata, on 2nd February, 2019.

TALKS BY CSIR-IICB FACULTY

POPULAR LECTURE on general awareness about viral diseases, especially dengue virus to visiting school students and their teachers: **Open House Day**, CSIR-IICB, Kolkata, 25th September 2018. Students from in and around Kolkata were also given live demonstration of day-to-day laboratory activities in a state-of-the-art virology laboratory at CSIR-IICB.

Dr. Sujoy K Das
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Biomimetic synthesis of functional nanomaterial to prevent biofilm formation and wound infection

Background:

Nosocomial or hospital acquired infection caused by bacterial colonization and biofilm formation is a major concern in the medical field at present. In particular, bacterial infection caused by ESCAPE pathogen *(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species)* is one of the leading causes of death, disability, and socioeconomic loss around the world. The most common bacterial infection includes pneumonia, pleuropulmonary, septicemia, surgical wounds, skin and soft tissue infection and other systemic infections that lead to morbidity and mortality in humans. According to the WHO report 1214 million people are infected by bacterial infection every year.

The spreading of life threatening infectious diseases through contact with biofilm contaminated surfaces poses a serious threat to public health. Owing to grave concerns about human health and huge economical loss, effective killing of bacterial pathogen and inhibition of biofilm formation is of the utmost importance. Biofilm protects the cells from external environment, requiring higher concentrations of antibiotics and prolonged treatment time to eradicate the biofilm in comparison to planktonic cells. The extensive use of antibiotics indeed promotes the generation of drug-resistant bacteria, which makes the situation more alarming. The third-generation antibiotics, such as cephalosporins, indeed are becoming ineffective in treatment of such nosocomial infections due to the increasingly acquired resistance against this antibiotic.

To prevent bacterial infection on wound an antibacterial dressing is applied on external wounds. The antimicrobial wound dressings either actively release antimicrobial agents or passively act through antiseptic surface properties. Recent studies however raised issues on the clinical efficacy of key antibacterial actives. Growing resistance against the antimicrobial wound care product often develops biofilm on the wound sites and delayed the wound healing.

Because of exceptionally high surface area, mechanical strength, electrical conductivity, excellent optical and thermal properties, nanomaterials have attracted much interest in biomedical fields to prevent bacterial growth and infection control. Despite its enhanced activity, the antibacterial activity of the nanomaterials potentially suffers from intractable limitations like dissolution, aggregation and accumulation in aqueous system. Various strategies have been adopted to improve the antimicrobial property of the nanomaterials through functionalization process and develop novel antibacterial agents.

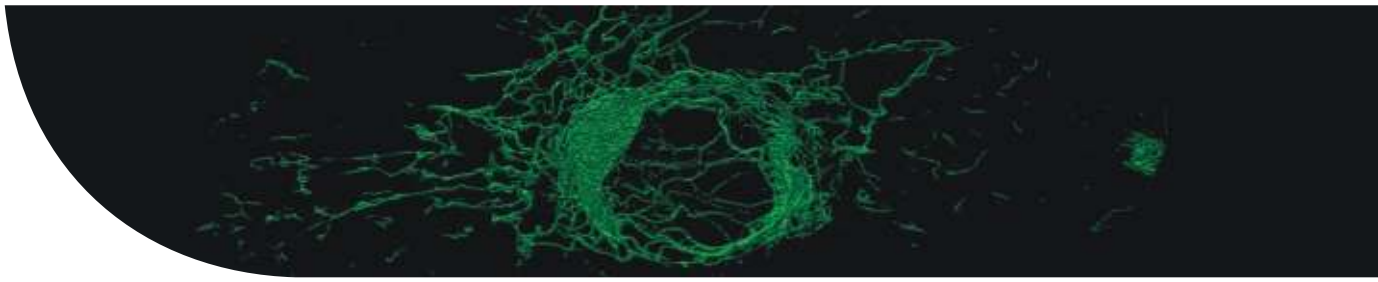
Aims and Objective:

Fabrication of poly-cationic peptide functionalized graphene nanocomposite as anti-biofouling material

Development of nanocomposite scaffold for antibacterial therapy and tissue regeneration

Work done:

Anti-biofiouling material: A safe-by-design strategy has been adopted for the synthesis of a polycationic peptide functionalized graphenesilver nanocomposite (GAPP) to enhance the biofilm inhibition and disruption properties and eliminate the biofilm development of Gram-negative bacteria. The polycationic peptide functionalized GAPP effectively killed the planktonic cells and biofilms of *Escherichia coli* and *Pseudomonas aeruginosa*. The polycationic peptide functionalized graphenesilver nanocomposite exerted bactericidal and biofilm inhibition activity through a "*contact-kil-lrelease*" mode of action. The net positive charge of polycationic peptide functionalized graphenesilver nanocomposite (ζ value = 15.4 ± 2.6 mV) promoted electrostatic interaction with the bacterial cells, and high redox potential of silver [$EH^0(Ag+/Ag^0)$ = 0.8 V] caused mechanical disruption of the cell membrane. Fluorescence microscopic and FESEM images clearly depicted damage of the cell wall. The pore formation on the cell wall and alteration of the transmembrane potential of the cells led to leakage of the cytoplasmic materials. The polycationic peptide functionalized graphenesilver nanocomposite also internalized into the cytoplasm through the damaged membrane and subsequently induced intracellular ROS production. The polycationic peptide functionalized graphenesilver nanocomposite mediated oxidative stress caused inactivation of the respiratory chain dehydrogenases and increased the lipid peroxidation activity, leading to metabolic imbalance in the cells (Fig. 1). The internalization of polycationic peptide functionalized graphenesilver nanocomposite into the cytoplasm through the



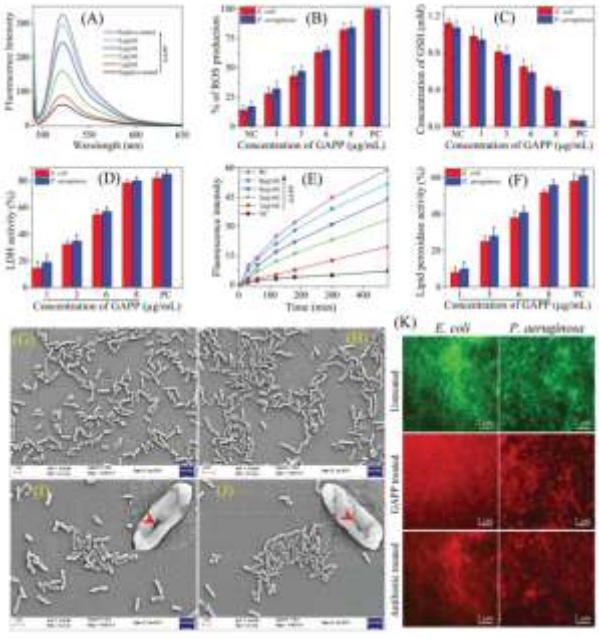


Fig. 1: Intracellular ROS production (A) upon treatment with different concentrations of polycationic peptide functionalized graphenesilver nanocomposite determined by H2-DCFDA assay. Concentration-dependent ROS production (B) and measurement of GSH concentration (C) following treatment of E. coli and P. aeruginosa with various concentrations of polycationic peptide functionalized graphenesilver nanocomposite. Determination of lipid peroxidase activity (D), LDH activity (E) and membrane potential (F) of E. coli and P. aeruginosa upon treatment with polycationic peptide functionalized graphenesilver nanocomposite. FESEM images of E. coli (G, I) and P. aeruginosa (H, J) before (upper panel) and after (lower panel) treatment with polycationic peptide functionalized graphenesilver nanocomposite; respective inset images depict the cell wall damage by polycationic peptide functionalized graphenesilver nanocomposite. Fluorescence microscopic images (K) of untreated (top panel), polycationic peptide functionalized graphenesilver nanocomposite (middle panel) and antibiotic treated (bottom panel) E. coli and P. aeruginosa following staining with SYTO 9 and PI. Data represent an average of five independent experiments, ±SD shown by error bars; *p value <0.003 with respect to negative control cells.

damaged membrane led to metabolic imbalance in the cells. The schematic presentation demonstrated that the antibacterial mechanism and biofilm inhibition and disruption activities of polycationic peptide functionalized graphenesilver nanocomposite occurred through a “contact-kill-release” route (**Fig. 2**). The peptide functionalization further prevented the dissolution of Ag+ ions, thus minimizing the cytotoxicity of the nanocomposite to adult zebrafish.

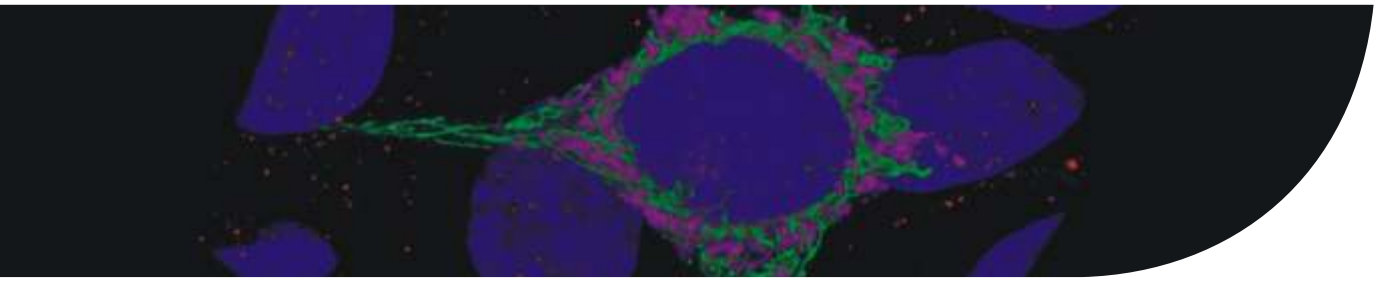
Ref. Das et al. Biomater. Sci., **2018**, 6, 33563372.

Antibacterial wound dressing:

A multidisciplinary approach has been developed for preparation of biomaterial reinforced graphene nanocomposite as a novel antibacterial wound dressing for infected wound care application. The physical and biochemical characteristics such as tensile strength, pore size distribution, swelling ability, fluid absorbability, elastomeric properties, and physiological stability were studied. The reinforcement of nanocomposite with biomaterial provided a stronger mechanical strength of the nanobiocomposite in the range of 40-48 MPa and enhanced the swelling property in the range 20-30%. The in-vitro antibacterial efficacy was tested against Gram-negative and Gram-positive bacteria such as E. coli, P. aeruginosa and S. aureus and demonstrated ~99.999% killing efficiency due to its ability to produce singlet oxygen ($^1O_2$). The cytotoxicity and hemolytic activities of the nanobiocomposite scaffold against L929 fibroblast cell line and red blood cells, respectively confirmed biocompatibility of the scaffold. The in-vivo experiment on bacterial infected wound model revealed that nanobiocomposite scaffold killed 99.9% bacteria within three days upon treatment (Fig. 3). In addition, the infected wound was healed within 18th days, which was far less in compared to that of antibiotic treated control group. Moreover, the nanocomposite scaffold did not exhibit any appreciable sign of abnormalities or damage to the major organs i.e. heart, liver, spleen, lung, and kidney during the wound healing process. The preliminary results therefore indicate that the developed nanobiocomposite scaffold would have a promising multimodal therapeutic approach for rapid and effective treatment of bacterial infected wound.

A patent has been filed for novel composition and process for the preparation of this nanobiocomposite material.

Ref. Das et al. Indian Patent Application No: **2018**11044089



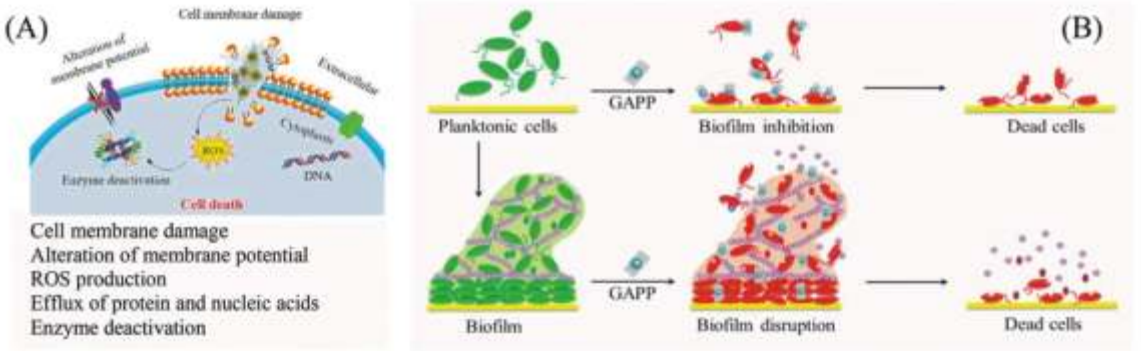


Fig. 2: Schematic illustration of antibacterial mechanism (A) of polycationic peptide functionalized graphenesilver nanocomposite and its biofilm inhibition and disruption (B) activities through a "contactkillrelease" route.

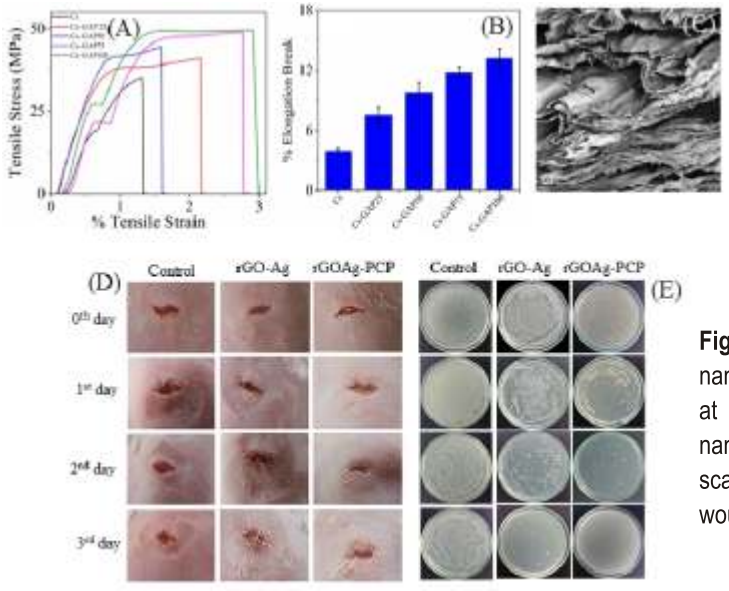


Fig. 3: Mechanical properties of pristine biomaterial and nanocomposite scaffold. Stress−strain curves (A), and elongation at break (B) point. SEM image (C) of cross-section of the nanocomposite scaffold. In-vivo efficacy of the nanocomposite scaffold in control of wound infection (D) and killing of E. coli (E) at wound site.

Future Research Work:

Photodynamic therapy for acute and chronic infected wounds
Development of hemostatic pad as a lifesaving bandage for faster blood arrest
Nanomaterial based antimicrobial peptide delivery for effective killing of bacteria and biofilm disruption

Dr. Upasana Ray
upasana.ray@iicb.res.in

Establishment of yeast (Klyuveromyces lactis) and mammalian expression systems for expression and assembly of Dengue virus proteins.

Participants

JRF : Debica Mukherjee, Feroza Begum, Sandeepan Das

Background

Our laboratory works on understanding the mechanism of viral particle assembly, studying host-viral interactions and using the molecular insight into host viral interactions to design antiviral candidates. We use knowledge about the mechanism of self assembly to assemble virus capsids/ virus particles without the genetic material and use them as vaccine candidates. To assemble virus particles we can use various assembly platforms out of which we are interested in (a) mammalian cells (b) yeast. Yeast is a robust protein production system. In our laboratory we are establishing yeast (Klyuveromyces lactis or K. lactis) expression system to assemble virus particles to be used to design vaccine candidates and to study virus entry.

Aims and Objectives

Cloning Dengue virus structural genes in mammalian and K. lactis expression vectors.

1. Integration of clones encoding viral proteins with the yeast genome to obtain integrants.
2. Expression of Dengue structural proteins in mammalian cells and yeast.

Work Achieved

We have cloned Dengue structural genes (capsid, membrane and envelope) with respect to all the four serotypes (1, 2, 3 and 4) in a mammalian as well as K. lactis expression vectors. The clones with respect to K. lactis expression are been used to generate yeast integrants expressing the structural proteins sperately as well as all in one integrant. We expect that an intergrant expressing all the structural proteins would lead to assembly of the virus particles and release. These particles will further be purified and used for downstream assays. Figure 1 shows representative PCR based screening to validate integration of capsid gene (serotype 1) in yeast genome. Figure 2 is western blot validation of expression of capsid protein in yeast. Figure 3 shows a representative picture of expression of serotype 1 capsid expressing plasmid in mammalian cell line (HEK 293T).

Future Research Plans

In future Dengue virus like particles without the genetic material will be assembled in yeast system followed by purification by density mediated ultracentrifugation. Such particles will be used to study virus entry in diverse human cell types. Dengue structural proteins cloned in mammalian expression plasmid will be used to assemble virus particles in mammalian cells and this system will be used to study the assembly mechanism of the particles.

FIGURE 1

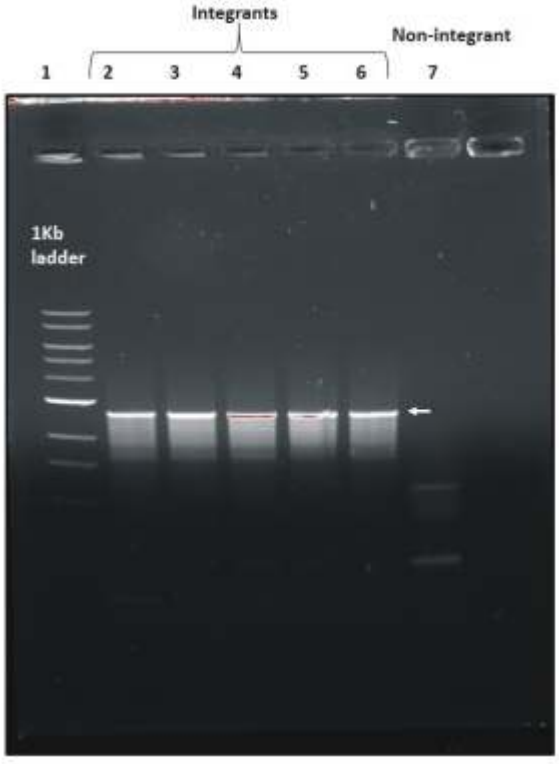


Fig. 1: PCR based screening of possible integrants (Lanes 2-6). Lane 7 is negative control (nonintegrated yeast genomic DNA)

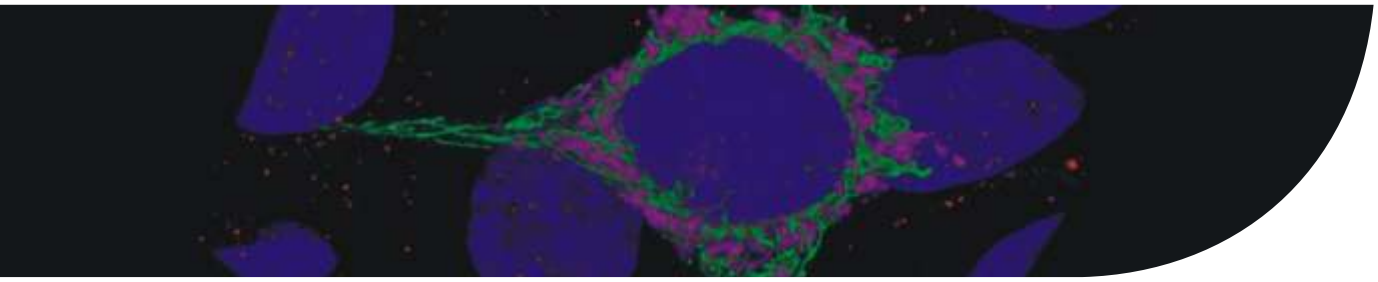


FIGURE 2

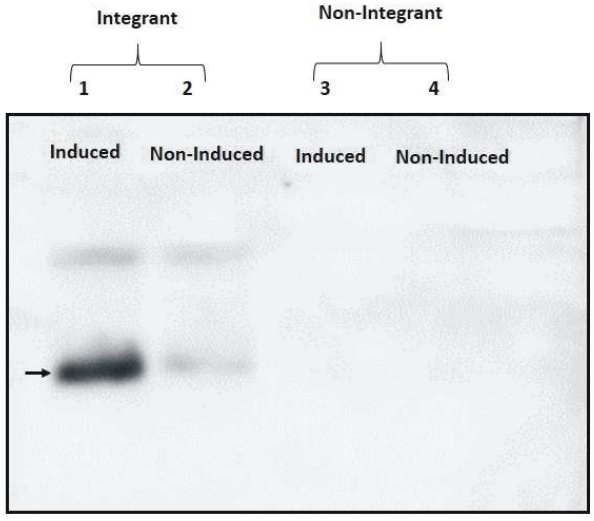


Fig. 2: Western blot validation of expression of serotype 1 capsid protein in yeast. Lane 1: Induced integrant; Lane 2: Uninduced integrant; Lane 3: Induced non-integrant control; Lane 4: Uninduced non-integrant

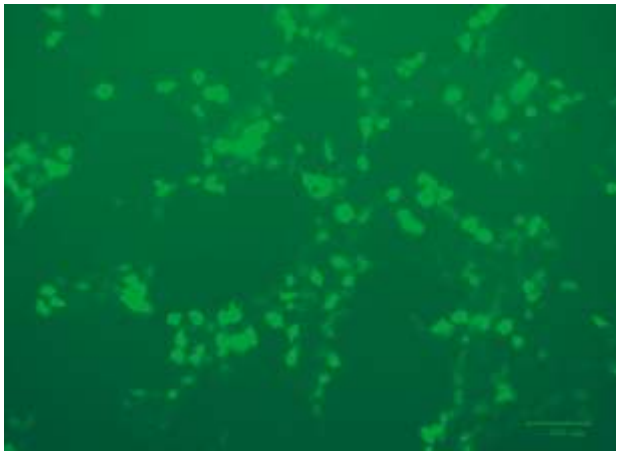


Fig. 3: Expression of serotype 1 capsid expressing mammalian expression plasmid in HEK 293T cells. Green Fluorescent Protein (GFP) is a reporter protein expressed from the expression plasmid.

PATENTS FILED / SEALED

Patent Title: Immunogenic JC polyomavirus compositions and methods of use.

Country(ies): United States
Patent No.: 9931393
Date filed / granted: 3rd April 2018 (Granted)
Co-inventors and their Institutes: Christopher B. Buck (National Institutes of Health), Upasana Ray (currently at CSIR-IICB), Diana V. Pastrana (National Institutes of Health)
Patent filed by DBT / CSIR-IICB / another organization: National Institutes of Health

AWARDS / HONOURS / MEMBERSHIPS

Scientist's Name Surname: Upasana Ray

Award

Early career research award; SERB; 2019

Membership

Full membership of the Royal Society of Biology (awarded designation of MRSB); Royal Society of Biology (RSB), 2018

EXTRAMURAL FUNDING

Name Surname: Upasana Ray

Grant Title: Understanding entry of Chikungunya virus and engineering self-assembly system based anti-Chikungunya vaccine
2019-2022
(Funding Agency: SERB, India)

Name Surname: Upasana Ray

Grant Title: Understanding the role of Dengue NS1 protein in endothelium leakage and therapeutic intervention of NS1 pathogenesis to design anti-Dengue antiviral candidate.
2019-2022
(Funding Agency: Department of Science & Technology and Biotechnology, Govt. of West Bengal, India)

CONFERENCES / WORKSHOPS

2

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

1. Immunology Day; 4.05.2018, 2018; Venue: CSIR-IICB; Convenor

2. 6th Molecular Virology Meeting; 28.02.2019-2.03.2019; Venue: IIT Kharagpur; Scientific Committee member

Dr. Sudipta Das

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Unraveling unique role of ribosomal protein in the cell division of Plasmodium falciparum

Participants

Dr. Sudipta Das

Students

Joining soon

Introduction

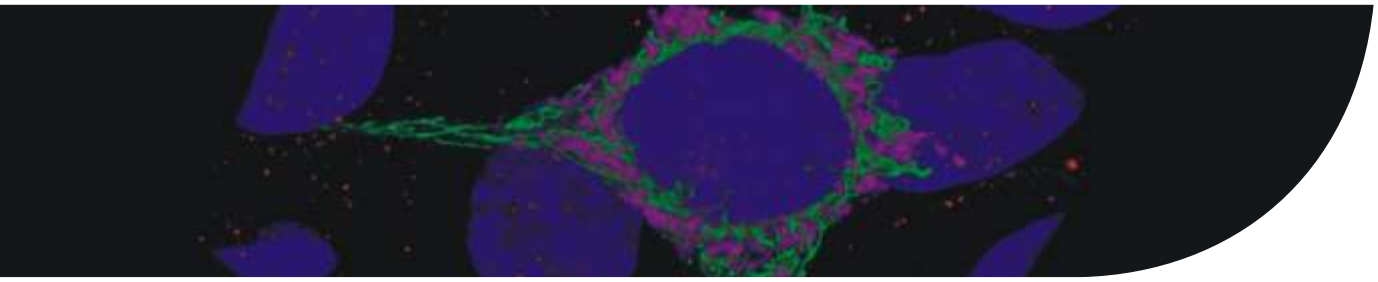
Plasmodium falciparum is a unicellular eukaryotic protozoan parasite which causes malaria, a catastrophic disease in many developing countries. Malaria alone is responsible for millions of deaths annually across the globe. In India, the cases of malaria are alarmingly increasing and the hope of prevention and cure is extremely challenging due to the emergence of drug resistant parasites. Drug resistance in malaria parasites is a grave concern, so in this situation the battle against malaria must go on by emphasizing on discovering new drug targets and inventing novel small molecules which can target multiple pathways together ensuring reduced chances of resistance. Thus, understanding the basic biology of malarial parasite is extremely important in devising novel drugs and drug targets. The peculiar proliferative cycles of apicomplexan parasites differ substantially from the hosts they inhabit and could offer novel molecular targets. To progress in this direction, we need a good understanding of the unique structural and molecular features of parasite proliferation. Apicomplexan parasites and many of their relatives undergo a complex developmental process in the cells of their hosts, which includes genome replication, cell division and the assembly of new invasive daughter cells. Plasmodium cells in particular, exhibit a peculiar cycle of cell division (schizogony), which is unique. In the vertebrate hosts, schizogony occurs in the liver and red blood cells. The growth of the parasite is mostly confined to the trophozoite stage during which nuclear and other organellar genomic division occurs followed by the formation of cell bodies. The mechanism and the regulation of schizogony are poorly understood.

Proposed work with Plasmodium falciparum P2 protein

a. Understanding the function of P2 on red cell surface

Localization of P2 on red cell surface appears to be an absolute requirement for parasite growth. Blocking red cell surface P2 using monoclonal antibody, and by inhibiting P2 using conditional degradation by allelic exchange using ribozyme construct (Fig.1) both showed nuclear division arrest. Pixel density quantification of ribozyme mediated P2 degradation showed 90-95% degradation and remarkably over 90% parasites were arrested at nuclear division stage, (Fig. 1). Despite this remarkable indispensability of P2 on red cell surface, it is an open question as to what might be the role of this protein in this 6-8h of window on red cell surface. During intraerythrocytic development and subsequent cell cycle progression, import of serum factors such as lipids into the parasite has been shown to be an absolute necessity. In particular, palmitic and oleic acids have been shown to be indispensable for cell cycle progression. Palmitic and oleic acids depleted serum did not support parasite growth and that resulted into the arrest of cell division. P2 on red cell surface appears to play a role as a sensor through the binding to some components in serum, hence, to check this possibility dot blot was performed and that came out astonishing. When recombinant tetrameric P2, but not the monomer, were checked for its binding ability to a set of lipid molecules, such as Phosphatidic acid (PA), Phosphatidyl ethanolamine (PE), Phosphatidylserine (PS), Sphingomyelin (SM), Sphingosine (Sph), Phosphatidyl inositol (PI), Phosphatidyl choline (PC), remarkably, P2 bound only to three lipids, PA, PS, and PC (Fig. 2Disha et al., unpublished data). To explore the possibility of P2-lipid interaction on red cell surface, several biochemical and biophysical experiments are needed to be performed using wild type and transgenic parasites

To understand the function of P2 on red cell surface, it is unquestionable to understand whether P2 tetramer alone is acting as a channel or as a pump or P2 is complexed with other parasite proteins to sense and/or transport lipid molecules into the parasites. To address this question, I propose to identify proteins interacting with and proximal to red cell surface P2 by applying proximity biotinylation approach developed by Roux et al. Using this method, biotinylating enzyme of E. coli can attach biotin to a subunit of acetyl CoA carboxylase but due to a mutation at R118G, it is capable of promiscuously biotinylating proteins in its proximity. By fusing the mutated enzyme (BirA*) to a protein of interest it is



possible to preferentially label other proteins either in complex with or proximal to the protein of study, which then is followed by affinity capture of the labeled proteins and identification by LC MS/MS (Fig. 3). This approach was originally developed for mammalian cells but now is being used for other organisms including Trypanosoma and Toxoplasma. Using this method, a transgenic P. falciparum line which will express P2-BirA* will be generated. With this fused protein, I will assess whether the pattern of proximity biotinylation of P2-BirA* changes during different stages of intraerythrocyticdevelopment. A catalogue of proteins identified through this study could then form the basis for further experimentation using a variety of biochemical and genetic tools. Overall, I believe that this proximity-biotinylation assay would reveal the identity of different molecular players which might be associated with P2 for its novel function on red cell surface and it would also provide inklings of the regulation of time dependent appearance and disappearance of tetrameric P2 on red cell surface.

Awards / Honour

Ramalingaswami Fellowship from the Department of Biotechnology (DBT), India

Core Research Grant, Department of Science and Technology (DST), SERB, India

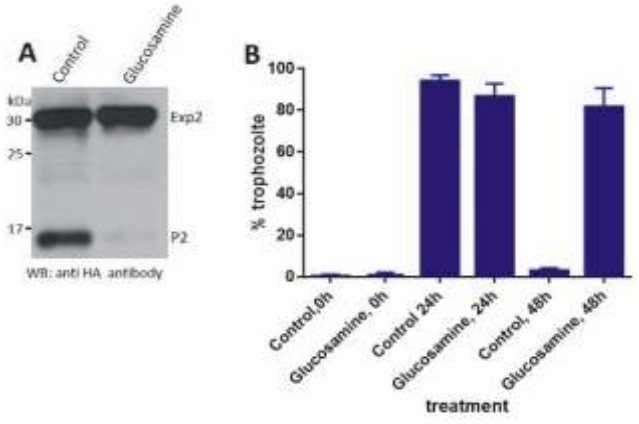


Fig. 1 (A) P2-HA-Ribozyme transfected transgenic parasite was treated with 5mM glucosamine in cRPMI for 24h (ring to trophozoite). Parasites were harvested by gentle saponinlysis. SDS-PAGE and Immunoblot was probed with HA antibody. Exp2 was used as a loading control. (B) Quantitation of arrested trophozoite morphology at 0h, 24h and 48h after glucosamine treatment post merozoite invasion (n=5).

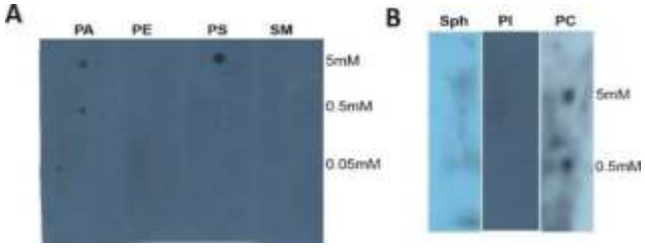


Fig.2 (A&B) Three different concentration of Phosphatidic acid (PA), Phosphatidyl ethanolamine (PE), Phosphatidyl serine (PS), Sphingomyelin (SM), Sphingosine (Sph), Phosphatidyl inositol (PI), Phosphatidyl choline (PC) were blotted and incubated with recombinant P2 protein. Subsequently, P2 protein was detected using anti-P2 monoclonal antibody E2G12) (Disha et al., unpublished data)

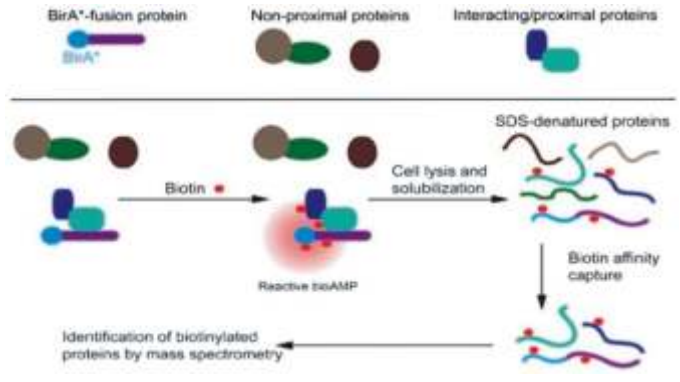


Fig. 3 Schematic of proximity-biotinylation method. In a cell expressing a protein fused with BirA*, biotin addition results in its activation and biotinylation of interacting and proximal proteins while non-proximal proteins are not labeled. Affinity capture of biotinylated proteins can be followed by their mass spectrometric identification. From Roux et al. 2013.

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Garcinol loaded novel cationic nanoliposomes: in vitro and in vivo evaluation for tumor targeting

Participants

Dr. Kakali De DST, WO Sct
Raghuvir Gaonkar (SRF, RGNF)
Ria Mukhopadhyay (SRF, DST Inspire)
Kazi Julekha (JRF, MANF)
Brahamacharry Paul (DST, JRF)
Ramkrishna Sen (DST, Project Assistant)

Collaborator(s)

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Thakurpukur cancer centre, Kolkata.

Background

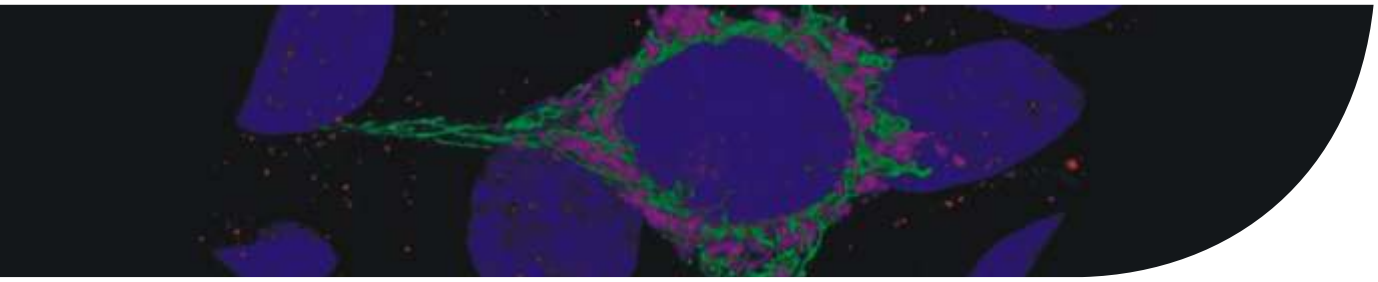
The development of drug formulations using nanotechnology (e.g. liposome, nanoparticle) has been recognized for many years to efficiently deliver drugs for cancer and other diseases. In our efforts to develop improved anticancer drug formulations, we fell back upon plant sources that are recognised to provide potential bioactive compounds for the development of new leads to combat cancer. Garcinol (GAR), a yellow crystalline polyisoprenylated benzophenone compound isolated from the extract of fruit rind of Garcinia indica contains both phenolic hydroxyl group and β-diketone moiety and exhibits a wide array of pharmacological properties, such as antioxidant, antiaging, anticarcinogenic and anti-inflammatory. But aqueous insolubility is the major barrier for GAR to be delivered in solution form or to achieve high bioavailability / target specificity using conventional solid or liquid dosage forms. Development of nanoparticle formulation in laboratory scale using vit-E TPGS as emulsifier has already been achieved by us (Sci. Rep. 7 : 530; 2017). In continuation of that we herein report for the first time the fabrication and characterisation of liposome encapsulated GAR and its use in treating melanoma as determined by in vitro and in vivo studies.

Aims and Objectives

- Fabrication and physicochemical characterization of GAR loaded DSPC and DPPC liposomal formulations developed using thin film hydration method
- 99mTc radiolabeling to track in vitro cellular uptake in B16F10 cells and in vivo biodistribution pattern of the formulations in Balb/C mice bearing B16F10 xenograft (subcutaneous implant)
- To ascertain tumour regression efficiency of GAR and its liposomal formulations in the above tumour bearing mice model.

Work Achieved

Garcinol loaded DSPC and DPPC liposomes were developed using thin film hydration technique to target melanoma. Addition of stearylamine during fabrication produced cationic liposomes with the expectation of better tumour uptake than non-ionic one. The liposomes were physico-chemically characterised by DLS, AFM, FESEM and cryo-TEM, while the compatibility of the formulation ingredients was analysed by FTIR and DSC. The % yields of dry powdered liposomes were found to be more than 90%. The mean particle sizes of GAR-DSPC and GAR-DPPC were 173.5±18.8 nm and 180.28±50.4 nm respectively and were consistent. Both the formulations exhibited moderately high encapsulation efficiency (61-65%). PDI values were also within the range (0.113±0.06 and 0.099±0.05 for GAR-DSPC and GAR-DPPC respectively), indicating narrowly dispersed nanostructure without any aggregation in water. FESEM and AFM images are shown in Figure 1. Study reveals that liposomes maintained a well-defined spherical shape in solution but AFM study reveals that the surfaces were flattened to some extent upon placing the soft lipid samples on the hard surface of mica sheet. Cellular uptakes of FITC loaded DSPC and DPPC liposomal formulations were observed on B16F10 melanoma cells. Under confocal microscope, cells treated with liposomal formulations revealed green fluorescence in cytoplasm confirming accumulation of liposomes inside the cells [Fig. 2A]. MTT study also demonstrated that IC50 values of GAR-DPPC liposomes (3.5±1.5 µg/mL) and GAR-DSPC liposomes (8.1±2 µg/mL) were five fold and two fold lower than that of free GAR (17.5±2.5 µg/mL) for 24 h treatment time. Apoptosis study in B16F10 melanoma cells also showed that GAR-DPPC induced a greater apoptosis of cells with 47% of cells in late apoptosis chamber as expected from the outcome of MTT assay. On the other hand the effect was not very significant in cells treated with GAR-DSPC, only 9.7% of cells were in late apoptosis chamber (Fig 2B) Biodistribution studies with radiolabeled formulations were performed to ascertain tumour localisation.



99mTc-GAR-DPPC exhibited substantially high tumour accumulation (2.81% ID/g) at 4 h post injection, and the tumour to muscle ratio was also significantly high (9.52). In contrast,99mTc-GAR-DSPC exhibited moderate tumour accumulation (1.76% ID/g at 4 h). 99mTc-GAR-DPPC permitted clear visualization of tumour mass during scintigraphic studies under gamma camera [Fig. 3(B)]. In vivo tumor efficacy study in B16F10 tumour bearing Balb/c mice showed % tumor growth inhibition was maximum in case of GAR-DPPC treated animals as compared to GAR-DSPC and free GAR treated ones. Prominent tumour uptake of 99mTc-labeled GAR-DPPC as observed in B16F10 tumour xenografts imaged under gamma camera as well as efficient tumour growth inhibition in B16F10 tumour bearing mice favours therapeutic application.

Future Research Plans

Fabrication of tumour targeting and tumour penetrating peptide decorated nanoformulation is in progress, this active targeting delivery approach will facilitate intracellular release of GAR to the desired site of action.

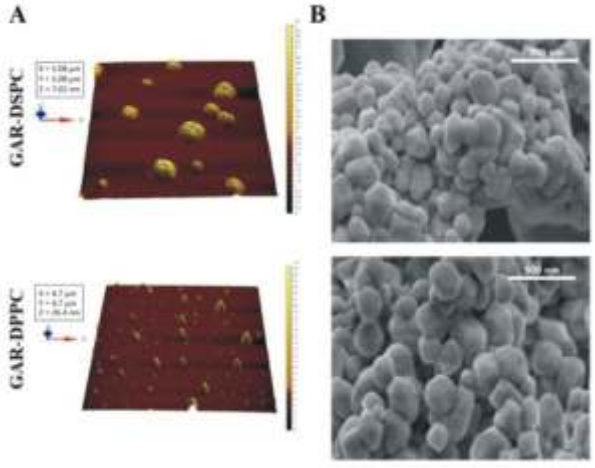


Fig 1. Atomic Force Microscopy (AFM) and Field Emission Scanning Electron Microscopy (FESEM) of GAR-DSPC and GAR-DPPC liposomes.

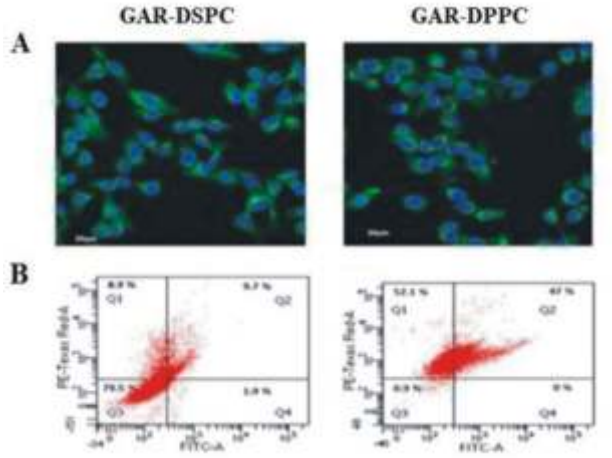


Fig 2: A. Confocal microscopy of B16F10 melanoma cells after incubating them with FITC loaded DSPC and DPPC liposomes. B. Apoptosis induction in B16F10 melanoma cells by GAR-DSPC and GAR-DPPC liposomes after 24 h of treatment.

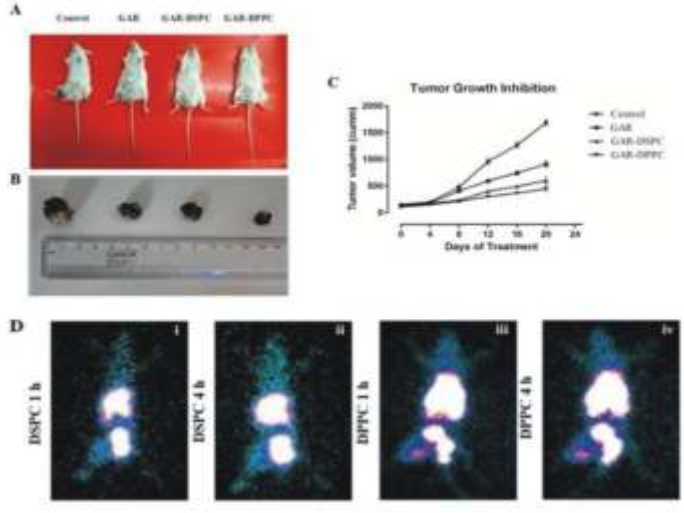
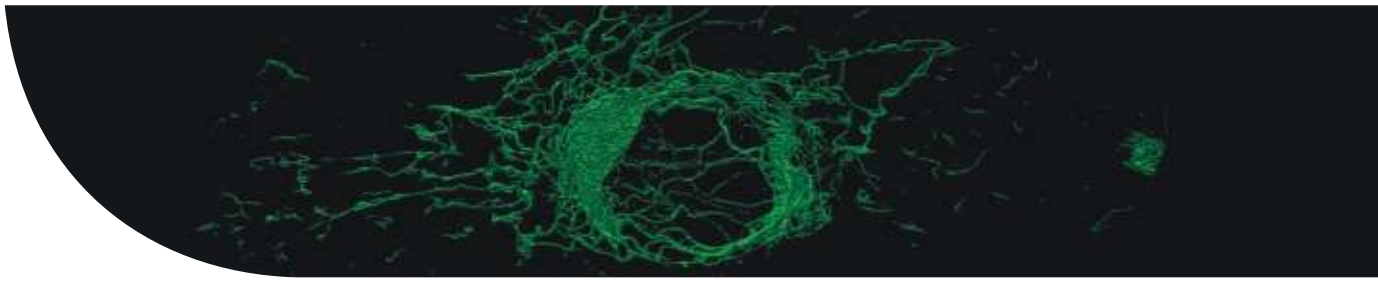


Fig 3: A. Representative images of B16F10 xenograft bearing mice; Control group and those receiving GAR, GAR-DSPC, and GAR-DPPC after completion of treatment. B. Tumors isolated from the animals aforementioned in panel A. C. Representative graph depicting growth of tumor in different group of B16F10 xenograft bearing mice throughout the time period of in vivo study. D. Distribution of 99mTc radiolabeled GAR-DSPC and GAR-DPPC liposomes in B16F10 tumor bearing mice at 1 h and 4 h post injection, as visualized under gamma camera.



Publications

1. Gaonkar, R.H., Baishya, R., Paul, B D4ewanjee S, Ganguly S, Debnath C Mita.(2018) Development of a peptide-based bifunctional chelator conjugated to a cytotoxic drug for the treatment of melanotic melanoma . Med chem. comm, **9**, 812-826.

2. Bhattacharya, S., Mondal, L., Mukherjee, B., Dutta, L., Ehsan, I., Debnath, M. C., Gaonkar, R. H., Pal, M. M., Majumdar, S. (2018) Apigenin loaded nanoparticle delayed development of hepatocellular carcinoma in rats. Nanomedicine, Nanotechnology, Biology and Medicine **14**, 1905-1917.

3. Sengupta, S., Paul, P., Mukherjee, B., Gaonkar, R. H., Debnath, M. C., Chakraborty, R., Khatun, N., Roy, S. (2018) Peripheral nerve targeting by procaine-conjugated ribavirin-loaded dual drug nanovesicle. Nanomedicine(London), **13**, 3009-3023.

4. Kazi, J, Mukhopadhyay, R, Sen, R, Jha, T, Ganguly, S, Debnath, C Mita (2019) Design of 5-fluorouracil (5-FU) loaded, folate conjugated peptide linked nanoparticles, a potential new drug carrier for selective targeting of tumor cells. Med Chem. Comm., **10**, 559-572.

5. Chakrabarty, S., Ehsan. I ., Mukherjee. B., Mondal, L., Roy, S., Saha, DK., Paul, B., Debnath, M.C., Bera, T., (2019) Therapeutic potential of andrographolide-loaded nanoparticles on murine asthma model. Nanomedicine, Nanotechnology, Biology and Medicine **20**, 1-14.

6. Paul ,B., Gaonkar, R.H., Mukhopadhyay, R., Ganguly, S., Debnath M.C. (2019) garcinol loaded novel nanoliposomes, in vitro and in vivo study against B16F10 melanoma tumor model. Just accepted in Nanomedicine (London) doi.org/10.2217/nnm-2019-0022 .

EXTRAMURAL FUNDING

Mita Chatterjee Debnath

In vitro and in vivo evaluation of 99mTc(CO)3- labelled RGD conjugated bioreductive pharmacophore and nucleoside analogue for potential use as tumor targeted SPECT radiopharmaceuticals September 2015 December 2018 (SERB, DST-India)

Molecular Genetics Division

Members :

Dr. Suvendra Nath Bhattacharyya, Dr. Debabrata Biswas

This department has the mandates to identify the importance of small RNA level -modulation in the mammalian cell physiology; to determine the molecular basis of gene delivery to mitochondria, and to understand the eukaryotic transcriptional regulatory mechanisms and their role in human diseases.

One objective of this department is poised to indentify the mechanisms that regulate activity of different microRNAs in mammalian cancer and immune cells and to relate these to disease onset and progression. Mechanistic understanding and regulation transcription process at molecular level is also under investigation. Using a combination of basic and applied approaches we will study the molecular basis of genetic disease and its probable therapy targeting diverse steps both in pre- and post-transcriptional events.

Dr. Suvendra Nath Bhattacharyya

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Regulation of miRNA Activity in Mammalian Cells

Participants

RA : Arnab Das, Debduti Datta

SRF : Bartika Ghoshal, Avijit Goswami, Dipayan De, Satarupa Ganguly, Saikat Banerjee, Susanta Chatterjee, Diptankar Bandyopadhyay

JRF : Syamantak Ghosh, Sourav Hom Choudhury, Ishani Banerji, Shreya Bhattacharjee, Sreemoyee Chakraborty

Collaborator(s)

Edouard Bertrand, IGMM, Montpellier, France

Mihaela Zavolan, BioZentrum, University of Basel, Basel, Switzerland

Saikat Chakrabarti, CSIR-IICB

Subhas Biswas, CSIR-IICB

Partha Chakraborty, CSIR-IICB

Krishnanada Chattopadhyay, CSIR-IICB

P Jaisankaar, CSIR-IICB

Background

The understanding of post-transcriptional regulation of mRNAs added an additional layer after the discovery of microRNAs (miRNAs). miRNAs, short tiny regulators of mRNA activity binds to the 3' UTR of mRNA with partial complementarities and represses its' expression either by target mRNA degradation or translational repression. miRNAs are 20-22 nucleotide long short RNAs contains 5' conserved seed sequence complementary to 3' UTR of target mRNA. miRNA biogenesis is a sequential modification process where miRNAs firstly transcribed from its' specific gene in the form of primary miRNA transcripts (pri-miRNAs) with the help of RNA polymerase II. Pri-miRNAs then processed into precursor miRNAs (pre-miRNAs) with the endonucleolytic activity of micro processor complex (DROSHA/DGCR8) to form a ~70nt. long cleaved pre-cursor miRNA (pre-miRNA) in the nucleus. Pre-miRNA then exported out from the nucleus with the anchorage of Exportin 5 protein complex. Pre-miRNA then further cleaved to form miRNA/miRNA* with the catalytic activity of DICER1. miRNAs then incorporated into RNA induced silencing complex (miRISC) consists of AGO and TRBP proteins for further miRNA activity on target mRNA. Exploring the effect of target mRNA on cognate miRNA, earlier we have observed there exists a target mRNA dependent miRNA biogenesis where target mRNA could regulate its' cognate miRNA biogenesis by modulating Dicer processivity. Then we were curious about how “target mRNA dependent miRNA biogenesis” manifests co-operative effect on other miRNAs that have binding sites on the same 3`UTR of target mRNA.

Aims and Objectives

Here, we have tried to understand if there exists any feedback relationship on miRNA biogenesis influenced by target mRNA abundance. Could target mRNA influences the biogenesis, activity and cellular compartmentalization of miRNA? Experimental observations suggests, there exists a target-mRNA dependent reciprocal relationship over miRNA biogenesis and its' activity.

Work Achieved

TLR4-activation dependent signalling pathway has been chosen for our study where multiple miRNAs fine-tune the immune responses and forming a miRNA-network to balance pro- and anti-inflammatory response. 3' UTR based study and global transcriptomics data analysis shows that the activity of one miRNA species with higher number of binding sites on TLR4 signalling mRNA influences the biogenesis and activity of other miRNAs with fewer binding sites on the same 3'UTR. We have found miR-146a, one of the prominent anti-inflammatory miRNA, cooperatively regulates the biogenesis and activity of other miRNAs that share the 3` UTR of common target mRNAs.

Future Research Plans

We are Eager to find how mechanistically the target mRNA dependent co-operative bio-genesis of miRNAs may play an important role to combat pro-inflammatory response that acts as a barrier against pathogenesis of many autoimmune, chronic inflammatory diseases or even inflammation-induced tumorigenesis.

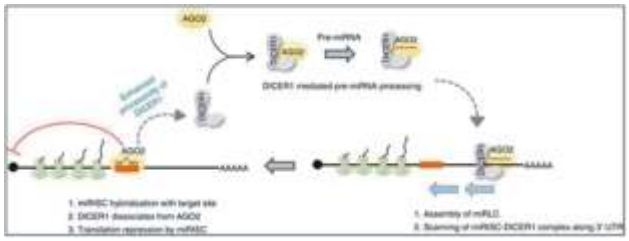

Fig. 1: Target dependent miRNA biogenesis process. Here the cartton shows how the processivity increase of the Ago2 associated Dicer1 can influence the cognate miRNA biogensis process. It is not suprizing that multipl miRNA binding sites on the same 3ÚTR will favoravle for biogensis of transcating miRNAs leading to change in gene expression profile.

PUBLICATIONS

Book Chapters / Invited Reviews

Mainak Bose and Suvendra N Bhattacharyya (2018) Target mRNA-Driven Biogenesis of Cognate MicroRNAs In Vitro In Methods in Molecular Biology. Human Press, Springer publishing group, USA, (Ed. Shao-Yao Ying), Vol. 1733, pp. 27-39.

AWARDS / HONOURS / MEMBERSHIPS

Students
Bartika Ghoshal
International RNA Society Travel Fellowship to attend the Annual RNA meeting in USA
Dipayan De
International Travel Award to attend the Annual meeting of the Amerian Cell Biology Society and EMBO, in USA

EXTRAMURAL FUNDING

Suvendra N. Bhattacharyya
Indo French CEFIPRA Fund 2019-2022 (CEFIPRA, India-France)

Indo Swiss Joint Research Fund 2019-2022 (DBT, Govt of India under Bluesky Research project funding in joint India-Switzerland funding)

CONFERENCES / WORKSHOPS

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

Name of event; Start date End date, Year; Venue; CSIR-IICB Organizing Committee

INVITED TALKS BY CSIR-IICB FACULTY

Suvendra N Bhattacharyya

MiRNA as gene regulator; SS Bhatnagar Lecture in CHARUSAT University, Anand Gujrat, 22nd September 2018

Regulation of miRNA activity in mammalian cells: Role of Organelles; Fellow's Lecture at 84th Annual Meeting of Indian Academy of Sciences, Bangalore (2-4 November) at Varanasi

miRNA activity Modulation in mmalian cells; Invited talk in Genome Architecture and Cell Fate Regulation conference hosted by the University of Hyderabad in partnership with CCMB, TIFR, CDFD and NIAB on December 3-6, 2018.

Exosomal export of miRNAs: A model of gene regulation; Invited talk in a conference on Protein, miRNA and Exosomes in Health and Disease 2018 in MS University Barodha, Gujrat December 11-13th,2018.

Cell biology of miRNA activity regulation; Invited talk in 49th All India Cell Biology Conference in BITS, Goa on 21-23rd December 2018.

Tiny RNA with big function; Invited Talk at Regional YIM Kolkata Chapter, Presidency University, Kolkata on 6th February 2019.

miRNA Actity regulation by Ev-mediated export; Invited talk in a symposium on 'Frontiers in Development and Molecular Medicine: Models to Insights' (FDMM2019) hosted by CSIR-Indian Institute of Chemical Biology, Kolkata, India, on March 1-3, 2019

Dr. Debabrata Biswas

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Understanding mechanisms of eukaryotic transcriptional regulation and leukemia development by MLL and MLL fusion partner proteins

Participants

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SRF: Mahesh Barad, Koushik Ghosh, Subham Basu, Nidhi Kumari, Dheerendra Pratap Mall, Md. Abul Hassan

Collaborator(s)

Name of collaborator outside CSIR-IICB

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Background

Human MLL protein is a histone H3-K4 methyl transferase that is associated with transcriptional activation. Balanced chromosomal translocations between MLL and variety of MLL fusion partners (>80) give rise to both acute myeloid and lymphoid leukemia with two-year survival rate of <50%. Recently, attempts have been made towards understanding molecular mechanisms of action of MLL fusion partners and corresponding MLL fusion proteins in transcriptional regulation and leukemia development. These studies have suggested a unified mechanism of action of common MLL fusion partners in regulating transcription through their presence in a large multi-subunit Super Elongation Complex (SEC). However, mouse models of MLL fusion proteins suggest distinct mechanisms of action of individual MLL fusion proteins and corresponding leukemia development.

In support of this hypothesis, our earlier studies and few recent studies have shown that, in contrast to a large megadalton static complex, the MLL fusion partners form various sub-complexes with overlapping subunits for dynamic regulation of different steps of transcription. Further, few recent studies have also shown different requirement of MLL fusion partners (outside the context of SECs) for transcriptional regulation and leukemia development. Therefore, for better understanding of overall mechanisms of functional regulation and disease pathogenesis, more detailed analyses are required.

In our lab, we are currently exploring detailed mechanisms of action of few MLL fusion partners in transcriptional regulation that is both dependent and independent of SECs. Further, we would extend our studies towards exploring importance of these novel mechanistic understanding in MLL fusion-mediated leukemogenesis.

Aims and Objectives

Detailed studies on role of human ZMYND8 protein in positive regulation of transcription

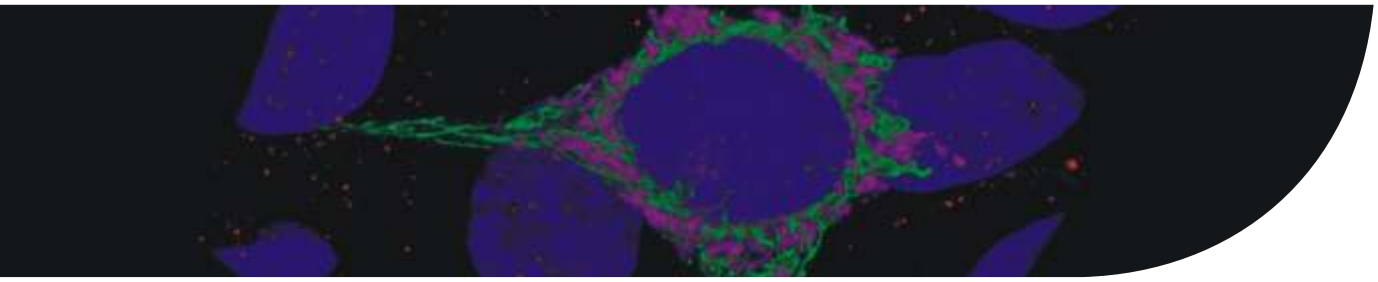
Understanding of role of human TFIID complex in regulation of elongation control through promoter proximal pausing

Mechanistic understanding of role of human DBC1 protein in regulation of ELL functions within mammalian cells

Work Achieved

Positive regulation of transcription by human ZMYND8 through its novel association with P-TEFb complex.

Although human ZMYND8 has been implicated as a transcriptional co-repressor of multiple targets, global association of ZMYND8 with active genes and enhancer regions predicts otherwise. Here, we report a novel function of ZMYND8 in transcriptional activation through its association with P-TEFb complex. Biochemical reconstitution analyses show that human ZMYND8, through direct association with CylcinT1, forms a minimal ZMYND8●P-TEFb complex. Importance of ZMYND8 in target gene activation, through P-TEFb complex recruitment, is demonstrated on chromosomally-integrated reporter gene as well as native target genes in vivo. Physiologically, we further show that the ZMYND8●P-TEFb complex-mediated transcriptional activation is required for All-Trans Retinoic Acid (ATRA)-mediated differentiation of neuronal precursor cells. Finally, to detail the dual activator and repressor nature, mechanistically we show that, through its putative coiled-coil domain, ZMYND8 forms homodimer that preferentially associates with the activator P-TEFb complex, whereas, monomer associates with CHD4 subunit of repressor NuRD complex (Fig. 1).



