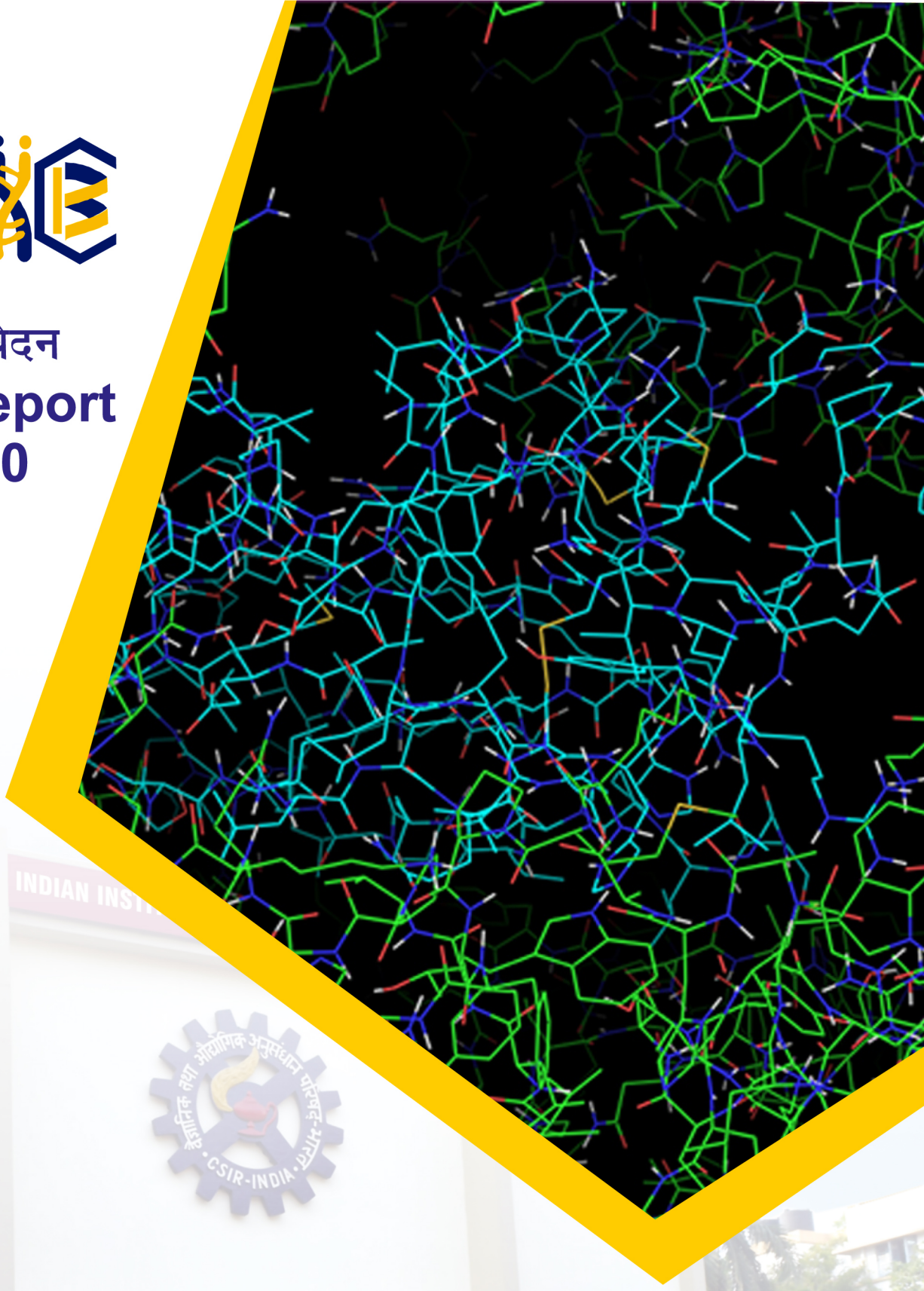


वार्षिक प्रतिवेदन
Annual Report
2019-20

CSIR-IICB

सी.एस.आई.आर – भारतीय रासायनिक जीवविज्ञान संस्थान
CSIR-Indian Institute of Chemical Biology