Multivalent role of human TFIID complex in recruiting elongation components at the promoter proximal region for transcriptional control

Despite substantial progress in understanding of players involved and regulatory mechanisms controlling initiation and elongation steps of transcription, little is known about recruitment of elongation factors at the promoter proximal region for initiation to elongation transition. In this report, we show evidence that human TFIID complex regulates recruitment of Super Elongation Complex (SEC) components at the promoter proximal region. Biochemical studies show that selected components of both TFIID and SEC are directly involved in this process. Fine mapping analyses show that specific domains of both TFIID and SEC components are involved in their recognition and recruitment processes. DNA template-based recruitment assay, using purified components, further show a direct role of TFIID in recruiting SEC components on target DNA. Finally, a role for this mechanism of action in factor recruitment and target gene expression is substantiated through ChIP and expression analyses in vivo (Fig. 2).

Mechanistic insight into role of DBC1 in stabilizing ELL through coordinated action of p300, HDAC3 and ubiquitylation machinery and its implication in Type 2 diabetes

Among all the Super Elongation Complex (SEC) components, ELL is the only bona fide elongation factor that directly stimulates transcription elongation by RNA polymerase II. However, mechanism of functional regulation of ELL, through its stabilization, is completely unknown. In this study, we report a novel function of human DBC1 in stabilization of ELL through a mechanism that involves inhibition of ELL deacetylation by HDAC3. Mechanistically, we show that p300-mediated site specific acetylation of ELL increases its stability by inhibiting ubiquitylation and subsequent proteasome-mediated degradation. HDAC3 enhances ELL deacetylation and subsequent degradation by ubiquitylation involving E3-ligase Siah1 that otherwise is incapable on its own. DBC1 increases ELL stability by inhibiting HDAC3 function and increasing ELL acetylation resulting reduced ubiquitylation. Furthermore, DBC1-mediated ELL stabilization is important for transcriptional regulation of important SEC components and thereby SEC functions for activating expression of EGF-induced immediate early genes as well as target genes at basal level (Fig. 3).

AFF1 acetylation by p300 temporally inhibits transcription during genotoxic stress response

Soon after exposure to genotoxic reagents, mammalian cells inhibit transcription to prevent collisions with repair machinery and to mount a proper DNA damage response. However, mechanisms underlying early transcriptional inhibition are poorly understood. In this report, we show that site-specific acetylation of Super Elongation Complex (SEC) subunit AFF1 by p300 reduces its interaction with other SEC components and impairs P-TEFb-mediated C-terminal domain phosphorylation of RNA polymerase II both in vitro and in vivo. Re-expression of wild type AFF1, but not an acetylation mimic mutant, restores SEC component recruitment and target gene expression in AFF1 knockdown cells. Physiologically, we show that, upon genotoxic exposure, p300-mediated AFF1 acetylation is dynamic and strongly correlated with concomitant global down-regulation of transcription and that this can be reversed by over-expression of an acetylation-defective AFF1 mutant. Therefore, we describe a novel mechanism of dynamic transcriptional regulation involving p300-mediated acetylation of a key elongation factor during genotoxic stress.

Future Research Plans

In future, majority of our research efforts would be directed towards addressing dynamic regulation of functional activity of different SEC factors during transcription-coupled DNA repair process. Especially we would like to focus more on regulation of SEC functional activity by various post-translational modification.

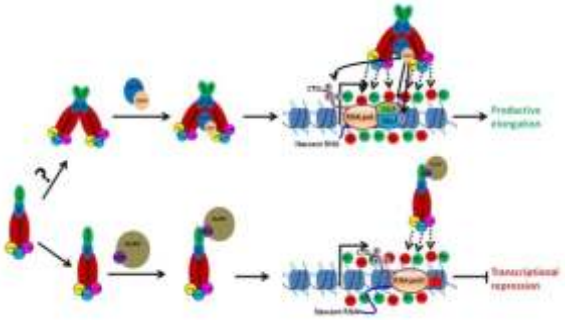


Fig. 1: Working model that describes mechanism of activator and repressor roles of ZMYND8 in transcriptional regulation in association with P-TEFb and NuRD complexes respectively. In a

coiled-coil domain dependent manner, ZMYND8 has the capability to dimerize. The dimerized ZMYND8 preferentially associates with the P-TEFb complex. Recognition of multiple histone modifications through its chromatin reader domains, the ZMYND8 helps in P-TEFb complex recruitment at the promoter proximal region of target genes for overcoming DSIF-NELF-mediated pausing of initiated RNA pol II and facilitates its entry into productive elongation for transcriptional activation, whereas, the monomeric ZMYND8 preferentially associates with the CHD4 subunit and helps in NuRD complex recruitment for repression of the target genes during DNA repair.

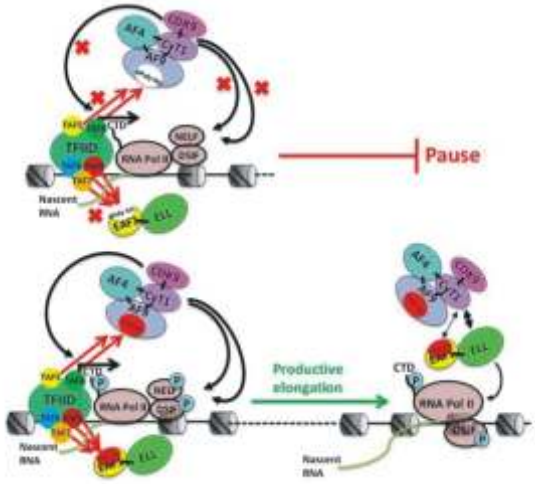


Fig. 2: Overall model showing regulation of pause and release of transcription event through TFIID complex-mediated AF9 and AF9-asscoiated SEC components. Poly-Ser domains present within the AF9 and EAF1 play a major role in TFIID-mediated SEC recruitment for overcoming DSIF and NELF-mediated pausing of RNA pol II and its entry into productive elongation.

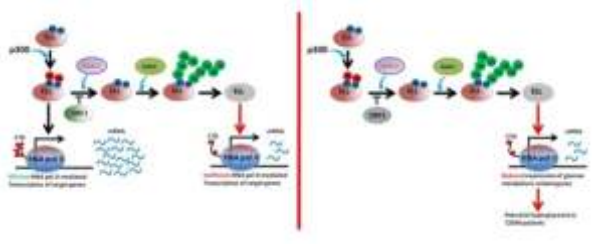


Fig. 3: Overall Model for coordinated action of DBC1, p300, HDAC3, and ubiquitylation machinery (through E3 ligase Siah1) in regulating ELL stability and its functions within mammalian cells. ELL protein is post-translationally acetylated by p300. This acetylation increases ELL stability through inhibition of ubiquitylation by Siah1. HDAC3, on the other hand deactlates ELL and thereby increases ubiquitylation for its degradation. The DBC1 protein inhibits the deacetylase activity of HDAC3 to increase ELL acetylation and thereby increasing its stability.

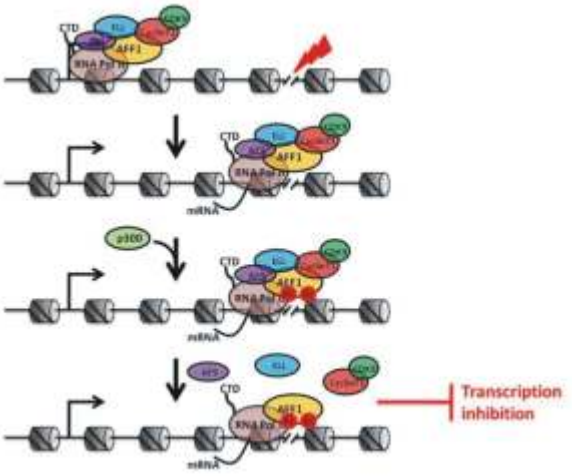
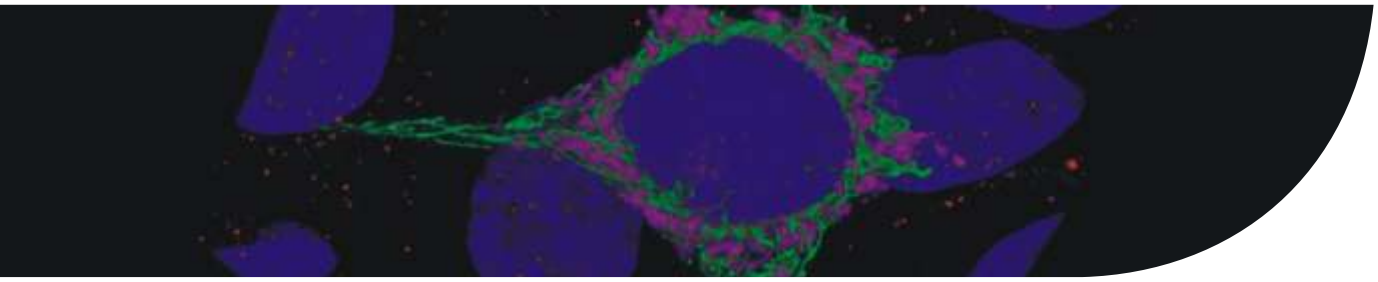


Fig. 4: Model for the role of dynamic AFF1 acetylation in transcription inhibition during exposure to genotoxic reagents. Exposure of cells to genotoxic reagents leads to AFF1 acetylation by p300 and a consequent decrease in AFF1 interactions with cognate SEC members. Since AFF1 plays a scaffolding role in overall SEC assembly, a reduction in AFF1 interactions with other SEC components potentially leads to disassembly of a functional SEC complex and, thereby, temporally inhibits transcription.

PUBLICATIONS

Koushik Ghosh, Ming Tang, Nidhi Kumari, Arijit Nandy, Subham Basu, Dheerendra Pratap Mall, Kunal Rai, and Debabrata Biswas: Positive regulation of transcription by human ZMYND8 through its novel association with P-TEFb complex. Cell Reports. 2018 Aug 21;24(8):2141-2154.e6. doi: 10.1016/j.celrep .2018. 07.064.

Dipika Yadav, Koushik Ghosh, Subham Basu, Robert G. Roeder, and Debabrata Biswas: Multivalent role of human TFIID complex in recruiting elongation components at the promoter proximal region for transcriptional control. Cell Reports. 2019 Jan 29;26(5):1303-1317.e7. doi: 10.1016/j.celrep.2019.01.012.



Subham Basu, Mahesh K. Barad, Dipika Yadav, Arijit Nandy, Bidisha Mukherjee, Jit Sarkar, Partha Chakrabarti, Satinath Mukhopadhyay, and Debabrata Biswas: DBC1, p300, HDAC3 and Siah1 coordinately regulate ELL stability and function for expression of Type 2 diabetes-linked genes (Under Review) PNAS, USA

Nidhi Kumari, Md. Abul Hassan, Xiangdong Lu, Robert G. Roeder, and Debabrata Biswas: AFF1 acetylation by p300 temporally inhibits transcription during genotoxic stress response PNAS, http://doi.org/10.1073/pnas/1907097116

Arijit Nandy, Subham Basu, Mahesh K. Barad, and Debabrata Biswas: Critical role for ELL-associated factor 1 and 2 in regulating SEC abundance and functions through regulation of ELL stability (Manuscript under preparation)

Extramural Funding:

1. Wellcome-Trust DBT India Alliance Intermediate Fellowship
2. Dept. of Science and Technology (DST)

CONFERENCES / WORKSHOPS

1. Dynamic regulation of transcription by p300-mediated site-specific acetylation of human Af4 during genotoxic stress response
   Transcription Assembly Meeting 2018, CDFD, Hyderabad, 26th July, 2019
2. Multivalent role of human TFIID in recruiting elongation components at the promoter proximal region for transcriptional control
   Saha Institute of Nuclear Physics Cancer Meet 2018, 26th Sept 2018
3. Dynamic regulation of transcription by p300-mediated site-specific acetylation of human AF4 during genotoxic stress response
   7th International Conference on Molecular Signalling, NCCS, Pune 24th Jan 2019
4. Dynamic regulation of transcription by p300-mediated site-specific acetylation of human Af4 during genotoxic stress response
   Frontiers in Developmental and Molecular Medicine, models to insight, CSIR-IICB, Kolkata, 1st March 2019

Organic & Medicinal Chemistry Division

Members :

Dr. P. Jaisankar (Head), Dr. Chinmay Chowdhury (Dy. Head), Dr. Sharmila Chattopadhyay, Dr. Surajit Ghosh, Dr. Biswadip Banerji, Dr. Ranjan Jana, Dr. Sanjay Dutta, Dr. Arindam Talukdar, Dr. R. Natarajan, Dr. Indu Bhusan Deb, Dr. Indrajit Das, Dr. Saraswati Garai, Dr V. S. Pragadheesh and Dr. Deepak Kumar.

The Organic and Medicinal Chemistry Division at CSIR-Indian Institute of Chemical Biology is composed of dedicated scientists with a diverse array of expertise in synthetic organic chemistry, catalysis, chemical biology, medicinal chemistry, natural product chemistry. Scientists from this division play a crucial role for the genesis of several research activitiesto address biological, environmental and other chemical problems which are burning issues of the nation. The department is actively engaged for the development of green chemical processes and technologies to boost up Indian pharma, agro and chemical industries for self-sustainability. Simultaneously, several biomedical challenges are tackled through a symbiotic collaboration between chemists and biologists to make Swasth Bharat.In this context, we are unravelling the molecular mechanism and potential therapies of human diseases through the structure/ligand-based design and synthesis of novel chemical entities. The division has a strong and proven track record of developing natural product based drugs 'Asmon' and 'Prostalyn' currently in the market. The divisional scientists are making a sincere stride in translational research to solve the healthcare issues of the national importance.

Besides extramural research projects from non-CSIR funding agencies such as DST, DBT, ICMR, WBDST etc. our scientists are also involved in mission mode projects (MMP) and fast track translation (FTT) schemes of CSIR for the development of Innovative Processes & Technologies for Indian Pharmaceutical and Agrochemical Sector Industries (INPROTICS).This initiative will provide cost effective processesof life saving drugsand agrochemicals for the nation. Our scientists also execute other crucial FTT projects of CSIR to develop therapeutic agents for sickle cell anaemia and nonalcoholicsteatohepatitis (NASH).We are also involved in the international (Indo-Australian) research projects for the development of therapeutics against Leishmaniasis.Several other niche creating and focused basic research projects such as RNA-targeted small molecules for Hepatitis C Virus (HCV) infection, rationally designed selective inhibitors for the nucleic acid-recognizing toll-like receptors (TLRs) for autoimmune diseases. We have immense contribution to the generation of skilled human resource in the fields of Chemistry, Chemical Biology and Medicinal Chemistry with an impressive number of PhDs, project fellows, master and bachelor students are trained, who contribute effectively to academic and industrial sectors. Furthermore, the knowledge generated in our division is either published in high impact journals or protected through patent filing for subsequent applications. We also provide technical support through consultancy services to the industries and other means to generate ECF.We are actively involved in developing analytical techniques/products for enhancement of income of the farmers as well as providing safe drinking water to the common people.

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Synthesis of potential lead molecular scaffolds by investigating their interactions with biological targets to understand their medicinal effects.

Participants

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Shrabanti Kumar (DST-Women Scientist)

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Dr. SuvendraNath Bhattacharyya

Background

Our research investigations towards the potential biological applications of 3-indolyl furanoids revealed that they have potent anti-ulcer property by inhibiting MMP-9, anti-proliferative activity by inhibiting mitochondrial complex III and biofilm disruption activities in Pseudomonas aeruginosa. Our group is engaged in the development of lead molecules havinganti-cancer, anti-leishmanial, anti-parkinsonian, anti-bacterial and anti-ulcer properties.Now-a-days, enzymatic reactions have become an attractive chemistry for the fabrication of advanced materials. Instead of chemical catalysts, enzymes can serve as cross-linking reagents for structurally diverse heterocyclic scaffold synthesis. We are actively engaged in isolating enzymes from edible sources and utilizing them towards organic reactions to construct specific epigenetic enzyme inhibitors by understanding the molecular targets.Apart from these we are curious to investigate asymmetric organic transformations by using chiral ligands/catalysts and their transition metal complexes to synthesis bioactive scaffolds. Introduction of stable atropisomerismis a general strategy to increase target selectivity of a promiscuous scaffold. This approach is dependent on the ability to incorporate steric bulk adjacent to the axis in order to rigidify it. This is most efficiently achieved through C-H functionalization, asymmetric transformative reaction on diverse aromatic scaffolds.

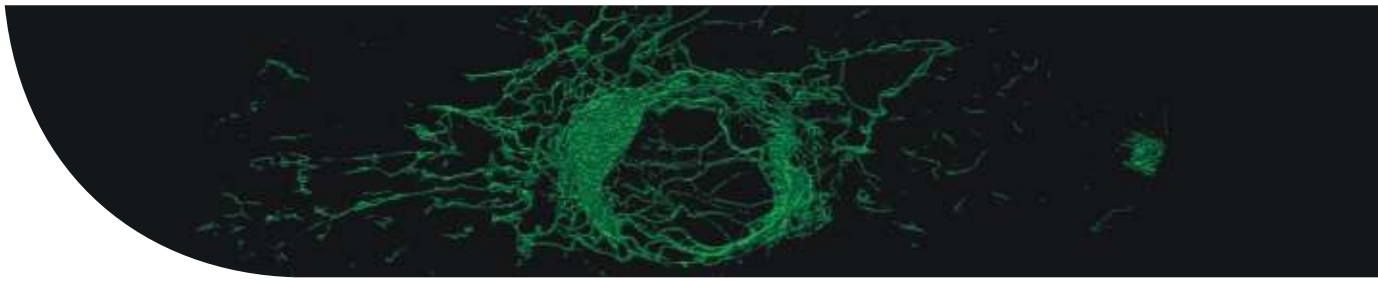
Aims and Objectives

- Our research revolves around asymmetric transformative reaction by using chiral catalysts,development of atropisomeric molecules and determination of their thermodynamic and racemization kinetics of enantiomers of bioactive molecules.
- Development of lead molecules from synthetic and natural origins with specific targets against various diseases.

Work Achieved

Establishment of atropisomerism in 3-indolylfuranoids: a synthetic, experimental and theoretical perspective

Atropisomerism is ubiquitous throughout drug discovery, however, is often overlooked as most examples exist as rapidly racemizing mixtures. While these molecules may be optically inactive, they will interact with their protein target in an atropselective fashion, with the nonrelevantatropisomer contributing little to the desired activities.Introduction of axial chirality in bioactive 3-indolyl furanoids has been achieved by systematic alteration of functional groups around the stereogenic axis, keeping in mind that atropisomerically pure analogues may possess different binding affinities and selectivity towards a target protein. The kinetics of racemization of axially chiral 3-indolyl furanoids have been studied through chiral HPLC analysis, electronic circular dichroism (ECD) spectroscopy, and computational modeling and significantly higher activation barrier to rotation (25.5 kcal mol-1) of 3-indolyl furanoids was found. The results identify the configurationalparameters for optically pure 3-indolyl furanoids to exist as stable and isolable atropisomeric form.



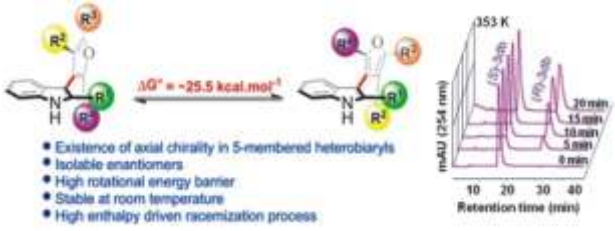


Fig. 1Racemization of axially chiral 3-indolyl furanoids

Orcinol Glucoside Loaded Polymer - Lipid Hybrid Nanostructured Lipid Carriers: Potential Cytotoxic Agents against Gastric, Colon and Hepatoma Carcinoma Cell Lines

Orcinol glucoside (OG) - loaded nanostructured lipid carrier (NLC), coated with polyethylene glycol-25/55-stearate (PEG-25/55-SA), were explored for delivering OG toimprove in vitro cytotoxicity against gastrointestinal tract (GIT), colon and hepatoma carcinoma cell lines. It is being expected that the PEGylated formulations would possess the sustainability in withstanding the adverse physiological extremities like the most significant metabolic activities and phase I / II enzymatic activities in the intestines.

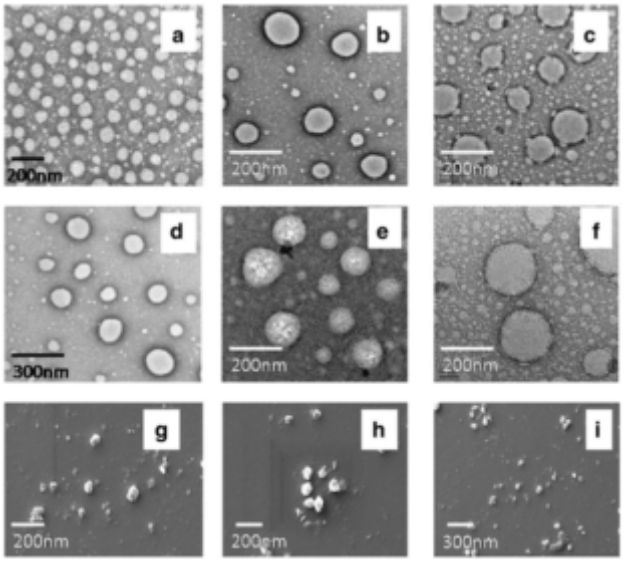


Fig. 2 TEM (a-f) and SEM (g-i) images of (A and G) TS + OA, (Band H) TS + PEG-25-SA + OA and (C, I) TS + PEG-55-SA + OA NLC respectively. D, E and F are the corresponding OG loaded formulations

Isobenzofuranone derivativeJVPH3, an inhibitor of L. donovanitopoisomerase II, disruptsmitochondrial architecture intrypanosomatid parasites

Kinetoplast DNA (kDNA) bearing unusual mitochondrion of trypanosomatid parasites ofers a new paradigm in chemotherapy modality. Topoisomerase II of Leishmaniadonovani(LdTopII), a key enzyme associated with kDNA replication, is emerging as a potential drug target. However, mode of action of LdTopII targeted compounds in the parasites at sub-cellular level remains largely unknown. Previously, we reported that an isobenzofuranone derivative, namely 3,5-bis(4-chlorophenyl)-7-hydroxyisobenzofuran- 1(3H)-one **(JVPH3)**, targets LdTopII and induces apoptosis-like cell death in L. donovani. Here, we elucidate the phenotypic changes and the events occurring at sub-cellular level caused by **JVPH3** in L. donovani. In addition, we have evaluated the cytotoxicity and ultrastructural alterations caused by **JVPH3** in two Brazilian trypanosomatid pathogens viz. L. amazonensisand Trypanosomacruzi. Despite killingthese parasites, JVPH3 caused significantly diferent phenotypes in L. donovaniand L. amazonensis. More than 90% population of parasites showed altered morphology. Mitochondrion was a major target organelle subsequently causing kinetoplast network disorganization in Leishmania. Altered mitochondrial architecture was evident in 7580% Leishmaniapopulation being investigated. Quantification of mitochondrial function using JC-1 fluorophore to measure a possible mitochondrial membrane depolarization further confirmed the mitochondrion as an essential target of the **JVPH3** corroborating with the phenotype observed by electron microscopy. However, the impact of **JVPH3** was lesser on T. cruzithanLeishmania. The molecule caused mitochondrial alteration in 40% population of the epimastigotes being investigated. To our knowledge, this is the first report to evaluate the proliferation pattern and ultrastructural alterations caused in Brazilian kinetoplastid pathogens by a synthetic LdTopII inhibitor previously established to have promising in vivo activity against Indian strain of L. donovani.

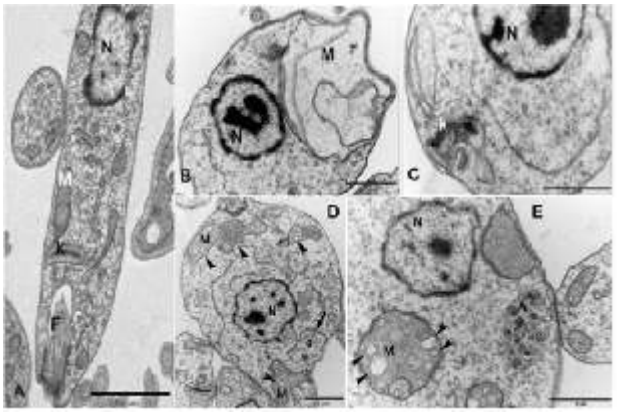


Fig. 3 Transmission electron micrographs of Leishmaniadonovani. **(A)** General overview of control parasites presenting a ramifed mitochondrion (M), kinetoplast (k), nucleus (N) and fagella (F). **(B)**Mitochondrial swelling followed by a loss of the matrix content at 15 µM**JVPH3**. **(C)** Disorganized kinetoplast at 15 µMJVPH3. **(D)** Intense vesiculation of the inner mitochondrial membrane (labelled as 'M')andphagophore formation (arrow-heads) surrounded by glycosome (g) at 20 µM JVPH3. **(E)** Presence of autophagosome containing several vesicles (labelled as 'A') at 20 µM**JVPH3.**

Future Research Plans

- The development of new enantiopure, axially chiral 3-indolyl based heteroaryl derivatives are currently being pursued in our laboratory.
- Synthesis of new lead compounds having indole/quinoline/isobenzofuran core and their analogues having various biological activities, with special focus on anticancer, anti-asthmatic, anti-microbial, and anti-inflammatory compounds are on-going.

PUBLICATIONS

Establishment of atropisomerism in 3-indolyl furanoids: a synthetic, experimental and theoretical perspective: S. Chatterjee, P. Bhattacharjee, G.L. Butterfoss, A. Achari, **P. Jaisankar*, RSC Adv.,(2019)** ,9, 22384.

Orcinol Glucoside Loaded Polymer Lipid Hybrid Nanostructured Lipid Carriers: Potential Cytotoxic Agents against Gastric, Colon and Hepatoma Carcinoma Cell Lines: P. Nahak, R. Gajbhiye, G. Karmakar, P. Guha, B. Roy, S. E. Besra, A. G. Bikov, A. V. Akentiev, B. A. Noskov, K. Nag, P. Jaisankar*, A. K. Panda, **Pharm Res.(2018)**, 35, 198.

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Book Chapters / Invited Reviews

Gajbhiye R.L., Mahato S.K., Achari A., Jaisankar P., Ravichandiran V. (2019) Cancer Chemoprevention by Dietary Polyphenols, Flavonoids, Terpenoids, and SaponinsIn: Sharma A. (eds) Bioactive Natural Products for the Management of Cancer: from Bench to Bedside. Springer, Singapore, pp 91-109,DOI: https://doi.org/10.1007/978-981-13-7607-8_5

Gajbhiye R.L., Mahato S.K., Achari A., Jaisankar P., Ravichandiran V. (2019) Immunogenic Potential of Natural Products. In: Sharma A. (eds) Bioactive Natural Products for the Management of Cancer: from Bench to Bedside. Springer, Singapore, pp 111-138, DOI: https://doi.org/10.1007/978-981-13-7607-8_6

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Parasuraman Jaisankar

(US20180230135) 3-Indolyl Furanoidsas Inhibitors of Matrix Metalloproteinase-9 For Prevention Of Gastric Ulcer And Other Inflammatory Diseases (2018): US Patent Appl. No.: 15897688, Publication Number: 20180230135, Publication Date: 16.08.2018
(IN201711005308) 3-Indolyl Furanoidsas Inhibitors of Matrix Metalloproteinase-9 For Prevention Of Gastric Ulcer And Other Inflammatory Diseases (2018):India patent, Appl. No. 201711005308, Publication Number: IN201711005308 and Publication Date: 17.08.2018.

Co-inventors:
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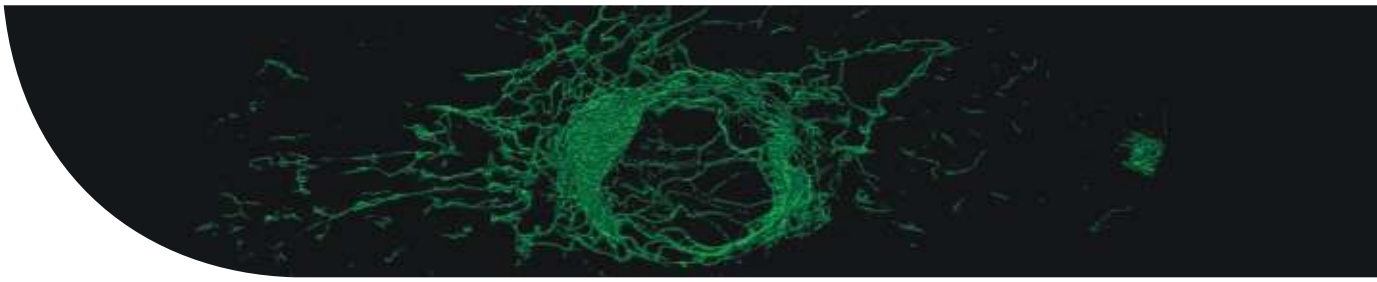


Madhumita Mandal: CSIR- Indian Institute of Chemical Biology
Susri Ray Chaudhuri: CSIR- Indian Institute of Chemical Biology
Patent filed by CSIR-IICB

AWARDS / HONOURS / MEMBERSHIPS
Faculty

Parasuraman Jaisankar

Awards / Honours
Fellow of West Bengal Academy of Science & Technology (FASc.T) awarded by West Bengal
Academy of Science and Technology (WAST) (2018)

Memberships
Member of the American Chemical Society

Students
Awards

EXTRAMURAL FUNDING

DST- SERB

Parasuraman Jaisankar

Development of axially chiral 3-indolyl based heterobiaryls: synthesis, separation, isolation of atropisomers and study of their physicochemical properties, applications in biology and materials science. 2017 - 2021. Science and Engineering Research Board (SERB); Department of Science & Technology, India.

CONFERENCES / WORKSHOPS

Parasuraman Jaisankar

7th International Conference on Molecular Signalling organized by SPPU and NCCS, Pune 411007, during 23-25th January 2019, India.

Andhra Pradesh Science Congress 2018 (APSC 2018) organized by Yogi Vemana University, Kadapa, AP during 9-11 November, 2018, India

Royal Society of Chemistry (RSC) Meeting of Eastern India Chapter at Visvabharati University, Shantiniketan, 28-09-2018, Shantiniketan, India.

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

Participated in JIGYASA 2019, organized by CSIR-IICB, Kolkata, India.

TALKS BY CSIR-IICB FACULTY

Parasuraman Jaisankar

Delivered an invited Lecture on “Unusual Chirality in Organic Molecules and their Diverse Applications” in the Royal Society of Chemistry (RSC) Meeting of Eastern India Chapter at Visvabharati University, Shantiniketan, 28-09-2018, Shantiniketan, India.

Delivered an Invited Lecture on “LCMSMS A Powerful Tool in Drug Development Research” in the UGC CAS Seminar organized by Pharmaceutical Technology Department, JadavpurUniversity, 01-03-2019, Kolkata.

Dr. Chinmay Chowdhury
chinmay@iicb.res.in

Synthesis of novel heterocycles of biological interests

Participants

RA: Dr. Gargi Pal
SRF: Moumita Jash, Amrita Mondal
JRF: Subhendu Pramanik, Sukanya De, Debasmita Mondal
Project Assistant: Arindam Kundu

Collaborator(s)

Dr. Santanu Paul, Calcutta University
Dr.Biswajit Mukherjee, Jadavpur University

Background

Benzo-fused benzofurans and indoles belong to the group of privileged structures in the area of drug discovery. In particular, naphtho[1,2-b]furans and benzo[g]indoles are structural components of a large number of biologically active natural and synthetic compounds. In particular, benzo[g]indoles were reported to be potent anti-cancer agents and inhibitors of microsomal prostaglandin E2 synthase-1 (mPGES-1), and expressed significant affinity for dopamine D2 like receptors. Besides, benzo[g]indoles have found various applications in material sciences such as yellow-light-emitting actitivity, high performance in electrochromic devices, and fluorescence "turn-off" sensing properties of metal ion etc. Surprisingly, there are only few reports on the general synthesis of naphtho[1,2-b]furans; on the other hand, scrutiny of the literature reveals only few methods for the general synthesis of benzo[g]indoles involving mostly multi-component reactions. Consequently, a straightforward and reliable method for the general synthesis of naphtho[1,2-b]furans and benzo[g]indoles continues to be fascinating.

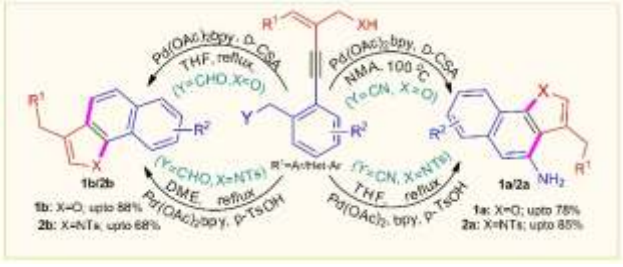
In addition, fused heterocycles are of great importance because of their broad applications in different areas. Among these compounds, 6H-dibenzo[c,h]chromenes are considered as privileged scaffolds and important substructures in modern drug discovery. Besides, benzo[c]phenanthridines and its 5,6-dihydro derivatives are of special interest because of their remarkable therapeutic efficacies. In view of the immense importance of the biological activities of these compounds, convenient syntheses of 6H-dibenzo[c,h]chromenes, benzo[c]phenanthridines and its 5,6-dihydro derivatives would assist the development of promising template(s) in drug discovery.

Aims and Objectives:

- To develop convenient methods for the synthesis of naphtho[1,2-b]furans and benzo[g]indoles of biological importance.
- To find out efficient reaction strategies for the synthesis of of 6H-dibenzo[c,h]chromenes, 5,6-dihydrobenzo[c]phenanthridines, benzo[c]phenanthridines and others relevant heterocycles.
- To achieve the straightforward synthesis of natural products (e.g, Arnottin I) and related natural products of biological interests.

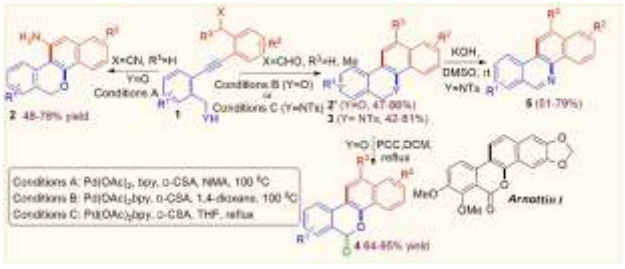
Work Achieved:

An efficient palladium (II) catalyzed cascade reaction of ene-yne substrates carrying cyano/aldehyde group was acheived. It involved successive hetero- and benz-annulations in one pot via trans-oxo/amino palladation onto alkyne followed by 1,2-addition to cyano/aldehyde, providing a convenient synthesis of both naphtho[1,2-b]furans and benzo[g]indoles (Scheme 1). The reaction constitutes a fast intramolecular assembly through several carbon-carbon and carbon-hetero atom bond formations



taking place in one pot. The reactions are operationally simple, compatible with a range of functional groups and atom economical in nature.

Besides, Facile and straightforward syntheses of dibenzo[c,h]chromen-6-ones 2/2' and 5,6-dihydrobenzo[c]phenanthridines 3 were accomplished via palladium (II) catalysed domino reactions of acetylenic substrates 1 through intramolecular trans-oxo/amino palladation onto the triple bond followed by nucleophilic addition of the generated carbon palladium bond to a tethered cyano/aldehyde



(Scheme 2). The scope of this reaction was further extended through one step conversion of some of these products into 6H-dibenzo[c,h]chromen-6-ones 4 and 5,6-benzo[c]phenanthridines 5 which are prevalent as core structures of many natural products and medicinally active compounds. A concise formal total synthesis of Arnottin I was easily achieved by utilization of this methodology.

Future Research Plans:

- Development of efficient metal catalysed methods for the synthesis of 1,2,3,4-tetrahydro-β-carbolines (THBCs) and their efficient conversion to carbolines.
- Development of a convenient palladium-catalysed method for the synthesis of 1,4-benzodiazepin-5-ones and their fused derivatives.
- Nanoparticulate targeted delivery of Betulinic acid derivative (BAD) to enhance therapeutic efficacy towards colorectal cancer.

Figures/Schemes (captions):

Scheme 1: Palladium-catalysed synthesis of naphtho[1,2-b]furans and benzo[g]indoles.

Scheme 2: Palladium-catalysed synthesis of 6H-dibenzo[c,h]chromenes 2/2' and 5,6-dihydro-benzo[c]phenanthridines 3, and their transformations to 6H-dibenzo[c,h]chromen-6-ones 4 and benzo[c]phenanthridines 5.

PUBLICATIONS:

Sarkar, S., Gopal, P. K, Chakraborty, B., Paul, M., Chowdhury, C. and Paul, S. (2019) 14- Deoxy-11,12-didehydroandrographolide: A novel compound isolated from Andrographis paniculata Nees. induces robust apoptosis in leukemic cells, Pharcognosy Mag., 15, 135-143.

Jash, M., De, S., Pramanik, S., Chowdhury, C. (2019) Palladium (II)-catalyzed cascade reactions of ene-ynes tethered to cyano/aldehyde: Access to naphtho[1,2-b]furans and benzo[g]indoles, Journal of Organic Chemistry, under minor revision.

AWARDS / HONOURS / MEMBERSHIPS

Elected as fellow of West Bengal academy of science and technology (WAST)

EXTRAMURAL FUNDING

A) Anti-leishmanial activity of a novel carbazole alkaloid mahanine: its mechanism of action and drug delivery through liposomal formulation. 2016-2019 (ICMR, New Delhi).

Dr. Sharmila Chattopadhyay

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POTENTIAL ROLE OF PLANTS TO SUSTAIN HUMAN LIFE

Participants

Asma Sultana, CSIR-SRF
Soumi Biswas, DBT-SRF
Priyanka Boro, CSIR-JRF
Kajal Mandal, SERB-JRF

Collaborator(s)

Prof. Adinpunya Mitra, Agricultural and Food Engineering IIT-KGP Kharagpur, WB
Dr. Riddhi Datta, Dr. A.P.J. Abdul Kalam Govt. College, Kolkata

Dr. Sucheta Tripathy

Background

Phytohormones like Salicylic acid (SA), jasmonic acid (JA), ethylene (ET) and abscisic acid (ABA) are generally present in low concentrations and are essential for the regulation of plant growth, development, reproduction and survival, besides being acting as signaling molecules for defence. Our previous proteo-genomic studies established the interplay of GSH with SA, ET and ABA to mitigate biotic and abiotic stress conditions in plants. However, the effect of phytohormones on GSH at transcriptional changes is yet to be explored.

Plants have been used in traditional medicine since ancient times and have been proved to be a source of valuable therapeutic substances. India has been known to be a great repository of diverse medicinal plants. Hence, re-exploring the natural resources for the betterment of human life is essentially reqquired.

Aims and Objectives

- Molecular mechanisn of GSH's interplay with established defese signaling phytohormones.
- Neutraceutical from Stevia rebaudiana leaves.

Work Achieved

Modulation of the phytohormonal concentration and their combination in plants under several kinds of biotic and abiotic stressed conditions, leads to a complex crosstalk that help the plants to undertake the required adaptive responses. In response to pathogenic invasion SA production is induced. SA has been known to play a pivotal role in the induction of local and systemic acquired resistance (SAR) in plants. SAR is characterized by activation of a set of PR (pathogenesis related)-genes which encode for proteins having antimicrobial properties. JA and ET are involved in deterring the effect of necrotrophic pathogens by acting synergistically. Plants response to abiotic stresses mainly occurs through ABA, though the potential involvement of SA, JA and ET were also reported. Here, to elucidate the involvement of GSH with various phytohormones at transcript level in Arabidopsis plant samples, exhibiting varied GSH content, viz. the transgenic AtECS1 line exhibiting enhanced GSH content and pad2-1, the GSH depleted mutant, along with the wild type Col-0, treated with SA, JA, ET and ABA content (Fig. 1), we performed transcripts analysis of various phytohormones treated plants with altered GSH content. Results showed that the external phytohormonal feeding might be beneficial to relay the downstream signals and to increase the expression of several stress responsive genes (Fig. 2). The presence of GSH found to be useful for plants to mitigate stresses as indicated through the differential responses of stress responsive genes in AtECS1 and pad2-1. Together, present study decipher the interactions of multi-tasker GSH with innate defense-responsive phytohormones viz. SA, JA, ET, ABA etc. to mitigate stress in planta.

On a different note, we are developing a NEUTRACEUTICAL from the leaves of the Stevia rebaudiana with its natural antioxidant potential.

Future Research Plans

Characterization of stress responsive microRNAs in Arabidopsis thaliana under altered GSH conditions and developing transgenic A. thaliana overexpressing selective miRNA for further confirmation.

Development of Stevia leaves as a steady source of natural non-calloric neutraceutical.

Fig. 1. Arabidopsis thaliana:Vegetative stage and Flowering stage.

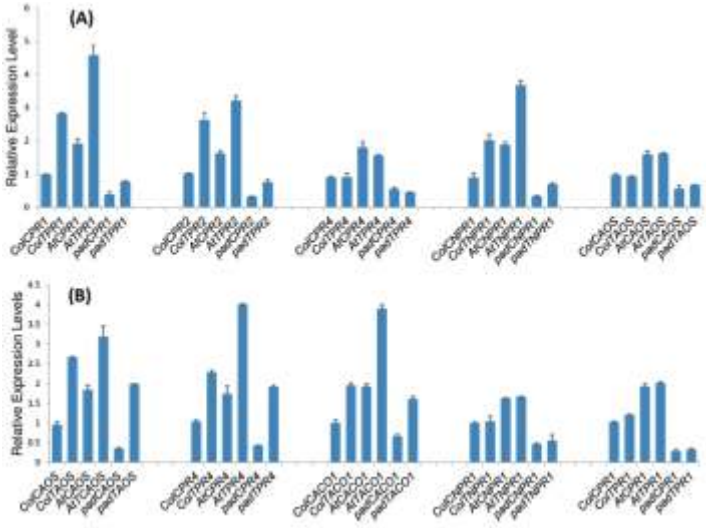


Fig. 2. Relative expression profile of stress-responsive transcripts after SA (a), JA(b), ET(c) and ABA(d) treatment in Col-0 (ColC, control and ColT, treated), AtECS1 (AtC, control and AtT, treated) and pad2-1 (padC, contol and padT, treated).

PUBLICATIONS

- Sultana, A., and Chattopadhyay, S. (2019) Deciphering the involvement of glutathione in phytohormone signaling pathways to mitigate stress in planta. The Nucleus DOI 10.1007/s13237-019-00288-x
- Kumar, D., and Chattopadhyay, S., (2018) Glutathione modulates transcription of heat shock proteins in response to stress via BZIP10 and MYB21 transcription factors in Arabidopsis thaliana. Jr of Experiment Bot 69, 37293743.
- Datta, R., and Chattopadhyay, S., (2018) "Glutathione as a crucial modulator of phytohormone signaling during pathogen defense in plants". Proc Ind Nat Sci Aca 84, 581-597.

Book Chapter

AWARDS / HONOURS / MEMBERSHIPS

Faculty

Dr. Sharmila Chattopadhyay

Award/Honour

Prof. F.C. Steward Memorial Award (2019), in the discipline of Plant Biotechnilogy, by the Plant Tissue Culture Association (India).

SERB Distinguished Investigator Award (2018), by the Science and Engineering Research Board, New Delhi, India.

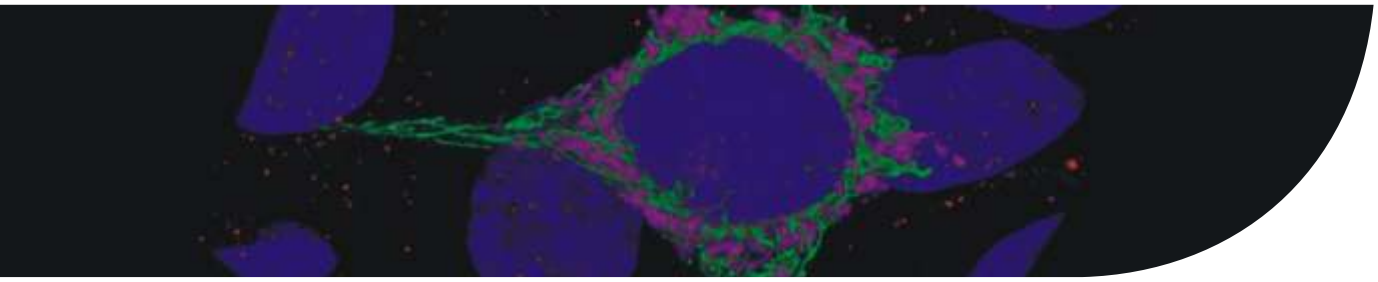
Dr. Sharmila Chattopadhyay
Membership
International Association of Plant Biotechnology
Plant Tissue Culture Association(India)
Chemical Biology Society, India

EXTRAMURAL FUNDING

"Identification of stress responsibe miRNAs in Arabidopsis under altered GSH conditions"
2017-2019 (SERB, New Delhi).

CONFERENCES:

4 abstracts presented in National/International conferences by the research scholars of my lab.



TALKS BY CSIR-IICB FACULTY

Sharmila Chattopadhyay
INTERNATIONAL

INVITED TALK

Podophyllum hexandrum- an endangered high-altitude plant of immense therapeutic importance

GORDON RESEARCH CONFERENCE- PLANT METABOLIC ENGINEERING, 15-21 June 2019, Italy.

INVITED TALK

Multistep interplay of glutathione with salicylic acid and ethylene to combat inevitable environmental stress

International Association for Plant Biotechnology Congress, August 2018, DUBLIN, IRELAND.

NATIONAL
INVITED TALK

Mechanistic insight on the interaction of GSH with phytohormes to endure environmental stress

4th International Plant Physiology Congress, December, 2018, CSIR-NBRI, Lucknow, India.

Interplay of GSH with salicylic acid, ethylene and absicisic acid in environmental stress tolerance

ICGEB Workshop on Plant responses to light and stress: emerging issues in climate change, October, 2018, New Delhi.

An insight on the cross talk of glutatione with other phytohormones to combat environmental stress

INDIA-EGYPT JOINT WORKSHOP ON AGRICULTURE BIOTECHNOLOGY, September 2018, NEHU, Shillong, India.

Dr. Biswadip Banerji

biswadip.banerji@gmail.com, biswadip@iicb.res.in

Design, Synthesis Small Organic Scaffolds as Selective Sensors

Participants

SRF : Saswati Adhikary, Leena Mazumder, R. Srinivas, SRF-NIPER

JRF : Saswati Ghosh, Debabrata Sarkar,

PA : Sourav Pakrashi, Suvankar Bera

Collaborator(s)

Dr.N.C. Maiti (Structural Biology & Bioinformatics)

Dr. S. C. Biswas (Cell Biology & Physiology)

Dr. Chitra Mandal (Cancer Biology & Inflamatory Disorder)

Dr. Shbhajit Biswas (Infectious Disease & Immunology)

Dr. Krishnananda Chattopadhyay

Background

Small organic scaffolds (ligands) which can selectively detect some important molecules or elements are of high demand. Particularly high selectively is the most essential part here and these have lots of Biological applications.

Work Achieved

(a) Efficient Detection of Early Events of α-Synuclein Aggregation Using a Cysteine Specific Hybrid Scaffold

In this work, we have designed and synthesized a new hybrid ligand (SCG) that can selectively detect cysteine in the free and protein-bound states within minutes at the subnanomolar level. Photoinduced electron transfer was the reason for the visible color change as well as a large increase in steady state fluorescence. In presence of other analytes and aminso acids, SCG showed high specificity for Cysteine amino acids only (Figure 1). This detection was further verified by using multiple model protein systems with differing cysteine environments and spatial arrangements. SCG has efficiently monitored the early events of the folding/aggregation kinetics of α-synuclein, a protein involved in the pathology of Parkinson's disease. The early events consisted of conformational changes between different forms of the protein and oligomer generation. SCG was found to be effective in detecting early isomers of α-syn in vitro and in live cell environments.

(b) Detection of Lysosome by a New, Fused, Fluorescent Heterocyclic Probe: Development of Pyrido-Imidazo-Indole Framework via Cu-Catalyzed Tandem N-Arylation

We have synthesized twenty different pyrido-imidazo-indole fused NEW heterocycles (6-5-5-6 ring) via copper catalyzed tandem N-arylation reaction in moderate-good yields (Figure 2). Due to decent fluorescent property of these molecules, lysosome-directing moieties were attached on two of these heterocycles. Delightfully, those molecules were able to visualze lysosome with bright blue fluorescence and co-localised with a known lysosome marker (Lysotracker Red) in human/murine cells. Therefore, it may be considered as a rapid (10 minutes) lysosome staining probe.

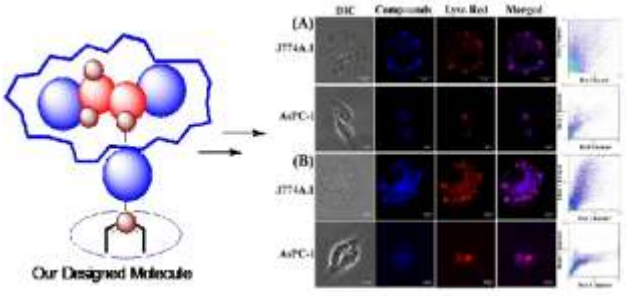
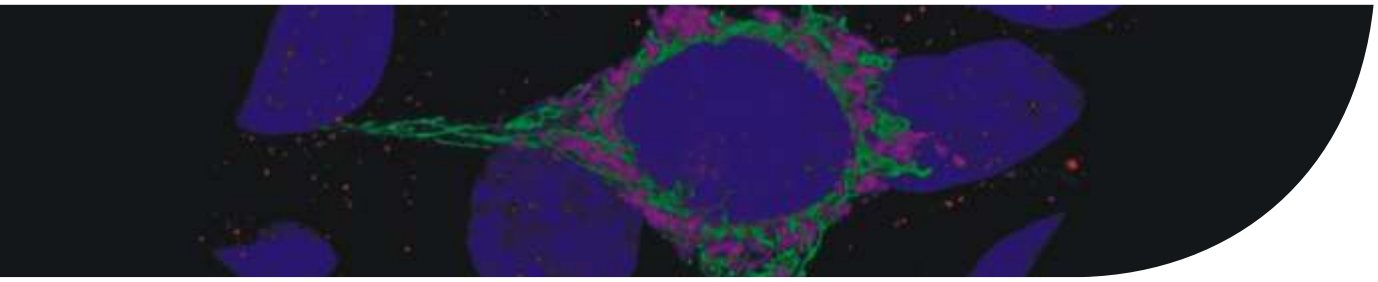


Fig. 1: Specificity towards Cysteine Amino acid by naked eye and under UV.

Fig. 2: Our representative design of Lysotracker and its affinity inside the cell .

FUTURE PLANS

Our laboratory is focused of making new organic molecules (NCEs) and look for their various applications in general. In future we will mostly engage in synthesizing fused heterocylces using



novel coupling methodologies, study their photophysical & other properties and finally go for their biological applications in various ways.

PUBLICATIONS

Efficient Detection of Early Events of α-Synuclein Aggregation Using a Cysteine Specific Hybrid Scaffold. Satadru Chatterjee, Sumanta Ghosh, Snehasis Mishra, Krishna Das Saha, Biswadip Banerji*, Krishnananda Chattopadhyay*; Biochemistry, 2019, 58, 1109-1119

A Green Synthetic Approach towards PolyarylatedOxazoles via IodineCatalyzed OnePot sp3 C−H Functionalization in Water: From Natural Product Synthesis ToPhotophysical Studies; Biswadip Banerji*, Saswati Adhikary, Leena Majumder, Saswati Ghosh; Asian Journal of Organic Chemistry; 2019, doi.org/10.1002/ajoc.201800742

Detection of Lysosome by a Fluorescent Heterocycle: Development of Fused PyridoImidazoIndole Framework via Cu-Catalyzed Tandem N-Arylation; Biswadip Banerji*, Satadru Chatterjee, Kadaiahgari Chandrasekhar, Saswati Ghosh, Kaustuv Mukherjee, Chitra Mandal; Journal of Organic Chemistry; 2018, 83, 13011-13018.

Synthesis of Triazole-Substituted Quinazoline Hybrids for Anticancer Activity and a Lead Compound as the EGFR Blocker and ROS Inducer Agent; Biswadip Banerji*, Kadaiahgari Chandrasekhar, Kancham Sreenath, Saheli Roy, Sayoni Nag, Krishna Das Saha; ACS Omega; 2018, 3, 16134-16142.

Cellular Detection of Hydrazine as Isoniazid Metabolite by a New TurnOn Fluorescent Probe: Synthesis, Live Cell Imaging and In Vitro Toxicity Studies; Biswadip Banerji*, Chandrasekhar K, Satadru Chatterjee, Sunil Kumar Killi, Chandraday Prodhan, Keya Chaudhuri. Chemistry Select; 2018, 3, 12816-12823.

EXTRAMURAL FUNDING

Biswadip Banerji

Grant Title: “Targeting HSP-90 as cancer therapy: Design and synthesis of mahanine-derived Second-Generation lead molecules”
Start year -2016, End year-2019. (DST-SERB, India)

Dr. Ranjan Jana

rjana@iicb.res.in

Molecular Diversity through Cascade C-H Activation

Participants

Dr. Suvankar Das, N-PDF

SRF : Samir Kumar Bhunia, Arghya Polley, Gurupada Bairy, Kartic Manna, Hasina Mamataj Begum, Pritha Das

Shantanu Nandi, JRF

Collaborator(s)

Dr. Mrinal K. Ghosh,
CSIR-IICB, Dr. S. Biswas, CSIR-IICB

Background

Development of previledged medicinal scaffolds is the key step in drug discovery program. We have initiated a cutting-edge C-H activation technology for the synthesis of heterocycles and other medicinally relevant molecules. Furthemore, this technology is particularly important for the late-stage diversification of functional molecules. C-H activation in organic synthesis (CHAOS) not only accelerate the synthesis but also allow us to achieve molecules which was unimaginable before. Furthermore, multiple C-H activation in a cascade manner will enable us to achieve molecular diversity as well as complexity from simple, readily available, inexpensive starting materials. This approach will generate a library of multifunctional molecules for Alzheimer's Disease, breast cancer etc. Furthermore, cost effective processes for the off-patent drug and agrochemicals will be developed.

Aims and Objectives

- Development of synthetic methodology for the synthesis of basic pharmacophores through cascade C-H activation.
- Late-stage diversification via site-selective C-H activations will be performed for the synthesis of unnatural amino acids.
- Chemical methodology and library development (CMLD) will be performed.
- Initial phenotypic screen of this library of compounds against MCF-7 primary breast cancer cell line and the corresponding MCF-10A normal cell line in 3D cell culture for hit optimization
- Affinity-based protein profiling for target identification, validation and hit to lead optimization through structure modifications
- Multi-functional molecular probe will be developed against Alzheimer's Disease

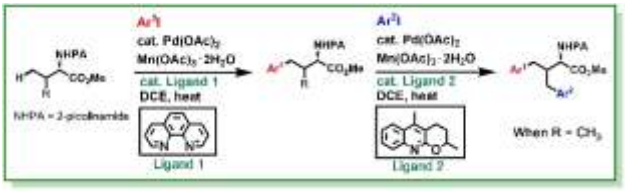
Work Achieved

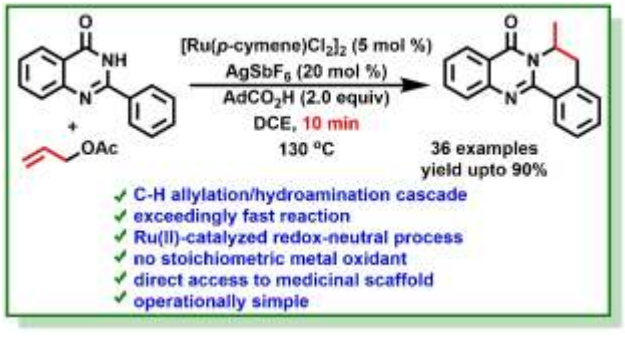
We have initiated and optimized the synthesis of basic scaffolds through C-H activation. We have accomplished a palladium-catalyzed synthesis of 2-arylindoles, and indolines from readily available and inexpensive aryl ureas and vinyl arenes merging C-H activation and alkene difunctionalization at room temperature. This strategy has been extended to the other pharmacophores such as 2-methyl indole and indolines, 2-quinazolinones etc. The 2-arylindole moiety has been extended to the dibenzofused carbazole system through multiple C-H activations. We have developed inexpensive copper-catalyzed C-H hydroxylation reaction to achieve a multifunctional molecular scaffold which is exhibiting neuroprotection in Alzheimer's Disease model. We have also identified a lead molecule against breast cancer cell lines.

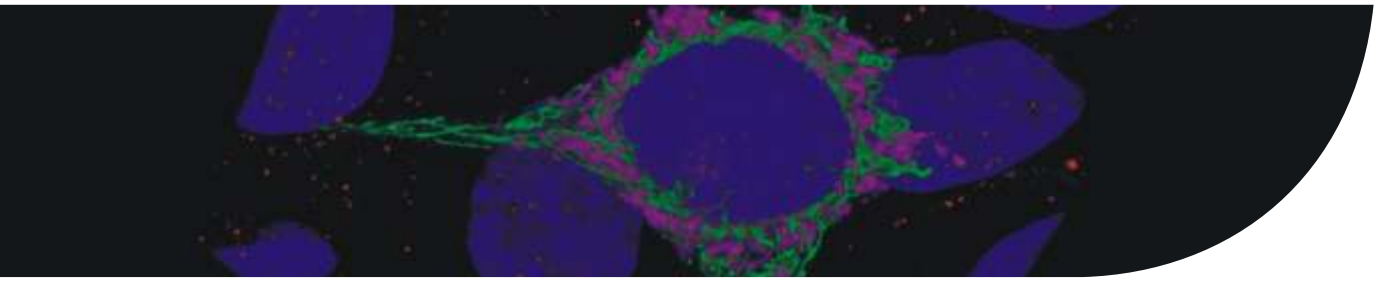
Future Research Plans

We like to apply this cutting-edge technology for the late-stage modification of amino acids to generate non-protinogenic amino acids for chemical biology and receptor specific drug delivery applications.

Figures







PUBLICATIONS

Bhunia, S. K.; Das, P.; Nanda, S.; Jana, R. (2019) Carboxylation of Aryl Triflates with CO2 Merging Palladium and Visible-Light-Photoredox Catalysts, Org. Lett. 21, 4632-4637.

Hasina, M. B.; Choudhury, R.; Behera, A.; Jana, R. (2019) Copper-Catalyzed Electrophilic Ortho C(sp2)-H Amination of Aryl Amines: Dramatic Reactivity of Bicyclic System, Org. Lett. 21, 4651-4656.