Front cover picture courtesy: **Dr. Arun Bandyopadhyay.**

A ball and stick view of the interaction between platelet protein soluble TREM like transcript 1(sTLT1) (sky blue) and Fcγ receptor 1 (FcγR1; Green). Interaction of sTLT1 with FcγRI initiates the SYK/MEK/ERK axis which results into chronic inflammation and atherosclerosis (Das et al. Clinical Science, 2019, 133,22)

वार्षिक प्रतिवेदन
Annual Report 2019-20

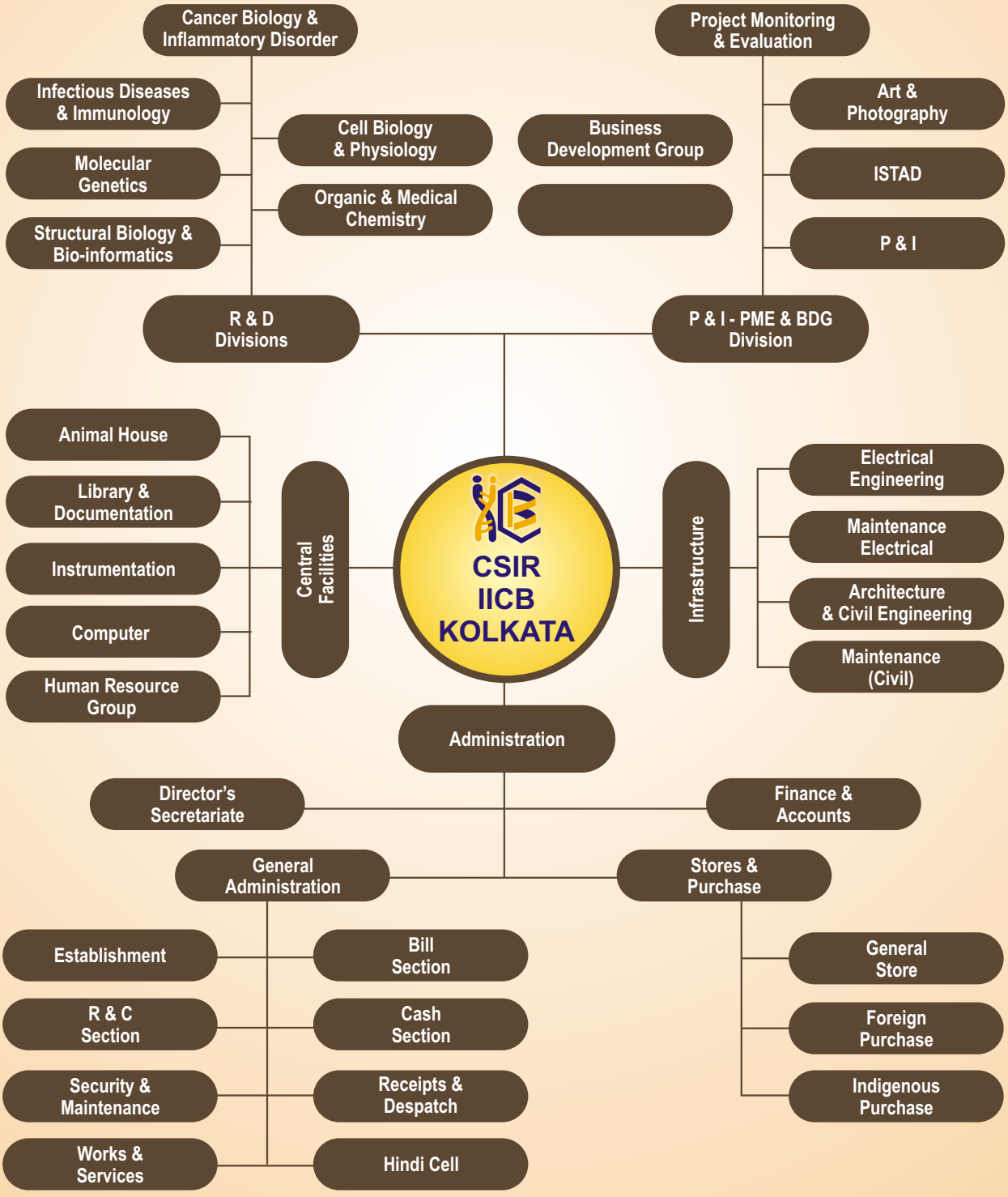


Jadavpur Campus



Salt Lake Campus

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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
Business Development Group
Art & Photography
ISTAD
P & I
P & I - PME & BDG Division
Animal House
Library & Documentation
Instrumentation
Computer
Human Resource Group
Central Facilities
CSIR IICB KOLKATA
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Architecture & Civil Engineering
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Administration
Director's Secretariate
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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 Desk



Dr. Arun Bandyopadhyay
CSIR-IICB, Kolkata

I am delighted to publish the annual report of CSIR-IICB for the period of 2019-2020. This annual report portrays a brief understanding of the overall activities of the institute in terms of its science and scientists, administrative services, service divisions, infrastructure, assets and other aspects of scientific management.

The journey of Indian Institute of Chemical Biology (IICB) began in the year 1935 as the 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 edge 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.

CSIR-IICB has grown from strength to strength due to the amalgamation of chemistry and biology. Like previous years, CSIR-IICB excels in quality research on diseases of biological importance. In order to strengthen the basic research and to attain translational objectives, a second campus, a four-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 an 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 the societal benefits of the common man. Six research divisions manage the research and development activities of CSIR-IICB.