Bairy, G.; Nandi, A.; Manna, K.; Jana, R. (2019) Ruthenium(II)-Catalyzed Migratory C-H Allylation/Hydroamination Cascade for the Synthesis of Rutaecarpine Analogues, Synthesis, 51, 2523-2531. Invited special issue "Ruthenium in organic synthesis."

Polley, A.; Varalaxmi, K.; Jana, R. (2018) Palladium-Catalyzed Ortho C-H Arylation of Aniline Carbamates with Diazonium Salts under Mild Conditions: Expedient Synthesis of Carbazole Alkaloids. ACS Omega, 3, 14503-14516.

Polley, A.; Bairy, G.; Das, P.; Jana, R. Triple Mode of Alkylation with Ethyl Bromodifluoroacetate: N, or O-Difluoromethylation, N-Ethylation and S-(ethoxycarbonyl)difluoromethylation. (2018) Adv. Synth. Catal., 360, 4161-4167.

Manna, M. K.; Bairy, G.; Jana, R. (2018) Sterically Controlled Ru(II)-Catalyzed Divergent Synthesis of 2-Methylindoles and Indolines through a C-H Allylation/Cyclization Cascade. J. Org. Chem. 2018, 83, 8390-8400.

Das, S.; Bairy, G.; Jana, R. Ligand-promoted γ-C(sp3)-H arylation and unsymmetrical diarylation to access unnatural amino acid derivatives. (2018) Org. Lett., 20, 2667-2671.

Bhunia, S. K.; Das, P.; Jana, R. (2018) Atom-economical selenation of electron-rich arenes and phosphonates with molecular oxygen at room temperature. Org. Biomol. Chem., 16, 9243-9250.

Bairy, G.; Das, S.; Begam, H. M.; Jana, R. (2018) Exceedingly Fast, Direct Access to Dihydroisoquinolino[1,2-b]quinazolinones through a Ruthenium(II)-Catalyzed Redox-Neutral C-H Allylation/Hydroamination Cascade. Org. Lett., 20, 7107-7112.

EXTRAMURAL FUNDING

Ranjan Jana

A Combined Late Stage C-H Functionalization and Affinity-Based Protein Profiling Strategy for the Identification of Highly Selective Kinase Inhibitors in Breast Cancer Cell Lines
2014-2018, DST, SERB, Govt of India, Project # SR/S2/RJN-97/2012

Molecular Diversity through Cascade C-H Activations
2015-2018, DST, SERB, Govt. of India, Project # EMR/2014/00469

CONFERENCES / WORKSHOPS

- Invited lecture at Aliah University on a national seminar on Molecular Diversity through Cascade C-H Activation.
- Popular Science Lecture in front of Jadavpur Vidyapith Students for Gigyasa program on Green Chemistry and Engineering from Societal Perspective
- Coordinating skill development program on LCMS training

Dr. Sanjay Dutta

sanjaydutta@iicb.res.in

Development of novel small molecules targeting Hepatitis C Virus RNA.

Participants

Subhadeep Palit (Chemistry, SRF), Dipendu Patra (Chemistry, SRF), Jeet Chakravarty (Biology, SRF), Chandra Sova Mandi (Biology, SRF), Ritesh Pal (Chemistry, SRF), Bhim Majhi (Chemistry, JRF),Sayanika Banerjee (CSIR-RA), Dr. Abhi Das (DST Women Scientist), Sayef Ahammed (DBT project fellow), Debajit Maiti (M. Tech thesis student, CU), Sravani Purnima Polnati (M.Pharm thesis student, NIPER).

Collaborator(s)

Prof. Saumitra Das, IISc Bangalore. Dr. Saikat Chakrabarti, CSIR-IICB (Structural Biology)

Background:

Hepatitis C Virus (HCV) infection is one of the major liver diseases and is a global health concern. HCV infection affects almost 180 million people worldwide which represent almost 3% of the world population. Absence of vaccine and inability to detect virus load in acute condition is major reason for liver transplantation. The available therapy for HCV is immunostimulatory pegylated interferon alfa (IFN-α) and in combination with guanosine analogue ribavirin which suffered from low efficacy and serious side effects. Recent studies have shown that the Internal Ribosome Entry Site (IRES) RNA of 5'-untranslated region (UTR) is a target for antiviral development due to the highly conserved region of HCV with unique structural features. Our laboratory is focused towards the development of novel small molecules targeting the RNA of HCV Virus.

Work Achieved:

Here we show by experimental and molecular dynamics simulations that destacking of RNA bases of domain IIa by designed quinoxaline small molecule leads to overall structural change and leads to inhibition of translation. These studies provide potential leads for the development of RNA targeting quinoxaline based ligands which alter structural features of functional HCV RNA molecule and has the ability to inhibit translation and replication of HCV. (manuscript currently under review)

Development of Novel Theranostics Targeting Nucleic acid

Abstract: Small molecules that intercalate DNA have tremendous therapeutic potential. Typically, DNA intercalators do not alter the overall DNA double-helical structure, except locally at the intercalation sites. In a previous report, we showed that a quinoxaline-based intercalator with a mandatory benzyl substitution (1d) induced an unusually large circular dichroism signal upon DNA binding, suggesting the formation of intercalated DNA superstructures (Angew. Chem. Int. Ed. 2016, 55, 7733-7736). However, no detailed structural studies have been reported. Using atomic force microscopy, we have probed the nature of the superstructure and report the formation of a plectonemically oversupercoiled structure of pBR322 plasmid DNA by 1d, where close association of distant DNA double-helical stretches is the predominant motif. Without the benzyl moiety (1a), no such DNA superstructure was observed. Similar superstructures were also observed with doxorubicin (dox), a therapeutically important DNA intercalator, suggesting that the superstructure is common to some intercalators. The superstructure formation, for both intercalators, was observed to be GC-specific. Interestingly, at higher concentrations (1d and dox), the DNA superstructure led to DNA condensation, a phenomenon typically associated with polyamines but not intercalators. The superstructure may have important biological relevance in connection to a recent study in which dox was shown to evict histone at micromolar concentrations.

Collaborator

Prof Gautam Basu, Department of Biophysics, Bose Institute P-1/12 CIT Scheme VIIM.

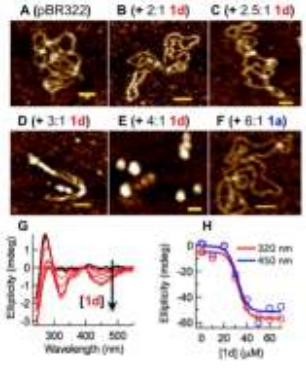
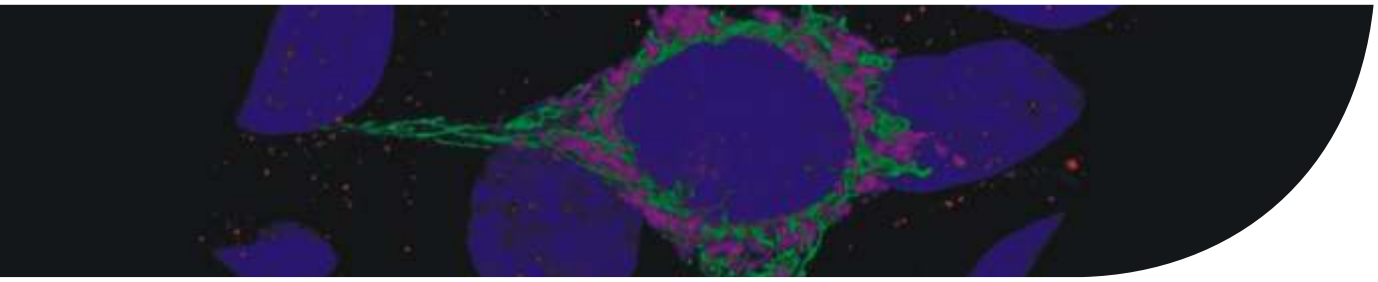


Fig. 1: AFM images and CD spectra of pBR322 in presence of 1d and 1a. AFM images (scale 50 nm) of pBR322 plasmid DNA, in absence (A) and in presence of 1d (B-E) and 1a (F) at varying ligand:DNA bp ratios (indicated in each panel). (G) CD spectra of pBR322 (10 M) with increasing concentrations of 1d. (H) Integrated ellipticity of the 320 nm and 450 nm band (panel G) as a function of [1d].



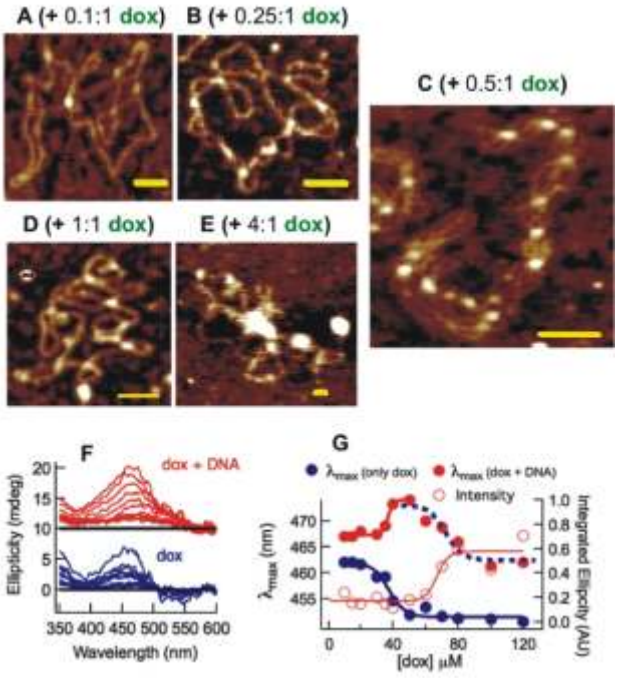


Fig 2. AFM images and CD spectra of pBR322 in presence of dox. (A-E) AFM images (scale 50 nm) of pBR322 plasmid DNA in presence of dox at varying ligand:DNA bp ratios (indicated in each panel). (F) Concentration dependent CD spectra of dox in presence and absence of pBR322 (40 M). (G) λmax shift and intensity difference (dox-DNA - dox) of the 450 nm band as a function of [dox].

Reduction of lipogenesis and lipid accumulation by small molecules in Hepatocytes.

Collaborator: Dr. Partha Chakrabarti, Principal Scientist, CSIR-Indian Institute of Chemical Biology, Kolkata

Abstract: Nonalcoholic fatty liver disease (NAFLD), which is characterized by excess accumulation of triglyceride in hepatocytes, is the major cause of chronic liver disease worldwide and no approved drug is available. The mechanistic target of rapamycin (mTOR) complexes has been implicated in promoting lipogenesis and fat accumulation in the liver, and thus, serve as attractive drug targets. The generation of non- or low cytotoxic mTOR inhibitors is required because existing cytotoxic mTOR inhibitors are not useful for NAFLD therapy. New compounds based on the privileged adenosine triphosphate (ATP) site binder quinoline scaffold conjugated to glucose and galactosamine derivatives, which have significantly low cytotoxicity, but strong mTORC1 inhibitory activity at low micromolar concentrations, have been synthesized.These compounds also effectively inhibit the rate of lipogenesis and lipid accumulation in cultured hepatocytes. This is the first report of glycomimeticquinoline derivatives that reduce lipid load in hepatocytes.

Future Research Plans

Development of an mTOR inhibitor in the nanomolar range which can reduce lipogenesis and lipid accumulation in hepatocytes with minimal cytotoxicities. Development of an effective small molecule targeting HCV IRES RNA which can work in nanomolar range and decrease viral translation. Design of small molecules which can sequence specifically target DNA and have anticancer properties which can be developed as therapeutics.

EXTRAMURAL FUNDING

1) "Discovery of RNA binding ligands-Targeting Hepatitis C Virus RNA", P.I: Dr. Sanjay Dutta, (July 2015 July 2018). (DBT, India)

2) "Synthesis of novel imipramine derivatives targeting Leishmania Donovani" (West Bengal DBT) in collaboration with Dr. Syamal Roy (NIPER Kolkata).

3) "Development of Novel Theranostics Targeting Nucleic acids" P.I: Dr. Sanjay Dutta (DST-SERB)

Inivited Lectures

1) Delivered an invited lecture-Title "Targeting Nucleic acids by Quinoxaline Small Molecules" at Viswa Bharati University, Shantiniketan during 4-6th October, 2018.

Publications

1. Tridib Mahata, Jeet Chakraborty, Ajay Kanungo, Dipendu Patra, Gautam Basu* and Sanjay Dutta* "Intercalator induced DNA superstructure formation: doxorubicin and a synthetic quinoxaline derivative" Biochemistry 2018, 57, 5557−5563

2. Subhadeep Palit,# Sanghamitra Mukherjee,# Sougata Niyogi,# Anindyajit Banerjee, Dipendu Patra, Amit Chakraborty, Saikat Chakrabarti, Partha Chakrabarti* and Sanjay Dutta* "Quinoline-glycomimetic conjugates reducing lipogenesis and lipid accumulation in hepatocytes" ChemBioChem, 2018, DOI: 10.1002/cbic.201800271. (#These authors contributed equally.)

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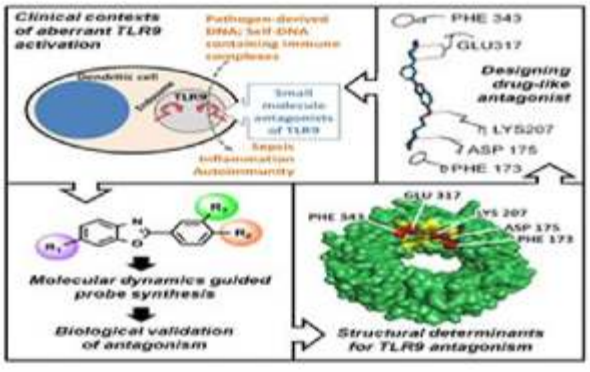
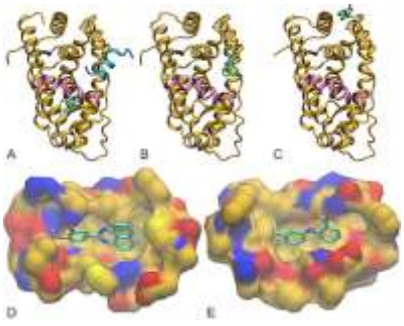
MEDICINAL CHEMISTRY LABORATORY

BACKGROUND

1) **Probing Endosomal Toll-like Receptors (TLRs):** TLRs are members of the larger family of evolutionary conserved pattern recognition receptors which are critical first line of defense for self-nonself discrimination by the host immune response. Aberrant endosomal TLR activation is implicated in auto-reactive inflammation in different autoimmune diseases. The goal is to rationally design selective inhibitors for the nucleic acid-recognizing TLRs (TLR7/TLR8/TLR9) for devising novel therapeutic strategies in relevant clinical contexts.



2) **Epigenetic modifying enzymes as novel therapeutic targets**:The main focus is to perform structure-based design and synthesis of small-molecule regulators of epigenetics modifying enzymes such as histone methyltransferases (HMT) as tools to unravel the complex biology of epigenetics and contribute towards epigenetic-based drugs for the treatment of a number of diseases such as cancer, autoimmunity, diabetes, or neurological disorders.



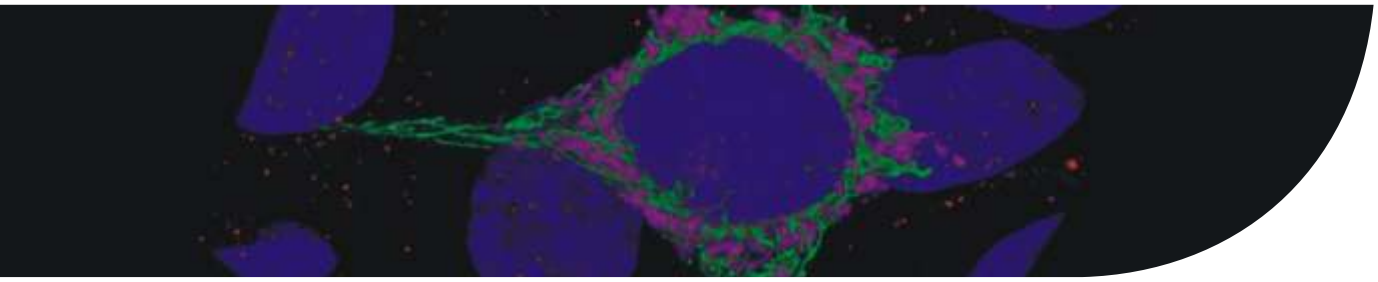
3) **Designing of Small molecules Topoisomerase 1 poison**: Topoisomerases are enzymes that participate in the overwinding or underwinding of DNA. The winding problem of DNA arises due to the intertwined nature of its double-helical structure. DNA becomes overwound ahead of a replication fork. If left unabated, this torsion would eventually stop the ability of DNA or RNA polymerases involved in these processes to continue down the DNA structure.Due to the presence of topoisomerase this topological problem is solved and cell proliferation runs continuously. So, our structure based designing and synthesis of small molecules is so rational to inhibit the topoisomerase for unwinding the overwound.

4) **Development of new drugs for Leishmaniasis**: Leishmaniasis is a disease caused by parasites of the Leishmania type which is spread by the bite of certain types of sandflies. Most prominently it can be observed on under developed area specially in Africa, Brazil, Nepal, Bangladesh. In India Bihar, Jharkhand, UP, West-Bengal are prevalent area for this disease. Skin ulcers, fever, low red blood cells, enlarged liver are the prominent indications occurred due to this. So our lab is focused for curing this traumatic disease by designing the small molecules in a rationalized way.

I've set up a bilateral collaboration between IICB, Monash University and University of Melbourne, Australia to develop new drugs for Leishmaniasis. A grant was approved under Australia-India Strategic Research Fund (AISRF) (Indo-Australian Biotechnology Fund stream to the Department of Biotechnology, Government of India.

AIMS AND OBJECTIVES

Our lab aims to answer fundamental questions that lie at the interface of chemistry and biology by integrating the concept of organic chemistry, biochemistry and molecular modeling to perform Structure-Based Design and Synthesis of novel chemical entity to unravel the molecular mechanism and develop affordable drugs for potential treatment for human diseases.



WORK ACHIEVED

We have successful developed potent anddual/selective TLR9 and TLR7 antagonists and filled two patents to protect the IP. We have also published a paper in European Journal of Medicinal Chemistry to establish our understanding in the autoimmune diseases. We have reported design, synthesis, and validation of "non-camptothecin" Topoisomerase 1 (Top1) poisons as anticancer agents.

The novel class of Top1 poisons is based on the quinoline core developed through an understanding of the structural features of ligands essential for binding in the active site.We provided compelling evidences that advocate for our novel Top1 poisons as a potential anticancer agent.We published the work in highly reputed ACS-Journal of Medicinal Chemistry. We have filed one patent related to the work.

I've set up a bilateral collaboration between IICB, Monash University and University of Melbourne, Australia to develop new drugs for Leishmaniasis. A grant was approved under Australia-India Strategic Research Fund (AISRF) (Indo-Australian Biotechnology Fund stream to the Department of Biotechnology, Government of India.

FUTURE DIRECTION

Preclinical development of rationally designed inhibitors for the nucleic acid-recognizing Toll-like receptors (TLRs) for which two patent has been filed. In vivo validation of our novel Topoisomerase 1 (Top1) poisons as anticancer agents.

Establish industrial partner to take forward our IP protected knowledge to commercialization.

To seek ways to extend a long term scientific collaboration on mutual strength between India and Australia(Monash University and University of Melbourne) in neglected disease drug discovery.

PUBLICATIONS

1. Discovery and Mechanistic Study of Tailor-Made Quinoline Derivatives as Topoisomerase 1 Poisons with Potent Anticancer Activity. BiswajitKundu, Subhendu Kumar Das, Srijita Paul Chowdhuri, Sourav Pal, DipayanSarkar, ArijitGhosh, Ayan Mukherjee, Debomita Bhattacharya, BenuBrata Das*, and **Arindam Talukdar*.** ***Journal of Medicinal Chemistry*****, 2019**, 62, 3428−3446.
2. Semisynthetic Quercetin Derivatives with Potent Antitumor Activity in Colon Carcinoma. Ayan Mukherjee, Snehasis Mishra, Naveen Kumar Kotla, Krishnendu Manna, Swarnali Roy, BiswajitKundu, Debomita Bhattacharya, Krishna Das Saha, and **Arindam Talukdar*.** ***ACS Omega*****, 2019,** 4, 7285−7298.
3. Understanding the Riboflavin Biosynthesis Pathway for the Development of Antimicrobial Agents. BiswajitKundu, DipayanSarkar, Namrata Ray, **Arindam Talukdar***. ***Medicinal Research Reviews*****, 2019, 1-34. Https://doi.org/10.1002/med.21576**
4. Ligand-based Pharmacophore Modeling, Virtual Screening and Molecular Docking Studies for Discovery of Potential Topoisomerase I Inhibitors. Sourav Pal, Vinay Kumar, BiswajitKundu, Debomita Bhattacharya, NagothyPreethy, MamindlaPrashanth Reddy and **Arindam Talukdar.** ***Computational and Structural Biotechnology Journal*****, 2019**, 17, 291310.
5. Activity-guided Development of Potent and Selective Toll-like Receptor 9 Antagonists. Barnali Paul, OindrilaRahaman, Swarnali Roy, Sourav Pal, SohalSatish, Ayan Mukherjee, Amrit R. Ghosh, DeblinaRaychaudhuri, Roopkatha Bhattacharya, Sunny Goon, Dipyaman Ganguly* and **Arindam Talukdar*.** ***European Journal of Medicinal Chemistry*****, 2018**, 159:187-205.

EXTRAMURAL FUNDING

1. Development of new drugs for leishmania- an australia-indianpartnershipAustralia-India Strategic Research Fund (AISRF): Start Year: June 2017. End Year: June 2020. Agency: DBT, Gov. of India.
2. Probing endosomal toll-like receptor 9 biology using novel small molecule antagonists. Start Year: September 2016. End Year: March 2019.Agency: EMR/2015/000117. Agency: DST-SERB, Gov. of India.
3. Exploring Therapeutic Efficacy of Novel Toll like Receptor 9 Antagonist in Type II Diabetes. Start Year: March 2017 End Year: March 2020. Agency: EMR/2016/003021, DST-SERB, Gov. of India.

CONFERENCES/WORKSHOP

Number of Abstract: 2

Dr. R. Natarajan

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Development of synthetic supramolecular receptors for targeted binding and design and discovery of therapeutic and diagnostic molecules

Participants

SRF : ShovanKumar Sen, KrishanuSamanta

JRF : Raju Biswas, SumanMaji, SandipanGorai

Collaborator(s)

Dr. P. S. Subramanian, CSIR-CSMCRI, Bhavanagar, and Dr. P. Murugesapandiyan, Bharathiyar University, Coimbatore. Dr. Subhas C. Biswas andDrKrishnanda Chattopadhyay (CSIR-IICB)

Background

Molecular materials capable of encapsulating large organic molecules, either drugs or toxins, are in demand to deliver the former in a targeted manner or to remove the later from the environment, respectively.

Structure determination using x-ray crystallography is a challenging task. Our group has vast and deep expertise in this.

Aims and Objectives

Development of novel synthetic scaffolds for the recognition of biologically relevant molecules through specific intermolecular interactions

Work Achieved

We have developed a novel cage-like organic receptor through a high-yielding synthetic method of azide-alkyne click chemistry. The click cage can efficiently bind carcinogenic polycyclic aromatic hydrocarbons with great affinity. The system has an excellent potential to be developed as a carcinogen trap. Subsequent work demonstrated that similar click cages can function as excellent sensor for nitro aromatic explosives.

We have developed a novel class of chiral cage molecules, based on metal-ligand coordination with a readily accessible chiral ligand. We have chosen bile acids such as cholic acid, deoxycholic acid and lithocholic acid as building blocks and functionalized them with pyridyl ligands. Subsequent self-assembly with Pd(II) ions resulted in the formation metal-organic cages. Among the three kind of ligands chosen, cholic acid resulted in inter-ligand hydrogen bond driven singular self-sorted product, whereas the other ligands resulted in a mixture of products. Essentially we have demonstrated that inter-ligand hydrogen bonding can facilitate self-sorting among different chiral isomers to select symmetrical and thermodynamically stable molecules.

In collaboration with others, we have contributed in structural determination of challenging molecular structures through single-crystal X-ray diffraction. The new found molecules exhibit excellent catalytic activities and fluorescent properties. The understanding of the molecular structure is essential in delineating their functions.

We take part in the CSIR Mission Mode Project of INPORTICS on the development of life-saving drugs in cost-effective way and contribute significantly.

Future Research Plans

Development of chiral supramolecular cages and conformationally lockedacylic receptors for recognition, transport and delivery.

PUBLICATIONS

Chinnaraja, E.; Arunachalam, R.; Suresh, E.; Sen, S. K.; Natarajan, R.; Subramanian, P. S. Binuclear Double-Stranded Helicates and Their Catalytic Applications in Desymmetrization of Mesodiols. Inorg. Chem. 2019, 58, 44654479.

Desymmetrization of meso diols using enantiopure zinc (II) dimers: Synthesis and chiroptical properties. Chinnaraja, E.; Arunachalam, R.; Samanta, J.; Natarajan, R.; Subramanian, P. S. Appl. Organomet. Chem. 2019, 33, e4327.

Santhiya, K.; Sen, S. K.; Natarajan, R.; Shankar, R.; Murugesapandian, B. DAD Structured Bis-Acylhydrazone Exhibiting Aggregation-Induced Emission, Mechanochromic Luminescence, and Al(III) Detection. J. Org. Chem.2018, 83, 1077010775.

Enantiomeric Resolution of Asymmetric-Carbon-Free Binuclear Double-Stranded Cobalt(III) Helicates and Their Application as Catalysts in Asymmetric Reactions. Arunachalam, R.; Chinnaraja, E.; Valkonen, A.; Rissanen, K.; Sen, S. K.; Natarajan, R.; Subramanian, P. S. Inorg. Chem.2018, 57, 1141411421.

Dr. Indu Bhusan Deb

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CHAOS* For Late Stage Functionalization and Synthesis Agrochemical / API (*C-H Activation in Organic Synthesis)

Participants

Aniket Mishra, CSIR-SRF
Writhabrata Sarkar CSIR-SRF
Sumit Das CSIR-SRF
Arup Bhowmik UGC-JRF
Aiswarya B. S. (project student)
Sudha Lahari Meduri (project student)
Ramkrishna Mandal (Project Student)

Collaborator(s)

Name of collaborator within CSIR-IICB: Dr. Subhas C. Biswas, Dr. Subhajit Biswas, Dr. Paulomi Ghosh.

Background

The ubiquitousness of azaindole, Benzosultam, Quinazolines as well as Quinazolinones skeletons in various natural products, pharmaceuticals and synthetic materials make them immensely valuable heterocycles. Hence, development of new and efficient methods for their synthesis and derivatization assumes high significance. Our group is actively involved in designing new and cost effective methodology to synthesize functionalized potential bioactive pharmacophore, API and agro chemicals employing transition metal (Pd, Fe, Co, Ni, Ru, Rh & Ir) catalyzed CH/CX bond activation concept.

Aims and Objectives

- Development of transition metal catalyzed cost effective, affordable and industry friendly C-H activation methodology for the late stage functionalization of pharmacophores such as benzosultams, azaindole and quinoline.
- Development of cost effective scalable process for the synthesis of API and agro chemicals.

Work Achieved:

1st row transition metal catalyzed C-H bond activation:

Cobalt-Catalyzed Directed sp2 C□H Acetoxylation of Arenes Employing Mn(OAc)3.2H2O as Acetoxy Source: The acetoxy group acts as a functional group modifier while imparting polar nature to a molecule. It is ubiquitous in a plethora of pro-drugs, natural products, antimicrobial agents, and herbicidal materials. An efficient catalytic method relying on the cheaper and earth-abundant first row transition metal catalysts in place of the expensive second row ones continues to be highly solicited in organic synthesis. Here, A cobalt-catalyzed sp2 C-H acetoxylation of amides having 8-aminoquinoline as a directing group has been achieved using manganese(III) acetate both as an oxidant and an acetoxy source. The method is scalable and does not require any additive. The mechanism of the reaction has been established by conducting a series of experiments. This work has been published in Advanced Synthesis and Catalysis 2018. (IF 5.123)

Fig. 1: Directed C□H Acetoxylation using cobalt catalysis

Rhodium-Catalyzed Direct and Selective ortho CH Chalcogenation of N-(Hetero)aryl-7-azaindoles: Employing C-H bond activation technology we have developed an efficient, highly regioselective and scalable rhodium-catalyzed ortho aryl CH mono chalcogenation of N-aryl-7-azaindoles and indolines through N-directed ortho CH activation in presence of silver triflate and silver carbonate in 1,4-dioxane. The scope of the reaction has been successfully tested with a wide array of medicinally important heterocyclic scaffolds with diverse functional group tolerance depicted in Fig.2. The products could have potential application in biological and/or materials science. This work has been published in Advanced Synthesis and Catalysis 2018. (IF 5.123).

Fig. 2: Chalcogen functionalized N-Aryl-7-azaindole via CH activation methodolgy

Employing C□H bond activation we also have developed C□H activation followed by annulations reaction for the synthesis of spirocyclic benzosultams scaffolds containing nitro and other groups (Manuscript in under minor revision in Org. Lett). An earth abundant copper mediated direct thiolation of quinazolineones has been achieved under operationally simple conditions via selective cleavage of a relatively inert C□H bond guided by a pyridine or pyrimidine moiety. The devised protocol does not require any toxic or reactive reagents and provides a direct access to a broad spectrum of pharmaceutically relevant heterocycles (Manuscript submitted).

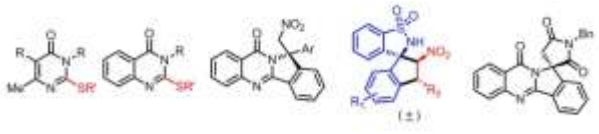

Fig. 3: Synthesized novel pharmacophore

Future Research Plans

Development of methodology for the synthesis of chiral molecules. Boactivity study of newly synthesized molecules will be pursued. Development of affordable process for API and agro chemicals.

PUBLICATIONS

1. Writhabrata Sarkar, Arup Bhowmik,† Aniket Mishra,† Tripta Kumari Vats and Indubhusan Deb* "Cobalt-Catalyzed Directed sp2 C□H Acetoxylation of Arenes Employing Mn(OAc)3. 2H2O as Acetoxy Source" Advanced Synthesis & Catalysis 2018, 360, 3228-3232 (†contributed equally). (IF: 4.785).
2. Tripta Kumari Vats,† Aniket Mishra† and Indubhusan Deb* "Rhodium-Catalyzed Direct and Selective ortho C-H Chalcogenation of N−)Hetero(aryl−7−azaindoles" Advanced Synthesis & Catalysis 2018, 360, 2291-2296 (†contributed equally).

Book Chapters / Invited Reviews:

AWARDS / HONOURS / MEMBERSHIPS

Faculty
Scientist's Name Surname Indu Bhusan Deb
Awards / Honours
Bristol Myers Squibb Research Fellowship-USA

Memberships
Life member of Chemical Biology society
ACS Cemical Society

EXTRAMURAL FUNDING

Name Surname: Deb, Indubhusan
Bristol Mayer Squibb research Grant. $ 20,000 (BMS-USA)

CONFERENCES / WORKSHOPS

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

TALKS BY CSIR-IICB FACULTY

Goa: The symposium "International Conference on Organometallics and Catalysis 2018.
" Invited Talk, Goa, Dec. 13-16, 2018:

Dr. Indrajit Das

indrajit@iicb.res.in

Visible-Light-Activated Divergent Reactivity of Dienones

Participants

SRF : Sandip Naskar
JRF : Rajib Maity, Jayanta Saha, Abhijit Bankura

Udayan Chaudhury, Sauvik Pandit, Project Assistant

Collaborator(s)

Prof. Sabyashachi Mishra
Department of Chemistry
IIT Kharagpur, India
Prof. Ayan Datta
School of Chemical Sciences
IACS, Kolkata, India

Background

Direct irradiation of reactant(s) with visible light in the absence of a catalyst has emerged as a powerful tool to generate structural complexity under green and sustainable reaction conditions and shows good functional group tolerance and regioselectivity. It has enabled the invention of a wide variety of novel new bond-forming protocols via a series of new activation modes. On the other hand, the capacity of cascade reactions to rapidly generate chemical complexity from simple starting materials with precise stereochemical control is unparalleled. By combining these two concepts and with thoughtful design of substrates, several elegant approaches have been developed recently for accessing diverse heterocycles. Recently, visible light-mediated E → Z isomerization of olefins in the presence or absence of a photocatalyst has been reported, but visible light-mediated photocatalyst-free regioselective E → Z isomerization in a conjugated diene remained to be achieved. Although the photochemical isomerization of fumarates or electronically different two-component alkenes of the dienes under UV-light has been well-established for decades, but its potential applications are somewhat restricted due to the high energy of UV-light, which can lead to the formation of undesired side products.

Aims and Objectives

2,4-Dienones undergo visible-light-promoted, photocatalyst-free dimerization in neat conditions to provide cyclohexene derivatives stereoselectively through cascade rearrangement pathways, whereas regioselective E → Z isomerization of the more dienophilic double bond takes place exclusively in nitromethane. On the basis of intermediate isolation and computational DFT studies, the dimerization reaction is proposed to proceed via s-trans to s-cis isomerization/regioselective E → Z isomerization/Diels–Alder cycloaddition.

Work Achieved

In continuation of our attempts to achieve regioselective E → Z isomerization of electronically different olefins in 2,4-dienones, we subjected dienones to visible light irradiation in neat conditions at ambient temperature to find that the substrate serendipitously underwent atom and step-economical dimerization through cascade rearrangement pathways to furnish a cyclohexene derivative stereoselectively. This unexpected observation triggered by visible light irradiation prompted us to undertake a thorough investigation. It is noteworthy that visible light-initiated cascade rearrangement of small molecules, particularly in the absence of any solvent and catalyst has never been achieved. Regioselective E → Z isomerization is the key to the success of this process. Further, the ability to control the alkene geometry provides a handle for diastereocontrol in the cycloaddition. The reaction is highly regio- and diastereoselective and does not require any organic solvent or photocatalyst. We now report that 2,4-dienones display a visible light-mediated divergent reactivity in neat conditions and in solution. They undergo atom and step-economical dimerization in neat conditions to provide stereoselective cyclohexene derivatives via cascade rearrangement pathways, whereas regioselective E → Z isomerization of olefins takes place exclusively in nitromethane solvent. To provide further support, the dimerization of neat (Z)-s-trans dienones under thermal conditions has also been performed (Figure 1).

Future Research Plans

Following our success in photocatalyst-free visible-light-mediated organic transformations, we are interested in further developing methodologies that harness the power of visible-light to mediate reactions that are useful in the synthesis of biologically active molecules and pharmaceuticals.

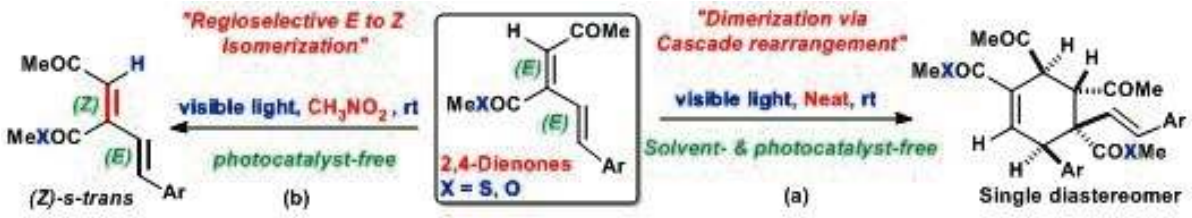

Fig. 1. Visible Light-Mediated and Photocatalyst-Free (a) Dimerization of Neat Dienones and (b) Regioselective E → Z Isomerization in Nitromethane Solvent

Publications

Naskar, S., Roy Chowdhury, S., Mondal, S., Maiti, D. K., Mishra, S., and Das, I. (2019) Visible-Light-Activated Divergent Reactivity of Dienones: Dimerization in Neat Conditions and Regioselective E to Z Isomerization in the Solvent. Org Lett 21, 1578-1582 Maity, R., Das, B., and Das, I. (2019) Transition-Metal-Free Reduction of α-Keto Thioesters with Hydrosilanes at Room Temperature: Divergent Synthesis through Reagent-Controlled Chemoselectivities. Adv Synth Catal 361, 2347 — 2353

Extramural Funding

α-Ketothioesters: An Indispensable Building Blocks for Accessing Diverse Heterocycles
via Sulfanyl Anions or Thiyl Radical Migration. File No: EMR/2016/001720, 2017-2019. (SERB, India)

Dr. V S Pragadheesh

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Exploring Anti-Asthmatic Compounds and Enantioselective Neuroprotective Property of Terpenoids from Plants

Participants

Ph.D Scholar: PriyaDarshani

Collaborator(s)
Name of collaborator within CSIR-IICB

Dr. U. Mabalirajan
Senior Scientist, Cell Biology and Physiology Division

Dr. Prem Tripathi
Scientist, Cell Biology and Physiology Division

Background

Natural product compounds are the chemical compounds produced by living organisms. Plant natural product compounds are the secondary metabolites synthesized in plants which involve in the protection of plants against herbivores, defend from microbes, attracting pollinators, etc. Structural and molecular differences in natural product compounds make them responsible for diverse physiological functions in other organisms as well. Further, enantiomers exhibit differential activity with enantiomerically pure enzymes and receptors. For instance, (R)-(−)-carvone possess the odor of spearmint whereas (S)-(+)-carvone smells like caraway. This dictates analytical chemists and natural product chemists to develop various methodologies for the resolution of enantiomers, interpret structures and also examine them biologically. Our lab is working towards the identification of new/novel natural product lead compounds having biological activity mainly in anti-asthma and neuroprotection. We employ bioactivity guided isolation procedure for the screening of fractions and pure isolates. We also exploit enantioselective chromatography to assess the bioactive compounds for their enantiomeric purity and will also extend to identify the function of enantiomeric natural product compounds in phytomedicine, therapeutics, healthcare, and aromatherapy.

Aims and Objectives

- To identify the anti-asthmatic compounds from Indian medicinal plants
- To explore the enantioselective biological activity of bioactive enantiomers from plants for neuroprotection
- Development of separation methodology for the enhancement of bioactive compounds in medicinal and aromatic plant extracts

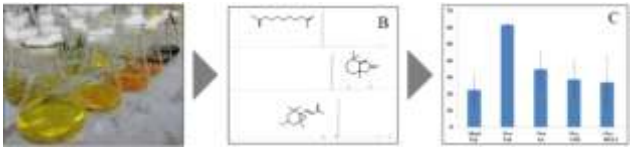
Work Achieved

A total of 20 compounds have been isolated and its enantiomeric composition was determined to evaluate the enantioselective biological activity. Two extracts developed in the lab showed significant anti-asthmatic activity and around 12 compounds were identified from these extracts. Around 13 pure compounds were isolated and further structural determination using GC-MS, NMR, and ESI-MS is in progress and five pure compounds were isolated for neuroprotective effects against kainic acid-induced seizure.

Future Research Plans

To study the mechanistic behavior of enantiomeric bioactive natural product compounds in neuroprotection and anti-asthma.

Fig.1: Bioactivity-guided isolation and screening of natural product compounds. (A) - Fractions of the plant extracts separated using



preparative chromatography, (B) Determining the purity of the compounds/fractions using analytical chromatography, (C) Evaluation of the biological activity of the extracts/fractions/compounds.

PUBLICATIONS

Popular Science Article

Pragadheesh, V.S., Olsson, S. (2018) The Scent Orchestra of Flowers. i wonder magazine (focusing middle school teachers), Sep. 2018

CONFERENCES / WORKSHOPS

1

TALKS BY CSIR-IICB FACULTY

Pragadheesh V S
Medicinal and Ecological Aspects of Aromatic Plants; Invited talk; “Current Research in Medicinal Plants Global Trends and Indian Scenario”; Durgapur, India March 2019

Pragadheesh V S
Floral Scent Pollinator attractant or herbivore deterrent?; Popular talk; JIGYASA-2018; CSIR Indian Institute of Chemical Biology; Kolkata, India, April 2018

Dr.Deepak Kumar
deepak@iicb.res.in

Chemical investigation of medicinal plants for potential bioactive leads

Participants

Priyanka Yatham, NIPER JRF
Yogita Dahat, JRF
Chayan Banerjee, JRF

Collaborator(s)

Name of collaborator outside CSIR-IICB
Dr Rinku Baishya, CSIR-NEIST Jorhat, Assam.

Name of collaborator within CSIR-IICB
Dr Amit K. Srivastava
Dr Joy Chakraborty

Background

Traditional medicines and natural products are of immense importance to human and are being used since inception of the human race. It is believed and also scientifically proven that the natural products have an immense role in healthcare. There are several drugs derived from the natural products and it is still considered as one of the potential source of bioactive leads. Aim of our group is to isolate and identify potential phytopharmaceutical leads from traditionally used medicinal plants against cancer stem cells (CSCs - A549 lung cancer) and neurological disorders (mono amine oxidase inhibitors - MAO). Also to develop strategies for bulk isolation of identified potent bioactive leads.

Aims and Objectives

Isolation and characterization of pentacyclic triterpenes and polyphenolic compounds against CSCs.

Isolation and characterization of flavonoids and sesqueterpene coumarins as potential MAO inhibitors.

Work Achieved

We have been successful in isolation and characterization of several compounds belonging to lupane triterpene, xanthone, flavonoids, coumarin, and sesqueterpene coumarin class. These molecules are being explored for their potential against CSCs and MAO.

Future Research Plans

- Isolation and characterization of more compounds from the selected plants.
- Evaluatation of these compounds against CSCs and MAO.
- Development of analytical methods as a standardization tool.
- Process development for bulk isolation of selected compounds.

INVITED TALKS BY CSIR-IICB FACULTY

Natural Product-Based Drug Discovery past, present and future : Indian perspective; Invited talk; Current Research in Medicinal plants - Global Trends and Indian Scenario; Durgapur Viswagandha Science Society and Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Bidhan Nagar, Durgapur, March 2019.

Structural Biology & Bioinformatics Division

Members :

Dr. Krishnananda Chattopadhyay (Head), Dr. Subrata Adak, Dr. Soumen Datta, Dr. Jayati Sengupta, Dr. Sucheta Tripathy, Dr. Saikat Chakraborty, Dr. Nakul C Maiti, Dr. Siddhartha Roy, Dr. G. Senthil Kumar, Dr. Poulomi Ghosh, Dr. Sandip Paul

With a view to understand cellular function and dysfunction in human health and disease, researchers at the Structural Biology & Bioinformatics Division studies attempt to probe into the structural and mechanistic features of various proteins, macromolecular complexes and cellular pathways, using integrative, trans-disciplinary approaches. Basic as well as translational research are being carried out on protein structure, functions, protein-protein interactions, protein-nucleic acid interactions, applying state-of-the-art technologies like X-ray crystallography, Nuclear Magnetic Resonance (NMR), Cryo-EM, single molecule fluorescence measurements and Fluorescence Correlation Spectroscopy, Raman spectroscopy, mass spectrometry, Nano-separation technology etc. Bioinformatic studies involving big data analysis, genome/proteome data mining, molecular dynamic simulations, molecular docking and pathway analysis are also being pursued. Special emphasis is given on macromolecules and small molecules of therapeutic interest against diseases like leishmaniasis, tuberculosis, malaria, multiple amyloid-related neurodegenerative diseases, systemic diseases like cancer and diabetes and microbial infections. Specific objectives of these studies include (i) identification of non-native conformers and oligomers in neurodegenerative diseases, (ii) delineation of the key processes/factors involved in protein misfolding, aggregation and amyloid formation (iii) elucidation of cellular defenses against aberrant protein folding, (iv) development of novel strategies for amelioration of protein misfolding disorders, (v) Studying sequence aspects of intrinsically disordered proteins and their plausible implications in diseases (vi) studying ribosomal RNA-assisted folding of denatured proteins in yeast and leishmania (vii) investigating oxidative stress responses in Leishmania (viii) harvesting cyanobacterial & fungal genomes in search of commercially important enzymes, (ix) metagenomic and pan-genomic analysis of human microbiome components in an attempt to explore their plausible roles in human health and diseases (x) studying parasitic (e.g.,malaria) and systemic disease (e.g., cancer) interactomes for identification of novel drug targets, (xi) development of novel software tools for NGS data mining, pathway analysis and other big data analysis and (xii) design and development of biological knowledgebase of clinical/societal relevance.

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Protein Folding, Dynamics and Aggregation….One Molecule at a Time

Participants

RA : Sayantani Chall
SRF : Achinta Sannigrahi, Ritobrita Chakraborty, Arnab Bandyopadhyay, Indrani Nandi, Anindita Mahapatra, Dwipanjan Sanyal

JRF : Sumangal Roychowdhury, Bidisha Das

Dr. Ramdhan Majhi, Technical Officer

Collaborator(s)

Professor Ujjwal MaulikDepartment of Computer Science, Jadavpur University, Kolkata

Professor Gautam De, Central Glass and Ceramic Research Institute, Kolkata

Dr. Subhash Chandra Biswas, CSIR-IICB, Kolkata

Background

Protein aggregation has been implicated in several neurodegenerative diseases. In addition, protein aggregation may create serious complications in Biologics formulations. One of the major bottlenecks of protein aggregation research arises from the heterogeneity of protein folding/aggregation landscape. In addition, the aggregation kinetics often goes through a lag phase and the present detection techniques seem to be inadequate to understand the events, which occurs in the lag phase of aggregation. We have been studying protein conformation, dynamics and aggregation using different biophysical methods including Fluorescence correlation spectroscopy (FCS). FCS is an important technique to measure the diffusional and conformational fluctuations of fluorescently labeled molecules at single molecular resolution. These fluctuations could be analyzed by using suitable correlation functions yielding useful information regarding the shape and/or conformational dynamics of a protein.

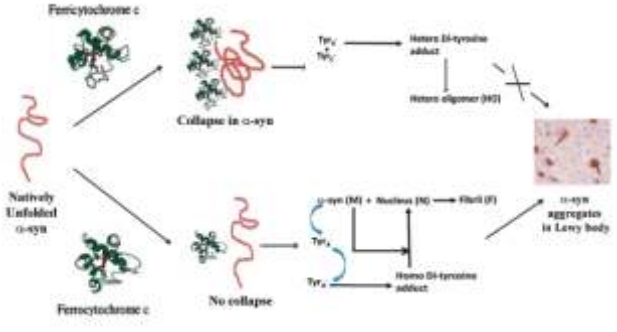
Aims and Objectives

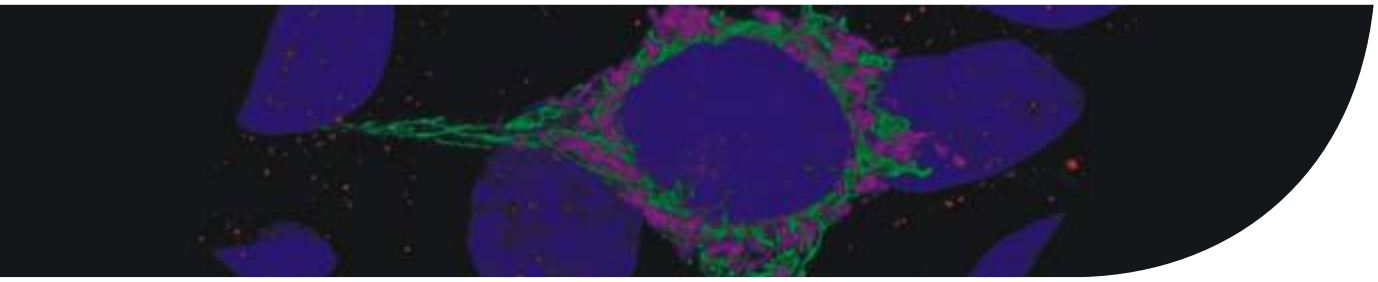
1. To detect, characterize and investigate in details the early folding pathways of proteins involved in different neurodegenerative diseases
2. To study early stages of aggregation of intrinsically disordered proteins (IDPs) in vitro and inside live cells using fluorescence correlation spectroscopy (FCS) and other biophysical methods.
3. To develop computational and experimental methods to investigate the protein conformation-aggregation landscape in a statistically significant manner.

Work Achieved

Investigation of the Modulation of Folding and Aggregation Landscape of Alpha-Synuclein by Cytochrome c, a Protein closely linked to Alpha-Synuclein induced Pathology in Parkinson's disease:

The α-Syn/cytochrome c (cyt c) system has important implications in the pathology of PD. α-Syn has been found to be immune-colocalized with the protein cyt c in Lewy bodies of patients with PD and other synucleinopathies, suggesting direct interactions between these two proteins inside the cells. Our investigations, using a compilation of biophysical techniques and FCS, revealed that the oxidized cytochrome was able to bind α-Syn and result in a significant compaction, and this early collapse inhibited aggregation of the latter. We also showed that the mechanism of inhibition of aggregation involved the formation of hetero-dityrosine bonds between α-Syn and cyt c III, which is in competition with the self-dimerization of α-Syn via homo-dityrosine adduct formation between two molecules of α-Syn. The interaction of α-Syn with reduced cyt c, on the other hand, did not result in a collapse and accelerate the process of its aggregation, which could again be correlated to the involvement of tyrosine free radicals. This study provides a clear modulation of the folding and aggregation landscape of the IDP by tuning of the oxidation states of a single interacting partner protein.





Investigation of the mechanism behind manifestation of latent Tuberculosis:

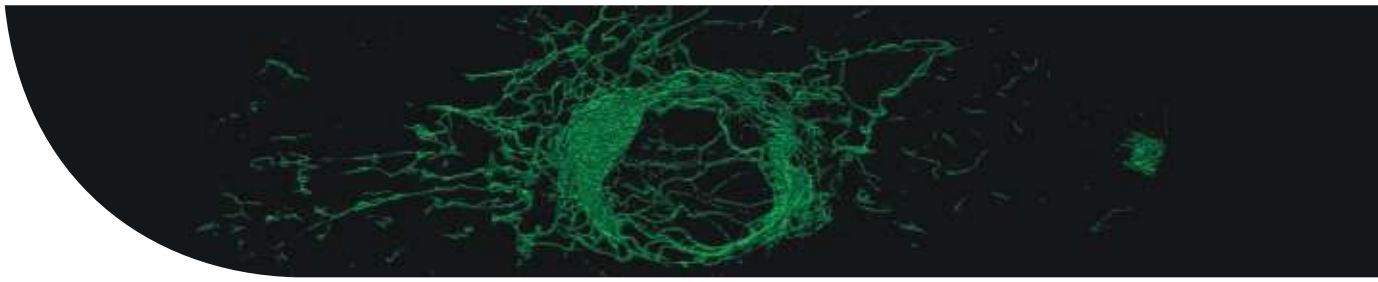
Pore forming toxins (PFTs) are the biological weapons utilized by pathogenic bacteria to evade the immune system of hosts leading to the survival of the pathogens and productive infections. Till date, no toxin is available in TB as evidenced from the genome analysis. Moreover, there is lack of understanding about the complex escape mechanism of MTB from the latent infectious stage in granuloma. Although a number of Mycobacterium secretory proteins are reported and MPT63 is the most abundant inside TB granuloma, the actual function of these proteins in the disease manifestation is missing. Recently, we investigated the role of MPT63 protein in terms of membrane binding activity, pore formation and macrophage cell death. It is interesting to note that MPT63 contains a number of chameleon sequences which can be utilized by MTB to change the native beta sheet conformation to alpha helical form under different environmental conditions. This 'conformational switch' is often used by pathogens for the infection purpose as reported earlier. Our study showed that MPT63 in its native beta sheet form neither binds with model membrane nor create pores in synthetic membrane or/and macrophage membrane as well. In contrast, when MPT63 is introduced to some modulating factors (e.g pH 5 mimicking the M2 Macrophages inside granuloma, specific W26F mutation and ct-GNP surface binding), there occurred conformational switch in MPT63 which consequently results the significant membrane affinity and the pore forming ability in macrophages as well as model membranes. We showed using fluorescence correlation spectroscopy (FCS) and atomic force microscopy (AFM), MPT63 oligomerises at pH 5, under ct-GNP bound condition and W26F mutation. Trypan blue assay and FACS analysis suggested that helical (and oligomer-forming) form induces the macrophage cell death whereas native form did not show any adverse effect on cell health. Collectively, our study emphasizes for the first time a toxin-like behavior of MPT63 induced by an environment-dependent conformational switch, resulting in membrane pore formation by toxic oligomers and M cell death.

Future Research Plans

- To study the conformational stability of SOD1, a key participant of anti-oxidant defense mechanism.
- To determine the structure of transient oligomeric species, which form early in the aggregation process of several proteins, using a host of structural biology techniques.

PUBLICATIONS

1. Sannigrahi, A; Nandi, I; Chall, S; Jawed, JJ; Halder, A; Majumdar, S; Chattopadhyay, K; Conformational switch driven membrane pore formation by Mycobacterium secretory protein MPT63 induces macrophage cell death. 2019, ACS chemical biology.
2. Chaudhury, SS; Sannigrahi, A; Nandi, M; Mishra, VK; De, P; Chattopadhyay, K; Mishra, S; Sil, J; Mukhopadhyay, CD; A Novel PEGylated Block Copolymer in New Age Therapeutics for Alzheimer's Disease. 2019, Molecular Neurobiology, 1-5
3. Sen, S; Dey, A; Chowdhury, S; Maulik, U; Chattopadhyay, K; Understanding the evolutionary trend of intrinsically structural disorders in cancer relevant proteins as probed by Shannon entropy scoring and structure network analysis. 2019, BMC bioinformatics, Feb;19(13):549
4. Chakraborty, R; Chattopadhyay, K; Cryo-Electron Microscopy Uncovers Key Residues within the Core of Alpha-Synuclein Fibrils. 2019, ACS chemical neuroscience, Feb 20
5. Ghosh, S; Chakraborty, B; Dey, S; Biswas, C; Chowdhury, R; Chattopadhyay, K; Sengupta, J; Electron microscopy reveals unique spore-like nano forms of Bacillus cereus. 2019, bioRxiv, Jan 1:228833.
6. Hazra, S; Bodhak, C; Chowdhury, S; Sanyal, D; Mandal, S; Chattopadhyay, K; Pramanik, A; A novel tryptamine-appended rhodamine-based chemosensor for selective detection of Hg 2+ present in aqueous medium and its biological applications. 2019, Analytical and bioanalytical chemistry, Jan 9:1-5
7. Ghosh, S; Mahapatra, A; Chattopadhyay, K; Modulation of Alpha-Synuclein Aggregation by Cytochrome c Binding and Hetero-di-Tyrosine Adduct Formation. 2019, ACS chemical neuroscience, Jan 8
8. Sannigrahi, A; Karmakar, S; Jawed, J; Majumdar, S; Chattopadhyay, K; An Interplay between KMP-11 Induced Phase Alteration of Macrophage Membrane and Immune Suppression Defines the Molecular Mechanism of Leishmaniasis. 2019, Biophysical Journal, Feb 15;116(3):373a
9. Chatterjee, S; Ghosh, S; Mishra, S; Das Saha, K; Banerji, B; Chattopadhyay, K; Efficient Detection of Early Events of Alpha Synuclein Aggregation using a Cysteine Specific Hybrid Scaffold. 2019, Biochemistry, Jan 29
10. Sannigrahi, A; Mullick, D; Sanyal, D; Sen, S; Maulik, U; Chattopadhyay, K; Effect of Ergosterol on the Binding of KMP-11 with Phospholipid Membranes: Implications in



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11. Sannigrahi, A; Chall, S; Jawed, JJ; Kundu, A; Majumdar, S; Chattopadhyay, K; Nanoparticle Induced Conformational Switch Between α-Helix and β-Sheet Attenuates Immunogenic Response of MPT63. 2018, Langmuir, Jul 9;34(30):8807-17
12. Ghosh, S; Kundu, A; Chattopadhyay, K; Small molecules attenuate the interplay between conformational fluctuations, early oligomerization and amyloidosis of alpha synuclein. 2018, Scientific reports, Apr 3;8(1):5481
13. Chakraborty, R; Sahoo, S; Halder, N; Rath, H; Chattopadhyay, K; Conformational-Switch Based Strategy Triggered by [18] π Heteroannulenes toward Reduction of Alpha Synuclein Oligomer Toxicity. 2018, ACS chemical neuroscience, Oct 19
14. Sarkar-Banerjee, S; Chowdhury, S; Sanyal, D; Mitra, T; Roy, SS; Chattopadhyay, K; The Role of Intestinal Fatty Acid Binding Proteins in Protecting Cells from Fatty Acid Induced Impairment of Mitochondrial Dynamics and Apoptosis. 2018, Cellular Physiology and Biochemistry, 51(4):1658-78
15. Mukherjee, S; Hazra, S; Chowdhury, S; Sarkar, S; Chattopadhyay, K; Pramanik, A; A novel pyrrole fused coumarin based highly sensitive and selective fluorescence chemosensor for detection of Cu2+ ions and applications towards live cell imaging. 2018, Journal of Photochemistry and Photobiology A: Chemistry, Sep 1;364:635-44

Proceedings:

Chowdhury, S., Banerjee, A., and **Chattopadhyay, K.** (2017) Metal ion co-factors sculpt the heterogeneity of conformational landscape in Superoxide Dismutase. in EUROPEAN BIOPHYSICS JOURNAL WITH BIOPHYSICS LETTERS, SPRINGER 233 SPRING ST, NEW YORK, NY 10013 USA

Book Chapters / Invited Reviews

None

PATENTS FILED / SEALED

AWARDS / HONOURS / MEMBERSHIPS

None

EXTRAMURAL FUNDING

- Investigation of the folding and aggregation landscape of superoxide dismutase in vitro and in live cells: its implications in Amyotrophic lateral sclerosis (ALS), 45.94 lakhs from the Department of Science and Technology, The Government of India
- Spatio-temporal mapping of membrane deformation induced by amyloid beta 40 during neurodegeneration, 49.2 lakhs from the Department of Biotechnology as a Co-PI

CONFERENCES / WORKSHOPS

- Poster Presentation at the National Conference on Fluorescence and Raman Spectroscopy, FCS2018 at Jawaharlal Nehru University, JNU, New Delhi. Nov 2018.
- Poster Presentation at the 63rd Annual Meeting of the Biophysical Society, BPS19, Baltimore, Maryland, USA. March 2019.
- Best Poster Award at the 43rd Indian Biophysical Society meeting, IBS19 at IISER Kolkata, India. March 2019.
- International Union of Pure and Applied Biophysics (IUPAB) Bursary awarded for attending and presenting at the 12th EBSA 10th ICBP-IUPAP Congress, Madrid, Spain, July 2019.