Our scientific productivity has been reflected in the publications in prestigious international journals. During the recent pandemic situation, CSIR-IICB was in the frontline of several research initiatives including the drug repurposing and the viral genome sequencing initiative. Our team has joined hands with Medical colleges in testing the Convalescent plasma therapy. We were applauded for deploying our RT-PCR machines for the detection of SARS Covid 19 virus to several hospitals including the command hospital. We have also commissioned a COVID testing center in Raiganj Medical College deploying some of our equipment.

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 the laboratory in supporting the scientific community and society, along with the development of public-private partnerships and human resource development.

CSIR-IICB has always remained as a center of choice for promising researchers with aspirations to work in biological and chemical fields. 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 potential answers to several burning biological questions.



Cancer Biology & Inflammatory Disorder Division

Members :

Dr. Mrinal K Ghosh (Head), Prof. Samit Chattopadhyay, Dr. Snehasikta Swarnakar, 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

Diverse arrays of aberrations are required before a normal cell will defy 'social behavior' to fulfill its only purpose – to proliferate – at the expense of life. By then, deep down at the molecular level crucial signalling pathways would have been extensively rewired. The long term goals of this division are to focus on the comprehensive understanding of cancer at many levels ranging from the investigation of molecular and genetic basis of cancer, the elucidation of cellular processes altered during development of cancers, immune response and inflammation.

Cancer has a multifaceted character which is inherent in its very origin.The faculties conduct both basic and translational research on a range of topics that include lung, brain, oral, breast, prostate, colon, pancreatic, cervical cancers and leukemia. Our current focus is on identification of pure herbal and/or synthetic compounds/herbal extracts having invitro anti-proliferative activities against different cancer cells, understanding alterations and cross-talks among signalling pathways in cancers. Emphasis is also given on characterization of novel targets, identification of target-specific leads and biologics using systems biology approaches. Optimization of lead molecules by development of in-silico library of compounds through pharmacophore modelling and structure-based drug designing, targeted drug delivery, invivo toxicity,in vivo efficacy assessmentandpharmacokinetics determination.

Following are some of the key research achievements:

- Promyelocytic Leukemia (PML) Gene Regulation: Implication towards curbing oncogenesis.• RNA helicase p68 deploys β-catenin in regulating RelA/p65 gene expression: Implications in Colon cancer.
- The interrelationship between cerebral ischemic stroke and glioma.
- Extracellular vesicles in Glioma: From Diagnosis to Therapy.
- Epigenetic regulation in AML pathogenesis & targeted therapy.
- Regulation of mitochondrial respiratory complex assembly and activity by CCN6. • Role mechano-sensing in immune cell function
- Cutting Edge: Dysregulated endocannabinoid-rheostat for plasmacytoid dendritic cell activation in a systemic lupus endophenotype.
- CRISPR/Cas-guided gene editing of sickle cell anaemia.
- Therapeutic Potential of some natural compounds and multifaceted nanomaterials towards cancer therapy.
- Bioengineered adipose-derived stem cells for targeted enzyme-prodrug therapy of ovarian cancer intraperitoneal metastasis.
- Big data analysis, Prognostic biomarker andEngineered cell based anti-cancer therapeutics or Suicidal gene-therapy.



Dr. Mrinal Kanti Ghosh

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The oncogenic interplay of cellular signaling networks for discovery of drug target and targeted delivery of nanotherapeutics in a combinatorial approach in cancer

Participants

Dr. Sibani Sarkar (WoS, DHR, ICMR)

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JRF : Partha Mohanta, Sunny Kumar, Subhojit Karmakar

Mr. Sourav Dey (Lab Manager)

Collaborator(s)

Name of collaborator outside CSIR-IICB

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Dr. Sandeep Chatterjee
Park Clinic, Kolkata

Dr. Suresh Bajoria
RTIICS (NH), Kolkata

Background

Cancer is a complicated diseased phenomenon, where the normal cells of our body override the cardinal hallmarks of normal growth and differentiation and transform themselves into benign or malignant tumors, through an elaborate process known as oncogenesis ("onco", the Latin word for "tumor" and "genesis" meaning "beginning"). Oncogenesis is characterized by perturbation of cellular signalling pathways leading to undue cellular proliferation, evading apoptosis, induced angiogenesis and metastasis, thereby leading to increased morbidity and mortality. At the molecular level context, tumor suppressor proteins such as p53, PML and PTEN lose their functionality whereas tumorigenic proteins such as STAT3, p68, β-catenin and c-Myc, get up-regulated. The emerging novel roles of protein kinases like Akt and CK2 in regulating phosphorylation of the molecular players involved, E3 ubiquitin ligases like CHIP and deubiquitinases like HAUSP in regulating their half lives are being enumerated in various research articles around the world. In our lab, we are actively involved in deciphering the mechanistic aspects of these proteins against the oncogeneic backdrop.

Moreover, there is a need for properly understanding the basis of the crosstalk between signalling pathways and interventional proteins involved so as to chalk out the course of cancer therapeutic interventions. Recent advances in the field of translational research and the use of novel targeted drug delivery approaches (liposome-based, exosome-based, inhibitory peptide-based, nanoparticle-based delivery systems) as well as combinatorial drug delivery methods are gradually gaining significance. Therefore, it is imperative to focus upon the basic science as well as the translational aspects so as to design proper routes of cancer treatment. Also, the advancements in genomics and proteomics in recent years has given significant boost to our understanding of roles of individual proteins in governing tumor growth, spread of cancer, interaction of cancer cells with surrounding cells, and response to the drugs and other therapies. Thus, it is also necessary to comprehensively understand the revolutionary aspects of proteomics and transcriptomics in the field of cancer.

Aims and Objectives

- To identify novel molecular targets leading to tumorigenesis.
- To gain mechanistic insights into the role and regulation of key molecular players such as p68, RelA, CHIP, HAUSP, PML and PTEN towards the process of curbing oncogenesis.
- To investigate the crosstalk between different signaling pathways such as Wnt, NF-κB and EGFR signaling in different types of cancer.
- To develop novel targeted drug delivery methods for therapeutic purpose.