International Awardship:

I. IUPAB Early Career Young Scientist Travel Award 2017 for attending and presenting at 19th IUPAB & 11th EBSA congress, Edinburgh, UK.
II. Finalist Speaker awardee at 3Rs in Bio-physics MAWA (medical advances in Bio-physics) at 19th IUPAB and 11th EBSA congress, July 2017
III. Best Poster Award, at International Conference on Intrinsically Disordered Proteins, IDP 2017, by Centre for Protein Science, Design and Engineering, Indian Institute of Science Education and Research, Mohali. Dec 2017.
IV. Carl Storm International Diversity Award Fellowship from Gordon Research Conference Jan 2018 (Protein Folding and Dynamics Session)

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

Science Day at CSIR-IICB on Feb 28, 2019

Dr. Subrata Adak

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New *Leishmania* specific protein: PAS domain containing phosphoglycerate kinase

Participants

SRF : Aditi Mukherjee, Ayan Adhikari, Saroj Biswas, Priya Das

JRF : Sumit Das

Rina Saha, ICMR-Women Scientist

Background

Leishmania infection results into severe, life-threatening disease and is a growing public health concern in many countries including India. Resistance to existing drugs has created demand for new drug targets. Our laboratory has had a long-standing interest in *Leishmania* biology for identifying new genes, specific for the parasite that can be potential target sites for drug development. Four new parasite specific proteins are heme containing adenylate cyclase, ascorbate peroxidase, pseudoperoxidase and NAD(P)H cytochrome b5 oxidoreductase. Recently we discover a new parasite specific protein, PAS domain containing phosphoglycerate kinase. It has been already established that Per-Arnt-Sim (PAS) domains carry out diverse functions within sensory proteins by signal transfer or supporting protein/protein interaction as well as by directly sensing environmental stimuli.

Aims and Objectives

The aim of our goals is the biochemical and functional characterization of these proteins in vitro as well as in vivo. For reaching our research goals, we have selected three different strategies (1) Cloning, expressing and purification of these proteins for biochemical studies in vitro. (2) The generation of over expressing, knockout and knockdown *Leishmania* cell line for the identification of the exact physiological role of these proteins in parasite. (3) Infection studies with macrophage cell lines as well as Balb/c mice for unraveling the role of parasite specific heme proteins regarding pathogenesis.

Work Achieved

We report the first PAS domain containing phosphoglycerate kinase in unicellular eukaryotic organisms, *Leishmania*. The PAS domain of this new protein exhibits structural properties similar to PAS domain of HIF 1α and this protein is present in the lysosome, where acidic pH directly stimulates phosphoglycerate kinase activity. Gene knock-out and overexpression studies suggest that pH dependent ATP generation from ADP plays a fundamental role in cell survival through the regulation of autophagosome. In addition, the knock-out cells display a marked decrease in virulence on infection with host macrophages as well as inoculation into BALB/c mice. Our work begins to clarify how acidic pH-dependent ATP generation by phosphoglycerate kinase is likely to function in cellular adaptability in *Leishmania*.

Future Research Plans

We are also interested to reveal the exact signaling pathways involved in PAS domain containing phosphoglycerate kinase deficient *Leishmania* infected macrophage. Deleting of PAS domain containing phosphoglycerate kinase causes dramatic drop in parasites infectivity. Thus, targeting PAS domain containing phosphoglycerate kinase gene could be a promising field for developing new drugs for treatment of leishmaniasis.

PUBLICATIONS

Mukherjee, A., Adhikari, A., Das, P., Biswas, S., Mukherjee, S., Adak, S. (2018) Loss of virulence in NAD(P)H cytochrome b5 oxidoreductase deficient Leishmania major. Biochem. Biophys. Res. Commun. 503, 371-377.

EXTRAMURAL FUNDING

Subrata Adak

Expression, intracellular localization and functional characterization of PAS domain containing phosphoglycerate kinase in *Leishmania*. 2017-2000 (DST, India)

CONFERENCES / WORKSHOPS

1) Adhikari, A., Biswas, S., Mukherjee, A., Das, S., Adak, S. Structure-function aspect of PAS Domain Containing Phosphoglycerate Kinase from *Leishmania* major. Presented at 87th annual meeting of Society of Biological Chemists (India) meeting at Manipal, Karnataka in Nov. 25-27, 2018.
2) Mukherjee, A., Adhikari, A., Das, P., Biswas, S., Mukherjee, S., Adak, S. Loss of pathogenicity in *Leishmania* major is associated with the deficiency of linoleate synthesizing enzyme, NAD(P)H cytochrome b5 oxidoreductase. Presented at 87th annual meeting of Society of Biological Chemists (India) meeting at Manipal, Karnataka in Nov. 25-27, 2018.

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

TALKS BY CSIR-IICB FACULTY

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ATPase of Type Three Secretion System

Participants

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JRF : Rajeev Kumar (SRF), Arkaprabha Choudhury (SRF), Bidisha Chakraborty, Angira Saha

Chittran Roy, SRF, ICMR

Background

Many gram-negative bacteria possess several different kinds of machinery to secrete their effector proteins into eukaryotic host cells and modulate host cell function, thereby enhancing bacterial survivability and pathogenicity. Till date nine such translocation machineries have been identified, namely type I-IX secretion systems. These systems are distinguished mainly by the translocation mechanism of their secreted protein. A wide range of pathogens, like Yersinia, Pseudomonas, Shigella, Xanthomonas, Bordetella, Erwinia, and Escherichia coli are equipped with Type Three Secretion System (T3SS) apparatus, a needle-like structure (injectisome) what protrudes out from the bacterial surface, pierces through the eukaryotic membrane, and finally reaches into the eukaryotic cell cytosol. This macromolecular apparatus is composed of over 20 different proteins that altogether form three basic components, namely, a large cytoplasmic complex, a transmembrane basal body, and an extracellular needle. Apart from the apparatus, a functional T3SS requires other proteins like effectors, chaperones, translocators, and regulatory proteins. Component proteins of T3SS injectisome are highly conserved among different bacterial clans, but their effectors vary significantly. These effectors are kept in semi-unfolded and inactive form inside the bacterial cytosol by a set of proteins known as chaperones. Attachment of the injectisome with the host cell membrane triggers the delivery of unfolded effectors through a hollow conduit formed inside the injectisome directly into the cytosol of host cells. T3SS ATPase assembles into a multimeric complex, either hexameric or dodecameric form, at the base of the injectisome and interacts with several other soluble and membrane-associated proteins. Hydrolysis of ATP by T3SS ATPase along with the proton motive force across the inner membrane provides the energy required for the uncoupling of the effectorchaperone complex and successive transport of the effectors into the host cell.

Aims and Objectives

Pseudomonas aeruginosa is an opportunistic pathogen which causes chronic lung infection in cystic fibrosis patients and several other types of infection like dermatitis, endocarditis, and infections of urinary tract, eye, ear, bone joints in immuno-compromised individuals. In P. aeruginosa the T3SS apparatus genes are distributed into four operons (pscNOPQRSTU, popNpcr1234DR, pcrGVHpopBD, and exsDpscBCDEFGHIJK). pscN from the pscNOPQRSTU operon is a putative ATPase that energies the P. aeruginosa secretion system and was envisaged to be regulated by an uncharacterized pscL. The aims of this project were to establish PscN as an ATPase and its functional oligomeric form, characterize PscL and its functional relevance in connection with PscN.

Work Achieved

We have characterized PscN as a T3SS ATPase and PscL as its regulator through several biochemical, biophysical, and microscopic techniques. Based on the available crystal structures of the homologous proteins, we could build in silico models of PscN and its regulator PscL. We established PscN interacts with dimeric PscL to form a trimeric complex. We could find an oligomeric form, which might be a biological functional form of the PscNPscL heterotrimeric complex. This oligomeric form of PscNPscL trimeric complex was further established by atomic force microscopy(AFM). So, in brief, this study characterizes PscN and PscL, gives 3D-structural details of both in isolation as well as in complex form and sheds some insights into the role of this ATPaseregulator complex in the proper functioning of T3SS.

Future Research Plans

Structural characterization of proteins PscN, PscL and PscN-PscL complex at atomic resolution.

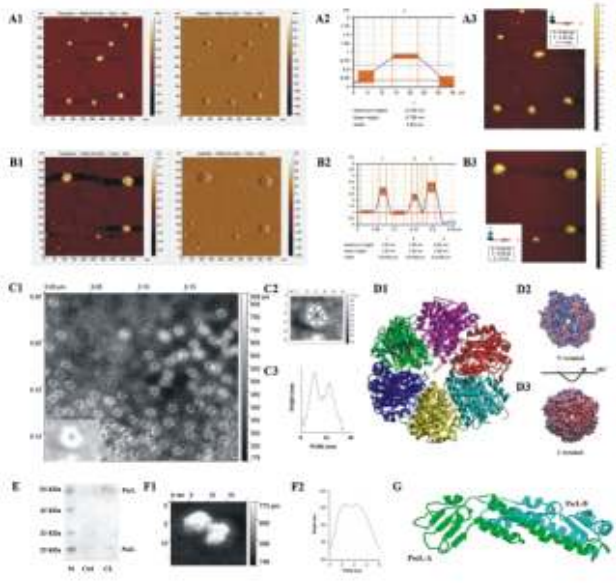

Fig. 1: Visualization of the oligomeric forms of PscN and PscL. (A) Monomeric form of PscN observed under AFM: A1-Topography and Amplitude, A2- Diameter, A3- 3D reconstruction. (B) Hexameric form of PscN observed under AFM: B1-Topography and Amplitude, B2- Diameter, B3- 3D reconstruction. (C) PscN hexamer observed under TEM: C1-TEM pic of PscN hexamer (Single hexamer unit-Inset), C2-Individual protomers in PscN Hexamer, C3-diameter. (D) Hexameric model of PscN developed in MODELLER. Electrostatic potential surface representation of PscN-His, N-terminal (D1) and C-terminal (D2). Positive potential represented by blue color and negative potential as red color. (E) Gluteraldehyde crosslinking profile of PscL in SDS-PAGE: M-Marker, Ctrl-Control, CL-Crosslinked PscL using gluteraldehyde. (F) PscL dimer viewed under AFM (F1) Diameter of PscL (G) MODELLER generated three dimensional model of PscL dimer.

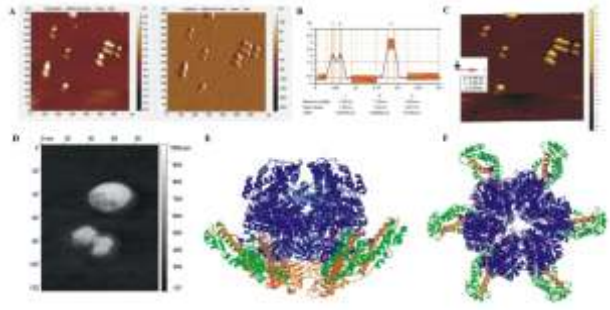

Fig. 2: Visualization of hexameric ring structure of PscN-PscL complex. (A)Topography and Amplitude, (B) Diameter, (C) 3D reconstruction of the AFM image. (D) Single hexameric ring unit view under AFM. MODELLER generated three dimensional model of hexameric ring: (E) lateral view and (F) Top view.

PUBLICATIONS

Halder PK, Roy C, Datta S. Structural and functional characterization of type three secretion system ATPase PscN and its regulator PscL from Pseudomonas aeruginosa. Proteins. 2018 Dec 18. doi: 10.1002/prot.25648. [Epub ahead of print] PubMed PMID: 30561072.

Mondal A, Chatterjee R, Datta S. Umbrella Sampling and X-ray Crystallographic Analysis Unveil an Arg-Asp Gate Facilitating Inhibitor Binding Inside Phosphopantetheine Adenylyltransferase Allosteric Cleft. J Phys Chem B.2018 Feb 8;122(5):1551-1559.

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High-resolution cryo-electron microscopy for elucidating 3D structures of molecular machines to infer functional mechanisms

Participants

JRF : Mr. Krishnamoorthi Srinivasan, Mr. Aneek Banerjee

SRF : Ms. Shirin Akbar, Ms Priya Baid, Ms. Rajanya Bhattacharya, Ms. Sukanya Mozumder, Mr. Sayan Bhattacharjee

Dr. Bani Pathak, DBT Postdoctoral fellow
Mr. Sayan Bhakta, (Thesis submitted)
Mr. Sandip Dey (Thesis submitted)

Collaborator(s)

Prof. Siddhartha Roy, Bose Institute, Kolkata
Prof. Ansuman Lahiri, University of Calcutta
Dr. Jhimli Dasgupta, St. Xavier's College, Kolkata
Dr. Chandana Barat, St. Xavier's College, Kolkata
Dr. Krishnananda Chattopadhyay, Structural Biology Division, CSIR-IICB, Kolkata

Background

The major focus of our lab research is to study the translational apperatus ribosome. All living organisms utilize ribosome to translate messenger RNA (mRNA) into proteins. The ribosome's function is one of the most fundamental processes of life, and intense efforts are going into elucidating the underlying mechanisms of ribosome-related processes.

Our group primarily employs cryo-electron microscopy (Cryo-EM) along with various biochemical and biophysical tools to delineate yet-unknown interactions of several regulatory factors (which could be potential targets for antimicrobial drugs) with the bacterial ribosome, particularly the proteins involved in different stress conditions for pathogenic bacteria.

In addition, we also have been pursuing structural studies employing cryo-EM on other macromolecular assemblies involved in disease-related crucial cellular functions (in collaboration with other groups). Major areas of collaborative researches are, metabolic diseases, neurodegerative diseases and cancer.

Work Achieved

A. Core lab research:
Ribosome at high resolution

A nascent polypeptide chain experiences deformylation of the N-terminal methionine by the enzyme peptide deformylase (PDF), followed by methionine excision catalyzed by methionine aminopeptidase (MetAP) when it emerges from the ribosome tunnel. The ribosome-associated chaperone trigger factor (TF) likely keeps the nascent protein shielded. We have determined 3D cryo-EM structures of E. coli 70S ribosome complexes with these nascent-polypeptide chain processing protein factors at ~10-12 Å resolutions. Our results unveiled remarkable dynamic interplay of the factors on the ribosomal tunnel exit during post-processing of the nascent polypeptide chain (published in JMB, 2019). Now, we aim to determine near-atomic resolution structures of these complexes to gain insight into the molecular interactions of the factors with the ribosome.

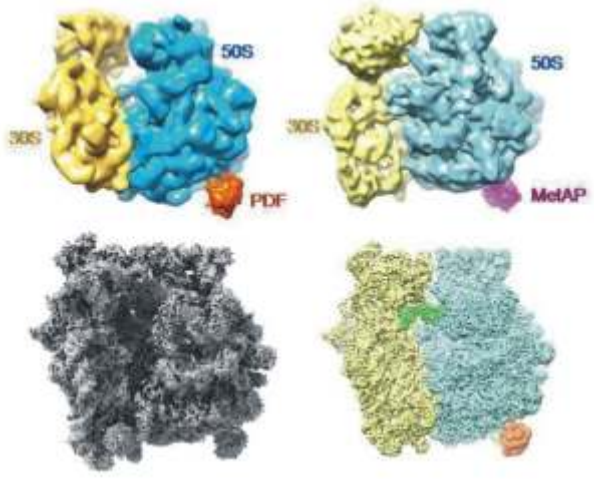
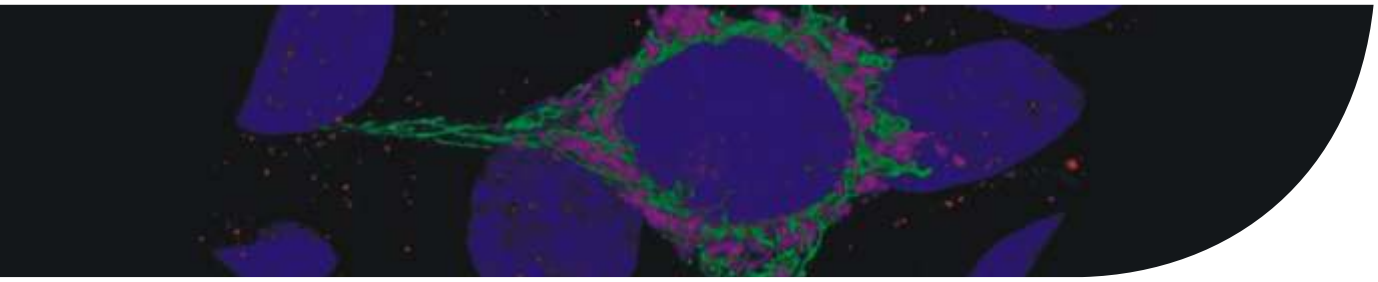


Figure 1: Cryo-electron microscopy (Cory-EM) structures revealed interactions of the nascent chain-processing enzymes peptide deformylase (PDF) and Methionine aminopeptidase (MetAP) with the ribosome (top panel, published in JMB, 2019). 3.8 Å cryo-EM map of a 70S ribosome complex with the nascent chain-processing enzymes (bottom panel, sincere thanks to: NCBS's cryo-EM National Facility, Dr. Vinothkumar Kutti Ragunath, Our Director, Prof. Samit Chattopadhyay).



B. Research in collaboration (Prof. Siddhartha Roy and Prof. Tapas Kundu):

Interaction between Tumor suppressor p53 and the transcriptional coactivator p300

We have reconstructed the 3D cryo-EM structures of free p300 and p300 in complex with p53 tetramer to gain insights into molecular interactions of p53 with the p300 protein. Despite the resolution limitation of the maps, global conformational changes in the p300 structure upon interaction with p53, particularly at the central domain (Bromo-RING-PHD-HAT), were clearly identifiable. Global conformational rearrangements in p53 domains also have been deciphered. Based on the structures we have proposed p53-induced allosteric activation mechanism of p300 (Accepted in Biochemistry, 2019). We are aiming at determining high resolution structure of the complex to understand the intricate details of the interactions leading to activation of p300.

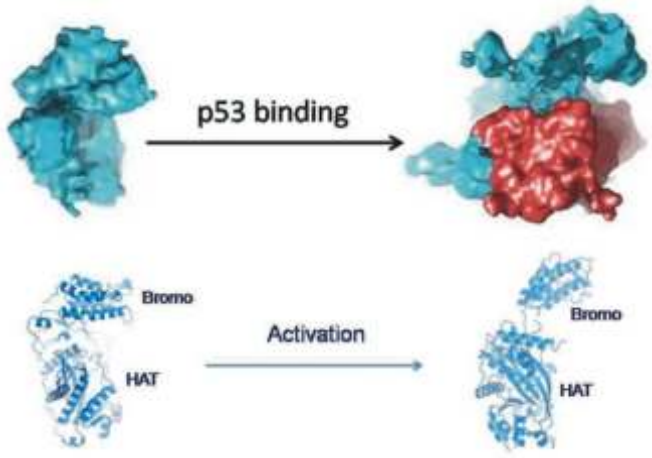


Figure 2: Cory-EM revealed conformational reorganization of p300 (blue) upon p53 (red) binding (top panel). In the 'un-activated' conformation, the HAT domain is buried inside the compact structure. Upon complex formation, the 'kink' angle between the Bromo and HAT domains opens up transforming the p300 in a conformation that can be characterized as 'open' and 'activated' (bottom panel).

Future Research Plans

Our lab is one of the first few labs to start 3D cryo-electron microscopy (cryo-EM) of biological molecules in India. We will continue to elucidate ribosome-related, yet-unknown mechanisms in pathogenic bacteria using primarily high-resolution cryo-EM. We also plan to employ this comparatively newer structural biology technique to elucidate structures of other macromolecular assemblies that participate in key cellular processes involved in human diseases and thus can be potential drug targets.

PUBLICATIONS

1. Sayan Bhakta, Shirin Akbar, Jayati Sengupta (2019) Cryo-EM Structures Reveal Relocalization of MetAP in the Presence of Other Protein Biogenesis Factors at the Ribosomal Tunnel Exit. J Mol Biol. Mar 29;431(7):1426-1439.
2. Krishnamoorthi Srinivasan, Sandip Dey, Jayati Sengupta (2019), Structural modules of the stress-induced protein HflX: an outlook on its evolution and biological role, Current Genetics, Apr;65(2):363-370. Review (Editor Invited).
3. Sandip Dey, Chiranjit Biswas, Jayati Sengupta (2018) The universally conserved GTPase HflX is an RNA helicase that restores heat-damaged E. coli ribosome J. Cell Biol. Jul 2; 217(7):2519-2529.

Aims and Scope:

One of the new strategies for fighting infection in this era of antibiotic resistance could be targeting novel pathways or mechanisms, particularly related to environmental stresses, in pathogenic organisms. In this regards identification of new targets in pathogenic organisms is of utmost importance. We aim at identifying hitherto-unknown ribosome-associated factors instrumental in various stress-related mechanisms of pathogenic bacteria and characterizing the ribosome-factor interactions using high-resolution3D cryo-EM.

Apart from deciphering bacterial ribosome structure, dynamics and function, other projects for structural characterization of molecular interactions related to different diseases, would reveal mechanistic details of the cellular processes and provide important clues for drug development.

Dr. Sucheta Tripathy

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Piecing together genomes of microbes for exploring thebiological treasure trove

Participants

RA:Aditya Narayan Sarangi

SRF: Subhadeep Das,Abhishek Das,Piush Das, Arijit Panda, Samrat Ghosh, Deeksha Singh, Mayuri Mukherjee.

JRFs : Shashikant,Asharani Prusty.

NIPER Masters students : MDevdas, Praveen Kumar, Rama Krishna

External Collaborator(s)

Prof. Anindita Seal, Calcutta University, West Bengal.

Dr. Shubho Choudhury, Bose Institute, West Bengal.

Dr. Swasthi Tiwari, PGI, Lucknow, UP.

Prof. Brett Tyler, Oregon State University, USA.

Dr. Takao Kasuga, University of California Davies, USA.

Dr. Ramesh Ventukuri, Sweedish University of Agricultural Sciences, Sweden.

Background

India is a major mega diverse nation with most of its microbial populations lying under explored. We work on a plethora of organisms belonging to different phylogenetic clades towards solving the biological riddles encoded in their genomes and exploiting them for beneficial purposes. We use existing and in house softwares and some custome made softwares in joining the shorter reads generated by the nextgen sequencing methods into larger contiguous segments. We use these contigs in predicting genes and assigning biological functions into them. We have already sequenced the genomes and transcriptomes of prokaryotic and eukaryotic organisms in discovering major genes including anti-freezing genes in endophytes that helps them sustain in sub-zero temperatures. These genes have huge economic significance. We have been able to over produce cell wall degrading enzymes in some fungal species that can have major implications in paper industry. We have predicted novel effectors that lie in the repeat rich regions of the genomes that evolve faster than other regions of the genomes - re-iterating the two speed genome evolution concept in pathogens. We have created computational resouces for genomic data analysis in forms of light weight genome analyzers. Our interest in prokaryotes centers around photosynthetic Cyanobacteria that grow in extreme environment. These organisms are shown to be extremely rich in signalling molecules that help them adapt quickly to changing environments. They also produce a plethora of secondary metabolites that has huge commercial significance. In future we would like to use this information for commercial level production of bio-enzymes and metabolites and bio-remediation agents.

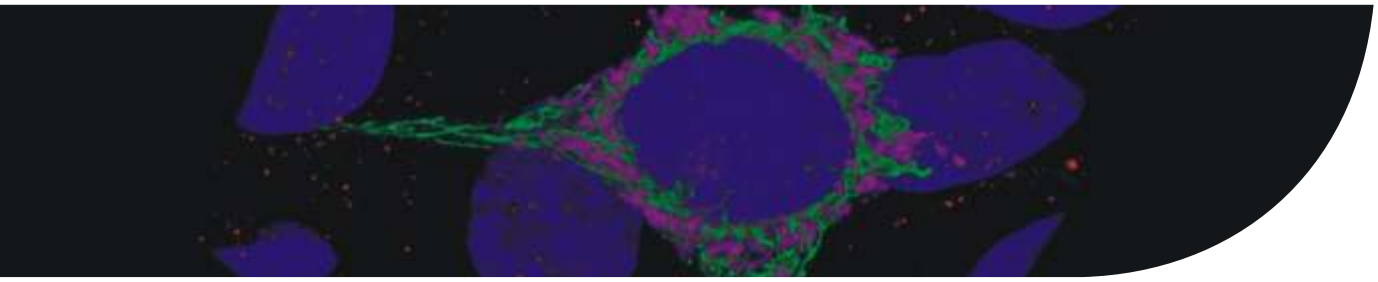
Aims and Objectives

Analyzing complex genomes in understanding the genomic re-arrangements.
Developing biological softwares for data analysis.

Work Achieved:

We have assembled and analyzed genomes of several virulent tree pathogens belonging to oomycetes groups such as Phytophthora ramorum ND886 and Phytophthora plurivora in collaboration with UC Davies and Swedish Agriculture University. Our analysis using cutting edge assemblers reveals that for a highly virulent heterozygous pathogen, long reads using P6-C4 chemistry of PacBio is best for capturing repetitive regions (mathumalar et. al 2019). We have also established that there is partial aneuploidy in some parts of the genome [Fig 1].Our genomic studies of nearly homozygous tree pathogen, Phytophthora plurivora reveals that the effectors are under purifying selection (Ventukuri et al 2018) [Fig 2]. In addition, we have also shown that the genomes of Leishmania donovani are under a state of flux and series of subculturing in lab environment causes the loss of virulence. We did deep genome and transcriptome sequencing of various passages and compared the results and found a co-relation in death of certain genes and loss of virulence. The copy number and function of several ABC transporters are changed in continuous passages in leading to loss of virulence (Sinha et. al 2018) [Fig 3].

While analyzing the genomes, we have created several bioinformatics resources and softwares and released them for the community consumption into the open source platform. Among our newest tools, we have Genome Annotator Lite (panda et. al



2019); SigFeature- An R package for feature selection using machine learning using support vector machine and t statistics. We have also developed another R package, OmicsPCA an multiomics data analysis R platform for dimension reduction in omics datasets.

Future Research Plans

We are now working towards over production of metabolites as well as other biologically active components from the Cyanobacterial cells. With the fungal dried cell wall, we wish to produce bio-materials that can be directly used for bio-remediation purposes.

PUBLICATIONS

1. Panda A, Chaudhari NM, **Tripathy S***. Genome Annotator Light (GAL): A Docker-based package for genome analysis and visualization. Genomics. **2019** Mar 26. pii: S0888-7543(18)30700-6. doi: 10.1016/j.ygeno.2019.03.012. PubMed PMID: 30926570.[IF: 3.327]
2. Malar C M, Yuzon JD, Das S, Das A, Panda A, Ghosh S, Tyler BM, Kasuga T, **Tripathy S***. Haplotype-phased genome assembly of virulent Phythophthora ramorum isolate ND886 facilitated by long-read sequencing reveals effector polymorphisms and copy number variation. Mol Plant Microbe Interact. **2019** Feb 22. doi: 10.1094/MPMI-08-18-0222-R. PubMed PMID: 30794480. [IF: 4.275]
3. Sen, D., K. Paul, C. Saha, G. Mukherjee, M. Nag, S. Ghosh, A. Das, A. Seal and **S. Tripathy* (2019)**. "A unique life-strategy of an endophytic yeast Rhodotorula mucilaginosa JGTA-S1a comparative genomics viewpoint." DNA Research.
4. Vetukuri RR, **Tripathy S#***, Malar C M, Panda A, Kushwaha SK, Chawade A, Andreasson E, Grenville-Briggs LJ, Whisson SC. Draft Genome Sequence for the Tree Pathogen Phytophthora plurivora. **Genome Biol Evol. 2018** Sep 1;10(9):2432-2442.doi: 10.1093/gbe/evy162. PubMed PMID: 30060094; PubMed Central PMCID: PMC6152947.
5. Sinha R1, Malar M C2, 3, Kumar R1,#a, Das S2, 3, Das S1, Shadab M1, Chowdhury R1, **Tripathy S**2, 3*, Nahid Ali1*. Genome plasticity in cultured Leishmania donovani: Comparison of early and late passages. Frontiers in Microbiology. 2018[IF-4.16]

[* Author for correspondence; # joint first author]

AWARDS / HONOURS / MEMBERSHIPS

Students

Full travel award to Shashikant for presenting his work in International conference Nextgen Genomics, Bioinformatics and Technologies in Jaipur, Rajasthan, Oct 2018.

EXTRAMURAL FUNDING

Sucheta Tripathy (PI)

Assessing the genome sequences of Termitomyces clypeatus for novel metabolite discovery through whole genome sequencing methods and characterization of the metabolites for application in biotechnology. 2016-2019. DBT, India

Sucheta Tripathy (PI)

Development of portable system with data analysis and relational data warehouse packages for high throughput structural and functional genomics data. 2017-2020. DBT, India.

Second and Third Generation Sequencing methods for unmadh the genome complicity. Jan 2019, Asansol

Students Graduated :

1. Dr. Lubna Sheikh, July, 2018
2. Mathumalas C., 2018
3. Dr. Arijit Panda, March 2019

CONFERENCES / WORKSHOPS : 3

INVITED TALKS BY CSIR-IICB FACULTY

- EumicrobeDBLiteV11: a lightweight genomic resource and analytic platform for draft oomycete genomes., April 2018, Taian, China.
- Big Data Analysis: Turn data and knowledge into actionable insights… International Conference on Molecular Medicine at SGPGI, Lucknow, December, 2018.
- A paradigm shift in understanding genomic biology by combining second and third generation sequencing technology. Invited talk at the Institute of Forest Genetics and Tree Breeding, Coimbatore., October 2018.

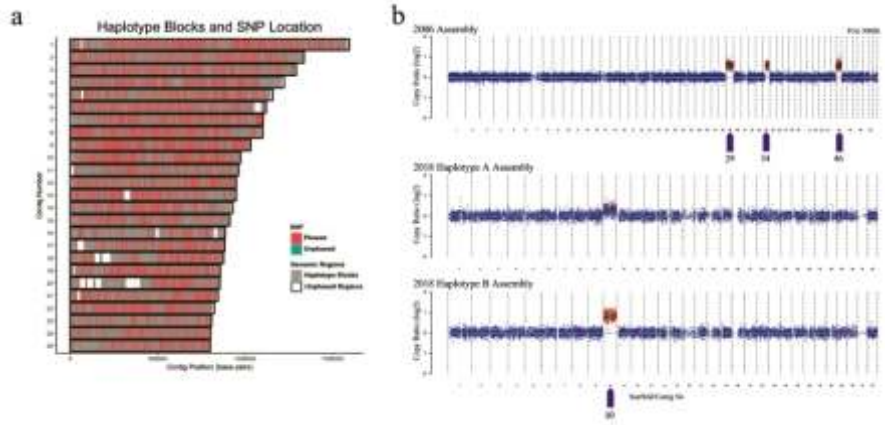


Figure 1: Haplotype blocks containing SNPs and CCNVs along with the phase information are represented.

a. Twenty-five largest contigs of P. ramorum ND886 assembly are shown with the positions of SNPs along the length of the scaffolds. Unphased SNPs are represented as blue lines and phased SNPs are represented as red lines. The grey color regions in the plot represent the haplotype blocks and white color represents unphased regions in the genome. SNPs are needed for phasing. Note that unphased regions (Sutton et al.) are devoid of SNPs (red).

b. CCNVs in Pr102 are mapped onto Pr102 and ND886 assemblies. The Y-axis is the log ratio of normalized read depths between Pr102 and ND886 for each heterozygous locus. Red and blue data points indicate, respectively, significant or non-significant read depth ratio differences between isolates. Top graph shows combined log ratios for both haplotypes mapped onto the Pr102 V1 unphased genome assembly. Lower graphs show individual log ratios for each haplotype (middle, A; bottom, B) mapped to the respective haplotypes of the ND886 phased assembly. Purple arrows refer to scaffolds or contigs that have CCNV in Pr102. The first 50 Mb of the Pr102 assembly (53 scaffolds) and the first 30 Mb of the ND886 assembly (largest 32 scaffolds) are shown. The remaining scaffolds are shown in Figures S4 and S5.

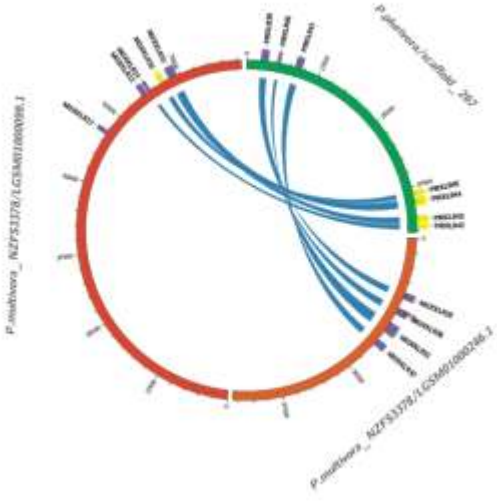


Fig: 2: Comparative genomics of regions of genomes between Phytophthora plurivora scaffold 267 and two other Phytophthora multivora speciesshowing duplication or loss of effector genes.

Fig: 3: Synonymous and non-synonymous substitution in early and late passages leading to altered ABC transporter genes in chromosome 31. (A)

A pair wise comparison between the protein coding genes in HTI4 and HTI5 showing single amino acid mismatches. (B) Nucleotide comparison in two genes indicates few substitutions, out of which the first one is a synonymous substitution and the second one is a non-synonymous substitution. A comparison between HTI4, HTI5 and Genbank strain (C) clearly indicates change of G to A in late passage same as the reference genome.

Dr. Saikat Chakrabarti

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Understanding the molecular mechanisms underlying systemic diseases and host-pathogen interactions

Participants

SRF : Ishita Mukherjee

JRF : Subhangshu Das, Krishna Kumar, Sarpita Bose, Priyanka Mullick

Raisa Bera, Project Fellow
Dr. Nupur Biswas Research Associate

Collaborator(s)

Simanti Datta, IPGMER, Kolkata
Oishee Chakrabarti, SINP, Kolkata
Siddhartha Roy, Bose Institute, Kolkata
Umesh Varshney, IISc, Bangalore
Subhabrata Sen, SNU, Delhi
Koustuv Panda, CU

Uday Bandyopadhyay, IICB
Soumen Dutta, IICB
Hemanta K Majumdar, IICB
Susanta RoyChaudhury, IICB
S N Bhattacharyya, IICB
Partha Chakrabarti, IICB
Dipyaman Ganguly, IICB
Chitra Mandal, IICB
Nahid Ali, IICB
SibSankar Roy. IICB
Sanjay Dutta, IICB
P. Jaishankar, IICB

Background

My team is actively involved in identification and subsequent analysis of important bio-molecular interactions involving proteins, DNA and other macro-molecules in systemic diseases like cancer and infectious diseases, like malaria, leishmaniasis, etc. The primary contribution of our research for the last five years is to develop a robust and efficient approach to understand the hidden properties of protein-protein interactions (PPI) systems leading to infection/systemic disease by a) integrating large scale "omics" data through network biology and graph theoretical algorithms and b) in-depth analysis of molecular interaction patterns using state-of-the-art molecular modeling, docking and dynamics strategies. In other words, we utilize large-scale genomics, transcriptomics, and proteomics data to construct bio-molecular interaction networks and further study them to understand and decipher their biological significance using meta-interactome analysis. Our group also develops various computational tools, techniques and web servers, which are freely available for users and are beneficial to the scientific community throughout the world.

Aims and Objectives

- To understand the hidden properties of systemic disease using network biology and graph theoretical approaches.
- To construct and analyze the protein-protein interactions (PPI) networks of host-pathogen system in order to identify novel targets.
- To validate the importance of the identified important target proteins using experimental techniques.
- To develop image processing, deep Learning and AI based non-invasive Diagnostics, Prognostics, and analytical Systems.

Work Achieved

Systems biology of cancer

We have developed a computational systems biology approach to build a meta-interaction network of signaling, metabolic and regulatory pathways within cellular systems using text mining, network assembly and graph theory approaches to understand complex molecular interplay in brain, breast, cervical and ovarian cancer scenarios, respectively. Our integrative "trans-omics" approach overlaid with network analysis aim to identify novel biomarker signatures specifically tuned towards metabolic reprogramming undergoing within the corresponding cancer types. Figure 1 shows the signaling-metabolic pairs and interconnecting paths between them filtered from a glioblastoma multiforme (GBM)-specific network.

Systems biology of host-pathogen interactions

We have studied the human pathogen, Leishmania sp. by compiling and analyzing the whole protein interactome data of Leishmania sp. The constructed network has been further considered for identifying important interacting leishmanial protein(s) of the network to understand their involvement in

pathogen survivability and pathogenicity. With the aim of studying protein interaction properties both at systems and molecular level, we have implemented bioinformatics tools towards identification and characterization of important virulence factors of the parasite. In this respect, we have identified a novel target protein using the network biology approach and its probable inhibitor using high throughput virtual screening (HTVS) technique.

Identification of Important Effector Proteins in the FOXJ1 Transcriptional Network Associated With Ciliogenesis and Ciliary Function.

Based on the assumption that FOXJ1-mediated regulatory and signaling networks are representative of the motile cilia interactome, we have constructed and analyzed the gene regulatory and proteinprotein interaction network (PPIN) mediated by FOXJ1. We have predicted important effectors in the motile cilia interactome, which are possibly associated with ciliary biology and/or function and are likely to further our understanding of the pathophysiology in ciliopathies like PCD. Figure 2 shows IIP-effector proteins in FOXJ1 regulatory network and their probable ciliary associations.

Image analysis for introspection of the damage caused by stroke

We have recently undertaken image analysis based studies where we are trying to estimate the impact of the damage caused by ischemic and hemorrhagic stroke, respectively. We started working with CT scan data, which are converted into a series of axial continuous 2D slices followed by implementation of morphological operations to segment the ischemic and hemorrhagic regions of the brain. These chronological segmented surface areas were further integrated to create a three-dimensional (3D) representation of the brain along with the volume and span of the ischemic and hemorrhagic regions (Figure 3).

Future Research Plans

We would like to explore metabolic reprogramming in cancer cells with a combination of network and systems biology approaches to understand the molecular mechanism of this metabolic switch.

Further, with the help of a multi-faceted research plan by integrating experimental information with subsequent development of computational techniques we will be able to better address systemic diseases and host-pathogen interactions. We will also like to explore the different avenues of image processing analysis using brain magnetic resonance imaging (MRI) data to develop tools and techniques to aid early detection of dementia.

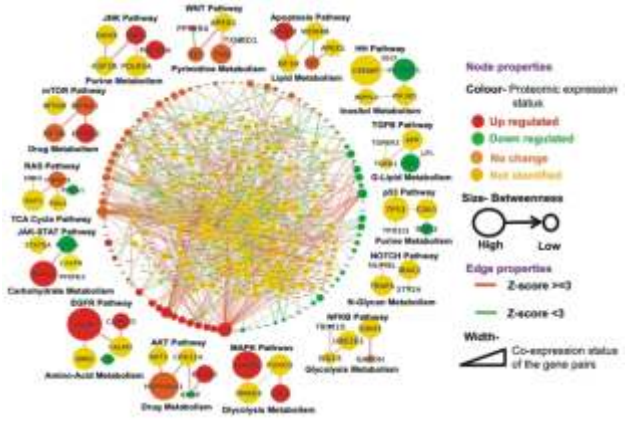

Figure 1: GBM-specific significant network along with signalling-metabolic (SM) pairs and interconnecting paths.

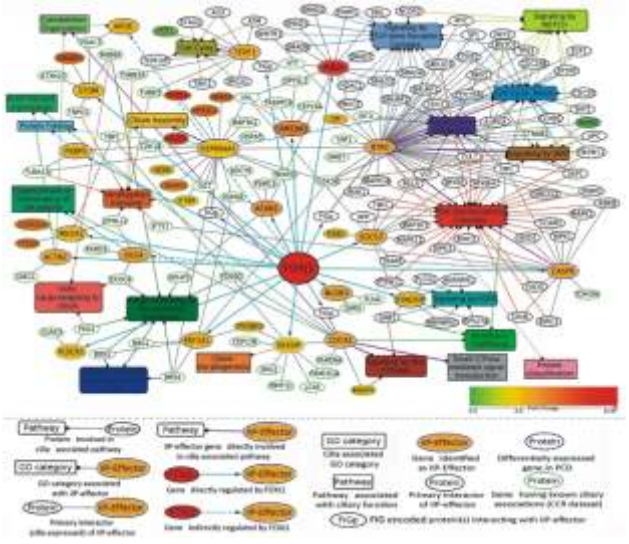

Figure 2: IIP-effector proteins in FOXJ1 regulatory network and their probable ciliary associations. Probable cilia associated pathways or processes that the IIP-effector proteins and their network interactors may participate in were determined with the help of pathway enrichment and GO analysis and such possible ciliary roles of each IIP-effector is depicted. The edge color denotes the ciliary processes or pathways the gene/protein is/are associated with.

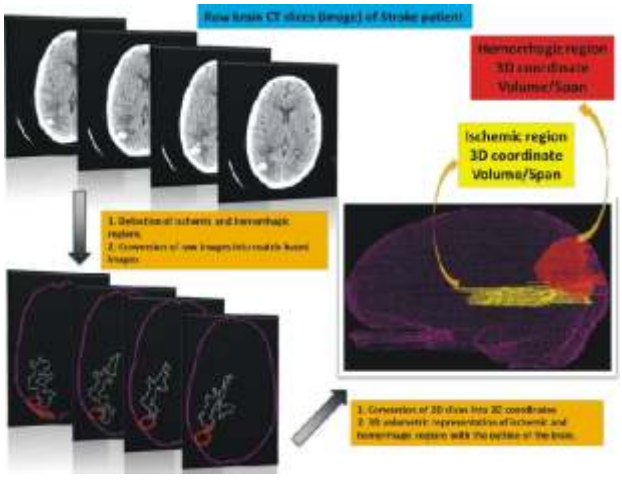

Figure 3: Schematics of the automated identification of ischemic and hemorrhagic stroke regions along with integrated 3D representation of the brain.

PUBLICATIONS

Bag, A.K., Mandloi, S., Jarmalavicius, S., Mondal, S., Kumar, K., Mandal, C., Walden, P., **Chakrabarti**, S.*, Mandal, C. (2019) Connecting signaling and metabolic pathways in EGF receptor-mediated oncogenesis of glioblastoma. PLoS Computational Biology 15, e1007090.

Mukherjee, I., Roy, S., **Chakrabarti,** S*. (2019) Identification of important effector proteins in the FOXJ1 transcriptional network associated with ciliogenesis and ciliary function. Front. Genet. 10, 23.

Luthra, T., Nayak, A.K., Bose, S., **Chakrabarti**, S., Gupta, A., Sen, S. (2019) Indole based antimalarial compounds targeting the melatonin pathway: Their design, synthesis and biological evaluation. European Journal of Medicinal Chemistry 168, 11-27.

Shadab, M., Banerjee, A., Sinha, R., Das, S., Asad, M., Kamran, M., Maji, M., Deepthi, M., Jha, B., Kumar, M., Tripathi, A., Kumar, B., **Chakrabarti**, S., Ali, N. (2019) RNA-seq revealed expression of many novel genes associated with Leishmania donovani persistence and clearance in the host macrophage. Front. Cell. Infect Microb 9, 17.

Mukherjee, R., Bhattacharya, A., Sau, A., Basu, S., **Chakrabarti**, S*., Chakrabarti, O. (2018) Calmodulin regulates MGRN1-GP78 interaction mediated ubiqitin proteasomal degradation system. FASEB Journal. 33, 1927-1945.

Chauhan, J., Dasgupta, M., Luthra, T., Aswasthi, A., Tripathi, S., Banerjee, A., Paul, S., Nag, D., **Chakrabarti**, S., Chakrabarti, G., Sen, S. (2018) Design, Synthesis and biological evaluation of antimitotic C2-aroyl/arylimino tryptamine derivatives that are also potent inhibitors of indoleamine-2,3-dioxygenase(IDO). European J. of Pharma Sc. 124, 249-265.

Palit, S., Mukherjee, S., Niyogi, S., Banerjee, A., Patra, D., Chakraborty, A., Chakrabarti, S., **Chakrabarti**, P., Dutta, S. (2018) Quinoline□glycomimetic conjugates reducing lipogenesis and lipid accumulation in hepatocytes. Chembiochem. June 13.

AWARDS / HONOURS / MEMBERSHIPS

Faculty

Saikat Chakrabarti

Awards / Honours

Invited selection of F1000Prime faculty
Invited selection as Research Advisor of NASS, Singapore

Dr. Nakul Chandra Maiti

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Protein Conformation Linked Human Diseases and Nano-Formulation for Cancer and Amyloid Human Disorder

Participants

Dr. Anupam Roy, SRF (PhD Awarded)
Mr. Sandip Dolui, SPF
Mr. Kaushik Bera, DST INSPIRE FELLOW SRF
Mr. Animesh Mondal, CSIR-SRF
Mr. Krishnendu Khamaru UGC-SRF
Ms. Lopamudra Das CSIR-JRF
Ms. Esha Pandit CSIR-JRF
Mr. Kaustav Mukherjee (co-guide, Prof. Chitra Mandal)

Project Trainees
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(ii) Aakriti Singh
(iii) Annaram Harika (NIPER)

Collaborator(s)
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National Institute of Immunology, New Delhi

Dr. Achinta Kumar Saha, University of Calcutta

Dr. Anirban Bhunia, Bose Institute, Kolkata

Name of collaborator within CSIR-IICB

Prof. Chitra Mandal
Cancer Biology and Inflammatory Disorder Division

Dr. Biswadip Banerji, Organic & Medicinal Chemistry Division

Dr. Snehasikta Swarnakar
Cancer Biology and Inflammatory Disorder Division

Background

Recent studies found that human proteome is enriched with intrinsically disorder regions (IDRs) in their sequence, which in turn reflect their indispensable role in cellular signalling and various other metabolic pathways. The number of disorder proteins known to be involved in cell signalling and regulation is growing rapidly. Various well characterized examples of individual disorder proteins involved in transcriptional regulation have been illustrated in literature. The performance of folded protein and intrinsically disordered protein are quite different. Intresnsically disorder proteins and regions maintain a unique stability between folded domain and disordered regions; it is required for proteins function. Certain instability in the cellular micro environment for both the types of protein cause protein misfolding and it has tremendous effect on multi component phase separation and some membrane less organel formation. Thus it is belived that protein disorder has tremendous implication on non-covalent epigenetic modification and cell regulation We investigate seeral proteins peptides linked to human disease and currently focused on the dynamics and role of disorder protein region on NS2-NS3 protease activity and the possible phase separation caused by disorder protein domain in gene regulation and cell disvission. Another area of research is to check how nano surfaces effect the protein phase separation and inhibition of amyloid formation. Our investigation attempts to provide the structural characterizations of intermediates which are formed in the processes of amyloid formation of disese linked proteins and peptides.

Work Achieved

1. Porphyrin Based Gold Nanomaterial for pH Responsive Efficient Drug Delivery to Cancerous Cells

With an aim to overcome multidrug resistance (MDR), non-targeted delivery and drug toxicity, we developed a new nano-chemotherapeutic system, based on meso-tetrakis (4-sulfonatophenyl) porphyrin (TPPS) with strong tumor localization potential, armored on gold nanoparticles (TPPS-AuNPs). The nanocarrier is able to be selectively internalized within tumor cells followed by endocytosis and therefore, delivers anti-tumor drugs doxorubicin (DOX) specifically to the nucleus of diseased cells. The TPPS segment attached strongly to the gold nanosurface and provides excellent stability and biocompatibility to the nanovalves. Such type of drug loaded nanosystem demonstrated enhanced cellular uptake with significantly reduced drug efflux in MDR brain cancer cells and thereby increasing retention time of drug within tumor cells. More importantly, DOX loaded nanoparticles exhibited nine times greater potency for cellular apoptosis via triggered release commenced by acidic pH. DOX has been successfully loaded on the porphyrin modified gold nanosurface with significant high capacity and tightly associated at normal physiological condition but capable of releasing ~81% of drug in low pH environment. Subsequently, DOX loaded TPPS-AuNPs exhibited higher inhibition of cellular metastasis, invasion and

angiogenesis suggesting that TPPS modified AuNPs could improve the therapeutic efficacy of drug. Unlike free DOX, drug loaded TPPS-AuNPs did not showed toxicity towards normal cells. Therefore, higher drug transport capacity with specific targeting potential and acidic pH-mediated intracellular release of DOX at the nucleus make TPPS-AuNPs as a "magic bullet" for implication in nanomedicine.

2. Modulation of Fe(III) Redox Potential via Biliverdin Protected Silver Nanosurface

Standard reduction potential of metal ion is an important descriptor of its redox property. Herein, we showed that silver nano-surface armored with biliverdin (BV), specifically reduce Fe(III) ion despite of their unfavorable reduction potential in aqueous medium. Biliverdin protected silver nanosurface (Ag-BV), having diameter ~10-15 nm, exhibited prominent surface plasmon resonance (SPR) band at 420 nm and produced straw yellow color in aqueous suspension. Flat BV moiety interacts strongly with the nano-surface and found to exist as face centered cubic lattice (FCC) in the solid state. The addition of Fe(III) to the Ag-BV suspension resulted an initial red shift in its SPR band indicating agglomeration of the nanoparticles and eventually the suspension became brown in color. Subsequently, a redox reaction caused the disappearance of deep brown color and the solution became colorless resulting blue shift of its SPR band. Our analysis suggested that aromatic π system of BV in Ag-BV nanosurface possibly made an electron carrier bridge that favored to transfer of electron from atomic silver to empty d orbital of Fe(III) following effective reduction of the ion and oxidation of silver atom. The oxidation and loss of the nanostructure was evidenced in transmission electron microscopy analysis. More importantly, Ag-BV could reduce ~ 74% of total Fe(III) in aqueous medium. The computational study revealed that the partial charge on Fe was +1.16 units in Fe(II)/biliverdin complex compared to +1.26 units in Fe(III)/biliverdin complex, suggesting a shift of electron density to the metal ion center. The electron transfer via conjugated π-electronic system of the ligand on metal nano-surface was unique in this process and the details are explored with surface plasmon resonance as well as density functional theory analysis.

Future Research Plans

(i) Formation of membrane less organels and its role as nono-covalent epigenetic modification
(ii) Understanding amyloid formation mechanism
(iii) Structural implication of protein oligomers in several disease formation
(iv) Nanao-biomeicine

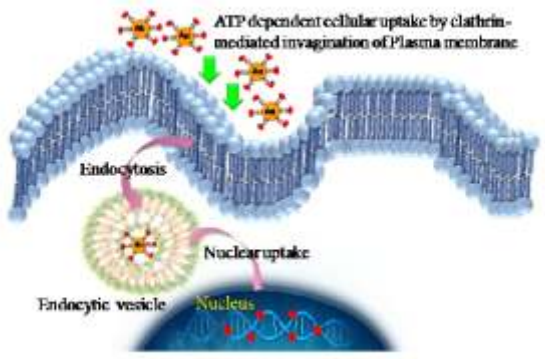


Figure 1: Delivery of Doxorubicin into Cancerous Cells by using Porphyrin Based Gold Nanocarrier.

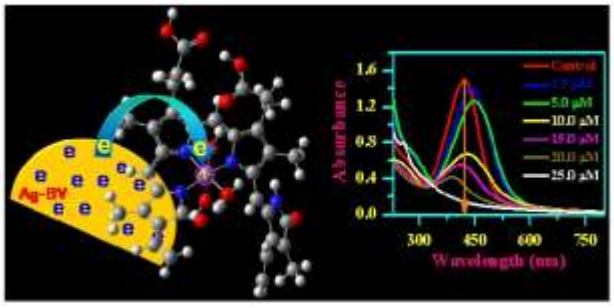
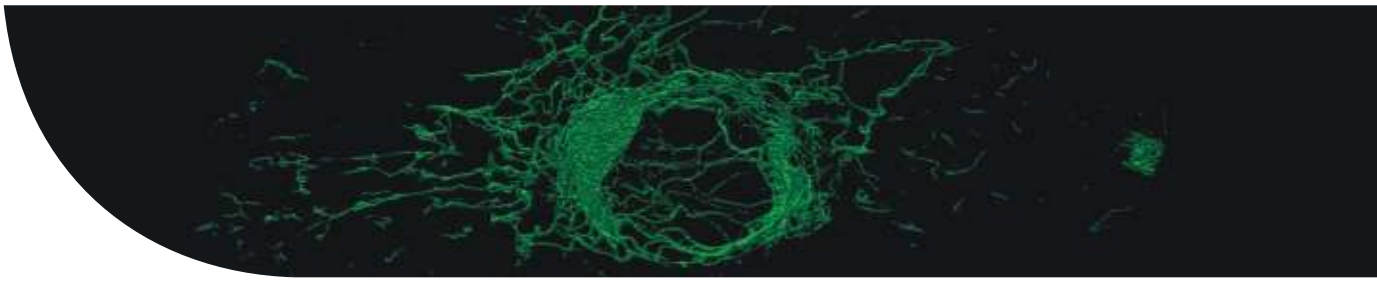


Figure 2: The Reduction Mechanism of Fe(III) Ion in Presence of Biliverdin Protected Silver Nanosurface

PUBLICATIONS:

1. Maity, M.; Bera, K.; Pal, U.; Khamaru, K. and Maiti N. C., Sensing of Fe(III) Ion via Modulation of Redox Potential on Biliverdin Protected Silver Nanosurface, ACS Appl. Nano Mater, 2018, 1, 60996111

2. Mondal A.; Pal U., Roy A. and Maiti, N. C., Structural Intricacy of Disordered Regions in Transcription Factors Imparting Colon Cancer, J. Proteins Proteomics, 2018, 9, 169-184.



3. Bera K.; Maiti, S. Maity,; M. Mandal and Maiti N. C., Porphyrin−Gold Nanomaterial for Efficient Drug Delivery to Cancerous Cells, ACS Omega 2018, 3, 4602−4619.

EXTRAMURAL FUNDING

1. Structural Implication of Amyloid Oligomers in Alzheimer's Disease, SERB, DST 2017-2020, 37 lacs, File No: EMR/2016/006322

CONFERENCES / WORKSHOPS

1. Divulging Characteristic Features of the Novel A-Synuclein Oligomers Augmenting Parkinson's Disease, 63rd Annual meeting of the Biophysical Society (BPS-19), Baltimore Convention Center, USA, March 2-6, 2019

2. Structural Intricacy and Raman Signature of Protein Prior to Their Transformation into Amyloid like Fibrillar State, National workshop on Fluorescence and Raman Spectroscopy, School of Physical Sciences, JNU, New Delhi, November 17-21, 2018 (Invited Talk)

3. Unveiling characteristic features of the toxic α-Synuclein Oligomers, National workshop on Fluorescence and Raman Spectroscopy, School of Physical Sciences, JNU, New Delhi, November 17-21, 2018 (Poster)

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

None

TALKS BY CSIR-IICB FACULTY

1. Structural Intricacy and Raman Signature of Protein Prior to Their Transformation into Amyloid like Fibrillar State, National workshop on Fluorescence and Raman spectroscopy, Indian Institute of Technology Guwahati, India, November 12, 2018

2. NeuroUpdate meeting, 2018 Saturday, Nov 24, 2018. CSIR-Indian Institute of Chemical Biology, Jadavpur, Kolkata

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Structural and functional characterization of Chromatin interacting proteins.

Participants

SRF : Dushyant Kr. Srivastava, Anirban Dasgupta, Shantanu Adhikary, Sambit Dalui, Sinjini Dhang
Senjuti Sen, NPDF

Collaborator(s)

Dr. Chandrima Das
Saha Institute of Nuclear Physics, Kolkata

Dr. Vasudevan Seshadri
National Centre for Cell Science (NCCS), Pune

Background

In eukaryotic organisms the genetic information is packaged into a compacted chromatin structure containing nucleosome core particles with 147bp of DNA wrapped around histone octamer. All the DNA-mediated activities, including transcription, replication, recombination, and DNA repair use the concerted efforts of histone chaperone protein that facilitates the assembly and disassembly of chromatin by deposition or eviction of histones. The NAP (Nucleosome Assembly Protein) family of histone chaperones is conserved from yeast to human and has been implicated in many biological functions including shuttling histones from the cytosol to the nucleosome, cell proliferation, cell-cycle regulation, transcription, replication, silencing, and apoptosis. TSPYL1, a new member of the NAP protein family, is identified by mapping of sudden infant death with dysgenesis of the testes syndrome (SIDDT) by a SNP genome scan. The primary sequence of TSPYL1 shows that it harbors Nterminal nucleosome assembly protein (NAP) domain. The sequence analysis of the TSPYL gene in affected individuals identified a homozygous frame shift mutation (457_458insG) at codon 153, resulting in truncation of translation at codon 169 and thereby leads to loss of NAP like domain. As the loss of NAP domain of TSPYL1 causes the disease in infants, NAP domain of TSPYL may play a role in development by altering regulation of specific developmental genes and contributing to region-specific chromatin remodeling (Puffenberger et al., 2004). In the present study we aim to elucidate the TSPYL1 NAP domain structure which may shed light on fundamental aspects of embryogenesis of the human nervous and reproductive systems and may also characterize the function through a previously not described epigenetic crosstalk and signaling mechanism of brainstem development. More important, studies of TSPYL structure will help in better understanding of its expression and function in the developing brain may provide new insight into the genetic basis of apnea, dysphagia, cardiac arrests, and sudden unexplained deaths in infancy.

Aims and Objectives

- Crystal Structure determination of NAP domain of TSPYL1 at atomic resolution using X-raycrystallography
- What is the three dimensional structure of TSPYL1 with histones/ modified histones?
- Does TSPYL1 possess chromatin assembly function?
- What is the interacting partner of TSPYL1 and what is the mechanism through which it regulates the chromatin assembly and altered gene expression?
- Role of TSPYL1 in cell proliferation, metastasis and cancer progression in human.

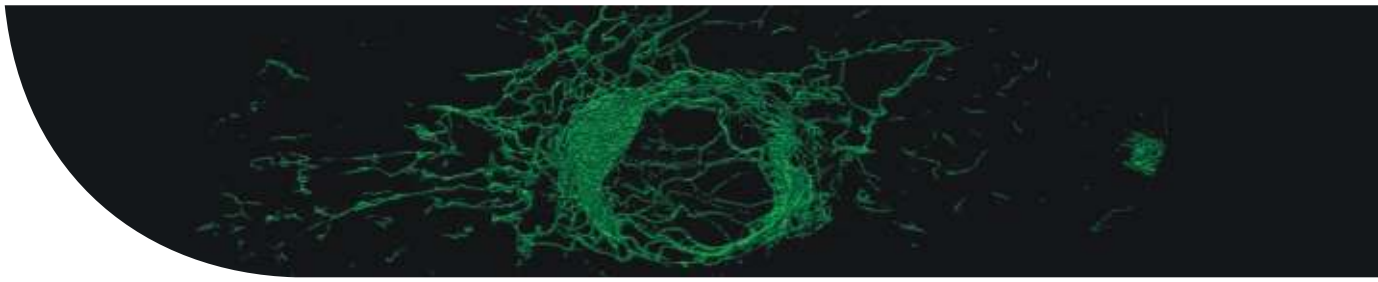
Work Achieved

Cloning

Initially attempts have been made to clone the human TSPYL1 gene from HEK human cell-line cDNA. But after cloning the gene the protein is not expressed with desired amount. So we opted for synthesis of TSPYL1gene. We cloned the C-terminal histone chaperone domain of NAP1 (residue 162-416) & (residue 198-416) from the codon optimized TSPYL1 gene in a pGEX 6p1 vector (Gateway Technologies) containing GST affinity tags. We also cloned full length TSPYL1 (residue 1-416) in pDEST-15 vector having N-terminal GST tag. All the vectors are further confirmed through sequencing.