Work Achieved

Promyelocytic Leukemia (PML) gene regulation: implication towards curbing oncogenesis -

Breast cancer is the most commonly encountered form of cancer and the second leading cause of cancer related mortality among women in the world. It is mostly diagnosed based upon the presence or absence of three receptors: ERα, PR and HER-2. Triple-negative BCa (TNBC) is defined by the lack of expression of

all the above three receptors and hence it is insensitive to hormone responsive treatments and frequently undergo local or systemic relapse. Promyelocytic Leukemia Protein (PML) is an essential component of PML Nuclear bodies (PML-NBs). They help in coordinated regulation of various processes such as transcriptional regulation, post-translational modifications, DNA replication, apoptosis, senescence, cell cycle regulation and DNA damage repairs. Dysregulation of PML, a significant tumor suppressor, is linked with cancers of different histological origins, with a decreased expression observed with a higher tumor grade especially in breast cancers. Thus, it is necessary to study about the mechanisms of PML regulation and stability.

In our lab, we established a compelling link in controlling oncogenesis where tumor suppressor PML is regulated by a pro-apoptotic molecule ERβ. We found that clinical expression of PML positively correlates with that of ERβ both in normal and breast carcinoma samples and inversely correlates with markers of cellular proliferation, hinting towards a possible mechanistic interdependence. Both mRNA and protein expression of PML were increased in response to ERβ overexpression on multiple human breast cancer cell lines. Mechanistically, luciferase reporter assays and ChIP assays demonstrated that ERβ can interact with the PML promoter via ERE and AP1 sites to enhance its transcription. ERβ induced stable PML expression causes a decline of its target protein Survivin and simultaneously stabilizes its target Foxo3a, further causing transcriptional upregulation of pro-apoptotic factors p21 and p27. Immunohistochemical analyses of cancer and normal breast tissues and functional assays conducted corroborated the findings. Thus ERβ-PML network interestingly curbs oncogenesis by inhibition of anti-apoptotic molecule and stabilizing a tumor-suppressor. Exploration of this novel 'ERβ-PML-(Foxo3a/Survivin)' signaling axis might hopefully provide a new direction in the clinical management of breast cancer. This work can also consider ERβ as a therapeutic target in ERα− tumors thus helping us to develop a new therapeutic network.

Future Research Plans

To focus upon the transcriptional and post-translational regulation of key molecular players such as PML, p68, HAUSP, CHIP and PTEN in different cancer systems.
To develop transcriptomics and proteomics-based study and delineating the oncogenic scenario using omics-based data.

To focus upon translational research via anti-cancer drug discovery from natural products and designing target based synthetic peptides for therapeutic purposes.
To develop novel targeted drug delivery-based systems to effectively alleviate tumorigenesis.

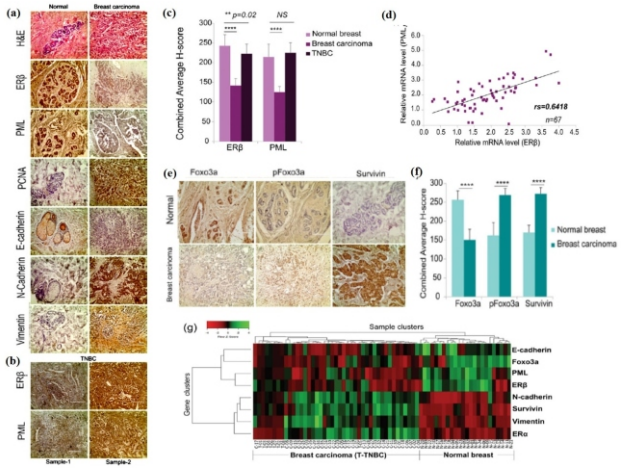


Fig. 1: Clinical sample-based study and IHC correlational analysis: (a), (b) & (c) Representative IHC and H&E images of the candidate proteins in human BCa and adjacent normal breast tissue samples and in two representative TNBC samples (Sample 1 & 2) & combined average H-scores**.** (d) Depiction of correlation coefficient from qRT-PCR data**.** (e) & (f) Representative IHC images of Foxo3a, pFoxo3a and Survivin of the human BCa and adjacent normal breast tissues and combined average H-scores**.** (g) Heat map of expression patterns from 24 normal (N) and 43 BCa (C) samples.

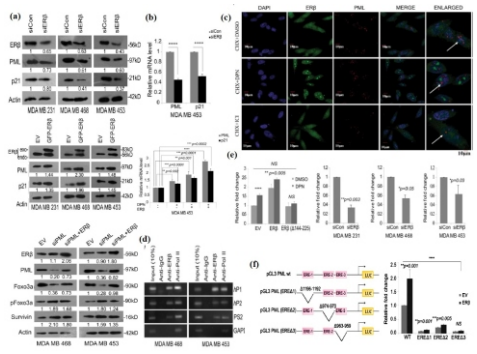


Fig. 2: Mechanistic regulation of PML by ERβ: (a) & (b) Immunoblot and qRT-PCR analysis delineating the ERβ-PML-(Foxo3a/Survivin) network in multiple breast cancer cell lines (c)

Expression of ERβ and PML treated with either DPN or ICI or DMSO control in combination with CHX, detected by immuno-cytochemistry. (d) Chromatin immunoprecipitation (ChIP) assay performed using the indicated antibodies. (e) Luciferase activity of PML promoter under ERβ. (f) Schematic depiction of ΔERE deletion constructs on PML promoter and mutational luciferase data analysis.

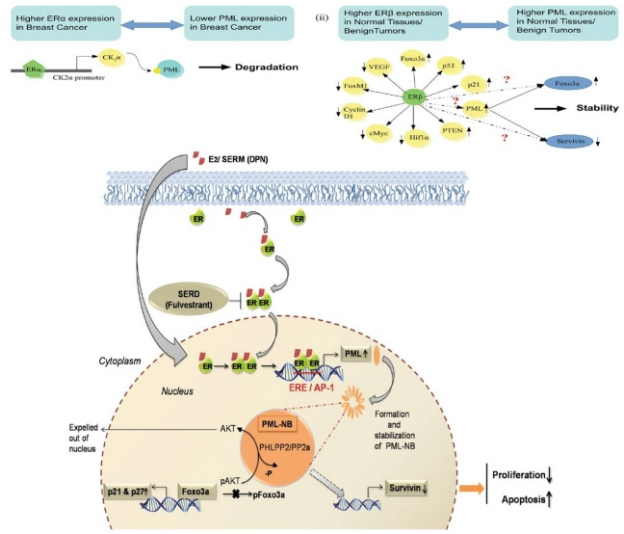


Fig. 3: Schematic illustration of ERβ mediated PML regulation in breast cancer.

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.
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- Basu B and Ghosh MK* (2019). Extracellular vesicles in Glioma: From Diagnosis to Therapy. BioEssays 41 (1800245): 1-9.
- 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.

Book Chapters / Invited Reviews

Basu M and Ghosh MK* (2019). Helicobacter Pylori Infection Leads to Colorectal Cancer Development: A Major Scientific Debate. Acta Scientific Cancer Biology 3(5): pg 22.

AWARDS / HONOURS / MEMBERSHIPS

Dr. Mrinal K Ghosh

Awards / Honours
Bharat Vikash Award - 2019

EXTRAMURAL FUNDING

Dr. Mrinal K Ghosh

A Novel Nanotechnology based Approach of Glioma Therapy by Targeting HAUSP -MDM2 axis in combination with Temozolomide. 2019 - 2022. (SERB, DST, India)

INVITED TALKS BY CSIR-IICB FACULTY

Dr. Mrinal K Ghosh

Establishment of drug target and targeted delivery of nanotherapeutics in cancer therapy. 5th International Conference on Translational Research (ICTR): Recent Trends in Pre-translational to Translational Research. National Centre for Cell Science, Pune, India. November 07– 09th, 2019.