Expression and purification:

DH5 alpha cell was transformed for propagation of the TSPYL1 clone and glycerol stock was maintained. Rossetta P-Lys strain of Escherichia coli were transformed with TSPYL1 clones and plated on LB agar plate containing ampicilin(100µg/ml) and chloramphenicol (34µg/ml). 3 liter culture was grown in LB media containing ampicillin and chloramphenicol by vigorous shaking at 180rpm @ 37°C till the culture reached an OD600nm value between 0.6 and 0.8. Afterwards TSPYL1 expression was induced



for a period of 16 hrs by adding 1mM IPTG and shaking at 180rpm @ 20°C. The cells were harvested by centrifuging @ 6000rpm at 40C and resuspended on ice in lysis buffer (20mM Tris-Cl pH 7.5, 150mM NaCl, 2 mM DTT, 0.05% NP-40). The cell lysate was sonicated and then clarified by centrifuging at 25000 rpm @ 4°C for 45mins for 2 times. The supernatant was collected and filtered with a 0.22 µ filter. The filtered supernatant was incubated with pre-equilibrated GST-Agarose beads (equilibrated in lysis buffer without adding NP-40) at 4°C for 4 hrs. After incubation, the beads were washed with wash buffer (20mM Tris-Cl pH 7.5, 250mM NaCl, 2mM DTT) thoroughly. The washed beads were then incubated with precision protease enzyme for 36 hrs @ 4°C to cleave the protein in precision protease buffer (20mM Tris-Cl pH 7.5, 150mM NaCl and 2mM DTT). All the samples from each step were then analyzed on SDS-PAGE gel. The cleaved protein was then eluted using the same precision protease buffer and then passed through a gel filtration column to remove impurities. After concentrating the protein to desired volume, protein concentration was estimated by Bradford assay (Figure 1).

MS-MS analysis of purified protein:
Confirmation of the purified protein to be TSPYL1 was done following standard protocol as given in Trypsin Gold Manual.

Crystallization:
Purified TSPYL1 (162-416) was dialyzed in high salt concentration buffer and concentrate up to 8-10mg/mL concentrations. Concentrated protein was used to set up several crystallization screens using sitting drop method. Initial hits obtained from selected drops were optimized and a crystal of considerable size was obtained in a crystallization condition containing 100mM Imidazole pH-8.0, 200mM Calcium Acetate and 20% PEG1000 (Figure 2).

Biochemical and Biophysical Characterization
Determination of Oligomer property of TSPYL1 by Analytical Size Exclusion Chromatography:
Analytical size exclusion chromatography (aSEC) with a HiLoad Superdex 200 16/600 column (GE healthcare) in different ionic strength buffer was used to determine molecular weights (MWs) in solution by comparison of the protein standards of precisely known MW values. The protein standards used here are mixture of Aldolase(157kDa), Conalbumin(75kDa), Ovalbumin(44kDa), Carbonic Anhydrase(29kDa), RibonucleaseA (13.7kDa), Apoprotenin (6.5kDa). The elution volumes of these proteins were used for calculation of standard curve since the separation range of the column is from 10 kDa to 600 kDa according to the instructions provided by the column manufacture.

In-vitro Histone interaction by GST Pull down assay:
For GST-pull down assays, GST-tagged TSPYL1 (162-416) was purified using affinity chromatography method. Briefly transformed Rosetta P Lys strain of E.coli was grown till log phase followed by induction using 1 mM IPTG and incubation @200rpm @20°C for 16 hrs. Post harvesting the cells, lysis was done in 20mM Tris, 200mM NaCl, 2mM DTT. Lysed cells were sonicated and GST-TSPYL1 was affinity purified using GSTSepharose Beads. Protein -protein interaction was set up by mixing GST-TSPTYL1 and Histones H2A, H2B, H3 & H4 in equimolar ratio and incubated in IP Buffer (20mM Tris, 200mM NaCl, using pre-blocked Glutathione Sepharose GST beads. After binding for 4 hours the bead was wash with Binding buffer for four times, the protein complex was resolved in SDS PAGE followed by western blotting. Pull down assay also performed with different ionic strength buffers to check the binding strength of the TSPYL1 and Histones.

DLS study of oligomer of TSPYL1:
Protein size was determined by dynamic light scattering (DLS) using the Nano ZS Malvern instrument (measurement range of 0.6 nm to 6 µm) using 2 micro molar of TSPYL1 oligomer protein. This technique measures the time dependent fluctuations in the intensity of scattered light that occur because particles undergo Brownian motion. The analysis of these intensity fluctuations enables the determination of the diffusion coefficients of particles, which are converted into a size distribution.

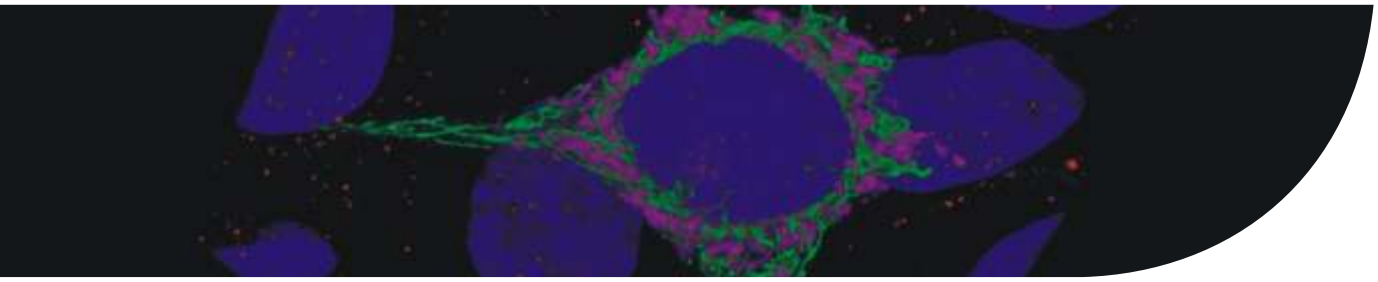
AFM study of TSPYL1 oligomer and Histone Interaction
TSPYL1 protein only and equimolar concentration of histone H3-H4 tetramer or H2AH2B
Dimer & TSPYL1 proteins were incubated and do AFM after drying 5 microliters of each sample in mica. Highest 400nm resolution picture ware taken and analyze (Figure 3).

Future Research Plans

Further biological characterization of TSPYL1 with Nucleosome Core by cryoEM

Co-crystallization with its binding partner/s

Detailed biophysical characterization of the effect of TSPYL1 mutants on its histone interaction properties.



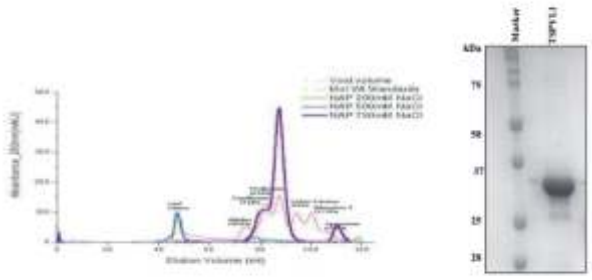


Fig. 1: Elution profiles of TSPYL1 NAP protein (~31kDA) protein and Calibration Kit proteins on HiLoad 16/600 Superdex 200 pg column in different salt strength buffer. Elution volumes (Ve) are found at maximum peak height of each respective protein.

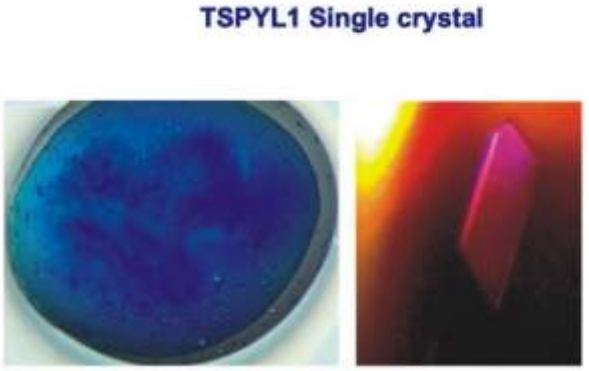


Fig. 2: Crystal of purified TSPYL1 NAP domain.

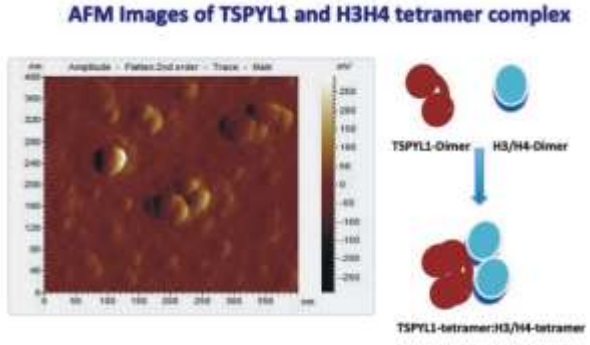


Fig. 3: AFM images in 400nm magnification TSPYL1& H3H4 complex

PUBLICATIONS

1. Adhikary S, Chakravarti D, Terranova C, Sengupta I, Maitituoheti M, Dasgupta A, Srivastava DK, Ma J, Raman AT, Tarco E, Sahin AA, Bassett R, Yang F, Tapia C, Roy S*, Rai K*, Das C*. Atypical plant homeodomain of UBR7 functions as an H2BK120Ub ligase and breast tumor suppressor. Nature Commun. 2019 Mar 28;10(1):1398.

EXTRAMURAL FUNDING

No.	Project No.	Funded by	PI/Co-PI	Amount (Lakh INR)
1	EMR/2016/006233	SERB	PI	43.0 (3 yrs, 2017-2020)
2	BT/PR23434/MED/29/1189/2017	DBT	PI	60.0 (3 yrs, 2017-2020)

Dr. G. Senthil Kumar

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Identification of epigenetic therapeutic targets to abolish the metabolic memory phenomenon in diabetic retinopathy.

Participants

Nidhi Kumari, CSIR-JRF
Aditi Karmakar, UGC-JRF

Collaborator(s)

Name of collaborators outside CSIR-IICB

Dr. Ashim Kumar Ghosh
Director, Regional Institute of Ophthalmology, Kolkata

Name of collaborator within CSIR-IICB
Dr. Saikat Chakrabarti
Principal Scientist, Structural Biology & Bioinformatics division

Background

Diabetic retinopathy (DR) is a major cause of vision loss among working-age adults in both the developing and developed countries. Landmark clinical trials have documented that retinopathy continues to develop in diabetic patients even after achieving and maintaining good glycemic control for many years, damage instilled by the prior poor glycemic control becomes hard to reverse. These results have suggested that the prior hyperglycemia leaves a legacy effect or “metabolic memory”. This phenomenon is also documented in experimental models of diabetic retinopathy. Epigenetic modifications such as DNA methylation, histone modifications, and non-coding RNAs are contributing to `metabolic memory' phenomenons. These modifications are accountable for deregulating various signaling pathways which are oxidative stress, inflammation, and apoptosis, etc.) in DR. Hence, identifying and understanding inter-relationship between various pathways, genes, enzymes, and proteins involved the disease progression after the termination of hyperglycemia will lead to developing the therapeutic targets.

Aims and Objectives

Identification of differentially methylated genes responsible for Diabetic retinopathy progression by An integrated omics analysis.

To Validate the identified candidate genes DNA methylation pattern (CpG islands of the promoter/5'-untranslated region) in the clinical samples.

Work Achieved

We have identified highly significant-top ten genes of each up-regulated and hypomethylated / down-regulated and hypermethylated which are associated with diabetic retinopathy progression.

We are recruiting clinical samples from the hospitals for the validation of the above-identified genes.

Future Research Plans

Validating the DNA methylation pattern of the identified candidate genes in human clinical samples.

Discovering the epigenetic predictive and prognostic biomarkers for diabetic retinopathy
Dissecting the molecular pathways the validated candidate genes using in vitro model

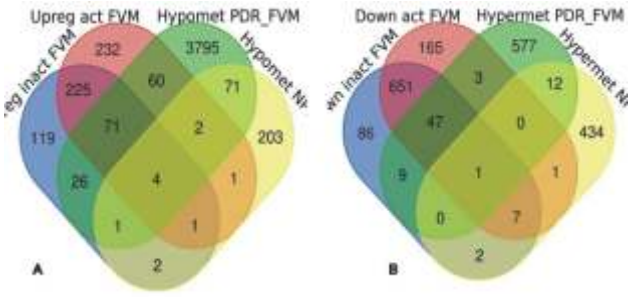

Fig. 1: Venn diagram showing the common genes involved in the diabetic retinopathy progression. A) Up-regulated & hypomethylated B) Down-regulated & hypermethylated

PUBLICATIONS

Kumari N, Karmakar A. Senthil Kumar G.Targeting epigenetic modifications as a potential therapeutic option for diabetic retinopathy. J Cell Physiol. 2019 Sep 17. DOI: 10.1002/jcp.29180.

Nalini D, Selvaraj J, Senthil Kumar G.Herbal nutraceuticals safe and potent therapeutics to battle tumor hypoxia. J Cancer Res Clin Oncol.2019 (Accepted)

CONFERENCES / WORKSHOPS

2

Dr. Paulomi Ghosh

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Development and characterization of biopolymer based fibers for biomedical applications

Participants

Project Assistant: Ashmita Mukherjee

Yogesh Kabutare (Alumni)

Collaborator(s)

Name of collaborator outside CSIR-IICB
Dr. Vamsi Krishna Balla and Dr. Subhadip Bodhak, CSIR-CGCRI, Kolkata, India

Name of collaborator within CSIR-IICB
Dr. Indubhusan Deb, Organic & Medicinal Chemistry

Background

Combination of medical science and textile technology has led to the emergence of medical textile industry. Applications of medical textile include wound dressing/gauze/surgical end-use/artificial ligament/hollow fibers for dialysis, etc. We have extracted keratin protein from Gallus gallus domesticus feathers/human hair and characterized it. Thereafter, we have chemically crosslinked keratin with other biopolymers to form dope. The dope prepared from varying the amount of keratin, alginate and the cross-linker was used to prepare uniform sized micro/nanofibers. An elaborate comparative study was done to evaluate the effect of the dual crosslinking on tensile strength, elastic modulus, swelling, thermal properties and diverse biomedical applications of the fibers.

Aims and Objectives

1. To fabricate microfibers from feather waste for applications in hygiene products
2. To develop fiber dressing for hemostatic applications

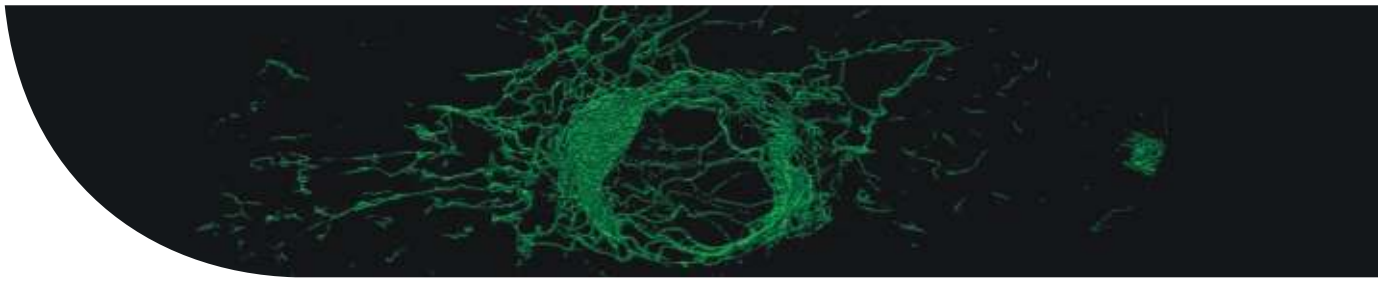
Work Achieved

We have developed tough dual crosslinked fibers with improved mechanical properties and stability by calcium ions to further cross-link the first amide network of alginate and keratin (Fig. 1a). Extracted keratin was chemically crosslinked with alginate in different ratios and crosslinker density to prepare dope respectively. Crosslinking density was assessed by the ninhydrin test (Fig. 1b). Uniform sized fibers were drawn in the coagulating bath of calcium chloride using the dopes of various ratios. FTIR plot confirmed fabrication of crosslinked fibers. Mechanical study showed the highest tensile strength for fibers with keratin/alginate ratios of 1:4, 10 mM EDC compared to that of the other fibers (Fig. 1c).

Human hair keratin is one of the most abundant and easily available natural protein sources. It is reported in previous studies that the hair keratin has great potential for cellular activities, has low immunogenicity and good haemostatic properties. However, as a biomaterial, handling of pure keratin is difficult owing to its low mechanical properties and therefore it is difficult to use the keratin alone in biomedical applications. To overcome this problem we have chemically crosslinked the hair keratin with alginate via 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC). In the current study, we have prepared novel keratin alginate crosslinked fibers by wet spinning technique. The hemolytic potential study concluded that the keratin-alginate crosslinked fibers had significantly lower haemolytic potential than the positive control. Blood clotting experiment showed that the keratin-alginate crosslinked fibers have good hemostatic potential (Fig. 2).

Future Research Plans

Our future plan is to develop 'smart' medical textile for applications, such as wound dressing, Hernia mesh, post-surgical adhesion preventive barrier, hygiene products, etc fabricated by rapid prototyping, weaving, knitting, nonwoven, and Fiber-hydrogel composite. We are also interested in understanding how fibrous extracellular matrix components such as collagen, keratin are organized within the tissue construct by simulating anatomical orientation, and how they influence cellular behavior.



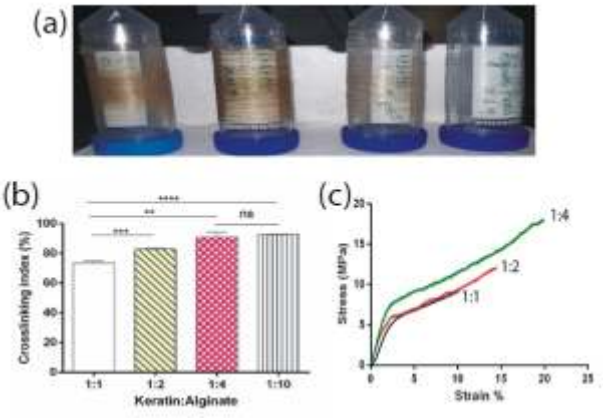


Fig. 1 (a) Fabricated crosslinked Keratin-alginate fibers. (b) Cross-linking index of dopes with various keratin: alginate ratio keeping crosslinker concentration constant at 10 mM. (c) Representative stress-strain graph of crosslinked keratin-alginate fibers.

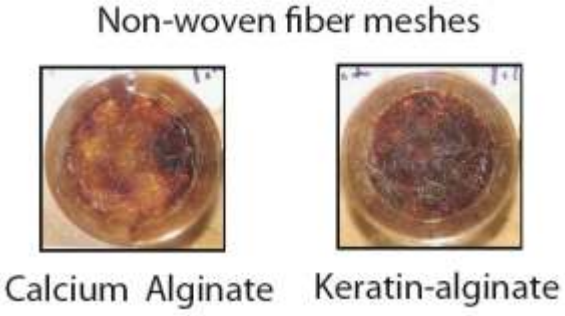


Fig. 2: Digital photographs of blood clotting experiment on the non-woven fiber meshes

PATENTS FILED / SEALED
Paulomi Ghosh

Patent Title: Microspheres containing decellularized donor tissue and their use in fabricating polymeric structures
Country(ies): US
Patent No. WO-2019084432-A1
Date filed / granted: 2019/05/02
Co-inventors and their Institutes:
Lin, Chia-Ying James, University of Cincinnati
Gruber, Stacey, University of Cincinnati
Whitlock, Patrick W., Cincinnati Children's Hospital Medical Center
Patent filed by DBT / CSIR-IICB / another organization: University of Cincinnati, USA

EXTRAMURAL FUNDING
Paulomi Ghosh (PI)

Local delivery of microspheres containing decellularized extracellular matrix for neo-cartilage formation and reduction in osteoarthritis inflammation in an animal model. 2017-2022. Sponsor: Inspire faculty research award, Department of Science and Technology, Govt. of India, India.

CONFERENCES / WORKSHOPS
No of abstract India: 2

INVITED TALKS BY CSIR-IICB FACULTY

Paulomi Ghosh, 3D Printed Construct Incorporating Decellularized Chondral Matrix for the Treatment of Large Cartilage Defects. 5th International Conference on Materials for the Millennium, Kochi, India, 14-16 March, 2019.

Dr. Sandip Paul

sandippaul@iicb.res.in

Understanding Human Microbiome in Health and Disease

Participants

Dr. Rachana Banerjee, RA
Abhishake Lahiri, SRF

Collaborator(s)

Narayana Superspecialty Hospital, Howrah

Background

The human body is home to numerous microorganisms, including bacteria, archaea, viruses, and fungi, collectively known as microbiome. In the past year, advances in the genomic technologies like high-throughput DNA sequencing and metagenomics, revealed the highly diverse nature of the microbial communities and their crucial role in human health and disease. Human microbiome related studies have revealed intriguing association between specific patterns of microbial diversity and several aspects of host health, including autoimmune disorders, inflammatory bowel disease and even psychiatric conditions. Several studies have indicated that the oral microbiome has a role in the maintenance of oral health and a dysbiosis may be associated with disease. In this study the oral microbiota was assessed in healthy individuals and patients suffering from oral cancer associated with tobacco chewing habits in the Eastern Indian population. Oral cancer is one of the leading causes of cancer deaths in India and its high prevalence in India is linked to several risk factors of which the most important is tobacco chewing habit.

Aims and Objectives

1. Exploration of microbial community and metabolite potential associated with the cancerous state.
2. Comparison of co-operation dynamics of oral microbial community between healthy and disease state.
3. Identification of microbial signatures associated with oral cancer.
4. Metabolic model based prediction of the host-microbiome cross talk in order to get more mechanistic insights into nature of these diseases.

Work Achieved

From initial analysis of changes in the oral microbiota associated with development of OSCC in individuals in comparison to healthy oral-microbiota, we explored enrichment of some genera in oral cancer patients, while simultaneously several other genera were significantly decreased. This pattern of relative abundance of these genera of bacteria can potentially distinguish the oral cancer samples from the healthy ones.

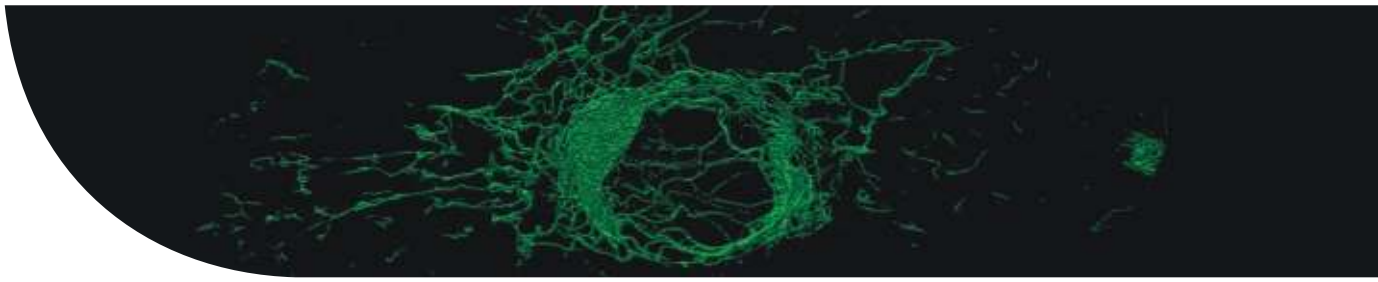
In another work by using comprehensive pan-genomic and functional approach we created a novel dynamic web-resource called PanGFR-HM (http://www.bioinfo.iicb.res.in/pangfr-hm/). The resource integrates genomic and functional characteristics of complete bacterial and archaeal genomes available from Human Microbiome Project and allows users to explore both genomic and functional diversity and phylogenetic relationships between human associated microbial genomes, not provided by any other resource. The two main features implemented here perform pan-genome and functional analysis of organisms based on taxonomy or body-site, and comparative analysis between groups of organisms. In addition, the first feature can pinpoint putative gene-loss events and significantly over/under represented KEGG/COG categories within pan-genome. The unique second feature can perform comparative genomic, functional and pathways analysis between 4 different groups of microbes. Options for user define parameters for orthologous clustering and selection of any set of genomes render the dynamic nature of this resource. We applied this resource for the body-site wise comparative analysis for 67 Lactobacillus genomes isolated from human gut, oral cavity and urogenital tract and identified body-site specific genes, enzymes and pathways.

Future Research Plans

Studying microbe-microbe interactions within clinical settings for cancer could play a pivotal role in the development of microbiome beneficial services to their host through identification of set of metabolites for which microbes compete. This will help us in the studies of dietary-based intervention efforts, safe drug development, early diagnosis, probiotics and prebiotics in cancer prevention.

PUBLICATIONS

Banerjee R., Shine O., Rajachandran V., Krishnadas G., Minnick M. F., Paul S., Chattopadhyay S. (2019) Gene duplication and



deletion, not horizontal transfer, drove intra-species mosaicism of Bartonella henselae. Genomics, S0888-7543(18)30730-4.

Chaudhari N. M., Gautam A., Gupta V. K., Dutta C., Paul S. (2018) PanGFR-HM: a dynamic web resource for pan-genomic and functional profiling of human microbiome with comparative features. Front. Microbiol. 9: 2322.

EXTRAMURAL FUNDING

Systems level metabolic model of human microbiota: prospective application in human health. 2016-21. (SERB, DST, Govt. of India)
Developments in Indian Genetic Disease Database: updation, analysis and inclusion of complex diseases. 2019-22. (DBT, Govt. of India - approved)

CONFERENCES / WORKSHOPS
Give numbers only: 3

INVITED TALKS BY CSIR-IICB FACULTY

March 2019: National Symposium on “Modern Perspective of Research & Development in 2019 Biochemistry & Biophysics”, Dept. of Biochemistry & Biophysics, University of Kalyani.

March 2019: “Kolkata Gynaecological Oncology Trials and Translational Research Group (KolGOTrg)” 1st annual meeting, Biswa Bangla Convention Center, Kolkata,

Business Development & Intellectual Property Management Group

Members :

Dr. Arun Bandyopadhyay (Head), Dr. Aparna Laksar (BD Nodal Officer), Mr. Arupesh Majumer, Mr. Madan Halder and Mr. Saibal Giri

Business Development

CSIR-IICB is essentially engaged in R&D activities on diseases and certain biological problems of global interest. It conducts basic and applied research on infectious diseases like leishmaniasis and cholera, and is also engaged in developing technologies for the diagnosis, immune-prophylaxis and therapy of various diseases. Over the past years CSIR-IICB has developed several successful products like Asmon and Prostalyn which are in the market. It is now putting more emphasis on quality basic research with strong emphasis on applied aspects. We are in constant dialogue with many industrial houses for closer partnership for translating its R&D to products of societal benefit. The BDG is the technology transfer arm of CSIR-IICB facilitating the protection of intellectual property and also for marketing the inventions and knowhow generated by the scientists.

BD division of CSIR-IICB strives to maintain strong relation with relevant industries in India and abroad and aim to help co-develop and also translate the technologies and innovations

Vision

To provide necessary support and encouragement of scientists and Technical Personnel's with the objective of converting basic R&D to products for commercial application and societal benefit.

Goals and objectives

To protect, promote and market commercially promising inventions and know how's developed at CSIR-IICB.
To scout for the right fit for each IP available with the institute
To deliver manage and optimize knowledge transfer to domestic and global market though various BD activities and services.

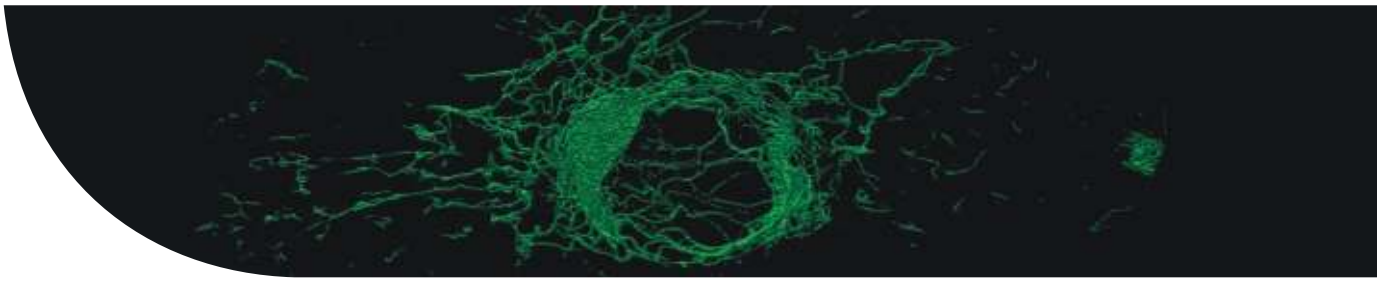
Major activities of BDG

- Liaison with private industries/R&D institutes/academic institutions and other potential clients.
- Negotiating business plans with industries and corporate houses and implementing them, and also drawing relevant MoAs ans MoU's for co-development and licensing
- Business partnership and co development negotiations.
- Arranging and conducting meetings between institute and industry/corporate clients, and interaction with scientists.
- Licensing/transfer of in house technologies and know-how's to industries and interested companies
- Preparation of knowledge base/products developed, dissemination of information on technologies developed etc.
- Distribution of royalty earned.
- Assistance for technical services and consultancy to companies and industrial houses.

Intellectual Property Management

CSIR-Indian Institute of Chemical Biology is continuously developing its knowledgebase through world class science and innovation. All innovations of CSIR-IICB having potential for commercialization are protected through patents and copyrights by its Intellectual Property Management (IPM) cell. The IPM cell of CSIR-IICB, in co-ordination with Innovation Protection Unit (IPU) of CSIR, is engaged in protecting the technologies developed with an objective to put forward these technologies towards the benefit of common people in our country and abroad. With the help of a new Comprehensive Patent Database prepared by this cell, now brief information about a patent filed by CSIR-IICB, since 1990 is just a click away.

This cell maintains liaison with Scientists of CSIR-IICB and IPU, CSIR to protect Intellectual Properties of CSIR-IICB/CSIR. The IPM Cell, CSIR-IICB provides all information, clarifications, explanations and reports to IPU, CSIR regarding patent applications, granted patents and renewal or lapsing of existing patents in consultation with concerned inventors within the prescribed time-limit. This cell functions with advice from Head, BDG & IPM Cell and Patent Advisory Committee whenever required. The IPM Cell always extends co-operation to the inventors, CSIR-IICB in writing and filing patent applications and prosecution of filed applications. IPM cell, CSIR-IICB provides necessary information to Business Development Group and Project Monitoring & Evaluation Division of CSIR-IICB for technologies developed, patents filed and granted; provides information on patent and technology to IPU, CSIR regarding Audit and Parliamentary Question; prepares year wise documents on total Patents of CSIR-IICB filed and granted.



Some of the significant works done are as follows:

1. Reviewed renewal and lapse of Indian and Foreign patents in force, patent applications and recommendations prepared for each patent/application. The documents sent to IPU, CSIR for necessary action.
2. Prepared Commercial Working Report for 10 Indian Patents in force of CSIR-IICB and sent to IPU, CSIR.
3. Response provided to IPU, CSIR regarding IPER, IPRP, OA, Designated Countries and other queries relating to patent application and filing.
4. Appropriate actions taken on execution of legal documents required for patent application, filing and prosecution.
5. Year wise documents prepared on total Patents of CSIR-IICB filed and granted.
6. Information on patent and technology transfer to IPU, CSIR regarding Audit and Parliamentary Questions.
7. Maintenance of CSIR-IICB Patent Database to keep it up-to-date

During reporting period, the performance at a glance of IPM Cell is as follows:

Patents Filed:

Indian Patents Filed

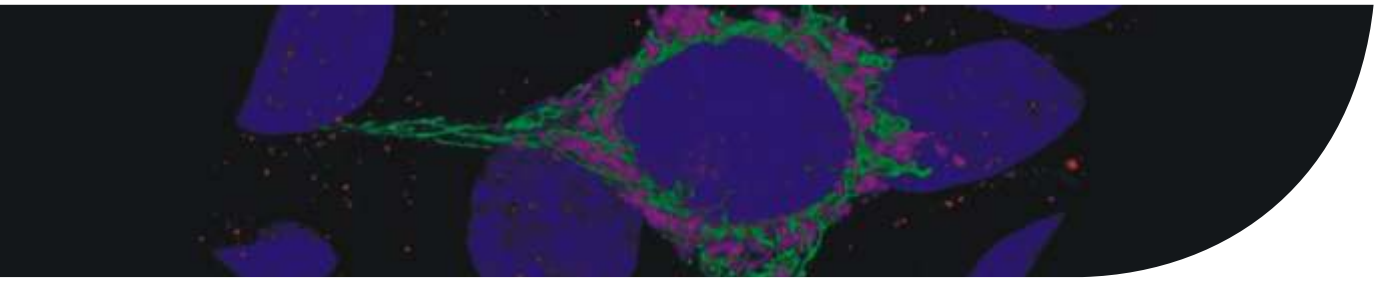
Complete Filed:	…	**4**
Provisionally Filed:	…	**1**
International Patents Filed	…	**6**

Patents Granted:

Indian Patents Granted	…	**2**
International Patents Granted	…	**2**

Complete Filed in India

SNo	Title	Inventors	Comp. Filing Date
1	PEPTOID OF FORMULA I, PHARMACEUTICAL COMPOSITIONS AND METHOD FOR PREPARATION THEREOF	SURAJIT GHOSH, KRISHNANGSU PRADHAN, GAURAV DAS, PRASENJIT MONDAL, SURAJIT BARMAN, SUBHAJIT GHOSH	04/May/2018
2	BICYCLE TOPOISOMERASE I INHIBITING COMPOUNDS, PROCESS FOR PREPARATION AND USE THEREOF	ARINDAM TALUKDAR, BENU BRATA DAS, BISWAJIT KUNDU, DIPAYAN SARKAR, SOURAV PAL, DEBOMITA BHATTACHARYA , AYAN MUKHERJEE, SUBHAJIT ROY, SRIJITA PAUL CHOWDHURI , SUBHENDU K DAS	29/May/2018
3	NONAPEPTIDE OF FORMULA I, PHARMACEUTICAL COMPOSITIONS AND METHODS FOR PREPARATION THEREOF	SURAJIT GHOSH, PRASENJIT MONDAL, GAURAV DAS, JUHEE KHAN, KRISHNANGSU PRADHAN	01/Jun/2018
4	PHARMACEUTICAL FORMULATIONS FOR MANAGEMENT OF CANCERS	CHITRA MANDAL, ESWARA MURALI SATYAVARAPU , BIKAS CHANDRA PAL	13/Dec/2018

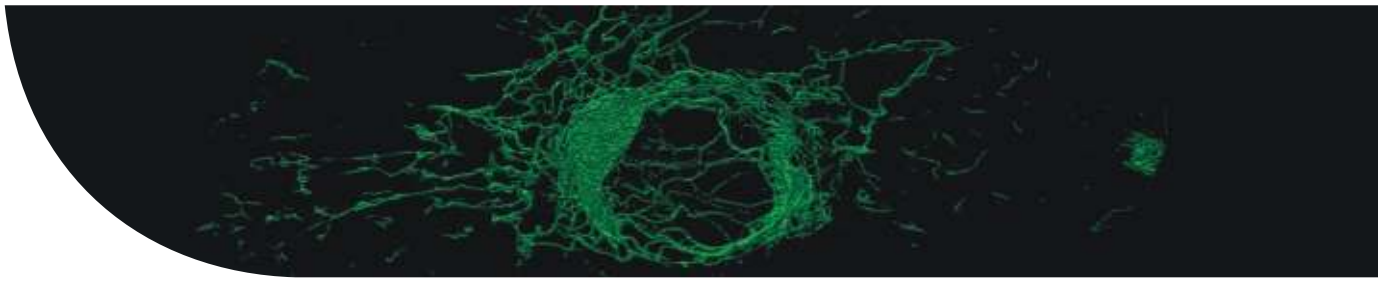


Provisionally Filed in India

SNo	Title	Inventors	Comp. Filing Date
1	BIOMARKER AND AN IN-VITRO METHOD FOR HEAD & NECK CANCER PROGNOSIS [NMITLI Project IICB/TCG/P Ally Hospital/ISI]	Sultan Pradhan, Susanta Roychoudhury, Surajit Ganguly, Rajan Kannan, Sucheta Tripathy, Sanjib Dey, Dipanjana Datta De, Pijush Das, Indranil Mukhopadhyay, R F Chinoy, Rajesh Munde, Arnab Chaudhry	15-May-2018

Filed in Foreign Countries

SNo	Title	Inventors	Country	Comp. Filing Date
1	BLOCKING TOLL-LIKE RECEPTOR 9 SIGNALING WITH SMALL MOLECULE ANTAGONIST	ARINDAM TALUKDAR, DIPYAMAN GANGULY, BARNALI PAUL, AYAN MUKHERJEE, SHOUNAK ROY, SWARNALI ROY, AMRIT RAJ GHOSH, ROOPKATHA BHATTACHARYA, OINDRILA RAHAMAN, BISWAJIT KUNDU	USA	20/Sep/2018
2	BLOCKING TOLL-LIKE RECEPTOR 9 SIGNALING WITH SMALL MOLECULE ANTAGONIST	ARINDAM TALUKDAR, DIPYAMAN GANGULY, BARNALI PAUL, AYAN MUKHERJEE, SHOUNAK ROY, SWARNALI ROY, AMRIT RAJ GHOSH, ROOPKATHA BHATTACHARYA, OINDRILA RAHAMAN, BISWAJIT KUNDU	CANADA	20/Sep/2018
3	BLOCKING TOLL-LIKE RECEPTOR 9 SIGNALING WITH SMALL MOLECULE ANTAGONIST	ARINDAM TALUKDAR, DIPYAMAN GANGULY, BAR NALI PAUL, AYAN MUKHERJEE, SHOUNAK ROY, SWARNALI ROY, AMRIT RAJ GHOSH, ROOPKATHA BHATTACHARYA, OINDRILA RAHAMAN, BISWAJIT KUNDU	AUSTRALIA	20/Sep/2018
4	BLOCKING TOLL-LIKE RECEPTOR 9 SIGNALING WITH SMALL MOLECULE ANTAGONIST	ARINDAM TALUKDAR, DIPYAMAN GANGULY, BARNALI PAUL, AYAN MUKHERJEE, SHOUNAK ROY, SWARNALI ROY, AMRIT RAJ GHOSH, ROOPKATHA BHATTACHARYA, OINDRILA RAHAMAN, BISWAJIT KUNDU	EUROPE	16/Oct/2018
5	PURINE BASED COMPOUNDS AS TOLL-LIKE RECEPTOR 9 ANTAGONIST	ARINDAM TALUKDAR, DIPYAMAN GANGULY, AYAN MUKHERJEE, BARNALI PAUL, OINDRILA RAHAMAN, BISWAJIT KUNDU, SWARNALI ROY, DEBLINA RAYCHAUDHURI	WORLD	05/Nov/2018
6	Pharmaceutical Formulations for Management of Cancers	CHITRA MANDAL, ESWARA MURALI SATYAVARAPU , BIKAS CHANDRA PAL	WORLD	13/Dec/2018

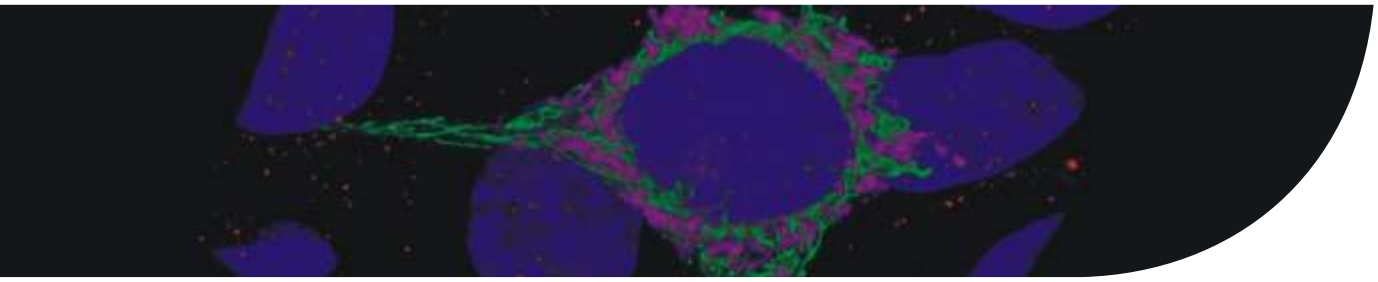


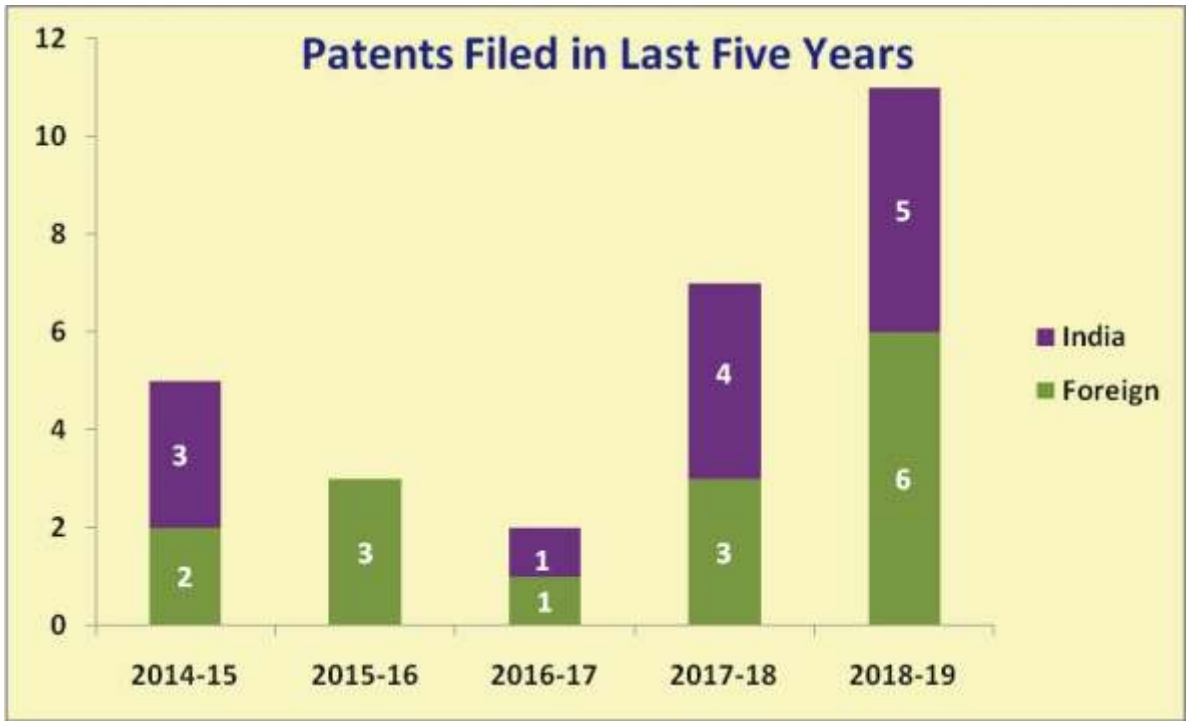
Filed in Foreign Countries

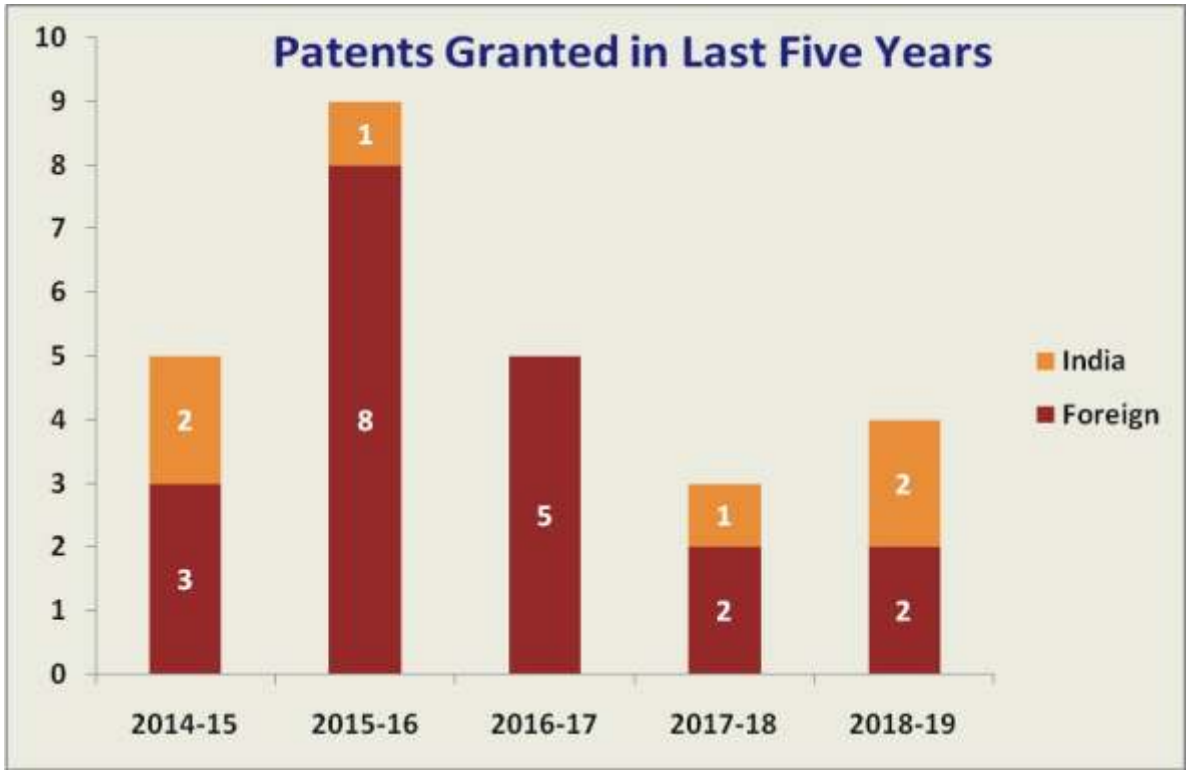
SNo	Title	Inventors	Grant Date	Patent No.
1	ANTI-LEISHMANIAL ACTIVITY OF PARAMOMYCIN ENTRAPPED IN CATIONIC LIPOSOMAL FORMULATION	NAHID ALI, ANTARA BANERJEE	27/Jun/2018	298145
2	COMPOSITIONS AND METHODS FOR DELIVERY OF PROTEIN-CODING RNAs TO CORRECT MITOCHONDRIAL DYSFUNCTION	SAMIT ADHYA	30/Jul/2018	299427

Granted in Foreign Countries

SNo	Title	Inventors	Country	Grant Date	Patent No.
1	A HEXAPEPTIDE INTERACTS WITH TUBULIN/MICROTUBULE AND EXHIBITS SIGNIFICANT NEUROPROTECTION AGAINST AB TOXICITY THEREOF	SURAJIT GHOSH, ATANU BISWAS, BATAKRISHNA JANA, SASWAT MOHAPATRA, SUBHAS CHANDRA BISWAS, SURAIYA SALEEM, PRASENJIT MONDAL, ANINDYASUNDAR ADAK, SUBHAJIT GHOSH, ABHIJIT SAHA, DEBMALYA BHUNIA	USA	16/Oct/ 2018	10100082
2	BIOMARKER FOR VALVULAR HEART DISEASE	ARUN BANDYOPADHYAY, TANIMA BANERJEE, SOMADITYA MUKHERJEE, SANTANU DUTTA	ARIPO	12/Feb/ 2019	AP 4731




Patents Filed in Last Five Years
12
10
8
6
4
2
0
3
2
3
1
1
4
3
5
6
2014-15
2015-16
2016-17
2017-18
2018-19
India
Foreign

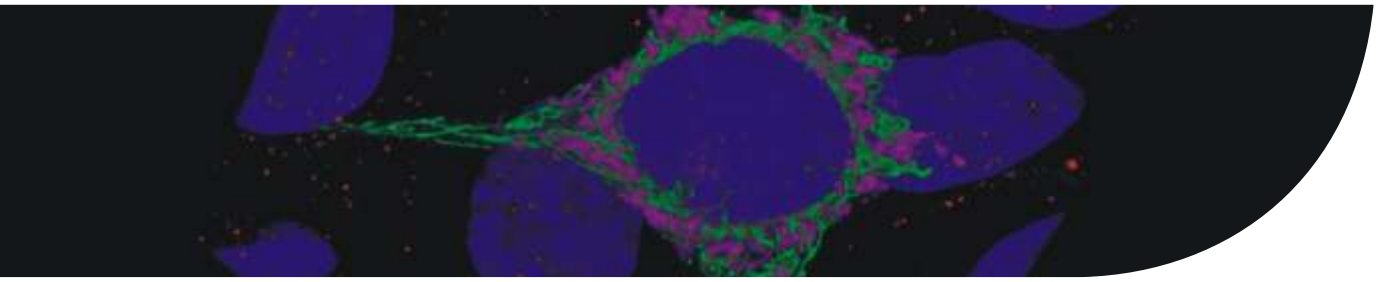

Patents Granted in Last Five Years
10
9
8
7
6
5
4
3
2
1
0
2
3
1
8
5
1
2
2
2
2014-15
2015-16
2016-17
2017-18
2018-19
India
Foreign

Central Instrumentation Facility Division

Members :

Dr. Sib Sankar Roy (Head), Dr. Indubhusan Deb (Deputy Head), Dr. Umesh Prasad Singh, Dr. Mrs Shila Elizabeth Besra, Dr. Tapas Sarkar, Dr. RamdhanMajhi, Dr. Ardhendu Kumar Mandal, Mr. R. N. Mandi, Dr. E. Padmanaban, Mrs. Banasri Das, Mr. Diptendu Bhattacharya, Mr. Sandip Chowdhury, Mr. Sandip Chakraborty, Mr. Jishu Mandal, Mr. T. Muruganandan, Mr. Bhaskar Basu, Mr. Binayak Pal, Mr. Sounak Bhattacharya, Mr. Soumik Laha, Mr. Sandip Kundu, Mr Anirban Manna, Mr. Santu Paul, Mr. M. Vigneshwaran, Smt. Dipika Roy, Mr. Tapas Chowdhury, Mr. K Suresh Kumar, Mr. Tarak Prasad Nandi, Mr. Hari Shankar Beni, Mr. Nimai Charan Pradhan and Mrs. Arpita Maji.

Central Instrumentation Facilities (CIF) Division not only provides facilities and support to researchers at CSIR-IICB, but it also offers services to researchers from different academic and R&D organizations, including Universities and Colleges. The objective of these state-of-the-art facilities is to provide accurate experimental data to the researchers with the help of sophisticated instruments. We now have about more than thirty high end and sophisticated instruments in CIF, which provides an excellent opportunity for researchers all over the country. Most of these instruments have dedicated and well-trained operators for smooth running and high-quality data acquisitions. This is indeed a pleasure for us to share that a few new types of equipment, like Single Crystal X-Ray Diffraction facility (small and macro), Label-free BLI detection system, Multimode Reader has been inducted to the facilities this year. The deionized water systems are kept under the CIF facility on both the campuses of IICB, which solved a lot of problems for the users. We plan to procure more high-end instruments in the coming years.



CIF-IICB organizes special hands-on training sessions in a regular fashion for students as well as staff members of our Institute as well as for the members from other Institutes to train them about the principle and application. CIF at IICB has also demonstrated and trained college students about different instruments. For the research fellows of our Institute, course work is mandatory to pursue PhD and in this course work, Instrumentation and techniques happen to be a paper each student must opt for. In this course, theoretical and practical aspects of relevant Instruments for Biology and Chemistry students are provided by the experienced faculty and the technical operators.

The list of the instruments of CIF is available on the IICB-webpage with their physical location. The process of booking the time slot to use the instruments are mentioned for most of the instruments. Now booking with AnalytiCSIR portal has been initiated. As per CSIR guideline, in due course all bookings will be made through this portal. CSIR's objective is to share all major R&D facilities to research community all over India in a transparent time-sharing manner, on a payment basis. “AnalytiCSIR” is a web-based portal and a gateway for common users to locate the nearest CSIR facility which is required for their R&D activities. CIF at IICB has the motto of providing service to each and every user of our Institute as well as external users, where maximum possible service is provided to satisfy the need of all. The process of booking instruments, data collection, etc have been simplified, which allows easy access to these instruments for all.

We still feel that there is a lot of scopes to further improve the service and CIF. We need a sophisticated TEM instrument, confocal microscopes, and some other high-end instruments. This year different rooms of the CIF unit are extensively renovated and this will provide better logistics for service to the researchers. We are planning to reorient the places of some instruments so that similar type of instruments is kept in close proximity.

Under Science dissemination and popularization Scheme by CSIR-IICB the CIF is taking care of extending all sorts of support to the recipient students and faculties. The instrument facility was showcased to many students came from colleges and Universities on several occasions and these instruments include NMR, LCMS, AFM, XRD, FACS, etc. In the 'Jigyasa' program, the instruments of CIF are shown to the school students. In addition, during the open day program, the school students visit our facility throughout the day.

It gives us immense pleasure that the data generated out of the instruments of CIF are included in many papers published by scientists at IICB and other Institutes. The number of such papers in each year is very high and it is increasing every year. Although our objective is to provide satisfactory service to the users, in parallel our division is earning a considerable amount of revenue. Finally, with the help of all concerned, CIF at IICB is dedicated to providing excellent service to the researchers of the nation.

Computer Division

CSIR-IICB Jadavpur Campus Members :

Dr. SuchetaTripathy, Principal Scientist, Head, Dr. Subhagata Ghosh, Principal Technical Officer, Deputy Head, Mr. Pradeep Sypureddi, Technical Assistant, Mr. Shiv Kumar Gupta, Technician (1)

CSIR-IICB TRUE Salt Lake Campus Members :

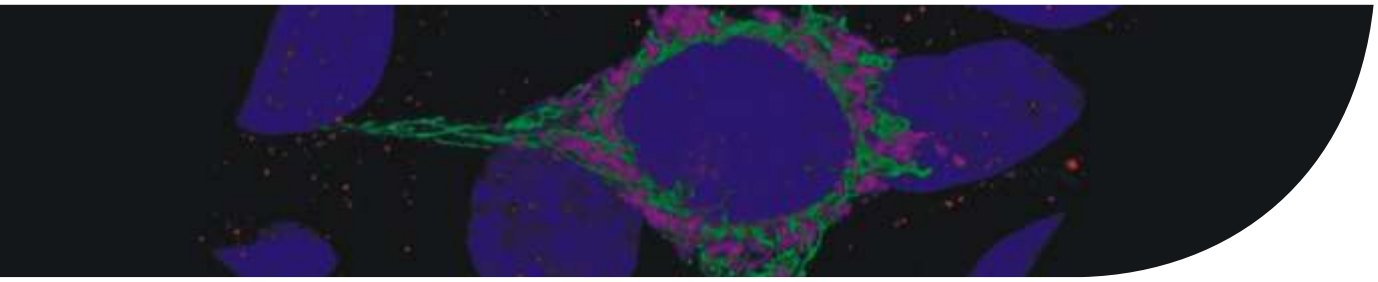
Dr. Saikat Chakrabarti, Principal Scientist, IT In-charge, Mr. Akash Gupta, Technician (1)

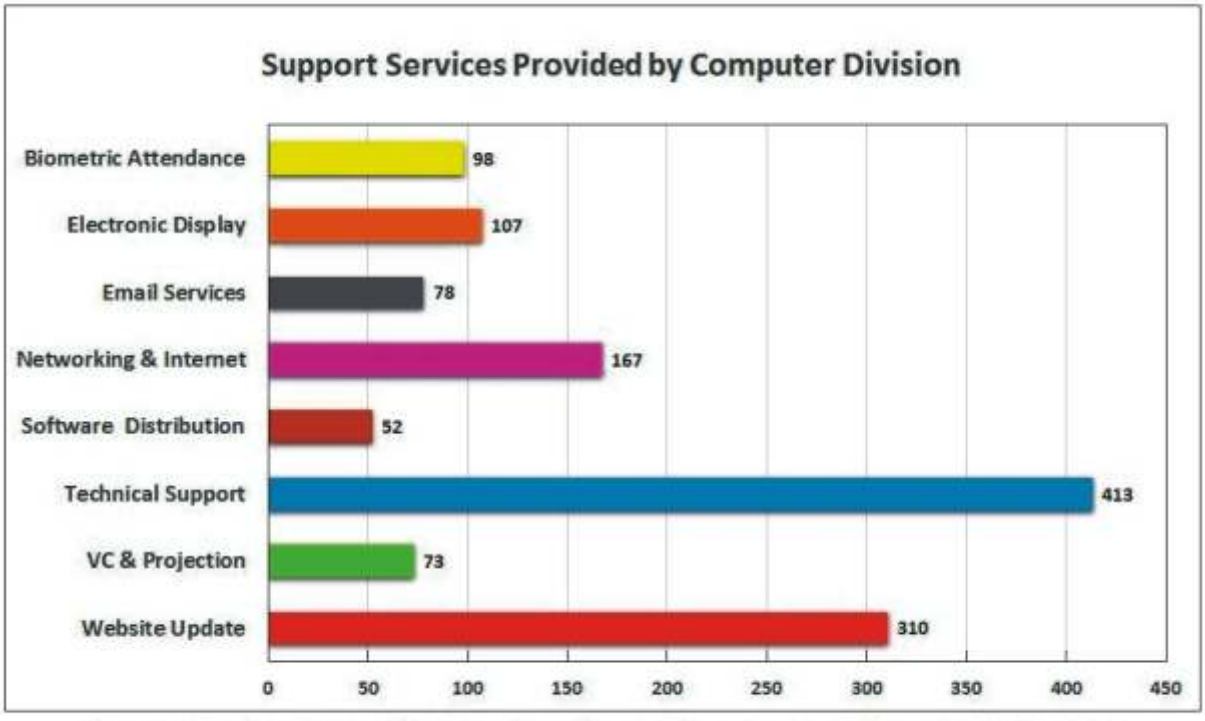
Introduction:

Computer Division provides the primary IT support to the scientists, students and staff members of CSIR-IICB. The IT group works towards maintaining the uninterrupted services to both the campuses of the Institute. It has been in the forefront of deploying information technologies towards modernizing the IT infrastructure.

The Division helps in providing support to Desktops, Laptops, Printers, Scanners, Software's, Video Conferencing, Biometric Attendance System and Network Infrastructure services from time to time along with setup, maintenance and procurement.

The Division also provides secured network services including the design of campus wide LAN/WAN solutions and internet/intranet solutions besides providing computing services to ongoing R&D projects and conducting periodical training programs. The Division has extended its services to CSIR-IICB TRUE, Salt Lake campus through Point to Point connectivity of bandwidth capacity 10 Mbps.





As per the back-end record of Online IT Service Booking Portal total jobs completed = 1298
During 15.10.2018 - 31.03.2019

MAJOR ACHIEVEMENTS IN 2018-2019: Few steps towards modernization

1. New CSIR-IICB Website & Intranet as per Government Website Compliance Rule Introducing and Representing the Institute to the World
2. New website has encryption technology for data security with SSL certificate Ensuring Digital Safety
3. In-House Designed Online Portal for registering job requests for technical support (Ticketing System) Time Management
4. Modernization of Digital Display Facility extending to IICB TRUE campus Quick Catering of In-house Information
5. Extension and Up-gradation of Video Conferencing Facility Faster Communication
6. High speed long range Wi-Fi connection within CSIR-IICB, Jadavpur Campus Uninterrupted Wireless Internet Support

NEW CSIR-IICB WEBSITE

The New Website of the Institute had been launched by the Dr. Sekhar C. Mande, Director General, CSIR on 21.01.2019.

DG CSIR Dr. Sekhar C. Mande Launching the new CSIR-IICB Website on 21st January 2019

Features in the New Website
Main Website: https://www.iicb.res.in

1. Govt. Compliances, Bi-lingual - English & Hindi (under construction), Multi Device Compatibility
2. Multiple Colour Theme, Font Size and higher contrast option for enhanced readability.

3. Multi Device Compatible and Dynamic behaviour
4. Fast loading of full site including images
5. Up arrowfor quickly reaching the main menu.
6. People Search options for
   (i) Faculties
      a. By name b. By campus
      c. By designation d. By division
   (ii) Administrative and Technical Staff
7. Quick Link to Research Division page
8. Research Divisional Page option for putting up list of publications of the specific division
9. Individual Faculty Page introduced new fields of information about the Faculties
   (i) Research Focus
   (ii) Research Interest
   (iii) Credentials
   (iv) Honours & Awards
   (v) Grant Supports
   (vi) Patents & Publications
   (vii) Products
   (viii) Research Group
   (ix) Alumni
   (x) Current photos
   (xi) Automatic Generation of CV
10. Introduced new areas containing quick information about the Institute in the home page:
   (i) Talks (ii) Conferences
   (iii) Events (iv) News
   (v) Awards (vi) Useful Info
   (vii) Tenders (viii) Careers
   (ix) Notices

Faculties can provide information about talks, conferences, any awards received by them for displaying in the website. Information about the above sections can also be provided by concerned division or person. All information can be listed by clicking Read all button below or can be read individually.

Recruitment or any other career related Advertisements will be found under career panel in the home page.

There is a sorting option for Tenders by specific date, date range and divisions. Expired Tenders can also be retrieved from the Tender archive called “Expired Tenders”. Tender Notices are also available in the home page.

11. In-House Software Links are accessible directly from the home page
12. Additional Information of Institute
   (i) Former Members
      a. Directors b. Faculties
      c. Staffs d. Alumni
13. Album-wise Photo Gallery and Video Gallery are introduced.Event-specific photos can also be uploaded in the event section in homepage.
14. Links for the social media (Facebook, Twitter, Youtube) of the Institute is at the homepage

New CSIR-IICB Website

Features in the New Intranet
Intranet: https://www.iicb.res.in/intranet

1. Can be accessed both Locally (Direct Access) and from outside the Institute (by User ID & Password)
2. Content Search options for Committees & Teams, Intra-news are under Office Memorandum
   (i) by keyword
   (ii) text
   (iii) date
   (iv) date range
3. A special feature called Forum introduced for faculties and students to discuss science, post comment etc. on any research topics or any other issues.
4. Introduced the Staff Directory
5. Categorized E-Forms download is also available in the left side menu.
6. Link to online service booking for Computer Division
7. Links to both Local (LBAS) and AADHAAR (AEBAS) based attendance system

8. A new feature the Event of the month is available in the Event Calendar
9. Latest Publication another new feature
10. CSIR-IICB main website and webmail link are available at the footer and quick links

New CSIR-IICB Intranet

SSL CERTIFICATE

As part of Accessible India Campaign (AIC) (Sugamya Bharat Abhiyan) and Compliance with Guidelines for Indian Government Websites; CSIR-IICB in fore front to install SSL certificate for the institute website. Generally, an SSL certificate is a bit of code on web server that provides security for online communication. When a web browser contacts secured website, the SSL certificate enables an encrypted connection. The SSL certificate for CSIR-IICB New Website has been successfully installed and Now it will accessible through https://iicb.res.in

ONLINE IT SERVICE BOOKING PORTAL

Online IT service booking system had been officially started on 15.10.2018. The above figure is, therefore, showing the data recorded during 15.10.2018-31.03.2019. Before this period the divisional documentation was done manually. The Portal was inaugurated by Prof. Samit Chattopadhyay, Director, CSIR-IICB on 10.08.2019.After the inauguration Computer Division conducted a series of training programs with different divisions of the Institute on the methods of using the portal as all service requests to Computer Division needed to be routed through this system. The software through which the portal was created had been designed in house. It enables the division to help submit online job requests, track their status and catalogue them. This system expedites the process of solving the problems related to malfunctioning of desktops/laptops and computer peripherals, internet connectivity, networking and other IT issues enabling the Institute to create a speedy, modern, scientific and favourable day to day working environment. This also serves the purpose of tracking and documenting day to day activities of Computer Division.

Online IT Service Booking Portal Launching by Prof. Samit Chattopadhyay, Director, CSIR-IICB on 10th August 2018

Training on Registering Job Requests Online at Salt Lake Campus on 4th October 2018

MODERNIZATION OF DIGITAL DISPLAY FACILITY

5 full high definition large Digital display board had been installed (4 in Jadavpur campus and 1 in Salt Lake campus of the Institute) for quick circulation of information. Those hi-end systems can display parallel multimedia content in a single panel and also different content display on different panels at a time. The in-built

content management software brings all 5 panels under central management through remote controlled operating technology.

EXTENSION AND UP-GRADATION OF VIDEO CONFERENCING FACILITY

One of the vital services provided by the Computer Division is Video Conferencing. The Video conferencing facility of Jadavpur Campus has been upgraded with state of art technology with HD Cameras and Display systems along with 7+1 Multi party license. There are three simultaneous VC Facilities installed at Jadavpur Campus to meet the increasing requirement of the Institute. It is also integrated with Video Conferencing facility of Salt Lake campus for frequent intercampus conferencing, meetings and research work.

HIGH SPEED LONG RANGE WI-FI CONNECTION WITHIN CSIR-IICB, JADAVPUR CAMPUS

Wireless Internet Service of the institute (Jadavpur campus) has been upgraded with high speed and long range signal support technology to access internet without cables or wires. The upgraded Wi-Fi system supports maximum wireless signal range of 40 meters with a speed of 1 Mbps to 1.3 Gbps and also works with both frequency Bands of 2.4 GHz & 5.0 Ghz.

Feature Plans:

- Upgradation of Point to Point Connectivity Link between Jadavpur Campus and Salt Lake Campus from 10 Mbps to 30 Mbps
- Extension of Electronic Display Services through Signage Software to Salt Lake Campus of CSIR-IICB, Kolkata via Point to Point Connectivity Link
- Up gradation or Extension of LAN and Wi-Fi System of Salt Lake Campus, CSIR-IICB
- Introducing New NIC Group Email for Student Communication
- Implementation of In house Network Monitoring System for Jadavpur campus and Salt Lake Campus
- Implementation of NIC Quick SMS Services
- Effective Information Portal for Skill Development Cell

Engineering Services Unit (ESU)

Members :

Dr. Rupak K. Bhadra (Head)

Civil Engineering: Sandip Saha, Susanta Ray, Nirali Bage, Debasish Banik, Avijit Paul, Shyamal K Ghosal

Electrical Engineering: Chirantan Debdas, Ujjal Roy, Sourin Ghosh, Saheb Ram Tudu, Abhijit Paul, Samir Majumder, Anup Karmakar, Tanmoy Biswas

Air-conditioning and Lab Supervision: Prosenjit Ganguly, Shubhendu Ghosh, Sanjib Biswas, Prabir Das, Sunil Nath, Manoranjan Adhikary

Works Section: Sujit Majumder and Muktar Ahamed

ESU of CSIR-IICB Kolkata having various techno-commercial activities related to buildings, building services and overall infrastructures of the Institute campuses located at Jadavpur and Salt Lake, Kolkata and Scientists' Apartment premise at P. A. Shah Road, Kolkata. This service section of the institute has three distinct functional Engineering Sections viz. Civil, Electrical and Mechanical (Air Conditioning and Refrigeration) to meet the various requirements related to Engineering Services of the Institute. Presently this section has all total nine Engineers (Junior Engineer to Sr. Superintendent Engineer) and ten Technicians (Technician-1 to Sr.Technician-2). This Engineering Unit always works as a team. Apart from this the Works Section plays important roles to complete all the official formalities of this Division. Beside Engineering and Technical works and services, ESU having various activities like, arranging different Institutional programs in Auditorium, Seminar Rooms, and Conference Rooms at two campuses of the Institute. This Engineering Unit also having direct as well as indirect involvements in providing the services for up-keeping of the Institute campuses including the Guest House (CSIR-IICB Guest House) located at Salt Lake campus.

Civil Engineering Section

The Civil Engineering Section under ESU of CSIR-IICB takes major role to render services in broad areas of infrastructural development, new construction, renovation and up-gradation of laboratories for Scientific Research Activities and common facilities, maintenance of campus, water supply, sewerage and drainage systems, routine and day to day maintenance at both the campuses at Jadavpur as well as Salt Lake.

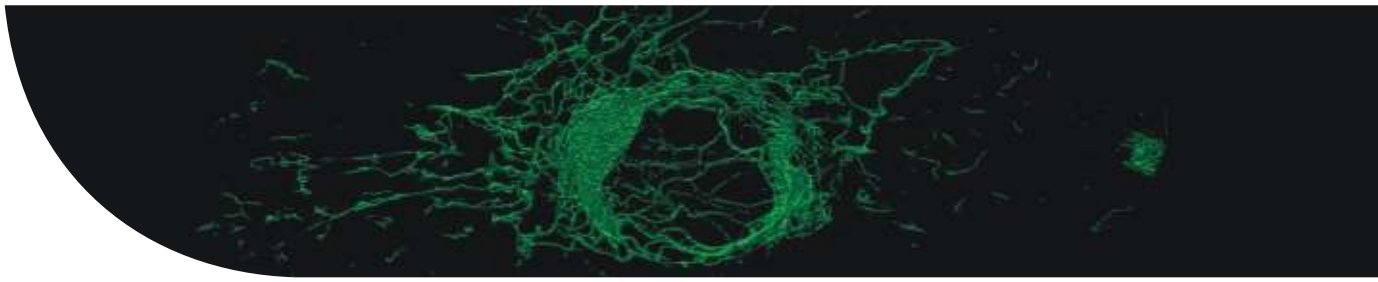
The major repair and renovation works taken up for the reporting year 2018-19 are as follows:

- External repair and renovation of CSIR-IICB building (Phase B) at Jadavpur Campus.
- External repair and renovation of CSIR-IICB building (Phase B balance portion) at Jadavpur Campus.
- Providing and fixing new steel ladder inside service ducts of RL and CF Blocks at CSIR-IICB, Salt Lake Campus.
- Civil works for repair and renovation of toilets at CSIR-IICB Jadavpur Campus.
- Repair and renovation of West side flooring of corridors (3 Nos.) at CSIR-IICB, Jadavpur Campus.
- Repair and renovation of different laboratories and rooms at CSIR-IICB, Jadavpur Campus (Phase A and B)
- Repair and Renovation of Roof Treatment work at Auditorium, Main Building, Nuclear Medicine, Main Library and Library Reading Room Roof at CSIR-IICB, Jadavpur Campus.
- Repair and renovation of boundary wall at CSIR-IICB, Jadavpur Campus.
- Construction of garbage vat at CSIR-IICB, Jadavpur Campus.
- Repair and painting of boundary wall at CSIR-IICB, Salt Lake Campus.
- Setting up of aluminium cubicles at Research Laboratories and other places at CSIR-IICB, Salt Lake Campus.
- Making a service toilet at CSIR-IICB, Salt Lake Campus.
- Replacement of wooden doors by aluminium doors in the Ground floor at CSIR-IICB, Jadavpur Campus.
- Repair and renovation of Conference Room at CSIR-IICB, Jadavpur Campus.

Electrical Engineering Section

Electrical Engineering Section under ESU has various activities and involvements towards overall management of Electrical Power Distribution systems installed at the campuses of CSIR-IICB at Jadavpur and Salt Lake. In addition to this ESU Electrical Section having regular activities for Estimation, Planning, Execution and Monitoring of all types of works related to Electrical Power and associated system including major modernization works.

Following are the particulars of major infrastructural jobs for which Works Proposals were initiated during the reporting period, which have been processed further for necessary implementation following the standard works procedures of CSIR.



1. **Proposal for up gradation of existing Electrical Substation and setting up of 11 KV HT Substation at CSIR-IICB Jadavpur Campus.**

   The Institute campus at Jadavpur having 6.0 KV HT Power with certain HT Switchgears which are about 30 years old and to some extent those is obsolete with respect to the modern system of HT Installations. For the purpose of modernization of existing HT Power system including setting up of more reliable 11 KV Electrical Substation Works proposal was placed in the meeting of Institute Management Council (MC) on 13th March 2019 and same was referred to CSIR-Engineering Services Division (ESD), New Delhi on 25th March 2019 for necessary Technical Sanction and other necessary formalities to go ahead for setting up 11 KV HT Electrical Substation and Modernization of existing LT Power Distribution Networks.

2. **Proposal for repair and renovation of research laboratory building for creation of animal experimentation facility at CSIR-IICB Salt Lake Campus.**

   For the purpose of creation of Animal Experimentation Facility within existing Research Laboratory Building at CSIR-IICB Salt Lake Campus elaborate Works proposal has prepared during the period under report by the team ESU personnel and same was sent to CSIR-ESD, New Delhi on 23rdJanuary 2019 for necessary approval and allocation of desired Fund. Engineers of ESU-Electrical Section modified or upgraded the Technical particulars of different systems and sub-systems in co-ordination with Engineers of CSIR-ESD New Delhi Technical representatives of the manufacturers of various equipment and installations.

3. **Implementation of grid connected roof Top solar photo voltaic (PV) system at CSIR-IICB Jadavpur Campus.**

   Under the major initiative of Ministry of New and Renewal Energy (MNRE) in coordination with CSIR- ESD, New Delhi for implementation of 5.481 MWp Grid Connected Roof Top Solar Photo Voltaic (PV) system at various premises of CSIR across India Feasibility Report has been prepared in January 2019 to install roof top Solar Power Plant at the Jadavpur Campus of CSIR-IICB, Kolkata. At this stage the projected capacity of Solar Electric Power Generation was decided as 222 KWp using the roof top of the main building of the Institute at Jadavpur campus. Later on after detailed survey and study and considering different practical aspects of installation of Solar PV Modules the revised capacity of generating Solar Electric Power has been finalized as 180 KWp, which is about one sixth of the Contract Demand of CSIR-IICB Jadavpur campus. For this purpose engineers of the ESU-Electrical Section kept on co-coordinating Technical representatives of CSIR-ESD, New Delhi, Central Electronics Limited, Sahibabad (UP) and Project Executing Agency M/s Atria Rooftop LLP , Bangalore for detail planning and necessary modifications in the existing Electrical Power Distribution System at CSIR-IICB Jadavpur campus. On implementation of this project of Solar Roof Top Power Plant CSIR-IICB will expected to save electricity consumption charges in the range of approximately Rs.1.50-2.0 Lac per month which will be significant with respect to overall expenditure of the Institute.

Air-conditioning and Lab Supervision Section

Air Conditioning and Lab Supervision section is one of the important functioning groups under ESU. This section has various activities at CSIR-IICB, Jadavpur and Salt Lake Campuses. The important activities performed by this section are as follows:

- Operation service and maintenance of Central Air-conditioning Plants of both the campuses of CSIR-IICB to ensure normal activities of the institute.
- More than 500 split/window ACs as well as ductable AC and VRV AC systems are maintained round the clock by this section.
- A total of 6 Nos. of Lifts are maintained round the clock at both the campuses of CSIR-IICB.
- Two Cold Rooms at different floors of CSIR-IICB Jadavpur campus are maintained properly throughout the year for different scientific purposes.
- Arranging different institutional programs at J. C. Ray Auditorium, Seminar Rooms of Jadavpur campus as well as Seminar Rooms of Salt Lake campus of the institute.
- Providing all necessary services at Salt Lake campus Guest House.
- Up-keeping of the entire institute including material/instrument/furniture shifting, RO Water Purifier maintenance, Pest Control services, garbage cleaning and house-keeping jobs are also under the purview of this section of ESU at both the campuses, Jadavpur and Salt Lake, of CSIR-IICB during the period under report.

Human Resource Group

Members :

Dr. Siddhartha Majumdar, Ms. Arti Grover, Ms. Debasree Das, Md. Ayub Shah

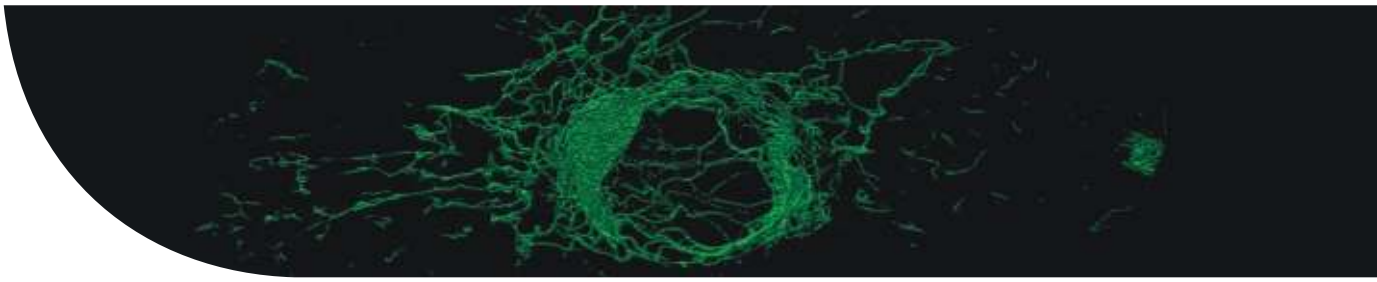
Human Resource Group (HRG) of CSIR-IICB promotes professional Human Resources Management in this institute by evolving and implementing HR development plan. The HRD group is involved in a wide range of Human Resources Development related activities in various areas of PhD student affairs, academic affairs and fellowship related activities. The major area where HR group contributes: Activities related to Academic Administration concerning PhD program, student affairs, post-graduate training programme, and different other training program. HRG co-ordinate in the class room teaching of PhD course work in various program critical to the mission of the Institute.

The functions include: Guidance and co-ordination of different HR development program & talent-management activities. HRG section function as a coordinating centre for the CSIR-IICB PhD course work for the PhD students. Head, HRG serves as the co-ordinator of the "Academic Affairs committee" and also member of the "Academic Committee" of ACSIR-IICB.

Activities, Guidance and Initiatives:

Student Affairs & Academic Affairs

1) PhD course work and PhD program: Management of Course work schedule, course administration and curriculum planning, attendance and class schedule, coordination with the teachers, management of semester examinations, evaluation, seminar, and publication of result, issuance of certificates and statement of marks.
2) Scrutinization of applications for PhD registration and documents of RFs/RAs related to academic affairs and maintenance of PhD registration related information.
3) Scrutinization of academic records, selection and placement of PG summer/winter trainees and co-ordination of this program.
4) Coordination of Academic Affairs committee meeting and content development in this regard.
5) NET JRF entrance interview: Information, web notification, list of number of NET JRFs intake. Maintenance of RFs record for the individual PhD supervisor and associated jobs.
6) Content development for Research fellow's handbook, publication of course catalogue, Teacher's guideline, academic Calendar and different guidelines related to IICB PhD program and PhD course work.
7) Organization of Orientation programme for PhD students.
8) Interacting and coordinating with CSIR HRDC/HRDG and with ACSIR, Lab-Co



Human Resourses : PhD students (as on March 2018)

At a Glance:
Number of existing Research Fellows: 256
(CSIR/UGC/DST/DBT/ICMR)

Summer Training / Project Work / Dissertation Work

HRG coordinates Summer Training Programme for the eligible Post Graduate students of different Universities, Institutions and Colleges for partial fulfilment of their degrees. The aim is to let young minds feel the thrill and excitement of science by working on a project requiring application and critical appreciation of scientific principles. It also aims at active participation in the learning process through experimentation and putting into practice the knowledge acquired in the classrooms.

The summer program is primarily designed to provide the opportunity to do basic research in top-notch research areas, in a supportive learning environment with plenty of interaction with PhD research fellows and faculty members. Detailed guidelines are made available in CSIR-IICB website.

Number of Summer Trainee/Project Trainee (2018-19): 88

Learning and instructional support: Academic Affairs

To conduct and coordinate the IICB PhD course work is the major focus of this Division which includes activities related to CSIR-IICB PhD Course Work program and academic-administrative guidance to the AcSIR activities in this institute.

The CSIR-IICB **"Academic Affairs Committee**" acts as an Advisory Committee to the Academic Affairs Division/HRG in connection with CSIR-IICB PhD program and the AcSIR programme.

CSIR-IICB PhD Course Work **(CW):** CSIR-IICB offers a mandatory PhD course work for the Research Fellows in their first year, taught by faculty members of in-house as well as from other Institutes/Universities. The framing of the course content & guidelines is designed in the line of AcSIR courses as well as per UGC requirement. The curriculum of Course work plays a pivotal role for rejuvenating the creative nature in the scientific area of research.

The existing CSIR-IICB PhD Course Work programme constitutes basic and advanced level courses. The basic course is for bridging the gap between M.Sc. and PhD. The advanced level course comprises of frontline areas of research and covers research methodology and review of current literature.

IICB PhD CW comprises of three level of courses viz 100, 200 & 300 level [total 12 credits]:

Level 100 [basic courses] (Total 4 credits, all compulsory): Computation / Bioinformatics; Basic Chemistry; Introduction to Chemical Biology; Research Methodology, Communication/ Ethics/ Safety; Biostatistics

Level 200 [mid level courses] (Total 4 credits): Biotechniques and Instrumentation, Biology of Macromolecules, Protein Science and proteomics, Molecular and Cellular Immunology, Cell Biology & Cell Signaling, Advanced Analytical Chemistry, Advanced Organic Chemistry, Green Chemistry, Advances in Nanoscience and Nanotechnology.

Level 300 [advanced level Course] (Total 4 credits): Cancer Biology, Eukaryotic Gene Regulatory Mechanism, Cell & Tissue Engineering, Chemical Biology, Natural Products and Drug Discovery, Total Synthesis, Supramolecular Chemistry.

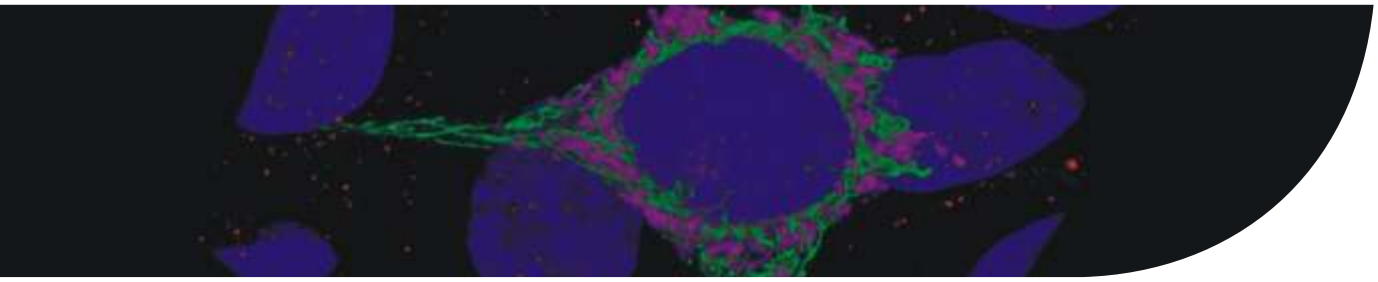
HRG functions as overall coordinating centre of CSIR-IICB PhD course work for PhD students. The PhD course work is carried out with the advice of Chairperson & members of Academic Affairs Committee and also the Examination committee constituted for this purpose.

Total number of Course work students for 2018: 44 (Chemistry - 18 , Biology - 26)

Program organized by HRG-IICB:

An Orientation Program for newly recruited CSIR-IICB PhD Research Fellows was organized on 28th February, 2019 at CSIR-IICB. About 57 students (2019 Course work batch) participated in this program. Dr. Arun Bandyopadhyay, Actg-Director CSIR- IICB, Dr. Uday Bandyopdhyay, Chairperson, AAC, Dr. S. Swarnakar, Dr. K. Chattopadhyay, Dr. Jayati Sengupta and Dr. Siddhartha Majumdar were present in the program. Dr. Majumdar presented about the course content and the overall structure of the course work. Students were provided with the course work materials with an overall guidance towards the new journey at CSIR-IICB.

The Orientation day on 28th Feb, and in commemoration with the National Science Day a Popular lecture was arranged. Prof. Soumitra Sengupta, Senior Prof. IACS delivered an exciting talk on "The Voice of the Cosmos: Einstein and the gravitational wave". Further, Prof. Sengupta motivated the Course work students and



presented the Course completion certificates to the 2018 batch of students.

Invited talk:

Dr. Majumdar was invited to attend and deliver a motivational talk on “At the Intersection of Science & Technology and Art” to enlighten the 8th batch of fresher B.Tech students of Gargi Memorial Institute of Technology, Baruipur, held on 21st August 2018.

Training Programme:

Several CSIR-IICB staff members participated in various training programs as follows:

A. 'Capacity building programme for Engineers & Architects' organized by CSIR-HRDC during 29th to 31st Oct 2018 at CSIR-IICB Salt lake campus. Members participated are:
   1. Mrs. Nirali Bage, Asst. Executive Engineer (Civil)
   2. Shri D. Banik, Asst. Executive Engineer (Civil)
   3. Shri Sourin Ghosh, Jr. Engineer (Electrical)
   4. Shri Ujjal Roy, Jr. Engineer (Electrical)
   5. Shri Shubhendu Ghosh, Jr. Engineer (Air cond.)

B. 'Taxation Laws: Direct & Indirect Taxes' organized by CSIR-HRDC during 26th to 27th Nov 2018 at HRDC Ghaziabad. Members participated are:
   1. Shri Alok Ray, ASO (G)
   2. Shri Atanu Moitra, Sr. Tech. (1)
   3. Shri V. Agarwal, SSA (F&A)

C. 'Capacity building programme for officials of Guest House' organized by CSIR-HRDC during 05th to 07th Dec 2018 at HRDC Ghaziabad. Members participated are:
   1. Shri. P. Gangopadhyay, Superintending Engineer (A.C).
   2. Shri Susanta Ray, Superintending Engineer (Civil)

D. 'Vigilance related matter' organized by CSIR-HRDC during 09th to 11th Jan 2019 at HRDC Ghaziabad. Shri S. Halder, Administrative Officer participated in this program.

Library & Documentation Division
Knowledge Resource Centre (KRC)

Members:

Dr. N. C. Ghosh (In Charge), Dr. Sankar Kumar Maitra, Mr. Swapan Kumar Naskar, Mr. Pallab Mukherjee, Mrs Mahua Bhattacharyya, Mr Shyamal Nath & Mr Asoke Ram

During this reporting period also the Library & Documentation Division (Knowledge Resource Centre) has been continuing its pivotal role as one of the important infrastructure division by providing literature supports to the users. As a growing organism, the division has marked growth in collection, systems, facilities and services.

Collections	Up to 31.03.2018
Books (including Hindi)	14,641
Journals (online only)	130
Bound volumes	33,860
Science-Direct (Back files) (Http://www.iicb.res.in/bkfiles_library.html)	202 journals full text up to 1994
Thesis (CDs)/online	336
Newspapers (English, Bengali & Hindi)	3

National Knowledge Resource Consortium (NKRC), NISCAIR, New Delhi is a very strong network of the CSIR & DST Institutions are jointly working towards catering best possible information services to their users. CSIR-IICB has been accessing in full text of about more than 1500 (thousand) STM journals through NKRC in addition to the subscribed content by IICB.

IThenticate – plagiarism detection service is available in the Library & Documentation Division for reviewing the manuscripts by the researchers.

IICB has been subscribing the **'Web of Science'** and providing various tailor-made services according to the needs of the Scientists.

The Library (KRC) is having a cosy Reading Room with a beautiful e-resources access corner for the users. The other services include photocopying service, Circulation service, Article delivery service through resource sharing, plagiarism checking for the manuscripts and the division has provided various other services during the period under reporting.

E-journals/database access corner with thirty desktop computers

CSIR Virtual Union Catalogue using KOHA

The functions and services of the KRC are computerized using 'LIBSYS'. The **Online Public Access Catalogue (OPAC)** is available at **http://14.139.223.107:8080/webopac/html/SearchForm** which has been utilized as a very useful tool for searching library holdings.

Open Access Repository (IR) maintaining in E-prints for archiving peer reviewed journals articles, Conference papers, Theses and other research documents produced by IICB researchers. The URL for accessing the repository is **http://www.eprints.iicb.res.in.** So far 1850 documents in full-text have been uploaded to the repository.

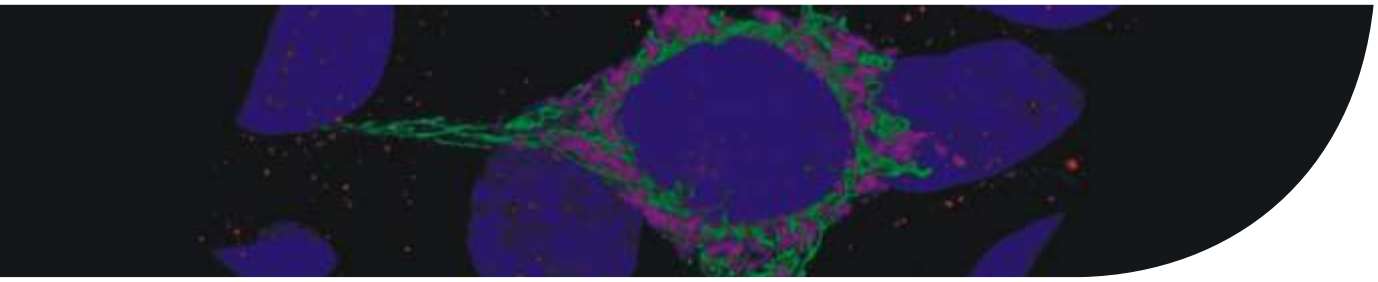
NIPER- Knowledge Resource Centre has been functioning as a separate unit in the library premises since its inception and catering services to the NIPER- Kolkata students and faculty members. The subscription to **'SciFinder Scholar'** was continued until February 2018.

Project Monitoring & Evaluation Section

Members:

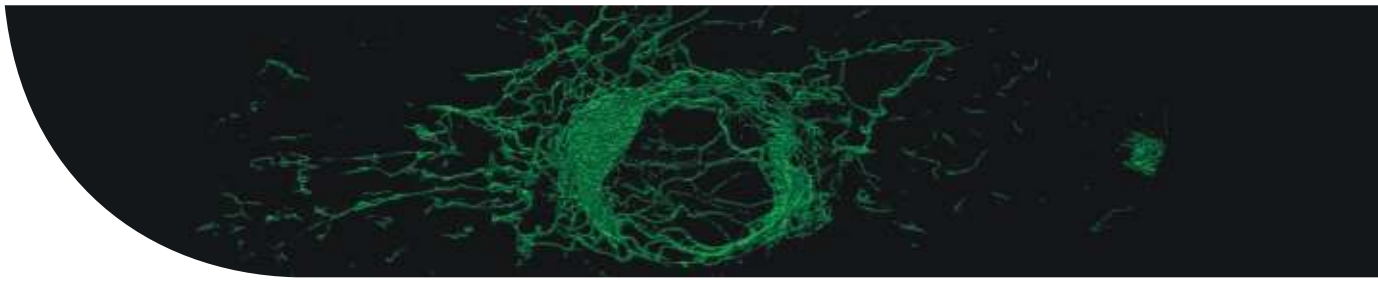
Dr. Rupak K. Bhadra (Head), Mrs. Purnima Chatterjee, Mr. Tapan Das, Mr. Soumalya Sinha and Mr. Samir Thami

The Planning, Monitoring and Evaluation (PME) Division manages the Institute's plan and non-plan projects, grant-in aid projects (GAP), sponsored and collaborative R&D projects, consultancy and technical service projects. This division maintains liaison with Scientists and Technical officers who are Investigators of these projects and liaison with the Finance and Purchase Sections and the funding agencies. PME provides proper logistic support for the management, monitoring and implementation of CSIR funded in house projects (Mission Mode, Fast Track Translational, Major Laboratory Projects etc.) and other externally funded projects that include those obtained from sponsored international agencies. PME's role is effective and successful implementations of the institute's commitments to all R&D endeavours. PME is also entrusted with appropriate dissemination of information regarding ongoing and completed projects to all statutory agencies like CSIR audit party, CAG audit etc. PME of CSIR-IICB, like other CSIR laboratories, is actively involved in the timely preparation and maintenance of databases for all intramural and extramural research projects, monitoring of project expenditure of projects, preparation of responses to Parliamentary queries in relation to the activities of the Institute, dissemination of information on all relevant National and International research program requests. PME from time to time provides information to scientists regarding terms and conditions of funding agencies, timely requirement of progress and completion reports, respectively, of ongoing and completed projects. PME division participates in the preparation of the Institute's annual plan and the budget and maintains the expenditure data, monitors and accounts the receipts of cheques as well as online transfer of fund by the sponsors against the project sanctioned, and request for sanctioned fund, and maintains proper record keeping of all aspects of projects. It does regularly interaction with finance division regarding the expenditure carried out against the projects and prepares the data on this a monthly basis. PME also processes all the relevant requirements for collaborative projects, approvals from competent authorities like Research and Management Councils and from Director enabling smooth and quick submission of new projects to external funding agencies. Details of CSIR and other extramural projects sanctioned during the reporting period (sanctioned, ongoing and completed) are provided as separate lists.



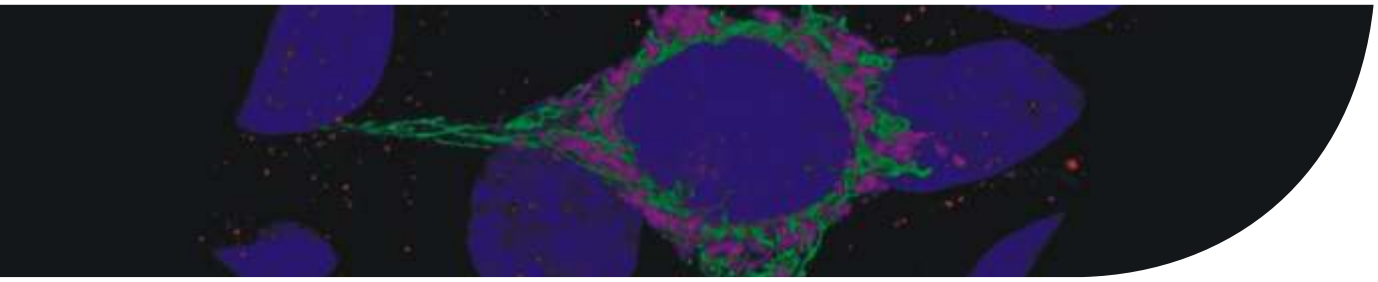
Completed Extramural Projects (2018-2019)

Sl. No	Name of the project	Project Code	Name of PI	Project Cost (Rs. In lakh)	Funding Agency	Start Date	Completion date
1	Identification of eight obligately halophilic cyanobacteria of the Sundarbans and molecular characterization of antimicrobial compounds therefrom	GAP-318	Dr. P Jaisankar	25.000	Minsitry of Earth Science, Govt. Of India	18.07.13	17.09.18
2	Discovery of RNA binding ligands-targeting Hepatitis C virus RNA	GAP-330	Dr. Sanjay Dutta	37.180	DBT, Govt. Of India	01.07.15	31.06.18
3	In vitro and in vivo evaluation of 99mTc(CO)3-labeled RGD conjugated bioreductive pharmacophore and nucleoside analogue for potential use as tumor targeted SPECT radiopharmaceuticals	GAP-331	Dr. Mita Chatterjee Debnath	32.910	SERB, Govt. Of India	13.10.15	31.12.18
4	Molecular Diversity through Cascade C-H activations	GAP-332	Dr. Ranjan Jana	26.900	SERB, Govt. Of India	09.10.15	31.03.19
5	Probing endosomal toll-like receptor 9 biology using novel small molecule antagonists	GAP-333	Arindam Talukder	32.900	SERB, Govt. Of India	26.10.15	25.10.18
6	An insight into the role and regulation of mitochondrial inner membrane upcoupling protein 2 in manipulating host-conducive oxidant-derived macrophage defense mechanism	GAP-334	Dr. Pijush Das/ Dr. Uday Bandyopadhyay	34.900	SERB, Govt. Of India	21.12.15	07.10.18
7	Targetting HSP-90 as cancer therapy: Design and synthesis of mathanine- derived Second-Generation lead molecules	GAP-336	Dr. Biswadip Banerjee	54.800	SERB, Govt. Of India	09.03.16	08.03.19
8	Modulatory role of Quercetin on radiation-induced oxidative stress in human colorectal carcinoma cells : Assessment of possible role of certain trace elements.	GAP-338	Dr. Krishna Das Saha	5.268	DAE, Govt. Of India	01.12.15	30.11.18
9	Evaluation of antileukemic and immunogenicity properties of engineered Escherichia coli asparaginase - II for the treatent of acute lymphatic leukemia in preclinical model	GAP-339	Dr. Chitra Mandal	8.400	SERB, Govt. Of India	12.02.16	11.02.19
10	Transiently formed non-native conformers of transthyretin : structure, function and their roles in formation of amyloid fibrils-[]	GAP-365	Dr. Sujoy Mukherjee	62.248	DBT, Govt. Of India	27.02.17	02.11.18
11	Sglt2 expression in human renal proximal tubular cells for predicting efficacy of Sglt2 inhibitors	SSP 373	Dr. Partha Chakraborti	9.900	RSSDI	10.08.17	09.08.18



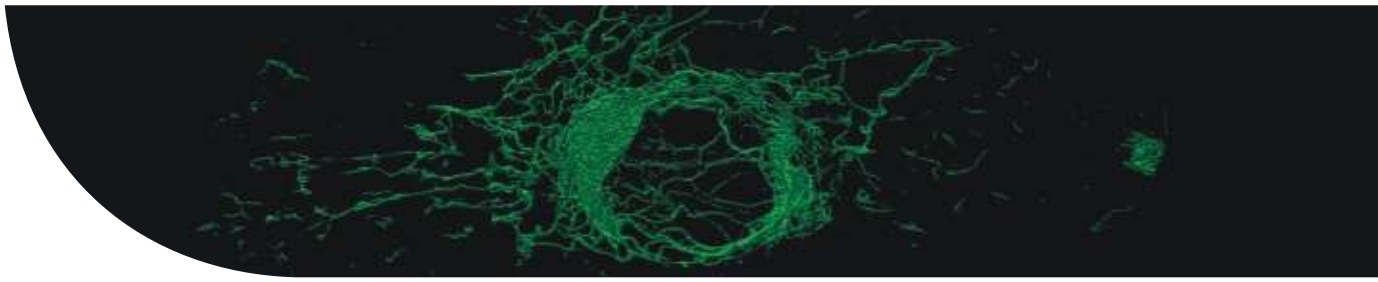
Ongoing Extramural Projects (2018-2019)

Sl. No.	Project Investigator	Title	Project Code	Funding Agency	Project Cost (Rs. In Lakh)	Start date	Completion Date
1	Dr. Debabrata Biswas	Functional characterization of human DBC1 complex in eukaryotic transcriptional regulation and leukemic transformation	GAP 319	Wellcome Trust & DBT	298.080	01.12.14	30.11.19
2	Dr. Rupasri Ain	Transgenic Over-Expression of Nostrin in Mice and Pregnancy - Induced Hypertension	GAP 326	ICMR	50.500	15.03.16	14.03.19
3	Dr. Biswadip Banerji	Targeting HSP-90 as cancer therapy: Design andsynthesis of mathanine- derived Second Generation lead molecules.	GAP 336	SERB, DST	54.840	09.03.16	08.03.19
4	Dr. Pijush K Das/Dr. Rupak K Bhadra	Targeting Deadenlation-Mediated Kinetoplastidae Prasite-Specific Polycistronic Gene Regulation for Therapeutic Intervention	GAP 337	DBT	48.950	13.05.16	12.05.19
5	Dr.Suvendra Nath Bhattacharya	Role of inter and subcelluar miRNA trafficking in controlling lipid metabolism in mammalian liver cells, Swarnajayanti Fellowship	GAP 341	SERB, DST	179.000	01.04.16	31.03.21
6	Dr. Sucheta Tripathi	Assessing the genome sequences of Termitomyces clypeatus for novel metabolite discovery through whole genome sequencing method and characterization of the metabolites for application in biotechnology	GAP 342	DBT	51.970	01.04.16	31.03.19
7	Dr. Rupasri Ain	MiRNAs in trophoblast stem cell differentiation	GAP 343	SERB, DST	46.480	03.06.16	02.06.19
8	Dr. Surajit Ghosh	Development of anti-alzheimer peptide from taxol binding pocket of B-tubulin	GAP 344	SERB, DST	57.240	11.07.16	10.07.19
9	Dr. Dipyaman Ganguly	Role or type I interferons in cerebral malaria	GAP 345	DBT	55.250	01.07.16	30.06.19
10	Dr. Saikat Chakrabarti	Role of sialylated glycan on Pseudomonas aeruginosa in interactuion with innate immune cells: A glyco-proteomics approach	GAP 346	DBT	67.020	27.07.16	26.07.19
11	Dr. Suvendra Nath Bhattacharya	Host Interactome analysis: Understanding the role of host molecules in parasitic Infection (HOPE) Indo-Belgian research proposal: Support of Networking Activities	GAP 347	BELSPO & DST	21.560	29.06.16	28.06.19
12	Dr. Partha Chakrabarti	A Prosperative study on the role of incertin hormones in patients undergoing bariatric surgery	GAP 348	DBT, Govt. of WB	23.980	24.08.16	23.08.19
13	Dr. Krishnanda Chattopadhyay	Investigation of the folding and aggregation landscape of superoxide dismutase invitro and in live cells : its implication in Amyotrophic lateral sclerosis (ALS)	GAP 349	SERB, DST	45.940	27.09.16	26.09.16
14	Dr. Subhajit Biswas	Molecular epidemiology and characterization of occult hepatitis B virus (HBV) infectious, particularly the role of S protein mutations leading toundetectable HBV surface antigen (HBsAg) in patient blood plasma	GAP 350	SERB, DST	31.320	30.09.16	29.09.19
15	Dr. Samit Chattopadhyay	Tumor suppressor SMART regulates transcription of Beta-catenin and protect from metastatic colon cancer	GAP 351	SERB, DST	80.130	29.09.16	28.09.19
16	Dr.Krishna Das Saha	Designing bioactive peptides from whey liquid waste of the dairy industry: Functionallyand health benifit in Obesity, obesity associated disorders with exploration of molecular mechanism	GAP 352	DBT	21.180	04.11.16	03.11.19



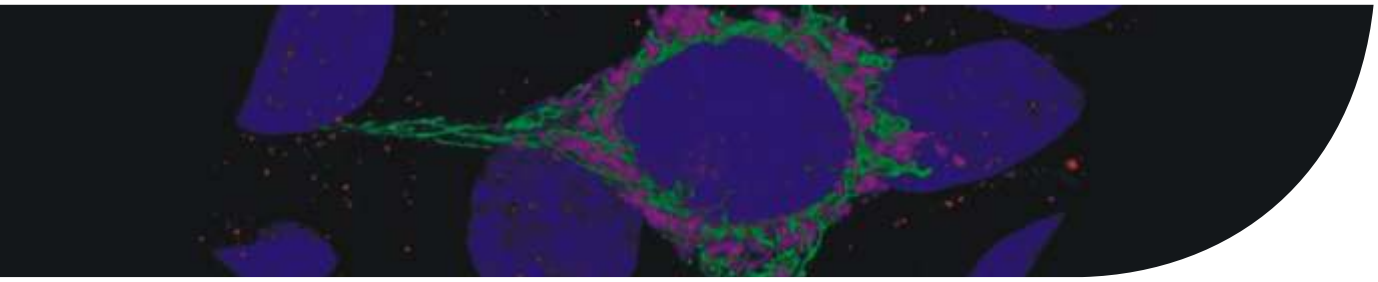
Ongoing Extramural Projects (2018-2019)

Sl. No.	Project Investigator	Title	Project Code	Funding Agency	Project Cost (Rs. In Lakh)	Start date	Completion Date
17	Dr. Partha Chakrabarti	Stereoselective Total Synthesis of Marine Macrocyclic Lactone Biseyngbyaside and its Variants and their Biological Activities	GAP 353	SERB, DST	9.700	01.11.16	31.10.19
18	Dr. Mrinal Kanti Ghosh	Development of nano-partical based directed delivery systems for peptide therapeutics	GAP 354	SERB, DST	68.560	04.12.15	03.12.18
19	Dr. P. Jaisankar	Development of Axially Chiral 3-Indolyl Based Heterobiaryls:Synthesis,Separation,Isolation of Atropisomers and Study of their physicochemical properties,applications in Biology and Materials Science	GAP 355	SERB, DST	41.810	20.02.17	19.02.21
20	Dr. Krishna Das Saha	Utilization of pomegranate for development of functional Medicinal ingredients	GAP 356	AYUSH	22.000	31.12.16	30.12.19
21	Dr. Samit Chattapadhyay	Multi dimensional Research to Enable Systems Medicine : Acceleration using a ClusterApproach	GAP 357	DBT	1818.000	07.03.17	06.03.21
22	Dr. Debabrata Biswas	Elucidation of functional role of FKBP5 in eukaryotic transcriptional regulation	GAP 358	SERB, DST	50.750	22.03.17	21.03.20
23	Dr. Indrajit Das	α- Ketothioesters : An Indispensable Building Blocks for Accessing Diverse Heterocycles via Sulfanyl Anions or Thiyl Radical Migration	GAP 359	SERB, DST	62.820	23.03.17	22.03.20
24	Dr. Sib Sankar Roy	Mechanism of Ets-1 transcription factor-mediated metabolic reprogramming and tumorigenesis in ovarian cancer	GAP 360	SERB, DST	39.040	29.03.17	28.03.20
25	Dr. Suvendra Nath Bhattacharyya	Characterization of exosomes released by macrophages infected with leishmania donovani	GAP 361	DBT	15.000	04.11.16	03.11.19
26	Dr. Suvendra Nath Bhattacharyya	Compartmentalization of micro RNA-Dependent Post-transcriptional Processes in Mammalian Cells: Role of Sub-cellular structures and Organelles	GAP 362	SERB, DST	40.370	29.03.17	28.03.20
27	Dr. Partha Chakrabarti	Elucidation of Roles of Inflammatory Mediators in Pancreatic Cell and hepatocyte dysfunction Type 2 Diabetes	GAP 363	ICMR	27.250	29.03.17	28.03.20
28	Dr. Surajit Ghosh	Muc1 receptor targeted nano-liposome containing peptide-drug-nanocage for breast cancer and cancer stem cell	GAP-364	DBT	129.736	01.04.17	31.03.20
29	Dr. Sujoy Mukherjee	Transiently formed non-native conformers of transthyretin: structure, function, and their roles in formation of amyloid fibrils	GAP-365	DBT	62.248	27.02.17	26.02.20
30	Dr. Sharmila Chattopadhyay	Identification of stress responsive microRNAs in Arabidopsis under GSH conditions	GAP-366	SERB	42.571	15.06.17	14.06.20
31	Dr. Amitava Sengupta	Deciphering epigenetic dysregulation in Hematopoietic stem cell transformation in human Myelogenous leukemia	GAP-367	DBT	68.400	29.06.17	28.06.20
32	Dr. Rupasri Ain	Regulation of Trophoblast-vasculogenic mimicry	GAP-368	DBT	40.068	29.06.17	28.06.20
33	Prof. Samit Chattopadhyay	Metabolic stress induced epigenetic changes in the transcriptional regulator gene SMAR1	GAP-369	DBT	59.748	01.06.17	31.05.20



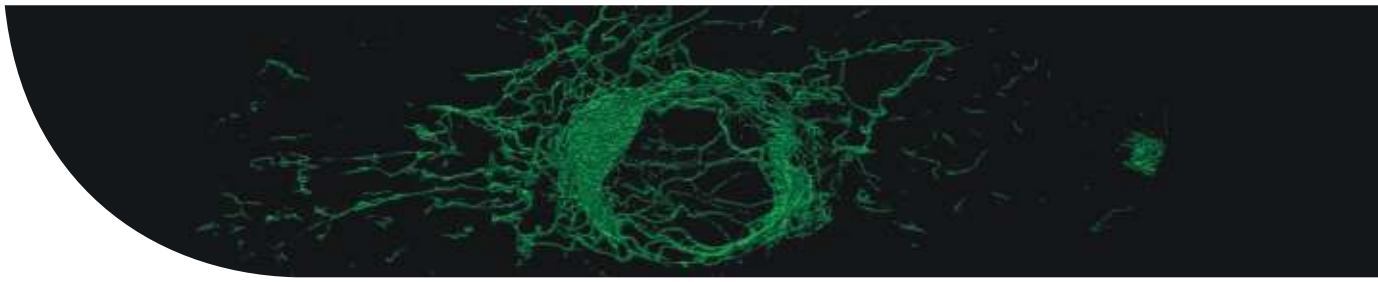
Ongoing Extramural Projects (2018-2019)

Sl. No.	Project Investigator	Title	Project Code	Funding Agency	Project Cost (Rs. In Lakh)	Start date	Completion Date
34	Dr. Krishna Das Saha	Anti-leishmanial activity of a novel carbazol alkaloid mahanine: its mechanism of action and drug delivery through liposomal formulation	GAP-370	ICMR	9.649	28.03.17	27.03.20
35	Dr. Surajit Ghosh	Development of novel extended λ-conjucated small molecules for generation of reactive oxygen species (ROS) inside the cancer cell	GAP-371	DST	5.360	14.07.17	13.07.19
36	Dr. Sucheta Tripathi	Development of portable system with data analysis and relational data warehouse packages for high throughput structural and functional genomics data	GAP-372	DBT	83.728	10.08.17	09.08.20
37	Dr. Subrata Adak	Expression, intracellular localization and functional characterization of OAS domain containing phosphoglycerate kinase in Leishmania	GAP-374	SERB	39.960	31.08.17	30.08.20
38	Dr. Arindam Talukdar	Development of new drugs for Leishmania- An Australian Indian Partnership	GAP-375	DBT	143.888	21.09.17	20.09.20
39	Prof. Samit Chattopadhyay	Production of Nanocarriers for theranostics	GAP-376	DBT	100.800	03.01.18	02.01.21
40	Dr. Malini Sen	Evaluating WISP3 and promoting societal benefit in the context of PPRD , a debilitating genetic disorder	GAP-377	DBT	44.424	13.02.18	12.02.21
41	Dr. Subhas Biswas	Alzheimer's diease: identification of common targets regulating both apoptosis and autophagy during neurodegeration	GAP-378	SERB	45.468	15.03.18	14.03.21
42	PI- Dr. Dipyaman Ganguly Co-PI- Dr. Arindam Talukdar	Exploring Therapeutic Efficacy of Novel Toll like Receptor 9 Antagonist in Type II Diabetes	GAP-379	SERB	48.076	21.03.18	20.03.20
43	Dr. Siddhartha Roy	Structural and functional characterization of TSPYL1, a novel histone chaperone implicated in Sudden infant death with dysgenesis of the tests syndrome (SIDDT) in human	GAP-380	SERB	42.360	22.03.18	21.03.21
44	Dr. Krishna Das Saha	Assessment of Virgin Pomegranate Seed Oil and its Encapsulated Form on the Management of Obesity and Associated Inflammation: A Molecular Approach	GAP-381	SERB	33.760	27.03.18	26.03.21
45	Dr. Aditya Konar	Developing nanoformulation of crstalline protein for rendering neuroprotection to cornea and retina	GAP-382	DST	22.468	07.02.18	06.02.21
46	Dr. Prem Prakash Tripathi	Role of endogenous intermediate progenitors in neurogenesis following neurodegeneration	GAP-383	SERB	33.966	24.05.18	23.05.21
47	Dr. Subhas Biswas	Research and development work for value addition of the product Parkers Medha Plus	SSP-384	Parker Robinson	9.003	02.07.18	01.07.21
48	Dr. Siddhartha Roy	Histone chaperon Asf1 in Plasmodium falciparum: Novel anti-malarial targets	GAP-385	DBT	52.500	04.07.18	03.07.21
49	Dr. Sanjay Dutta	Synthesis of Novel Imipramine derivatives targeting Leishmania Donovani	GAP-386	DBT, Govt. Of West Bengal	40.920	17.01.18	16.01.21
50	Dr. Krishnanda Chattopadhyay	Spatio-temporal mapping of membrane deformation induced by Amyloid-beta 40 during neurodegeration	GAP-387	DBT, Govt. Of India	16.950	19.03.18	18.03.21
51	Dr. Aditya Konar	Developing new strategies to prevent corneal and retinal Blindness in Dogs	GAP-388	DBT, Govt. Of India	8.000	13.07.18	12.07.20



Ongoing Extramural Projects (2018-2019)

Sl. No	Name of PI	Title	Project Code	Funding Agency	Project Cost (Rs. In lakh)	Start date	Completion Date
1	Dr. Prem Prakash Tripathi	Role of endogenous intermediate progenitors in neurogenesis following neurodegeneration	GAP-383	SERB	33.966	24.05.2018	23.05.2021
2	Dr. Subhas Biswas	Research and development work for value addition of the product Parkers Medha Plus	SSP-384	Parker Robinson	9.003	02.07.2018	01.07.2021
3	Dr. Siddhartha Roy	Histone chaperon Asf1 in Plasmodium falciparum: Novel anti-malarial targets	GAP-385	DBT	52.500	04.07.2018	03.07.2021
4	Dr. Sanjay Dutta	Synthesis of Novel Imipramine derivatives targeting Leishmania Donovani	GAP-386	DBT, Govt. Of West Bengal	40.920	17.01.2018	16.01.2021
5	Dr. Krishnanda Chattopadhyay	Spatio-temporal mapping of membrane deformation induced by Amyloid-beta 40 during neurodegeration	GAP-387	DBT, Govt. Of India	16.950	19.03.2018	18.03.2021
6	Dr. Aditya Konar	Developing new strategies to prevent corneal and retinal Blindness in Dogs	GAP-388	DBT, Govt. Of India	4.000	13.07.2018	12.07.2020
7	Dr. Dipyaman Ganguly	Mechanistic exploration of the pathogenic role of type I interferons in metabolic syndrome and preclinical validation of the therapeutic targeting	GAP-389	DBT, Govt. Of India	273.720	30.08.2018	29.08.2023
8	Dr. Mrinal Kanti Ghosh	Development of a combinatorial nano-vehicales assisted therapeutic system for the effiecient treatment of Glioma	GAP-390	DST, Govt. Of India	41.982	23.08.2018	22.08.2021
9	Dr. Malini Sen	Role of Wnt5A Signaling in Bacterial Infection	GAP-391	DBT, Govt. of India	67.060	15.09.2018	14.09.2021
10	Dr. Subhajit Biswas	Characterization of herpesvirus in clinical samples from Eastern India in terms of their growth kinetics and sensitivity to available antivirals together with screening for novel herpes	GAP-392	DBT, Govt. Of West Bengal	26.466	14.09.2018	13.09.2019
11	Dr. Mrinal Kanti Ghosh	Glucocorticoid Receptor-Assisted Drug Sensitization (GRADS) in colorectal cancer therapy: Nano-therapeutic strategy towards repurposing of anti-cancer drugs	GAP-393	SERB, Govt. Of India	12.420	18.09.2018	17.09.2021
12	Dr. Sanjay Dutta	Development of Novel Theranostics Targeting Nucleic acids	GAP-394	SERB, Govt. Of India	25.300	06.11.2018	05.11.2021
13	Dr. Nakul Chandra Maiti	Structural implication of Amyloid Oligomers in Alzherims disease	GAP-395	SERB, Govt. Of India	22.140	05.11.2018	04.11.2021
14	Dr. Malini Sen	Potential of Wnt5a Signalling in Promoting Host Defense against Leishmania Donovani infection	GAP-396	ICMR, Govt of India	17.401	15.12.2018	
15	Dr. Joy Chakraborty	USP14 level in different brain regions: Correlation between differential neurodegenration and mitophagy	SSP-397	International Society for Neurochemistry	3.226	30.11.2018	29.11.2019
16	Dr. Mrinal Kanti Ghosh	A Novel Nanotechnology based Approach of Glioma Therapy by Targeting HAUSP-MDM2 axis in combination with Temozolomide	GAP-398	SERB, GOVT. Of India	40.14	15.01.2019	14.01.2022
17	Dr. Sib Sankar Roy	To evaluate the effect of black tea intake on chronic anovulation and insulin resistance in polycystic ovarian syndrome (PCOS)	GAP-399	NTRF, Govt. Of India	34.45	19.12.2018	18.12.2021
18	Dr. Subhas Biswas	Alzheimer's disease: is age related subtle DNA damage the trigger of the sporadic Alzheimer's disease?	GAP-400	SERB. Govt. Of India	30.39	04.03.2019	03.03.2022
19	Dr. Dipyaman Ganguly	Exploring the mechanistic link between type I interferons, gut dysbiosis and regulatory T cell abundance in obesity associated metaflammation and insulin resistance	GAP-402	DBT, Govt. Od India	15.00	18.03.2019	17.03.2022
20	Dr. Upasana Ray	Understanding the role of Dengue NS1 protein in endothelium leakage and therapeutic intervention of NS1 pathogens	GAP-403	DBT, Govt. Of West Bengal	23.75	30.03.2019	29.03.2022
21	Dr. Upasana Ray	Understanding entry of Chikungunya virus and engineering self-assembly system based anti-Chikungunya vaccine	GAP-404	SERB. Govt. Of India	35.88	30.03.2019	29.03.2022
22	Dr. Suvendra Bhattacharya	Elucidation of the interplay of cell autonomous and pathogen-derived factors on the susceptibility of individual host cells to infection by a protozoan pathogen	GAP-406	DBT. Govt. Of India	191.806	04.06.2020	03.06.2023



Ongoing In-house projects (2018-19)

Sl. No	Title	Project Code	Nodal Scientist	Project cost (Rs. In Lakh)	Start date	Completion Date
1	CSIR Sickle Cell Anaemia Mission	HCP-0008	Dr. Amitava Sengupta	434.964	22.09.17	21.09.20
2	CSIR Phytopharmaceutical Mission	HCP-0010	Prof. Samit Chattopadhyay	629.240	08.02.17	07.12.20
3	INPROTICS-Pharma and Agro	HCP-0011	Dr. Indu Bhusan Deb	300.000	12.02.18	11.02.21
4	Nano Biosensors and Microfluidics for Healthcare	HCP-0012	Dr. Subhajit Biswas	292.072	13.03.18	12.03.20
5	Crop Protection Chemicals	HCP-0021	Dr. Indrajit Das	190.000	09.01.19	31.03.20
6	CSIR Integrated Skill Initiative Program	NWP-0100	Dr. P. Jaisankar/Dr. Arun Bandyopadhyay	98.200		
7	JIGYASA Project	NWP-101	Dr. Neeta Khalkho	30.200	25.02.18	31.03.20
8	Rapid Assay System and Clinical Validation of Biomarker for Reumatic Heart Disease	MLP123	Dr. Arun Bandyopadhyay	133.000	11.08.2019	10.08.2018
9	Serum and urine-based kits for diagnosis of human and canine visceral leishmaniasis (VL) and post kala-azar dermal leishmaniasis (PKDL) in field settings	MLP124	Dr. Subrata Adak Dr. Nahid Ali	199.832	08.09.2019	31.03.2019
10	Non-alcholoic Steatohepatitis (NASH)	MLP125	Dr. Partha Chakrabarti	80.000	Sep' 2018	March' 2020
11	Chronic Respiratory Disease Innovation and Solution Program (CRISP)	MLP126	Dr. U Mabalirajan	75.000	14.08.18	31.03.20
12	Genomics and Epigenomics in Health and Disease (GEHeaD) EXOsomal MIRna INhibitor:	MLP127	Dr. Arun Bandyopadhyay	15.000	14.08.18	31.03.20
13	Identification of the new classes of inhibitors of miRNA trafficking via exosomes (EXOMIRIN)	MLP128	Dr. S N Bhattacharya	50.000	24.09.18	31.03.20

Publication & Information Division

Members :

Dr. Snehasikta Swarnakar (Head), Dr. Neeta V. M. Khalkho (Deputy Head), Mr. Sankar Bhakta upto 31st March 2019), Mrs. Sutapa Ganguly, Mr. P. C Dehuri

This section deals with diverse informational activities, publication and monitoring of reports and dissemination of information in electronic and printed forms. The major contribution of this section lies in assisting scientists in day to day maintenance of the institute activities and innovations, project profiles, publication records and research utilization data. The section was involved in the following wide spectrum of programmes during the reporting.

Preparation of CSIR-IICB Annual Report 2017-2018 English Version . Preparation of documents released during events. Dissemination of information to scientific milieu on relevant subjects. Assistance to scientists, fellows and staff members for participation in seminars, symposia and conferences. Maintenance of database for testing and calibration. Preparation of a new up-to-date brochure for CSIR-IICB. Updated information's regarding section for CSIR-IICB website. Public relations news and views forum. Organization display of exhibition and science news dissemination. **Monthly Report of CSIR-IICB for PPD, CSIR**. Compilation of CSIR-IICB News for CSIR News Letter. Scientist Visit & Events **Management of Laboratory Visit for Students** On the occasion of CSIR Foundation Day celebration-2018, the members of this section have actively helped for the arrangement of 'OPEN HOUSE' programme where 165 number of students from 9 schools & colleges within and around Kolkata visited CSIR-IICB. A large number of students from different schools and colleges with their teachers visited various laboratories and interacted with the scientists expressing great interest and enthusiasm. Members of this section also arranged the laboratory visit for students of colleges and universities from outside Kolkata particularly from North East States. Two(2) numbers of students visits were organized in year (2018-19). **CSIR-IICB Organized 'JIGYASA'**: An interactive training camp for KV students as a part of the above initiative of CSIR, a group of 50 students of class XII and 4 teachers from Kendriya Vidyalaya, Salt Lake No1& No2 , Kolkata took part in the secound training camp, **JIGYASA 2018** was, organized by CSIR-Indian Institute of Chemical Biology (CSIR-IICB), Kolkata in its Jadavpur and Saltlake campus for three days during **April 2018**

Exhibition Unit has participated in exhibitions and out reach programmes at local level such as 6th Indian national exhibition cum fair at Patuli ground, from 26th -29th July 2018,and at national level in India international science festival at Lucknow from 5th - 8th October and at Kisan mela at Lucknow on 31st October 2018 for dissemination of science.

6th Indian National Exhibition Cum Fair at Patuli ground, from 26th -29th July 2018

MSc. Zoology Sreeram college students one day visit to CSIR-IICB, Jadavpur Campus, On 20th June 2018

JIGYASA 2018 held during 24th -26th April 2018 in Jadavpur and Saltlake Campus

Scientist giving demonstration during JIGYASA

PhD scholar giving demonstration during JIGYASA

Scientist during soap making session during JIGYASA

Administration

In its endeavour to bring about a healthy, transparent and vibrant administrative mechanism at the Institute, the Administration has taken a number of steps of facilitating the smooth functioning of the activities of the Institute by availing digital technology wherever available, providing for easy access to online forms, implementing new Purchase procedure etc.

IICB TRUE Campus at Salt Lake has successfully hosted important meetings like RC, RAB Assessments, training programmes on administrative issues in co-ordination with the CSIR-HRDC etc.

In accordance with directions from CSIR from time to time, it has been the aim of the Institute to have an efficient preventive vigilance system in practice and thus a number of checks and balances have been implemented in the system to this effect.

As a part of the celebrations of the Vigilance Awareness Week, a number of lectures and workshops had been organised in the Institute. A team from Institute also visited some Kendriya Vidyalaya Schools at Kolkata where the lectures on the importance of remaining vigilant, short talks on popular science as well as informal quiz programmes on the Indian Constitution, saw the enthusiastic participation of the students.

For the first time, CSIR-IICB had also been organised a Gram Sabha as a part of the Vigilance Awareness Week at Village Mukutshila PO Krishnanagar Dist East Midnapore wherein a discussion on the role of an effective vigilance mechanism was initiated by the team from the Institute which was followed by a round of quiz on general knowledge matters. It was heartening to see the active and whole hearted participation of the local people in the discussion as well as the quiz.

Hindi Activities 2018-19

Official Language in the Institute is being implemented with regular meetings, everyday Hindi words and phrases displayed in the electronic boards, Hindi workshops, observance of Hindi week, publication of Hindi patrika Sanjivani etc.

The year 2018 saw many activities of the Official Language with workshop every quarter (three months).

Regular Hindi classes were arranged in the Institute (both campuses) wherein some students passed Hindi praveen & pragya examination conducted by the Home Ministry. Above 80% of the employees have passed Hindi and attained working knowledge / proficiency in the Official language of the government.

Official Language meetings are held regularly with Director being the Chairman of all the OLIC meetings.

This quarterly Hindi workshop was held on 27th June 2018, where scientist staff members were imparted training topic on 'Interesting glass: from tomorrow to tomorrow' in Hindi language.

Hindi week was celebrated from 10 to 14 September 2018. During this week many competitions were held in Hindi. The judges of these competitions were eminent professors, teachers and other noted personalities in Hindi language.

On the 10th September 2018 the inaugural ceremony was opened by the Administrative Officer of the Institute. Assistant Director (Rabha) Shri Bhaskaranand Jha from Variable Energy Cyclotron Center and Dr. Geeta Dubey, Chief, Hindi Department from Scottish Church College were the judges guests of that day. The ceremony was followed by recitation & extempore competitions in Hindi where many employees and research scholars took active part in large numbers.

On the 11th September 2018 Hindi essay, noting & drafting competitions were held where many employees and research scholars participated.

On 12 September 2018 forenoon, a one-day Hindi seminar was organized in the institute which three lectures were arranged. In these achievements, the Director of our institute give statement on the official language. He encouraged everyone to work on Hindi and directed to follow the orders of the Government / President on the official language. The Principal Scientist of the institute, Dr. Sucheta Tripathi, delivererd a popular lecture on science and the Store and Purchase officer, Sri Anjani Kumar Pandey, presented his lectures on the subject of Hindi as a enriched language. The seminar was conducted by Sri Naveen Prajapati, Senior Manager (Rabha), DVC. Sri Naveen Prajapati discussed the questionnaire of the Parliamentary Committee on Official Language. He imparted training to all about the importance of Parliamentary questionnaire and how to fill it properly. All the permanent employees of the institute were present in this Hindi seminar.

On 12 September 2018 afternoon, a debate competition was organized in which a large number of employees and research scholars participated. Mrs. Rita Gupta, Bharat Heavy Electricals Limited Senior Manager (Rabha) and Mr. Rajesh Kumar Singh Roshan Administrative Officer CSIR -Central Glass and Ceramic Research Institute were judges of the competition.

On 13 September 2018 forenoon a Hindi quiz competition was organized in J. C. Ray Auditorium. The competition was conducted by Dr. Umesh Prasad Singh, Principal Scientist and Sri Manoj Kumar, Section Officer (Finance and Accounts). Eight (8) teams participated in this competition. Each team had three participants. In which employees and researchers participated with excitement and joy.

September 13, 2018 afternoon, a Hindi drama was organized at J. C. Ray auditorium. A play named 'Atmaj' was staged under the direction of well-known playwright Usha Ganguly. The play was based on victimized women. All the employees were overwhelmed by the moral of the play.

Hindi day - last and final day of the week and the closing ceremony was organized on 14th September 2018. The prize distribution of the program was organized on the same day. The program organized on this occasion was presided over by Dr. P. Jaishankar, Chief Scientist of the institute. Dr. P. Jaishankar, while addressing everyone in his welcome speech, welcomed everyone warmly. The Principal of Calcutta Girls' College, Dr. Satya Upadhyay was the Chief Guest at the program. Dr. Satya Upadhyay, the Chief Guest, expressed his views about Hindi and appreciated the work being done in the institute. Dr. Satya Upadhyay inspired everyone to adopt Hindi and shared their life experiences with everyone in this context. The annual Hindi patrika of the institute 'Sanjivani' was also released by the Chief Scientist, Dr. P. Jaishankar.

The Hindi Officer A. Nag and team organised the programme.

This quarterly Hindi workshop was held on 18th December 2018, The Assistant Director of Hindi teaching scheme Mrs. Manju Shireen conducted the training on official language implementation. The administrative officials took part in this

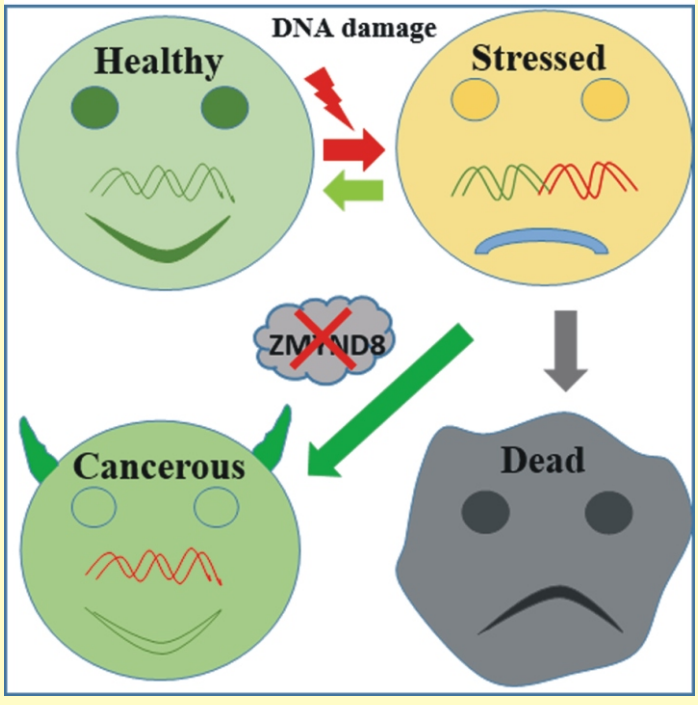
workshop. Madam Shireen started with the meaning of workshop - she explained how to work in Hindi at office and abide by the rules of official language.

This quarterly Hindi workshop was held on 18th March 2019, Technical staff members were trained in Hindi workshop to work efficiently in Official Language.

Annual report of the institute was published in Rajbhasha in compliance with the official language policy of the government.

ZMYND8: A new player in cancer prevention

Cancer is one of the leading cause of death in India. It is an outcome of the interplay between oncoproteins (bad proteins) and tumour suppressor proteins (good proteins). PTEF-b, is positively associated with both good and bad protein synthesis machinery. But targeting PTEF-b activity is still a challenging issuesince it is associated with good protein synthesis as well.

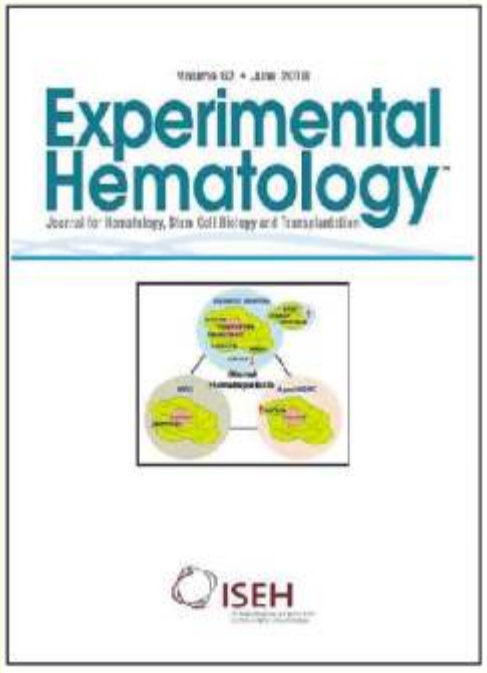


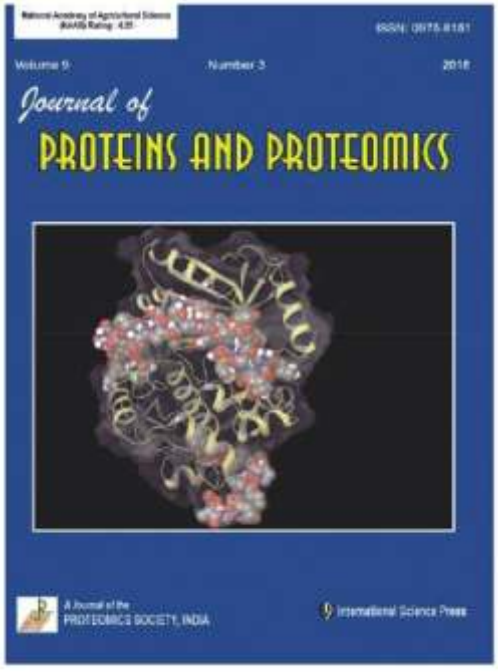
Therefore, P-TEFb-associated factors that modulate its activity could be a good target for this purpose. In that regard, our study has uncovered a novel role of human ZMYND8 in P-TEFb functions for target gene expression and protein synthesis. This study would serve as the foundation for designing molecule-based targeting of ZMYND8 in cancerous cells. Further, we have also established ZMYND8-PTEF-b axis in theneuronal development that has the potential to throw some light on several neuronal dysfunction-associated congenital disorder. In our daily life, cells are often exposed to toxic substances that causes DNAlesion and cancer. Through our study, we have also shown the mechanisms by which ZMYND8 could serve dual roles of protein synthesis in normal cells as well as repairing the damaged DNA to prevent progression of normal cells to cancerous cells. This mechanistic study has been published in highly reputed journal ***Cell Reports.***

Reference:

Koushik Ghosh, Ming Tang, NidhiKumari, ArijitNandy, SubhamBasu, DheerendraPratap Mall, KunalRai, and Debabrata Biswas "Positive regulation of transcription by human ZMYND8 through its association with P-TEFb complex." Cell reports 24.8 (2018): 2141-2154.

Cover Page Articles - 2018





CSIR-IICB in News

THE TIMES OF INDIA
CITY

Kolkata researchers develop molecule for TB vaccine

KOLKATA: A team of researchers from the city has zeroed in on a protein which could be used as a vaccine against tuberculosis (TB), a deadly disease that takes an estimated two lives every five minutes in India.

The six-member team from the Indian Institute of Chemical Biology (IICB) and the Bose Institute claims to have successfully tweaked the protein to develop a 'stable and active' protein-based molecule that will provide immunity against the disease, which can spread through coughing or sneezing.

THE HINDU
SUNDAY, JUNE 17, 2018

Novel gold nanocomplex for cancer drug delivery

Anti-tumour drugs could target the diseased cell

ASWATHI PACHA

Using gold nanoparticles coated with a simple organic molecule (porphyrin), researchers from CSIR-Indian Institute of Chemical Biology, Kolkata, have designed an efficient drug nanocarrier. The nanocarrier was found to effectively deliver drug to the nucleus of the diseased cell and bring about programmed cell death.

Porphyrin was armoured on the gold nanosurface via continuous stirring method. "Porphyrin is a simple organic compound and it gives the necessary protection and stability to the nanosurface. Porphyrins are essential co-factors in many human proteins such as hemoglobin and so it can escape from the macrophages in our body," explains Dr. Nahid C. Maiti, Senior Scientist at the Structural Biology and Bioinformatics Division of CSIR-IICB and one of the corresponding authors of the paper published in *ACS Omega*.

The porphyrin molecule was found to be uniformly distributed on gold nanoparticles and the porphyrin-gold complex was stable.

The anti-tumour drug doxorubicin was then successfully loaded on the porphyrin-gold nanosurface. "Doxorubicin is selectively released when it reaches the low-pH environment seen in cancerous cells," explains Koushik Bera, research scholar at the institute and one of the first authors of the paper.

We are trying to design a system that can release the drug more efficiently, says Chitra Mandal (left).

Activity of the complex

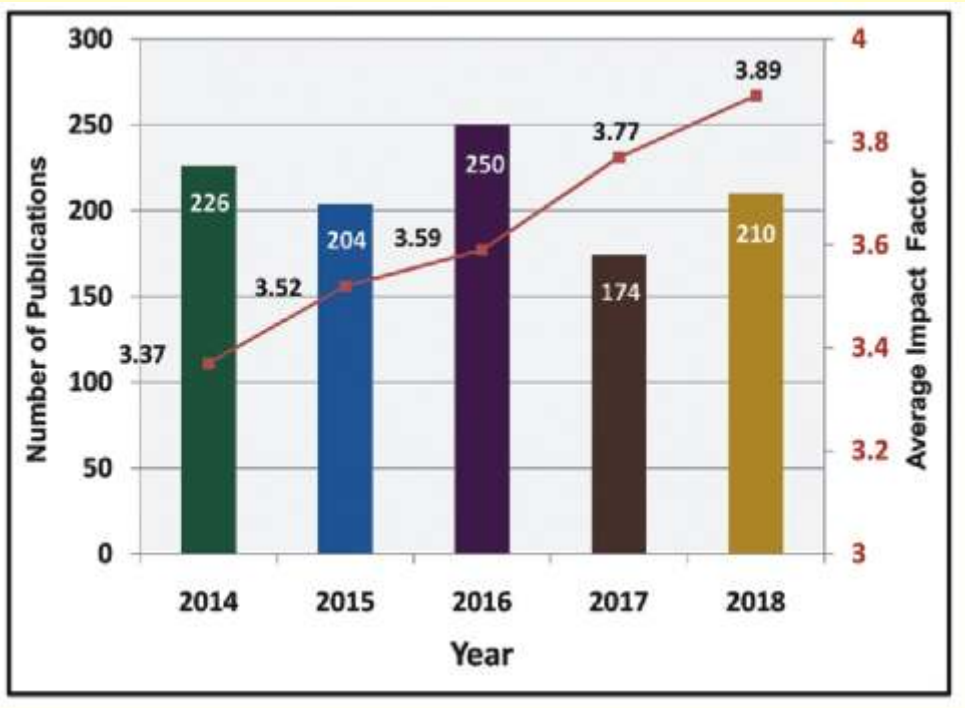
Its activity was then tested on brain and lung cancer cells and normal healthy cells. The porphyrin-gold complex without the drug showed no toxicity to healthy and cancerous cells. The nanoparticles coated with the drug showed very low toxicity to normal cells and caused programmed cell death both in brain and lung cancer cells.

Multidrug resistance is one of the major barriers in cancer cells, where the drug is quickly ejected out, reducing the effective drug concentrations within the cells and thus decreases its sensitivity.

"We found that the drug-coated nanoparticles were retained well inside the cells thus showing higher activity," says Samarpan Maiti, another research scholar at the institute and one of the first authors of this paper in an email to *The Hindu*.

"There are several pathways by which the drug can damage the DNA. Currently we are studying the pathways, and trying to design a system that can release the drug more efficiently. We are also studying how the system works in real scenario of tumour model," says Prof. Chitra Mandal from the Cancer Biology & Inflammatory Disorder division of this institute and one of the corresponding authors of the paper.

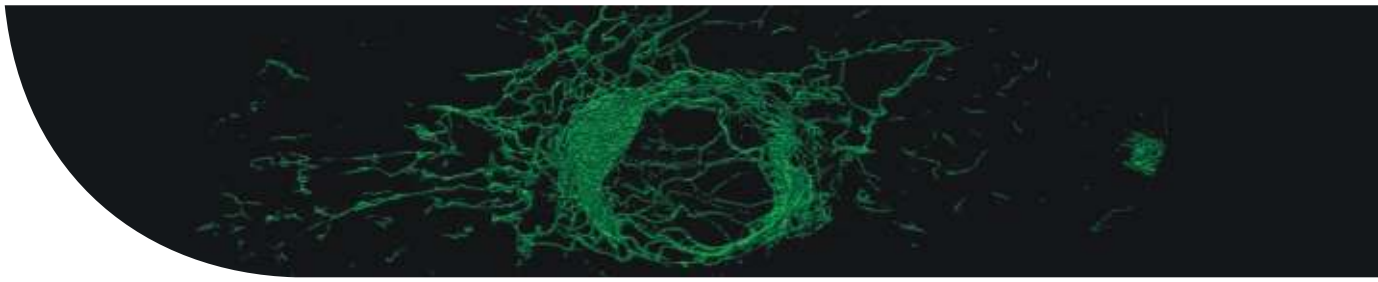
CSIR-IICB Publication Profile



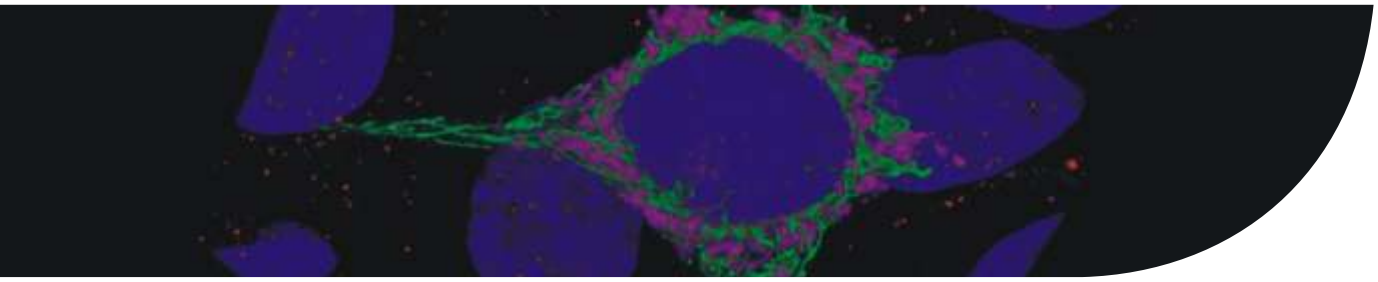
Total Number of Publications	210		
	36	Non SCI Publications	
SCI Publications	174		
	03	No. of Papers with IF ≥ 10	
No. of Papers with IF ≥ 5 < 10	33		
	32	No. of Papers with IF ≥ 4 < 5	
No. of Papers with IF ≥ 3 < 4	48		
	37	No. of Papers with IF ≥ 2 < 3	
No. of Papers with IF ≥ 1 < 2	19		
	02	No. of Papers with IF < 1	
Total IF (2018)	677.48		
	3.89	IF per Research Publication (SCI)	

CSIR-IICB List of Publications - 2018

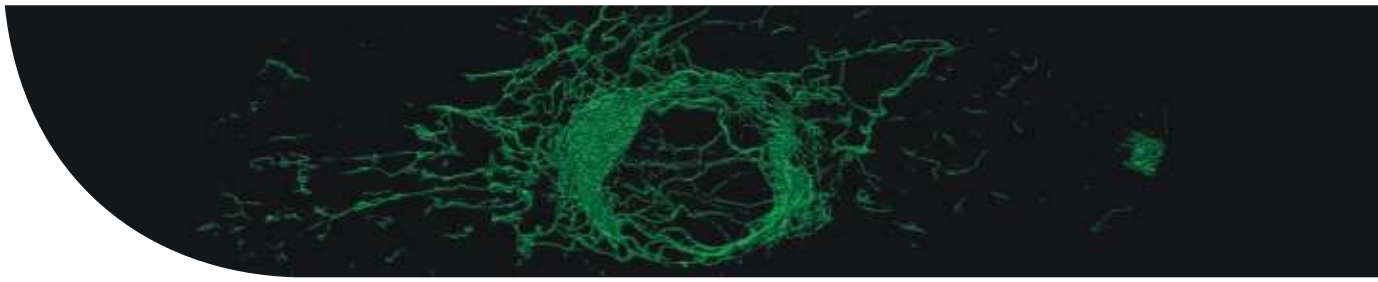
Sl. No.	Publications	IF
1.	Bhunia, D., Mondal, P., Das, G., Saha, A., Sengupta, P., Jana, J., Mohapatra, S., Chatterjee, S., Ghosh, S. (2018) Spatial position regulates power of tryptophan : Discovery of a major-groove-specific nuclear-localizing, cell-penetrating tetrapeptide. *Journal of the American Chemical Society,* 140, 1697-1714.	14.357
2.	Ganguly, D. (2018) Do type I interferons link systemic autoimmunities and metabolic syndrome in a pathogenetic continuum? *Trends in Immunology,* 39, 28-43.	14.188
3.	Sengupta, P., Banerjee, N., Roychowdhury, T., Dutta, A., Chattopadhyay, S., Chatterjee, S. (2018) Site-specific amino acid substitution in dodecameric peptides determines the stability and unfolding of c-MYC quadruplex promoting apoptosis in cancer cells. *Nucleic Acids Research*, 46, 9932-9950.	11.561
4.	Dey, S., Biswas, C., Sengupta, J. (2018) The universally conserved GTPase HflX is an RNA helicase that restores heat-damaged *Escherichia coli ribosomes. Journal of Cell Biology,* 217, 2519-2529.	8.784
5.	Behera, S., Xu, Z., Luoni, L., Bonza, M. C., Doccula, F. G., De Michelis, M. I., Morris, R. J., Schwarzlander, M., Costa, A. (2018) Cellular Ca2+ signals generate defined pH signatures in plants. *The Plant Cell,* 30, 2704-2719.	8.228
6.	Ghosh, K., Tang, M., Kumari, N., Nandy, A., Basu, S., Mall, D. P., Rai, K., Biswas D. (2018) Positive regulation of transcription by Human ZMYND8 through its association with P-TEFb complex, *Cell Reports*, 24, 2141-2154, e6.	8.032
7.	Bhattacharya, S., Mondal, L., Mukherjee, B., Dutta, L., Ehsan, I., Debnath, M. C., Gaonkar, R. H., Pal, M. M., Majumdar, S. (2018) Apigenin loaded nanoparticle delayed development of hepatocellular carcinoma in rats. *Nanomedicine: Nanotechnology, Biology and Medicine*, 14, 1905-1917.	6.500
8.	Das, S., Bairy, G., Jana, R. (2018) Ligand-promoted g-C(sp3)-H arylation and unsymmetrical diarylation to access unnatural amino acid derivatives. *Organic Letters*, 20, 2667-2671.	6.492
9.	Bairy, G., Das, S., Begam, H.M., Jana, R. (2018) Exceedingly fast, direct access to dihydroisoquinolino[1,2-b]quinazolinones through a ruthenium(II)-catalyzed redox-neutral C–H allylation/hydroamination cascade. *Organic Letters*, 20, 7107–7112.	6.492
10.	Roy, K., Mazumder, A., Ghosh, P., Naiya, G., Ghosh, B., Roy, S. (2018) A peptide-based synthetic transcription factor selectively activates transcription in a mammalian cell. *Chemical Communications*, 54, 1611-1614.	6.920
11.	Bhunia, D; Pradhan, K., Das, G., Ghosh, S., Mondal, P., Ghosh, S. (2018) Matrix metalloproteinase targeted peptide vesicles for delivering anticancer drugs. *Chemical Communications*, 54, 9309-9312.	6.290
12.	Das, S. K., Mishra, S., Manna, K., Kayal, U., Mahapatra, S., Das Saha, K., Dalapati, S., Das, G. P., Mostafa, A. A., Bhaumik, A. (2018) A new triazine based ? -conjugated mesoporous 2D covalent organic framework: its in vitro anticancer activities. *Chemical Communications*, 54, 11475-11478.	6.290
13.	Ramalingam, B. M., Moorthy, N. D., Roy Chowdhury, S., Mageshwaran, T.,Vellaichamy, E., Saha, S., Ganesan, K., Rajesh, B. N., Iqbal, S., Majumder, H. K., Gunasekaran, K., Siva, R., Mohanakrishnan, A. K. (2018) Synthesis and biological evaluation of Calothrixins B and their deoxygenated analogues. *Journal of Medicinal Chemistry*, 61, 1285-1315.	6.253
14.	Das, P. P., Pramanik, S., Chatterjee, S., Roy, A., Saha, A., Devi, P. S., Suresh Kumar, G. (2018) Multiband fluorescent graphitic carbon nanoparticles from queen of oils. *ACS Sustainable Chemistry & Engineering*, 6, 10127-10139.	6.140
15.	Chatterjee, K., Jana, S., Choudhary, P., Swarnakar, S. (2018) Triumph and tumult of matrix metalloproteinases and their crosstalk with eicosanoids in cancer. *Cancer and Metastasis Reviews*, 37, 279-288.	6.081
16.	De, M., Ghosh, S., Sen, T., Shadab, M., Banerjee, I., Basu, S., Ali, N. (2018) A novel therapeutic strategy for cancer using phosphatidylserine targeting stearylamine-bearing cationic liposomes. *Molecular Therapy-Nucleic Acids*, 10, 9-27.	5.660
17.	Nath, S., Mandal, C., Chatterjee, U., Mandal, C. (2018) Association of cytosolic sialidase Neu2 with plasma membrane enhances Fas-mediated apoptosis by impairing PI3K-Akt/mTOR-mediated pathway in pancreatic cancer cells. *Cell Death & Disease*, 9, Article No. 210.	5.638
18.	Satyavarapu, E. M., Das, R., Mandal, C., Mukhopadhyay, A., Mandal, C. (2018) Autophagy-independent induction of LC3B through oxidative stress reveals its non-canonical role in anoikis of ovarian cancer cells. *Cell Death & Disease*, 9, Article No. 934.	5.638
19.	Patranabis, S., Bhattacharyya, S. N. (2018) P-body-induced inactivation of let-7a miRNP prevents the death of growth factor-deprived neuronal cells. *FASEB Journal*, 32, 1493-1509.	5.638
20.	Chatterjee, K., Jana, S., DasMahapatra, P., Swarnakar, S. (2018) EGFR-mediated matrix metalloproteinase-7 up-regulation promotes epithelial-mesenchymal transition via ERK1-AP1 axis during ovarian endometriosis progression. *FASEB Journal*, 32, 4560-4572.	5.595



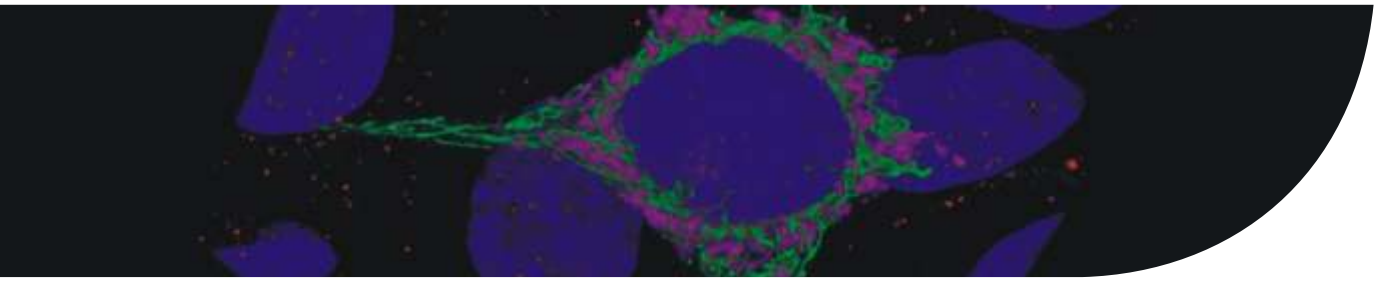
Sl. No.	Publications	IF
21.	Adak, M., Das, D., Niyogi, S., Nagalakshmi, C., Ray, D., Chakrabarti, P. (2018) Inflammasome activation in Kupffer cells confers a protective response in nonalcoholic steatohepatitis through pigment epithelium-derived factor expression. *Faseb Journal,* 32, 6510-6524.	5.595
22.	Sabur, A., Bhowmick, S., Chhajer, R., Ejazi, S. A., Didwania, N., Asad, M., Bhattacharyya, A., Sinha, U., Ali, N. (2018) Liposomal elongation factor-1? triggers effector CD4 and CD8 T cells for induction of long-lasting protective immunity against visceral leishmaniasis. *Frontiers in Immunology,* 9, Article 18.	5.551
23.	Jati, S., Kundu, S., Chakraborty, A., Mahata, S. K., Nizet, V., Sen, M. (2018) Wnt5A signaling promotes defense against bacterial pathogens by activating a host autophagy circuit. *Frontiers in Immunology*, 9, Article 679.	5.551
24.	Kar, D., Bandyopadhyay, A. (2018) Targeting peroxisome proliferator activated receptor ? (PPAR ?) for the prevention of mitochondrial impairment and hypertrophy in cardiomyocytes. *Cellular Physiology and Biochemistry*, 49, 245-259.	5.550
25.	Sarkar-Banerjee, S., Chowdhury, S., Sanyal, D., Mitra, T., Roy, S. S., Chattopadhyay, K. (2018) The role of intestinal fatty acid binding proteins in protecting cells from fatty acid induced impairment of mitochondrial dynamics and apoptosis. *Cellular Physiology and Biochemistry*, 51, 1658-1678.	5.550
26.	Kumar, D., Chattopadhyay, S. (2018) Glutathione modulates the expression of heat shock proteins via the transcription factors BZIP10 and MYB21 in Arabidopsis. *Journal of Experimental Botany,* 69, 3729-3743.	5.354
27.	Ayyub, S. A., Dobriyal, D., Shah, R. A, Lahry, K., Bhattacharyya, M., Bhattacharyya, S., Chakrabarti, S., Varshney, U. (2018) Coevolution of the translational machinery optimizes initiation with unusual initiator tRNAs and initiation codons in mycoplasmas. *RNA Biology,* 15, 70-80.	5.216
28.	Maity, S., Parshi, N., Prodhan, C., Chaudhuri, K., Ganguly, J. (2018) Characterization of a fluorescent hydrogel synthesized using chitosan, polyvinyl alcohol and 9-anthraldehyde for the selective detection and discrimination of trace Fe3+ and Fe2+ in water for live-cell imaging. *Carbohydrate Polymers,* 193, 119-128.	5.158
29.	Vats, T. K., Mishra, A., Deb, I. (2018) Rhodium-catalyzed direct and selective ortho C-H chalcogenation of N-(Hetero)aryl-7-azaindoles. *Advanced Synthesis & Catalysis*, 360, 2291-2296.	5.123
30.	Sarkar, W., Bhowmik, A., Mishra, A., Vats, T. K., Deb, I. (2018) Cobalt-catalyzed directed sp2 C-H acetoxylation of arenes employing Mn(OAc)3.2H2O as acetoxy source. *Advanced Synthesis & Catalysis*, 360, 3228-3232.	5.123
31.	Polley, A., Bairy, G., Das, P., Jana, R. (2018) Triple mode of alkylation with ethyl bromodifluoroacetate: N, or O-difluoromethylation, N-Ethylation and S-(ethoxycarbonyl)difluoromethylation. *Advanced Synthesis & Catalysis*, 360, 4161-4167.	5.123
32.	Khan, M. W., Layden, B. T., Chakrabarti, P. (2018) Inhibition of mTOR complexes protects cancer cells from glutamine starvation induced cell death by restoring Akt stability. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1864, 2040-2052.	5.108
33.	Dutta, D., Ali, N., Banerjee, E., Singh, R., Naskar, A., Paidi, R. K., Mohanakumar, K.P. (2018) Low levels of prohibitin in substantia nigra makes dopaminergic neurons vulnerable in Parkinson's disease. *Molecular Neurobiology*, 55, 804-821.	5.076
34.	Bhagat, P. N., Jadhav, S. H., Chattopadhyay, S., Paknikar, K. M. (2018) Carbon nanospheres mediated nuclear delivery of SMAR1 protein (DNA binding domain) controls breast tumor in mice model. *Nanomedicine (London)*, 13, 353-372.	5.005
35.	Paul, P., Sengupta, S., Mukherjee, B., Shaw, T. K., Gaonkar, R. H., Debnath, M. C. (2018) Chitosan-coated nanoparticles enhanced lung pharmacokinetic profile of voriconazole upon pulmonary delivery in mice. *Nanomedicine (London)*, 13, 501-520.	5.005
36.	Sengupta, S., Paul, P., Mukherjee, B., Gaonkar, R. H., Debnath, M. C., Chakraborty, R., Khatun, N., Roy, S. (2018) Peripheral nerve targeting by procaine-conjugated ribavirin-loaded dual drug nanovesicle. *Nanomedicine (London)*, 13, 3009-3023.	5.005
37.	Paul, B., Rahaman, O., Roy, S., Pal, S., Satish, S., Mukherjee, A., Ghosh, A. R., Raychaudhuri, D., Bhattacharya, R., Goon, S., Ganguly, D., Talukdar, A. (2018) Activity-guided development of potent and selective toll-like receptor 9 antagonists. *European Journal of Medicinal Chemistry*, 159, 187-205.	4.816
38.	Maity, R., Naskar, S., Das, I. (2018) Copper(II)-catalyzed reactions of ?-keto thioesters with azides via C-C and C-S bond cleavages: Synthesis of N-acylureas and amides. *The Journal of Organic Chemistry*, 83, 2114-2124.	4.805
39.	Mishra, A., Mukherjee, U., Vats, T. K., Deb, I. (2018) Ir(III)/MPAA-catalyzed mild and selective C-H amidation of N-sulfonyl ketimines: Access to benzosultam-fused quinazolines/quinazolinones. *The Journal of Organic Chemistry*, 83, 3756-3767.	4.805
40.	Manna, M. K., Bairy, G., Jana, R. (2018) Sterically controlled Ru(II)-catalyzed divergent synthesis of 2-methylindoles and indolines through a C-H allylation/cyclization cascade. *The Journal of Organic Chemistry*, 83, 8390-8400.	4.805



Sl. No.	Publications	IF
41.	Santhiya, K., Sen, S. K., Natarajan, R., Shankar, R., Murugesapandian, B. (2018) D-A-D structured bis-acylhydrazone exhibiting aggregation-induced emission, mechanochromic luminescence, and Al(III) detection. *The Journal of Organic Chemistry*, 83, 10770-10775.	4.805
42.	Banerji, B., Chatterjee, S., Chandrasekhar, K., Ghosh, S., Mukherjee, K., Mandal, C. (2018) Detection of lysosome by a fluorescent heterocycle: Development of fused pyrido–imidazo–indole framework via Cu-catalyzed tandem N-arylation. *The Journal of Organic Chemistry,* 83, 13011–13018.	4.805
43.	Mukherjee, S., Ganguly, S., Manna, K., Mondal, S., Mahapatra, S., Das, D. (2018) Green approach to synthesize crystalline nanoscale ZnII coordination polymers: Cell growth inhibition and immunofluorescence study. *Inorganic Chemistry*, 57, 4050-4060.	4.700
44.	Arunachalam, R., Chinnaraja, E., Valkonen, A., Rissanen, K., Sen, S. K., Natarajan, R., Subramanian, P. S. (2018) Enantiomeric resolution of asymmetric-carbon-free binuclear double-stranded cobalt(III) helicates and their application as catalysts in asymmetric reactions. *Inorganic Chemistry,* 57, 11414-11421.	4.700
45.	Bhattacharjee, P., De, D., Bhattacharyya, D. (2018) Degradation of fibrin-? amyloid co-aggregate: A novel function attributed to ubiquitin. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, 1865, 1465-1478.	4.651
46.	Chatterjee, S. S., Biswas, M., Boila, L. D., Banerjee, D., Sengupta, A. (2018) SMARCB1 deficiency integrates epigenetic signals to oncogenic gene expression program maintenance in Human acute myeloid leukemia. *Molecular Cancer Research,* 16, 791-804.	4.597
47.	Ghosh, B., Boila, L. D., Choudhury, S., Mondal, P., Bhattacharjee, S., Pal, S. K., Sengupta, A., Roy, S. (2018) A potent conformation-constrained synthetic peptide mimic of a homeodomain selectively regulates target genes in cells. *ACS Chemical Biology*, 13, 2003-2009.	4.592
48.	Liu, C. S. C., Raychaudhuri, D., Paul, B., Chakrabarty, Y., Ghosh, A. R., Rahaman, O., Talukdar, A., Ganguly, D. (2018) Cutting edge: Piezo1 mechanosensors optimize human T Cell activation. *Journal of Immunology,* 200, 1255-1260.	4.539
49.	Ray, U., Roy, S. S. (2018) Aberrant lipid metabolism in cancer cells - the role of oncolipid-activated signaling. *FEBS Journal*, 285, 432-443.	4.530
50.	Jain, M.R., Giri, S.R., Bhoi, B., Trivedi, C., Rath, A., Rathod, R., Ranvir, R., Kadam, S., Patel, H., Swain, P., Roy, S.S., Das, N., Karmakar, E., Wahli, W., Patel, P.R. (2018) Dual PPAR?/g agonist saroglitazar improves liver histopathology and biochemistry in experimental NASH models. *Liver International*, 38, 1084-1094.	4.500
51.	Paul, P., Chatterjee, S., Pramanik, A., Karmakar, P., Bhattacharyya, S. C., Suresh Kumar, G. (2018) Thionine conjugated gold nanoparticles trigger apoptotic activity toward HepG2 cancer cell line. *ACS Biomaterials Science & Engineering*, 4, 635-646.	4.432
52.	Chatterjee, D., Bandyopadhyay, A., Sarma, N., Basu, S., Roychowdhury, T., Roy, S. S., Giri, A. K. (2018) Role of microRNAs in senescence and its contribution to peripheral neuropathy in the arsenic exposed population of West Bengal, India. *Environmental Pollution*, 233, 596-603.	4.358
53.	Chowdhury, K., Kumar, U., Das, S., Chaudhuri, J., Kumar, P., Kanjilal, M., Ghosh, P., Sircar, G., Basyal, R. K., Kanga, U., Bandyopadhaya, S., Mitra, D. K. (2018) Synovial IL-9 facilitates neutrophil survival, function and differentiation of Th17 cells in rheumatoid arthritis. *Arthritis Research & Therapy,* 20, 18.	4.269
54.	Mondal, P., Das, G., Khan, J., Pradhan, K., Ghosh, S. (2018) Crafting of neuroprotective octapeptide from taxol-binding pocket of β-tubulin. *ACS Chemical Neuroscience*, 9, 615–625.	4.211
55.	Mondal, P., Gupta, V., Das, G., Pradhan, K., Khan, J., Gharai, P. K., Ghosh, S. (2018) Peptide-based acetylcholinesterase inhibitor crosses the blood-brain barrier and promotes neuroprotection. *ACS Chemical Neuroscience*, 9, 2838–2848.	4.211
56.	Khan, J., Das, G., Gupta, V., Mohapatra, S., Ghosh, S., Ghosh, S (2018) Neurosphere development from hippocampal and cortical embryonic mixed primary neuron culture: A potential platform for screening neurochemical modulator. *ACS Chemical Neuroscience,* 9, 2870–2878.	4.211
57.	Pradhan, K., Das, G., Mondal, P., Khan, J., Barman, S., Ghosh, S. (2018) Genesis of neuroprotective peptoid from Aβ30-34 inhibits Aβ aggregation and AChE activity. *ACS Chemical Neuroscience*, 9, 2929-2940.	4.211
58.	Panda, A., Sen, D., Ghosh, A., Gupta, A., Mathu Malar, C., Mishra, G. P., Singh, D., Ye, W., Tyler, B. M., Tripathy, S. (2018) EumicrobeDBLite: a lightweight genomic resource and analytic platform for draft oomycete genomes. *Molecular Plant Pathology*, 19, 227-237.	4.188
59.	Bhattacharya, S. S., Mandal, C., Albiez, R. S., Samanta, S. K., Mandal, C. (2018) Mahanine drives pancreatic adenocarcinoma cells into endoplasmic reticular stress-mediated apoptosis through modulating sialylation process and Ca2+- signaling. *Scientific Reports,* 8, Article No. 3911.	4.122
60.	Dey, T., Saville, A., Myers, K., Tewari, S., Cooke, D. E. L., Tripathy, S., Fry, W. E., Ristaino, J. B., and Guha Roy, S. (2018) Large sub-clonal variation in Phytophthora infestans from recent severe late blight epidemics in India. *Scientific Reports,* 8, Article No. 4429.	4.122



Sl. No.	Publications	IF
61.	Ghosh, S., Kundu, A., Chattopadhyay, K. (2018) Small molecules attenuate the interplay between conformational fluctuations, early oligomerization and amyloidosis of alpha synuclein. *Scientific Reports*, 8, Article No. 5481.	4.122
62.	Chakraborty, S., Islam, S., Saha, S., Ain, R (2018) Dexamethasone-induced intra-uterine growth restriction impacts NOSTRIN and its downstream effector genes in the rat mesometrial uterus. *Scientific Reports*, 8, Article No. 8342.	4.122
63.	Roy Chowdhury, S., Godinho, J. L. P., Vinayagam, J., Zuma, A. A., De Macedo Silva, S. T., Jaisankar, P., Rodrigues, J. C. F., De Souza, W., Majumder, H. K. (2018) Isobenzofuranone derivative JVPH3, an inhibitor of L. donovani topoisomerase II, disrupts mitochondrial architecture in trypanosomatid parasites. *Scientific Reports*, 8, Article No. 11940.	4.122
64.	Ejazi, S. A., Bhattacharyya, A., Choudhury, S. T., Ghosh, S., Sabur, A., Pandey, K., Das, V. N. R., Das, P., Rahaman, M., Goswami, R. P., Ali, N. (2018) Immunoproteomic identification and characterization of leishmania membrane proteins as non-invasive diagnostic candidates for clinical visceral leishmaniasis. *Scientific Reports*, 8, Article No. 12110.	4.122
65.	Dutta, S., Das, J. K., Maganti, L., Bhattacharyya, M., Bhattacharyya, D., Mukherjee, S., Sengupta, K. (2018) Skeletal muscle dystrophy mutant of lamin A alters the structure and dynamics of the Ig fold domain. *Scientific Reports*, 8, Article No. 13793.	4.122
66.	Sinha, R., Mathu Malar, C., Raghwan., Das, S., Shadab, M., Chowdhury, R., Tripathy, S., Ali, N. (2018) Genome plasticity in cultured Leishmania donovani: Comparison of early and late passages. *Frontiers in Microbiology*, 9, Article 1279.	4.019
67.	Chaudhari, N. M., Gautam, A., Gupta, V. K., Kaur, G., Dutta, C., Paul, S. (2018) PanGFR-HM: A dynamic web resource for pan-genomic and functional profiling of Human microbiome with comparative features. *Frontiers in Microbiology*, 9, Article 2322.	4.019
68.	De, R., Sarkar, S., Mazumder, S., Debsharma, S., Siddiqui, A. A., Saha, S. J., Banerjee, C., Nag, S., Saha, D., Pramanik, S., Bandyopadhyay, U. (2018) Macrophage migration inhibitory factor regulates mitochondrial dynamics and cell growth of human cancer cell lines through CD74-NF-kB signaling. *Journal of Biological Chemistry*, 293, 19740-19760.	4.010
69.	Vetukuri, R. R., Tripathy, S., Malar, C. M., Panda, A., Kushwaha, S. K., Chawade, A., Andreasson, E., Grenville-Briggs, L. J., Whisson, S. C. (2018) Draft genome sequence for the tree pathogen Phytophthora plurivora. *Genome Biology and Evolution*, 10, 2432-2442.	3.940
70.	Ghosh, P., Bhoumik, A., Saha, S., Mukherjee, S., Azmi, S., Ghosh, J. K., Dungdung, S. R. (2018) Spermicidal efficacy of VRP, a synthetic cationic antimicrobial peptide, inducing apoptosis and membrane disruption. *Journal of Cellular Physiology*, 233, 1041-1050.	3.923
71.	Ghosh, P., Mukherjee, S., Bhoumik, A., Dungdung, S. R. (2018) A novel epididymal quiescence factor inhibits sperm motility by modulating NOS activity and intracellular NO-cGMP pathway. *Journal of Cellular Physiology*, 233, 4345-4359.	3.923
72.	Basu, A., Bhattacharya, S. C., Suresh Kumar, G. (2018) Influence of the ionic liquid 1-butyl-3-methylimidazolium bromide on amyloid fibrillogenesis in lysozyme: Evidence from photophysical and imaging studies. *International Journal of Biological Macromolecules*, 107, 2643-2649.	3.909
73	Bhoumik, A., Saha, S., Payghan, P. V., Ghosh, P., Dungdung, S. R. (2018) Localization of MIF :-II on mammalian spermatozoa: A study revealing its structure, function and motility inhibitory pathway. *International Journal of Biological Macromolecules*, 116, 633-647.	3.909
74.	Mukherjee, A., Banerjee, S., Gachhui, R. (2018) Investigation of conformational changes of levansucrase isolated from Acetobacter nitrogenifigens strain RG1 by mercuric and cadmium ion. *International Journal of Biological Macromolecules*, 120, 189-194.	3.909
75.	Das, G., Chattoraj, S., Nandi, S., Mondal, P., Saha, A., Bhattacharyya, K., Ghosh, S. (2018) Probing the conformational dynamics of photosystem I in unconfined and confined spaces. *Physical Chemistry Chemical Physics*, 20, 449-455.	3.906
76.	Roy, N. S., Debnath, S., Chakraborty, A., Chakraborty, P., Bera, I., Ghosh, R., Ghoshal, N., Chakrabarti, S., Roy, S. (2018) Enhanced basepair dynamics pre-disposes protein-assisted flips of key bases in DNA strand separation during transcription initiation. *Physical Chemistry Chemical Physics*, 20, 9449-9459.	3.906
77.	Pramanik, S., Chatterjee, S., Suresh Kumar, G., Devi, P.S. (2018) Egg-shell derived carbon dots for base pair selective DNA binding and recognition. *Physical Chemistry Chemical Physics*, 20, 20476-20488.	3.906
78.	Dutta, D., Das, R., Mandal, C., Mandal, C. (2018) Structure-based kinase profiling to understand the polypharmacological behavior of therapeutic molecules. *Journal of Chemical Information and Modeling*, 58, 68-89.	3.804
79.	Jana, B., Mondal, P., Saha, A., Adak, A., Das, G., Mohapatra, S., Kurkute, P., Ghosh, S. (2018) Designed tetrapeptide interacts with tubulin and microtubule. *Langmuir*, 34, 1123-1132.	3.789



Sl. No.	Publications	IF
80.	Sannigrahi, A., Chall, S., Jawed, J. J., Kundu, A., Majumdar, S., Chattopadhyay, K. (2018) Nanoparticle induced conformational switch between α-helix and β-sheet attenuates immunogenic response of MPT63. *Langmuir*, 34, 8807-8817.	3.789
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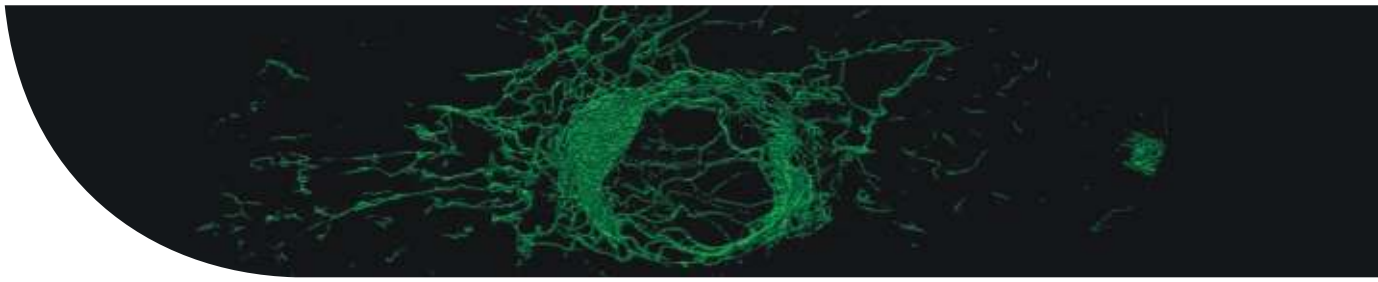

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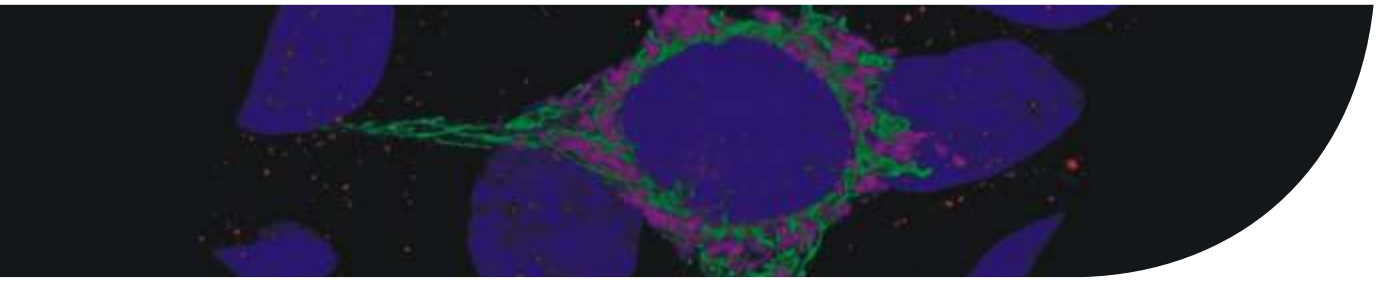

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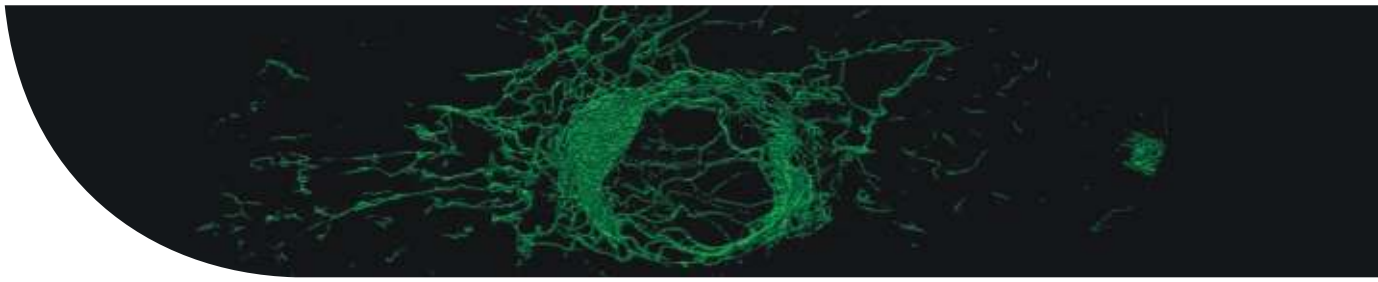

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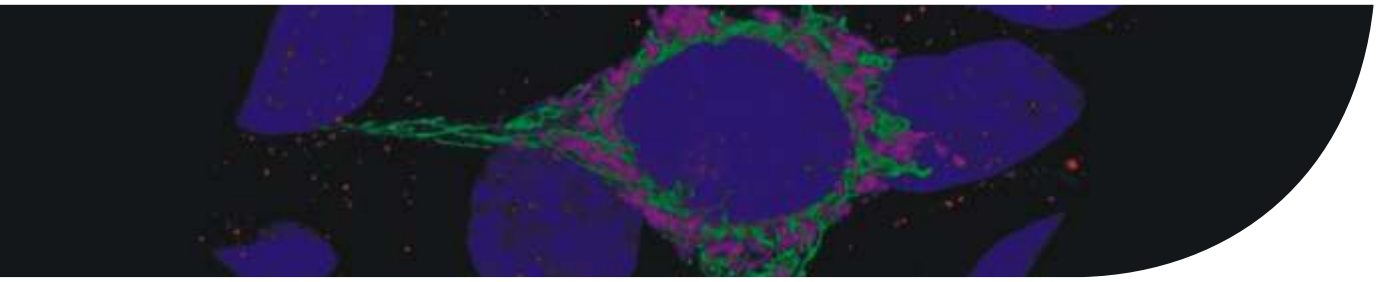

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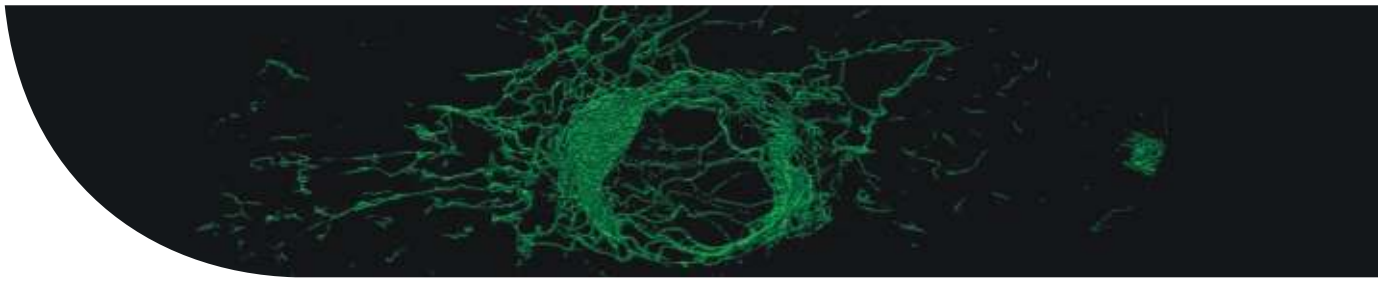
168.	Ratha, I., Anand, A., Chatterjee, S., Kundu, B., Suresh Kumar, G. (2018) Preliminary study on effect of nano-hydroxyapatite and mesoporous bioactive glass on DNA. *Journal of Materials Research,* 33, 1592-1601.	NIL
169.	Ghosh, P., Rameshbabu, A. P., Das, D., Subramanian, B (2018) Single-pot biofabrication of living fibers for tissue engineering applications. Journal of *Materials Research*, 33, 2019-2028.	NIL
170.	Gomes, A., Ghosh, S., Sengupta, J., Saha, K., Gomes, A. (2018) Nanotechnology in snake venom research an overview. *Indian Journal of Experimental Biology*, 56, 707-715.	NIL
171.	Chakraborty, S., Maruthanayagam, V., Achari, A., Mahansaria, R., Pramanik, A., Jaisankar, P., Mukherjee, J. (2018) Oxynema aestuarii sp. Nov. (Microcoleaceae) isolated from an Indian mangrove forest. *Phytotaxa*, 374, 24-40.	NIL
172.	Mahesh, G., Jaiswal, P., Dey, S., Sengupta, J., Mukherjee, S. (2018) Cloning, expression, purification and characterization of oligomeric states of the native 5HT2A G-protein-coupled receptor. *Protein and Peptide Letters*, 25, 390-397.	NIL
173.	Mukherjee, D., Bhattacharjee, P., Bhattacharya, R., Dutta, A. K., Bhattacharyya, D. (2018) Degraded products of stem bromelain destabilize aggregates of ?-amyloid peptides involved in Alzheimer's disease. *Current Science*, 115, 2133-2141.	NIL
174.	Pandit, A., Begum, Y., Chatterjee, K., Swarnakar, S. (2018) Hormonal regulation of endometriosis and clinical significance. *Indian Journal of Biochemistry and Biophysics*, 55, 351-360.	NIL
175.	Taye, N., Alam, A., Ghorai, S., Chatterji, D. G., Parulekar, A., Mogare, D., Singh, S., Sengupta, P., Chatterjee, S., Bhat, M. K., Santra, M. K., Salunkhe, P. B., Finston, S. K., Chattopadhyay, S. (2018) SMAR1 inhibits Wnt/*β*-catenin signaling and prevents colorectal cancer progression. *Oncotarget,* 9, 21322-21336.	NIL
176.	Tripathi, P. P., Arami, H., Banga, I., Gupta, J., Gandhi, S. (2018) Cell penetrating peptides in preclinical and clinical cancer diagnosis and therapy. *Oncotarget*, 9, 37252-37267.	NIL
177.	Bhanja, P., Mishra, S., Manna, K., Das Saha, K., Bhaumik, A. (2018) Porous polymer bearing polyphenolic organic building units as a chemotherapeutic agent for cancer treatment. *ACS Omega*, 3, 529-535.	NIL



Sl. No.	Publications	IF
178.	Dolui, S., Roy, A., Pal, U., Saha, A., Maiti, N. C. (2018) Structural Insight of amyloidogenic intermediates of Human insulin. *ACS Omega*, 3, 2452-2462.	NIL
179.	Saha, B., Chowdhury, S., Sanyal, D., Chattopadhyay, K., Suresh Kumar, G. (2018) Comparative study of toluidine blue O and methylene blue binding to lysozyme and their inhibitory effects on protein aggregation. *ACS Omega*, 3, 2588-2601.	NIL
180.	Bera, K., Maiti, S., Maity, M., Mandal, C., Maiti, N. C. (2018) Porphyrin?Gold nanomaterial for efficient drug delivery to cancerous cells. *ACS Omega*, 3, 4602-4619.	NIL
181.	Khandelwal, P., Alam, A., Choksi, A., Chattopadhyay, S., Poddar, P. (2018) Retention of anticancer activity of curcumin after conjugation with fluorescent Gold quantum clusters: An in vitro and in vivo xenograft study. *ACS Omega*, 3, 4776–4785.	NIL
182.	Das, S., Mukhopadhyay, S., Chatterjee, S., Devi, P. S., Suresh Kumar, G. (2018) Fluorescent ZnO-Au nanocomposite as a probe for elucidating specificity in DNA interaction. *ACS Omega*, 3, 7494-7507.	NIL
183.	Nandi, I., Chall, S., Chowdhury, S., Mitra, T., Roy, S. S., Chattopadhyay, K. (2018) Protein fibril-templated biomimetic synthesis of highly fluorescent gold nanoclusters and their applications in cysteine sensing. *ACS Omega*, 3, 7703-7714.	NIL
184.	Chatterjee, S. M., Jain, C. K., Singha, S., Das, P., Roychoudhury, S., Majumder, H. K., Das, S. (2018) Activity of CoII-quinalizarin: A novel analogue of anthracycline-based anticancer agents targets human DNA topoisomerase, whereas quinalizarin it elf acts via formation of semiquinone on acute lymphoblastic leukemia MOLT-4 and HCT 116 cells. *ACS Omega*, 3, 10255-10266.	NIL
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186.	Banerji, B., Chandrasekhar, K., Sreenath, K., Roy, S., Nag, S., Saha, K.D. (2018) Synthesis of triazole-Substituted quinazoline hybrids for anticancer activity and a lead compound as the EGFR blocker and ROS inducer agent. *ACS Omega*, 3, 16134–16142.	NIL
187.	Maity, P., Naskar, B., Goswami, S., Prodhan, C., Chaudhuri, T., Chaudhuri, K., Mukhopadhyay, C. (2018) Pyrrolo[3,4- c]pyridine-based fluorescent chemosensor for Fe 3+ /Fe 2+ sensitivity and their application in living HepG2 cells. *ACS Omega*, 3, 18646-18655.	NIL
188.	Maity, M., Bera, K., Pal, U., Khamaru, K., Maiti, N. C. (2018) Sensing of Iron(III) ion via modulation of redox potential on biliverdin protected silver nanosurface. *ACS Applied Nano Materials*, 1, 6099-6111.	NIL
189.	Das, A., Asad, M., Sabur, A., Didwania, N., Ali, M. (2018) Monophosphoryl lipid A based cationic liposome facilitates vaccine induced expansion of polyfunctional T cell immune responses against visceral leishmaniasis. *ACS Applied Bio Materials*, 1, 999-1018.	NIL
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191.	Bhattacharya, P., Swarnakar, S., Ghosh, S., Banerjee, S. (2018) Disinfection of drinking water via algae mediated green synthesized copper oxide nanoparticles and its toxicity evaluation. *Journal of Environmental Chemical Engineering*, 7, 102867.	NIL
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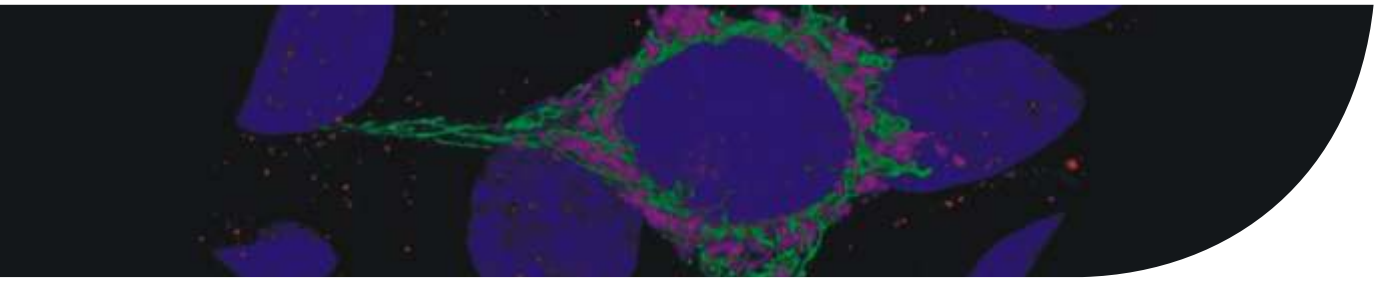
193.	Bose, R., Ain, R. (2018) Regulation of transcription by circular RNAs. *Advances in Experimental Medicine and Biology*, 1087, 81-94.	NIL
194.	Saleem, S., Saha, A., Akhter, R., Biswas, S. C. (2018) Cooperation of BH3-only proteins in killing neurons. *Biomedical Research and Clinical Practice*, 3, 1-3.	NIL
195.	Katarkar, A., Prodhan, C., Mukherjee, S., Ray, J.G., Chaudhuri, K. (2018) Role of matrix metalloproteinase-9 polymorphisms in basement membrane degradation and pathogenesis of oral submucous fibrosis. *Meta Gene*, 16, 255-263.	NIL
196.	Pal, U., Maiti, N. C. (2018) Pattern based detection of potentially druggable binding sites by ligand screening. *Journal of Proteins and Proteomics*, 9, 1-9.	NIL
197.	Mondal, A., Pal, U., Roy, A., Maiti, N. C. (2018) Structural intricacy of disordered regions in transcription factors imparting colon cancer. *Journal of Proteins and Proteomics*, 9, 169-184.	NIL
198.	Ghosh, S., Roy, A., Singhania, A., Chatterjee, S., Swarnakar, S., Fujita, D., Bandyopadhyay, A. (2018) In-vivo & in-vitro toxicity test of molecularly engineered PCMS: A potential drug for wireless remote controlled treatment. *Toxicology Reports*, 5, 1044-1052.	NIL



Sl. No.	Publications	IF
199.	Raychaudhuri, S., Ghosh, S., Roy, A., Swarnakar, S. (2018) Protective role of black tea flavonoids against ethanol-induced gastropathy via matrix metalloproteinase pathway. *Indian Journal of Clinical Biochemistry*, Pages 1-16.	NIL
200.	Yelamanchi, S. D., Tyagi, A., Mohanty, V., Dutta, P., Korbonits, M., Chavan, S., Advani J., Madugundu, A. K., Dey, G., Datta, K. K., Rajyalakshmi, M., Sahasrabuddhe, N.A., Chaturvedi, A., Kumar, A., Das, A. A., Ghosh, D., Jogdand, G. M., Nair, H. H., Saini, K., Panchal, M., Sarvaiya, M. A., Mohanraj, S. S., Sengupta, N., Saxena, P., Subramani, P. A., Kumar, P., Akkali, R., Reshma, S. V., Santhosh, R. S., Rastogi, S., Kumar, S., Ghosh, S. K., Irlapati, V. K., Srinivasan, A., Radotra, B. D., Mathur, P. P., Wong, G. W., Satishchandra, P., Chatterjee, A., Gowda, H., Bhansali, A., Pandey, A., Shankar, S. K., Mahadevan, A., Prasad, T. S. K. (2018) Proteomic analysis of the Human anterior pituitary gland. *OMICS*, 22, 759-769.	NIL
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202.	Sinha Roy, J., Chatterjee, D., Das, N., Giri, A. K. (2018) Substantial evidences indicate that inorganic arsenic is a genotoxic carcinogen : A review. *Toxicological Research*, 34, 311-324.	NIL
203.	Roy, C., Datta, S. (2018) ASBAAC: Automated salt-bridge and aromatic-aromatic calculator. *Bioinformation*, 14, 164–166.	NIL
204.	Bhattacharya, S., Chakraborty, D., Basu, M., Ghosh, M. K. (2018) Emerging insights into HAUSP (USP7) in physiology, cancer and other diseases. *Signal Transduction and Targeted Therapy*, 3, Article No. 17.	NIL
205.	Singh, S., Mishra, P., Banga, I., Parmar, A. S., Tripathi, P. P., Gandhi, S. (2018) Chemiluminescence based immunoassay for the detection of heroin and its metabolites. *Bioimpacts, 8, 53-58.*	NIL
206.	Naskar, A., Bera, S., Bhattacharya, R., Roy, S.S., Jana, S. (2018) Solution based PEG and PVP capped maghemite–reduced graphene oxide nanocomposites: Cell viability study. *Biointerface Research in Applied Chemistry*, 8, 3751-3757.	NIL
207.	Boro, P., Sultana, A., Mandal, K., Chattopadhyay, S. (2018) Transcriptomic changes under stress conditions with special reference to glutathione contents. *The Nucleus*, 61, 241-252	NIL
208.	Datta, R., Chattopadhyay, S. (2018) Glutathione as a crucial modulator of phytohormone signalling during pathogen defence in plants, Proceedings of the *Indian National Science Academy,* 84, 581-597.	NIL
209.	Kognou, A. L. M., Tchamgoue, A.D. , Tchokouaha,L. R. Y., Nthenge-Ngumbau,D. N., Fokou, P. V. T., Tchinda, A. T., Agbor, G. A. , Etame, R. M. E. , Mouokeu, R. S., Gueiffier,C. E., Pawar, R. S., Mouelle, A. S., Ngane, R. A. N. (2018) Acute and sub-chronic toxicity studies of Dichaetanthera africana (Hook. F.) Jacq. Fel. (Melastomataceae) stem bark ethanol extract. *Journal of Applied Pharmaceutical Science*, 8, 147-155.	NIL
210.	Das, T., Mahato, B., Chaudhuri, K. (2018) Effect of areca nut on rabbit oral mucosa: evidence of oral precancerous condition by protein expression and genotoxic analysis. *Oral Science International*, 15, 7-12.	NIL

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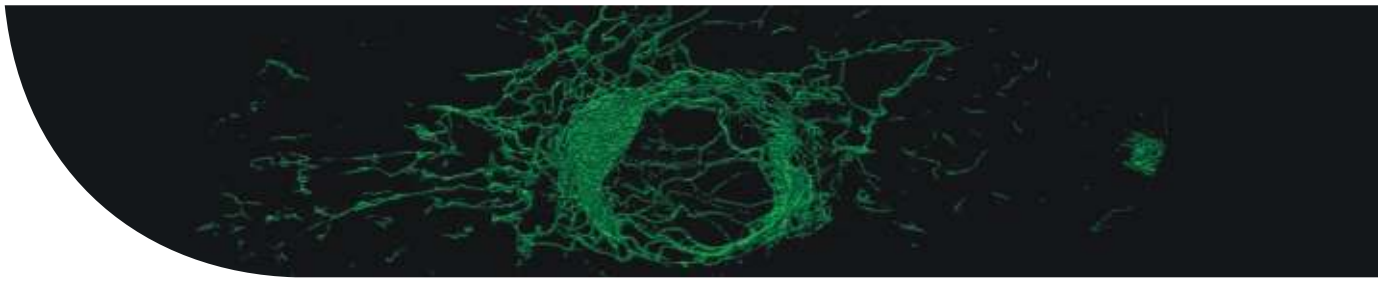


Books / Book Chapters

1. Molecular Biology of Kinetoplastid Parasites
H. K. Majumder (Ed.), Caister Academic Press, United Kingdom.

2. Sinha., Boila, L.D., Chatterjee, S. S., Sengupta, A. (2018)
miRNA and Cancer: A Deadly Liaison? In : Cancer and Noncoding RNAs,
Chapter 2, Pages 27-46.
J. Chakrabarti and S. Mitra (Eds.), Academic Press.

3. Mukherjee, S., Adhikary, S., Roy, S., Das, C. (2018)
Noncoding RNAs Act as a Chromatin Scaffold of Histone Modification Complexes in Cancer, In : Cancer and Noncoding RNAs
Chapter 18, Pages 329-357.
J. Chakrabarti and S. Mitra (Eds.), Academic Press.

4. Das, M., Ghosh, M., Gharami, K., Das, S. (2018)
Thyroid Hormone and Astrocyte Differentiation, In : Vitamins and Hormones,
Volume 106, Chapter 12, Pages 283-312.
G. Litwack (Ed.), Elsevier.

5. Basu, A., Suresh Kumar, G. (2018)
Binding of Food Colorants to Functional Protein Hemoglobin , In : Natural and Artificial Flavoring Agents and Food Dyes (Handbook of Food Bioengineering Series).
Chapter 5, Pages 133-163.
A. M. Grumezescu, and A.M. Holban, (Eds), Academic Press.

6. Mukhopadhyay, S., Dutta, D., Ganguly, D. (2018)
Lipid-Induced Insulin Resist ance: Molecular Mechanisms and Clinical Implications , In : Nutritional and Therapeutic Interventions for Diabetes and Metabolic Syndrome (Second Edition)
Chapter 14, Pages 181-191.
D. Bagchi and S. Nair, (Eds.), Academic Press.

7. Laskar, A., Jana, S., Mazumdar, A., Swarnakar, S. (2018)
Premalignant and Malignant Lesions of the Oral Cavity: Tobacco as an Etiological Factor ,
In : Tobacco Addiction: Effect on Human Health.
Chapter 2, 17 Pages.
Y. Lakew, S. Agrawal and Wanxia (Eds.), Open Access e -Books.

8. Bose, M., Bhattacharyya S.N. (2018)
Target mRNA -Driven Biogenesis of Cognate MicroRNAs In Vitro, In : MicroRNA Protocols. Methods in Molecular Biology.
Vol. 1733. Pages 27 -39.
S.Y. Ying (Ed .), Springer /Humana Press .

9. Mondal, K., Roy, S. (2018)
Response of B Lymphocyte During Leishmania Infection,
In : Molecular Biology of Kinetoplastid Parasites.
Chapter 3, Pages 39-66.
H. K. Majumder (Ed.), Caister Academic Press.

10. Saha, A. and Ukil, A. (2018)
Leishmania Exploits Host's Defence Machineries for Survival: A Tale of Immune Evasion , In : Molecular Biology of Kinetoplastid Parasites.
Chapter 6, Pages 97-110.
H. K. Majumder (Ed.), Caister Academic Press.

11. Dolai, S., Adak, S. (2018)
The Role of Hemeproteins in Different Life Cycle Stages of Leishmania, In : Molecular Biology of Kinetoplastid Parasites.
Chapter 8, Pages 119-136.

Awards & Recongnitions - 2018

Fellowship of the National Academy of Sciences (FNASc)-2018

Dr. Arun Bandyopadhayay
Chief Scientist

Fellowship of the West Bengal Academy of Sciences & Technology (FAScT)-2018

Dr. Chinmay Chowdhury
Senior Principal Scientist

Fellowship of the West Bengal Academy of Sciences & Technology (FAScT)-2018

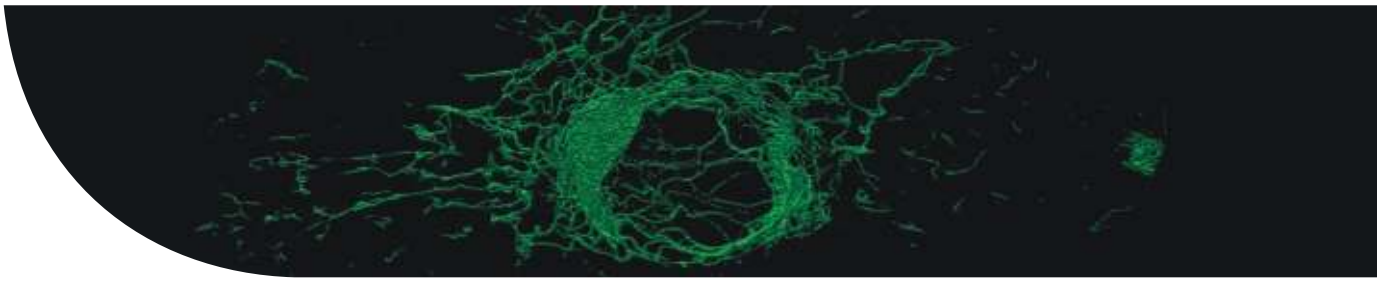
Dr. Surajit Ghosh
Principal Scientist

S. Ramachandran-National Bioscience Award for Career Development - 2018

Dr. Dipyaman Ganguly
Senior Scientist

Doctorates from CSIR-IICB

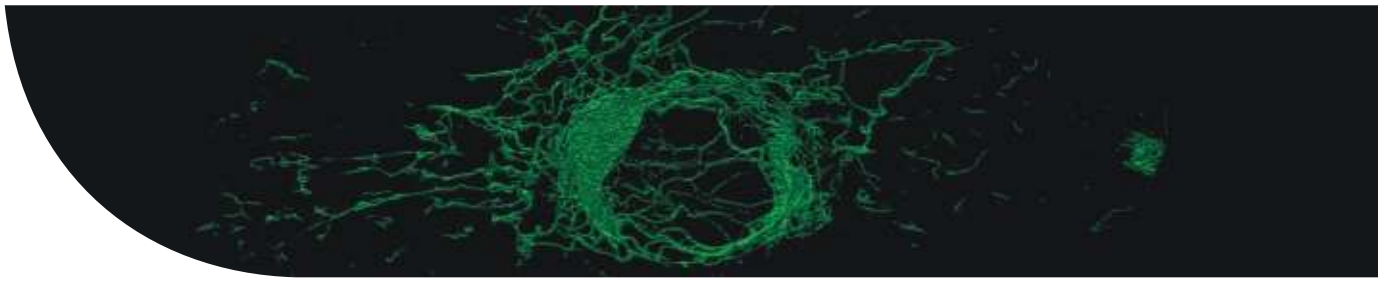
Sl. No.	Recipient's Name	Title of Thesis	University	Dt. of Award	Supervisor's name	Division
1	**Dr. Bijaya Kumar Singh**	Direct Syntheses of Drug or Drug-like Molecules via Copper Mediated/Catalyzed C-H Activation	AcSIR	4/4/2018	Dr. Ranjan Jana	Organic and Medicinal Chemistry
2	**Dr. Madhumita Bhattacharyya**	Structural and Functional analysis of Host Parasitic Interaction Network using Plasmodium as case study	University of Calcutta	5/8/2018	Dr. SaikatChakrabarti	Structural biology and Bioinformatics
3	**Dr. AsikHossian**	Development of Decarboxylative Cross-coupling Reactions	AcSIR	5/15/2018	Dr. Ranjan Jana	Organic and Medicinal Chemistry
4	**Dr. Ramesh Kumar Paidi**	Novel neuroprotective strategies in Alzheimer's disease	AcSIR	6/8/2018	Dr. Subhas C Biswas	Cell Biology and Physiology
5	**Dr. Dipayan Bose**	A mechanistic approach of anticancer and antimetastatic potential of attenuated *L. donovani* and its membrane lipoprotein	University of Calcutta	6/11/2018	Dr. Krishna Das Saha	Cancer Biology & Inflammatory Disorder
6	**Dr. Dharmendra Kumar Yadav**	Studies on bioactive molecules from Neem leaf extract and their mechanism of action against gastric ulcer	University of Calcutta	7/4/2018	Dr. SnehasiktaSwarnakar	Cancer Biology & Inflammatory Disorder
7	**Dr. Upasana Ray**	The invasion and metastasis in ovarian carcinoma through metabolites and growth factors-mediated signaling	University of Calcutta	7/9/2018	Dr. Sib Sankar Roy	Cell Biology and Physiology
8	**Dr. SomnathMazumder**	Studies on the mechanism of non-steroidal anti-inflammatory drugs (nsaids)-induced mitochondrial pathology and altered dynamics during gastric injury	University of Calcutta	7/10/2018	Dr. UdayBandyopadhyay	Infectious Diseases and Immunology
9	**Dr. Deepak Kumar**	To unravel the dynamic complexity of defense signaling network in respect to glutathione to combat environmental stress *in planta*	AcSIR	7/13/2018	Dr. Sharmila Chattopadhyay	Organic & Medicinal Chemistry
10	**Dr. Kasturi Chatterjee**	Studies on the role of matrix metalloproteinase-7 in understanding the invasiveness in endometriosis	University of Calcutta	7/16/2018	Dr. SnehasiktaSwarnakar	Cancer Biology & Inflammatory Disorder
11	**Dr. PallabiBasu**	Studies on the role of stringent response regulator DksA in controlling major virulence genes of *Vibrio cholera*	University of Calcutta	7/19/2018	Dr. Rupak K. Bhadra	Infectious Diseases and Immunology
12	**Dr. Ajay Kanungo**	Design and synthesis of novel quinoxaline small molecules and evaluation of their biophysical and nucleic acid binding properties	AcSIR	7/28/2018	Dr. Sanjay Dutta	Organic and Medicinal Chemistry Division
13	**Dr. TulikaMitra**	Factors Regulating Signaling Pathways involved in Epithelial-Mesenchymal Transition And Chemoresistance in Ovarian Cancer Cells	University of Calcutta	8/8/2018	Dr. Sib Sankar Roy	Cell Biology and Physiology
14	**Dr. SuraiyaSaleem**	Role of TRB3 in Neuronal Cell Death in Alzheimer's Disease Model	University of Calcutta	8/8/2018	Dr. Subhas Chandra Biswas	Cell Biology & Physiology
15	**Dr. Manash K. Manna**	Divergent Synthesis of Heterocycles Through Cascade C−H Bond Activation	AcSIR	8/20/2018	Dr. Ranjan Jana	Organic and Medicinal Chemistry
16	**Dr. Lubna Sheikh**	Biomimmetic hydroxyapatite composites for bone repair	AcSIR	8/29/2018	Dr. SuchetaTripathy	Structural Biology and Bioinformatics Division
17	**Dr. Manjarika De**	Stearylamine-bearing cationic liposomes for targeted anti-cancer therapy and its role in immunomodulation	University of Calcutta	9/6/2018	Dr. Nahid Ali	Infectious Diseases & Immunology
18	**Dr. Mathu Malar C.**	Perils of genome assembly: Datatypes and sequencing platform defines optimal genome assembly in prokaryotes and eukaryotes	AcSIR	9/26/2018	Dr. SuchetaTripathy	Structural Biology and Bioinformatics Division



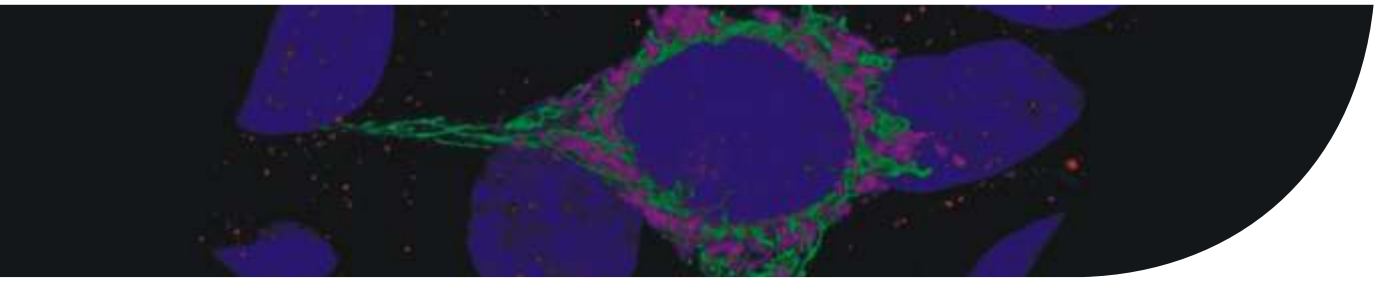
Sl. No.	Recipient's Name	Title of Thesis	University	Dt. of Award	Supervisor's name	Division
19	**Dr. Barnali Paul**	Design. Synthesis and biological evaluation of small molecule immunomodulators targeting endosomal TLRs and Piezo-type mechanosensitive ion channel	AcSIR	11/26/2018	Dr. ArindamTalukdar	Organic and Medicinal Chemistry Division
20	**Dr. Rahul Bhattacharya**	Understanding the role of growth factors and their receptors to regulating the epithelial to mesenchymal transition and invasion of ovarian cancer cells	University of Calcutta	12/5/2018	Dr. Sib Sankar Roy	Cell Biology and Physiology
21	**Dr. TridibMahata**	Study of the interactions of novel quinoxaline based small molecules with nucleic acids and their potential applications	University of Calcutta	12/5/2018	Dr. Sanjay Dutta	Organic and Medicinal Chemistry Division
22	**Dr. Raghuvir Haridas Gaonkar**	Synthesis, physicochemical and biological evaluation of novel site specific spect-radiopharmaceuticals based on 99mTc(CO)3(H2O)3-synthon core.	Jadavpur University	12/6/2018	Dr. (Mrs.) Mita Chatterjee Debnath	Infectious Diseases and Immunology
23	**Dr. JayantaSamanta**	Covalent Organic Cages and Molecular Recognition	AcSIR	12/26/2018	Dr. R. Natarajan	Organic & Medicinal Chemistry
24	**Dr. Yogaditya Chakrabarty**	Interaction Of miRNP Machinery With Subcellular Structures And Organelles: Implications In miRNA Mediated Gene Repression Process In Mammalian Cells	University of Calcutta	1/7/2019	Dr. SuvendraNath Bhattacharyya	Molecular Genetics
25	**Dr. Anindyajit Banerjee**	Determining the structural and functional importance of Bio-molecular complexes of microbial proteins using network biology, molecular modelling and docking approaches	University of Calcutta	1/9/2019	Dr. SaikatChakrabarti	Structural biology and Bioinformatics
26	**Dr. Prasanta Ghosh**	Isolation Functional Characterization And Insights Into Molecular Mechanism Of A Sperm Motility Quiescence Factor From Caprine Epididymis	University of Calcutta	1/18/2019	Dr. S. R. Dungdung	Cell Biology & Physiology
27	**Dr. Basavraj Khanppnavar**	Structural and Functional Analysis of Type Three Secretion System (T3SS) Effectors and Key Metabolic Proteins from *Pseudomonas aeruginosa*	AcSIR	2/4/2019	Dr. SaumenDatta	Structural Biology and Bioinformatics
28	**Dr. TitliNargis**	Etiopathological study of type 2 diabetes patient from India	University of Calcutta	2/18/2019	Dr. ParthaChakrabarti	Cell Biology and Physiology
29	**Dr. SamarpanMaiti**	Signal Cross-Talking Of Mammalian Target Of Rapamycin Complex 2 (mTORC2) in Glioblastoma Multiforme: Focusing Targeted Therapy	University of Calcutta	2/21/2019	Prof. Chitra Mandal	Cancer Biology & Inflammatory Disorder
30	**Dr. Somenath Roy Chowdhury**	Targeting topoisomerase(s) for antileishmanial chemotherapy and understanding the mechanism of topoisomerase related dna damage repair machineries in *Leishmaniadonovani*	University of Calcutta	3/19/2019	Dr. Hemanta K. Majumder Co-Supervisor: Dr. ParasuramanJaisankar	Infectious Diseases & Immunology
31	**Dr. Anupam Roy**	Structural Aspects of Amyloid Aggregates	Jadavpur University	March 2019	Dr. Nakul C Maiti	Structural Biology and Bioinformatics

Staff List of CSIR-IICB as on March 1, 2019

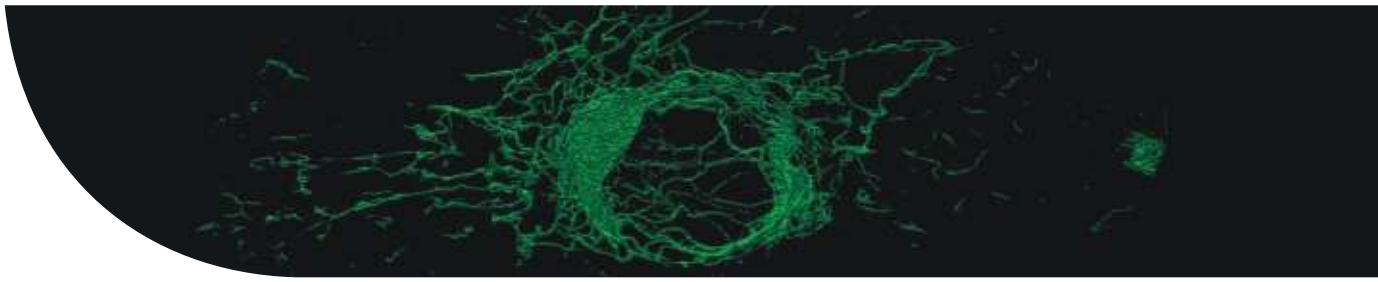
	Sl. No.	Details of the Staff Member			Pay Structure of 6th CPC		Level of Pay as per 7th CPC
		EMP.ID	Employee's Name	Designation	Pay Band	Grade Pay	
1	1	**592**	**Samit Chattopadhyay Dr.**	**Director**	**HAG 67000-79000/**		Level 15
2	1	445	Arun Bandyopadhyay Dr.	Chief Scientist	PB-4 37400-67000/-	10,000/-	Level 14
3	2	124	Rupak Kr. Bhadra Dr.	Chief Scientist	PB-4 37400-67000/-	10,000/-	Level 14
4	3	112	P. Jaisankar Dr.	Chief Scientist	PB-4 37400-67000/-	10,000/-	Level 14
5	1	443	Sibsankar Ray Dr.	Senior Principal Scientist	PB-4 37400-67000/-	8900/-	Level 13 A
6	2	441	Aditya Konar Dr.	Senior Principal Scientist	PB-4 37400-67000/-	8900/-	Level 13 A
7	3	521	Uday Bandopadhyay Dr.	Senior Principal Scientist	PB-4 37400-67000/-	8900/-	Level 13 A
8	4	473	S. Swarnakar Dr.(Miss)	Senior Principal Scientist	PB-4 37400-67000/-	8900/-	Level 13 A
9	1	520	Chinmay Chowdhury Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
10	2	563	Rupasri Ain Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
11	3	570	Sucheta Tripathy Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
12	4	503	Soumen Datta Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
13	5	523	K.N. Chattopadhyay Dr	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
14	6	524	Mrinal Kanti Ghosh Dr	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
15	7	447	S. Chattopadhyay Dr.(Mrs)	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
16	8	472	Subrata Adak Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
17	9	530	S. N. Bhattacharya Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
18	10	122	N. V. M. Khalkho Mrs. Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
19	11	580	Saikat Chakrabarti Dr	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
20	12	581	Surajit Ghosh Dr	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
21	13	582	Debabrata Biswas Dr	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
22	14	584	Umesh Prasad Singh Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
23	15	527	Malini Sen Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
24	16	532	Jayati Sengupta Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
25	17	540	Biswadip Banerji Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
26	18	547	Subhas Ch. Biswas Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
27	19	551	Nakul Ch. Maiti Dr.	Principal Scientist	PB-4 37400-67000/-	8700/-	Level 13
28	1	561	Partha Chakrabarti Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
29	2	566	Sanjoy Datta Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
30	3	568	Siddhartha Ray Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
31	4	571	Ranjan Jana Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
32	5	572	Arindam Talukdar Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
33	6	574	Ramalingam Natarajan Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
34	7	576	Indu Bhusan Deb Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
35	8	577	Dipyaman Ganguly Dr	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
36	9	578	Amitava Sengupta Dr	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
37	10	583	Subhajit Biswas Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
38	11	607	Upasana Ray Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
39	12	612	U. Mabalirajan Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12



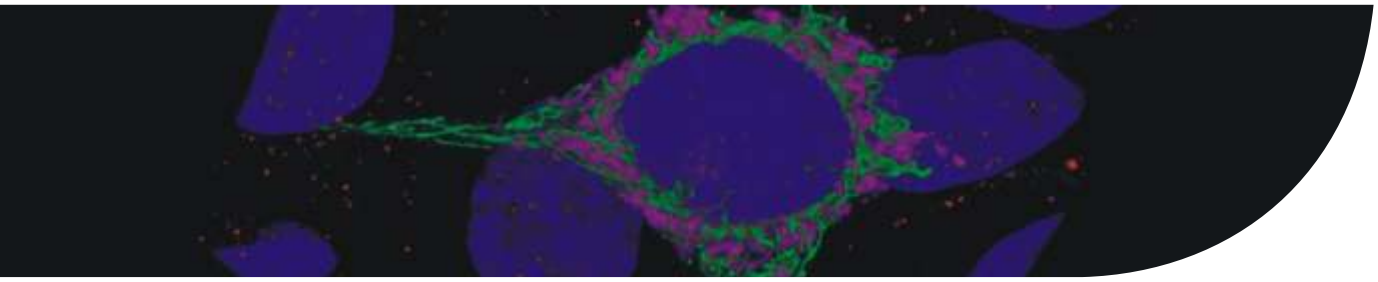
	Sl. No.	Details of the Staff Member			Pay Structure of 6th CPC		Level of Pay as per 7th CPC
		EMP.ID	Employee's Name	Designation	Pay Band	Grade Pay	
40	13	613	Shilpak Chatterjee Dr.	Senior Scientist	PB-3 15600-39100/-	7600/-	Level 12
41	1	528	Saraswati Garai Dr.	Scientist	PB-3 15600-39100/-	6600/-	Level 11
42	2	560	Indrajit Das Dr.	Scientist	PB-3 15600-39100/-	6600/-	Level 11
43	3	605	G. Senthil Kumar Dr.	Scientist	PB-3 15600-39100/-	6600/-	Level 11
44	4	608	Prem Prakash Tripathi Dr.	Scientist	PB-3 15600-39100/-	6600/-	Level 11
45	5	609	Pragadheesh VS	Scientist	PB-3 15600-39100/-	6600/-	Level 11
46	6	611	Siddik Sarkar Dr.	Scientist	PB-3 15600-39100/-	6600/-	Level 11
47	7	614	Amit Kr. Srivastava Dr.	Scientist	PB-3 15600-39100/-	6600/-	Level 11
48	8	615	Deepak Kumar Dr.	Scientist	PB-3 15600-39100/-	6600/-	Level 11
49	9	616	Joy Chakraborty Dr.	Scientist	PB-3 15600-39100/-	6600/-	Level 11
50	10	618	Sujoy Kr. Das Dr.	Scientist	PB-3 15600-39100/-	6600/-	Level 11
51	1	143	Krishna Das Saha Mrs. Dr.	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
52	2	145	S.E. Besra Dr. (Mrs.)	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
53	3	432	M Chatterjee Debnath Dr.	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
54	4	535	Chirantan Debdas Sri	Sr. Superintending Engineer (Electrical)	PB-4 37400-67000/-	8700/-	Level 13
55	5	162	Kshudiram Naskar Sri	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
56	6	164	S. Majumdar Dr.	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
57	7	494	Sandip Saha Sri	Sr. Superintending Engineer (Civil)	PB-4 37400-67000/-	8700/-	Level 13
58	8	499	Narayan ch. Ghosh Dr.	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
59	9	448	Binayak Pal Sri	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
60	10	449	Aparna Laskar Mrs. Dr.	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
61	11	173	Purnima Chatterjee Mrs.	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
62	12	175	Ardhendu Kr. Mandal Dr.	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
63	13	177	Tapas Sarkar Dr.	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
64	14	179	Subhagata Ghosh Miss Dr.	Principal Technical Officer	PB-4 37400-67000/-	8700/-	Level 13
65	1	174	Sankar Kumar Maitra Dr.	Sr. Technical Officer (3)	PB-3 15600-39100/-	7600/-	Level 12
66	2	180	Arupesh Majumder Sri	Sr. Technical Officer (3)	PB-3 15600-39100/-	7600/-	Level 12
67	3	185	R.N.Mandi Sri	Sr. Technical Officer (3)	PB-3 15600-39100/-	7600/-	Level 12
68	4	184	Ramdhan Majhi Dr.	Sr. Technical Officer (3)	PB-3 15600-39100/-	7600/-	Level 12
69	5	186	P. Gangopadhyay Sri	Superintending Engineer (Air Cond.)	PB-3 15600-39100/-	7600/-	Level 12
70	6	188	Dipika Roy Mrs.	Sr. Technical Officer (3)	PB-3 15600-39100/-	7600/-	Level 12
71	7	176	Banasri Das Mrs.	Sr. Technical Officer (3)	PB-3 15600-39100/-	7600/-	Level 12
72	8	178	Diptendu Bhattacharya Sri	Sr. Technical Officer (3)	PB-3 15600-39100/-	7600/-	Level 12
73	9	182	Pratap Ch. Kayal Sri	Sr. Technical Officer (3)	PB-3 15600-39100/-	7600/-	Level 12
74	10	496	E. PadmanabanDr.	Sr. Technical Officer (3)	PB-3 15600-39100/-	7600/-	Level 12
75	11	514	Susanta Ray Sri	Superintending Engineer (Civil)	PB-3 15600-39100/-	7600/-	Level 12



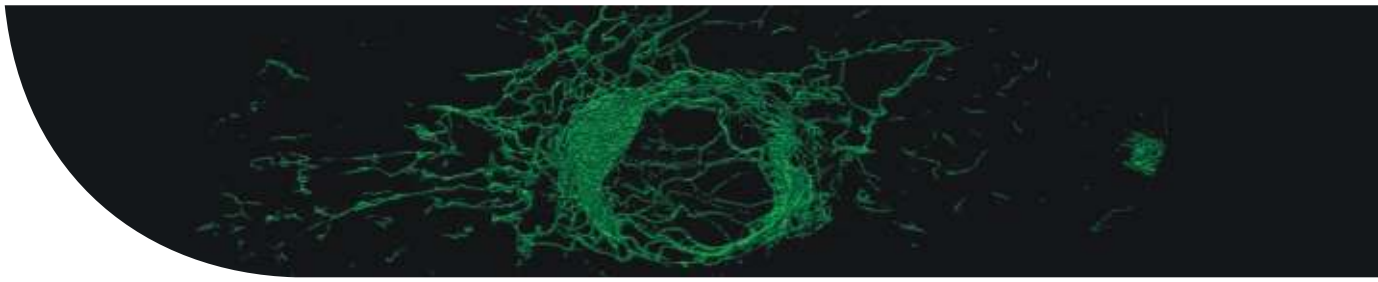
	Sl. No.	Details of the Staff Member			Pay Structure of 6th CPC		Level of Pay as per 7th CPC
		EMP.ID	Employee's Name	Designation	Pay Band	Grade Pay	
76	1	411	Sandip Chowdhury Sri	Sr. Technical Officer (1)	PB-3 15600-39100/-	5400/-	Level 10
77	2	466	Nirali Bage Mrs.	Asst. Executive Engineer (Civil)	PB-3 15600-39100/-	5400/-	Level 10
78	3	463	Arti Grover Mrs.	Sr. Technical Officer (1)	PB-3 15600-39100/-	5400/-	Level 10
79	4	465	Swapan Kr. Mondal Sri	Sr. Technical Officer (1)	PB-3 15600-39100/-	5400/-	Level 10
80	5	513	Debashis Banik Sri	Asst. Executive Engineer (Civil)	PB-3 15600-39100/-	5400/-	Level 10
81	6	516	Sandip Chakraborty Sri	Sr. Technical Officer (1)	PB-3 15600-39100/-	5400/-	Level 10
82	1	495	Jishu Mandal Sri	Technical Officer	PB-2 9300-34800/-	4600/-	Level 7
83	2	604	Sounak Bhattacharya Sri	Technical Officer	PB-2 9300-34800/-	4600/-	Level 7
84	3	539	Muruganandan T. Sri	Technical Officer	PB-2 9300-34800/-	4600/-	Level 7
85	4	552	M. Vigneshwaran Sri	Technical Officer	PB-2 9300-34800/-	4600/-	Level 7
86	5	556	Santu Paul Sri	Technical Officer	PB-2 9300-34800/-	4600/-	Level 7
87	6	557	Sandip Kundu Sri	Technical Officer	PB-2 9300-34800/-	4600/-	Level 7
88	7	559	Debasree Das Ms	Technical Officer	PB-2 9300-34800/-	4600/-	Level 7
89	1	550	Karri Suresh Kumar Sri	Technical Assistant	PB-2 9300-34800/-	4200/-	Level 6
90	2	569	Pradeep Sypureddi	Technical Assistant	PB-2 9300-34800/-	4200/-	Level 6
91	3	579	Soumik Laha Sri	Technical Assistant	PB-2 9300-34800/-	4200/-	Level 6
92	4	589	Sourin Ghosh Sri	Junior Engineer (Electrical)	PB-2 9300-34800/-	4200/-	Level 6
93	5	529	Ujjal Roy Sri	Junior Engineer (Electrical)	PB-2 9300-34800/-	4200/-	Level 6
94	6	600	Shubhendu Ghosh Sri	Junior Engineer (Air Cond.)	PB-2 9300-34800/-	4200/-	Level 6
95	7	610	Arpita Maji Ms.	Technical Assistant	PB-2 9300-34800/-	4200/-	Level 6
96	1	251	S. R. Tudu Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
97	2	244	Swapan Kumar Naskar Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
98	3	344	Ayub Shah Md.	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
99	4	242	Sheo Shankar Verma Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
100	5	246	Tapas Chowdhury Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
101	6	383	Pradip Mondal Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
102	7	247	Tarak Prasad Nandi Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
103	8	248	Sutapa Ganguly Mrs.	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
104	9	249	Sanjib Biswas Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
105	10	250	R. P. Gorh Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
106	11	252	Nishikanta Naskar Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
107	12	345	Ranjit Das Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
108	13	450	Abhijit Paul Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
109	14	410	Anirban Manna Sri	Sr. Technician (2)	PB-2 9300-34800/-	4600/-	Level 7
110	1	426	Samir Majumder Sri	Sr. Technician (1)	PB-2 9300-34800/-	4200/-	Level 6
111	2	360	M. Ahmed Md.	Sr. Technician (1)	PB-2 9300-34800/-	4200/-	Level 6
112	3	409	Paresh Sarkar Sri	Sr. Technician (1)	PB-2 9300-34800/-	4200/-	Level 6



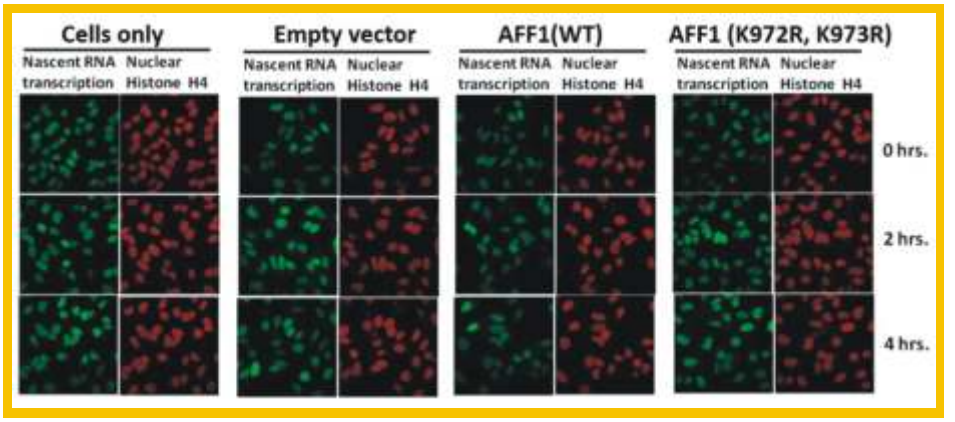
	Sl. No.	Details of the Staff Member			Pay Structure of 6th CPC		Level of Pay as per 7th CPC
		EMP.ID	Employee's Name	Designation	Pay Band	Grade Pay	
113	4	416	Sujit Kr. Majumdar Sri	Sr. Technician (1)	PB-2 9300-34800/-	4200/-	Level 6
114	5	419	Mahua Bhattacharjee Mrs.	Sr. Technician (1)	PB-2 9300-34800/-	4200/-	Level 6
115	6	418	Prabir Kr. Das Sri	Sr. Technician (1)	PB-2 9300-34800/-	4200/-	Level 6
116	7	460	Tapan Das Sri	Sr. Technician (1)	PB-2 9300-34800/-	4200/-	Level 6
117	8	417	Atanu Maitra Sri	Sr. Technician (1)	PB-2 9300-34800/-	4200/-	Level 6
118	1	534	Anup Karmakar Sri	Technician (2)	PB-1 5200-20200/-	2800/-	Level 5
119	2	546	Soumalya Sinha Sri	Technician (2)	PB-1 5200-20200/-	2800/-	Level 5
120	1	553	Nita Chakraborty Ms	Technician (1)	PB-1 5200-20200/-	1900/-	Level 2
121	2	554	Akash Gupta Sri	Technician (1)	PB-1 5200-20200/-	1900/-	Level 2
122	3	555	Samir Thami Sri	Technician (1)	PB-1 5200-20200/-	1900/-	Level 2
123	4	585	Avijit Paul Sri	Technician (1)	PB-1 5200-20200/-	1900/-	Level 2
124	5	586	Tanmoy Biswas Sri	Technician (1)	PB-1 5200-20200/-	1900/-	Level 2
125	6	590	Shiv Kumar Gupta Sri	Technician (1)	PB-1 5200-20200/-	1900/-	Level 2
126	7	591	Hari Sankar Beni Shri	Technician (1)	PB-1 5200-20200/-	1900/-	Level 2
127	1	272	Sunil Nath Sri	Lab. Assistant	PB-1 5200-20200/-	2800/-	Level 5
128	2	440	Bhaskar Basu Sri	Lab. Assistant	PB-1 5200-20200/-	2800/-	Level 5
129	3	479	Madan Halder Sri	Lab. Assistant	PB-1 5200-20200/-	2800/-	Level 5
130	4	282	Nimai Charan Prodhan Sri	Lab. Assistant	PB-1 5200-20200/-	2800/-	Level 5
131	5	351	Sambhu Raul Sri	Lab. Assistant	PB-1 5200-20200/-	2800/-	Level 5
132	6	353	Suresh Balmiki Sri	Lab. Assistant	PB-1 5200-20200/-	2800/-	Level 5
133	7	361	S. K. Banik Sri	Lab. Assistant	PB-1 5200-20200/-	2800/-	Level 5
134	8	352	Nanda Lal Routh Sri	Lab. Assistant	PB-1 5200-20200/-	2800/-	Level 5
135	1	501	Ashoke Sardar Sri	Lab. Attendant (2)	PB-1 5200-20200/-	1900/-	Level 2
136	2	502	Ram Kumar Sarkar Sri	Lab. Attendant (2)	PB-1 5200-20200/-	1900/-	Level 2
137	3	519	Shyamal Nath Sri	Lab. Attendant (2)	PB-1 5200-20200/-	1900/-	Level 2
				Lab.Attendant (1)	PB-1 5200-20200/-	1800/-	Level 1
				ADMINISTRATION			
138	1	606	Suprokash Halder Sri	Administrative Officer	PB-3 15600-39100/-	6600/-	Level 11
139	2	602	A.K. Pandey Sri	Stores & Purchase Officer	PB-3 15600-39100/-	6600/-	Level 11
140	3	617	Asim Kr. Jha Sri	Finance & Accounts Officer	PB-3 15600-39100/-	6600/-	Level 11
141	4	587	V.K. Gond Shri	Section Officer (G)	PB-3 15600-39100/-	5400/-	Level 10
142	5	525	Shampoo Sengupta Mrs.	Section Officer (G)	PB-3 15600-39100/-	5400/-	Level 10
143	6	392	Kanu Mondal Sri.	Section Officer (G)	PB-3 15600-39100/-	5400/-	Level 10
144	7	588	Monoj Kumar Sri	SO(F&A)	PB-3 15600-39100/-	5400/-	Level 10
145	8	397	Ratan Bage Sri	SO(SP)	PB-3 15600-39100/-	5400/-	Level 10
146	9	428	M. Bhattacharya Mrs.	Assistant Section Officer (Gen)	PB-2 9300-34800/-	4800/-	Level 8
147	10	427	Sanhita Ganguly Mrs.	Assistant Section Officer (Gen)	PB-2 9300-34800/-	4800/-	Level 8
148	11	335	Prem Singh Sri	Assistant Section Officer (Gen)	PB-2 9300-34800/-	4800/-	Level 8
149	12	340	D. K. Kisku Sri	Assistant Section Officer (Gen)	PB-2 9300-34800/-	4600/-	Level 7



	Sl. No.	Details of the Staff Member			Pay Structure of 6th CPC		Level of Pay as per 7th CPC
		EMP.ID	Employee's Name	Designation	Pay Band	Grade Pay	
150	13	396	Alok Ray Sri	Assistant Section Officer (Gen)	PB-2 9300-34800/-	4600/-	Level 7
151	14	510	Jayanta Pal Sri	Assistant Section Officer (Gen)	PB-2 9300-34800/-	4600/-	Level 7
152	15	511	Saugata Das Sri	Assistant Section Officer (Gen)	PB-2 9300-34800/-	4600/-	Level 7
153	16	508	Tarun Kr. Sinha Roy Sri	Assistant Section Officer (Gen)	PB-2 9300-34800/-	4600/-	Level 7
154	1	507	Raju Pal Sri	Sr. Secretariat Assistant (Gen)	PB- 1 5200-20200/-	2400/-	Level 4
155	2	509	Ranjit Debnath Sri	Sr. Secretariat Assistant (Gen)	PB- 1 5200-20200/-	2400/-	Level 4
156	3	512	Sukhendu Biswas Sri	Sr. Secretariat Assistant (Gen)	PB- 1 5200-20200/-	2400/-	Level 4
157	4	565	Anirudha Das Sri	Sr. Secretariat Assistant (Gen)	PB- 1 5200-20200/-	2400/-	Level 4
158	5	593	Tanumoy Sen Shri	Sr. Secretariat Assistant (Gen)	PB- 1 5200-20200/-	2400/-	Level 4
159	6	594	Raju Kumar Shri	Sr. Secretariat Assistant (Gen)	PB- 1 5200-20200/-	2400/-	Level 4
160	7	595	Debtanu Pal Shri	Sr. Secretariat Assistant (Gen)	PB- 1 5200-20200/-	2400/-	Level 4
161	8	596	Sumit Kumar Singh Shri	Sr. Secretariat Assistant (Gen)	PB- 1 5200-20200/-	2400/-	Level 4
162	9	597	Ram Kanai Mondal Shri	Sr. Secretariat Assistant (Gen)	PB- 1 5200-20200/-	2400/-	Level 4
163	1	343	Sanjoy Kr.Mukhopadhyay Sri	Assistant Section Officer (F&A)	PB-2 9300-34800/-	4800/-	Level 8
164	2	336	Asit Kr. Roy Sri	Assistant Section Officer (F&A)	PB-2 9300-34800/-	4800/-	Level 8
165	3	338	M. K. Dutta Sri	Assistant Section Officer (F&A)	PB-2 9300-34800/-	4600/-	Level 7
166	1	506	Vishal Agarwal Sri	Sr. Secretariat Assistant (F&A)	PB-1 5200-20200/-	2400/-	Level 4
167	2	598	Chaitali Sarkar Miss	Sr. Secretariat Assistant (F&A)	PB-1 5200-20200/-	2400/-	Level 4
168	1	328	A. B. S. Roy Sri	Assistant Section Officer (S&P)	PB-2 9300-34800/-	4800/-	Level 8
169	2	536	Rajib Ray Sri	Assistant Section Officer (S&P)	PB-2 9300-34800/-	4800/-	Level 8
170	3	342	Bisweswar Das Sri	Assistant Section Officer (S&P)	PB-2 9300-34800/-	4600/-	Level 7
171	4	363	Bula Pal Mrs.	Assistant Section Officer (S&P)	PB-2 9300-34800/-	4600/-	Level 7
172	1	505	Pradipta Sarkar Sri	Sr. Secretariat Assistant (S&P)	PB-1 5200-20200/-	2400/-	Level 4
173	2	504	Arnab Sen Sri	Sr. Secretariat Assistant (S&P)	PB-1 5200-20200/-	2400/-	Level 4
174	3	599	Shyama Chanran Bose	Sr. Secretariat Assistant (S&P)	PB-1 5200-20200/-	2400/-	Level 4
175	1	324	Pratima Banerjee Mrs.	SR. STENOGRAPHER	PB-2 9300-34800/-	5400/-	Level 9
176	2	325	Shankar Bhakta Sri	SR. STENOGRAPHER	PB-2 9300-34800/-	4800/-	Level 8
177	3	393	Rabindranath Das Sri	SR. STENOGRAPHER	PB-2 9300-34800/-	4800/-	Level 8
178	4	490	Sankar Santra	SR. STENOGRAPHER	PB-2 9300-34800/-	4600/-	Level 7
179	5	453	Gautam Saha Sri	SR. STENOGRAPHER	PB-2 9300-34800/-	4600/-	Level 7
180	6	491	Moumita Majumdar Mrs.	SR. STENOGRAPHER	PB-2 9300-34800/-	4600/-	Level 7
181	1	405	Saibal Giri Sri	JR. STENOGRAPHER	PB-1 5200-20200/-	2400/-	Level 4
				ISOLATED POST			
182	1	321	Ambalika Nag Mrs.	Hindi officer	PB-3 15600-39100/-	5400/-	Level 10
183	2	567	Sabyasachi Karmokar Sri	Security Officer	PB-2 9300-34800/-	4600/-	Level 7
				Gr-C (NT) / MTS			
184	1	348	Ashok Ram Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2400/-	Level 4

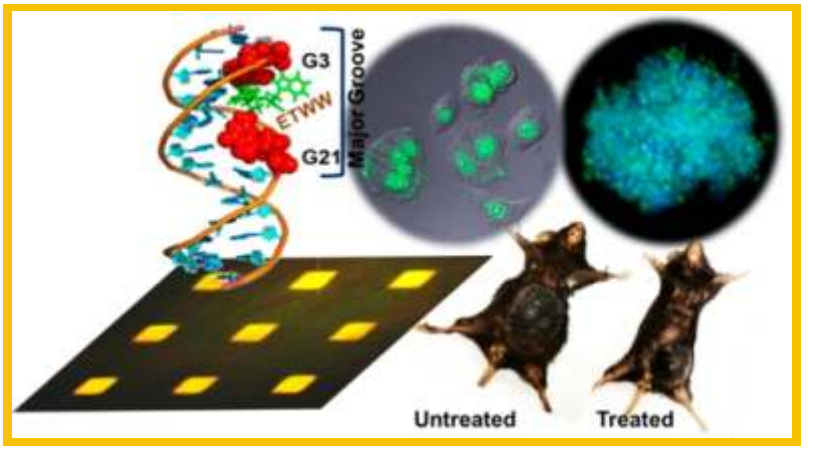


	Sl. No.	Details of the Staff Member			Pay Structure of 6th CPC		Level of Pay as per 7th CPC
		EMP.ID	Employee's Name	Designation	Pay Band	Grade Pay	
185	2	365	Kailash Ch. Nayak Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
186	3	401	Soma Devi Sharma Mrs	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
187	4	412	Gopal Ch. Mandal Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
188	5	413	Asit Mitra Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
189	6	431	Janmanjoy Midya Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
190	7	430	Pasupati Midya Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
191	8	423	Shyamal Kr. Ghosal Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
192	9	414	P. C. Dehury Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
193	10	425	Manoranjan Adhikary Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
194	11	424	Tapan Sarkar Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	2000/-	Level 3
195	12	451	Dinesh Mahali Sri	GR-C (NT) / MTS	PB-1 5200-20200/-	1900/-	Level 2
Canteen							
196	1	371	Ashok Sadhukhan Sri	BEARER	PB-1 5200-20200/-	2400/-	Level 4
197	2	370	Badal Haldar Sri	BEARER	PB-1 5200-20200/-	2400/-	Level 4
198	3	374	Jagabandhu Biswas Sri	WASH BOY	PB-1 5200-20200/-	2400/-	Level 4
199	4	375	Nirapada Halder Sri	SWEEPER	PB-1 5200-20200/-	2400/-	Level 4
200	5	376	Mantu Das Sri	SWEEPER	PB-1 5200-20200/-	2000/-	Level 3



Nascent RNA transcription in mammalian cells in presence of WT and mutant (K972A, K973A) AFF1 proteins.

Courtesy : Dr. Debabrata Biswas



A top-down approach to show how spatial positions of two tryptophans regulate the cellular entry and nuclear localization.

Courtesy : Dr. Surajit Ghosh

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