Glioma therapy: Targeting RNA helicase p68 and Post-translational modifier HAUSP for translation of peptide & small molecule based nanotherapeutics in a combinatorial approach. INDO-JAPAN bilateral program meeting at Sister Nivedita University (SNU), Oct 30, 2019.

Glioma Diagnosis: Early diagnosis using Tc-labelled mutated somatostatin peptide probe against SSTR2 receptor. INDO-JAPAN bilateral program meeting at Sister Nivedita University (SNU), Oct 30, 2019.

Glioma Therapy: Targeted Delivery of Nanotherapeutics across the Blood Brain Barrier (BBB). Symposia on Molecular Diagnostics and Therapeutics. College of Medicine & JNM Hospital, WBUHS, Kalyani, West Bengal with Association of Clinical Biochemists of India (ACBI), June 21-22, 2019.



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Role of WNT and WISP in Health and Disease.

Participants

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Background & Work Achieved:

In view of the potential of WNT5A signaling to influence cytoskeletal dynamics and immune homeostasis, we are evaluating the interrelationship between WNT5A signaling and microbial infection. WNT5A is a member of the large family of WNT glycoprotein ligands that transmit signals to the cell cytoskeletal network upon binding to Frizzled and/or ROR cell surface receptors. Frizzled5, Frizzled4, Frizzled2 and ROR1 are putative receptors for WNT5A. The molecular mechanism of WNT5A signaling may vary with cell type. Although in many cases the signaling can ensue independent of the transcriptional coactivator beta-catenin, the involvement of beta-catenin, which is actually conferred by the existing stoichiometry of WNT5A receptors, cannot be totally ruled out. In light of the ever-increasing emergence of drug resistant pathogens, evaluation of the role of WNT5A in host defense against pathogen incursions may lead to the development of new ways of preventing the progression of drug resistant infections.

We are also studying the function of Cell Communication Network Factor 6 (CCN6) in the context of the debilitating skeletal disorder Progressive Rseudo Rheumatoid Disorder (PPRD). Although it is known that mutations in the CCN6 gene coding sequence lead to the development of PPRD, the molecular mechanism of disease pathogenesis is not understood. Furthermore, several features of CCN6 function also remain unknown. CCN6 being a multimodular protein is expected to exert its characteristics through interacting with other proteins. Since CCN6 localizes to several organelles in the cell including mitochondria, we are evaluating the role of CCN6 in mitochondrial function. A proper characterization of the role of CCN6 in the mitochondria should help us in analyzing PPRD causing CCN6 mutants and understanding PPRD pathogenesis.

Objectives

To investigate the role of WNT5A signaling in interaction of macrophages with both pathogenic microbes (e.g. Pseudomonas aeruginosa, Streptococcus pneumonia, E.coli K1), and non pathogens (lab strains of Escherichia.coli and commensals).

To decipher the role of CCN6 in mitochondrial function.

Work Achieved
We have found that the effect of WNT5A signaling on bacterial phagocytosis and sustenance in macrophages varies with the type of infection. Interestingly, while non pathogenic lab strains of E.coli were only increasingly internalized by activation of WNT5A signaling, the pathogenic bacteria were both internalized and killed. Our experimental results suggest that WNT5A signaling in macrophages activates a Rac1-Dishevelled dependant host autophagy circuit to initiate killing of bacterial pathogens. The Wnt5A-Actin axis directs the outcome of infection by pathogen and nn-pathogen.

Our experiments focused on the functional characterization of CCN6 have documented that CCN6 localizes to the mitochondria, remains as a component of mitochondrial respiratory complexes and regulates mitochondrial respiration. We have seen that cells partially depleted of CCN6 have increased mitochondrial complex activity. However, mutations in CCN6 similar to those linked to PPRD result in collapse of mitochondrial respiratory activity and function. Our results suggest that CCN6 plays an important role in the regulation of mitochondrial metabolism.

Future Research Plan:

To find out if regulation of WNT5A signaling restrains drug resistant bacterial infections.

To characterize PPRD causing CCN6 mutants in zebrafish.

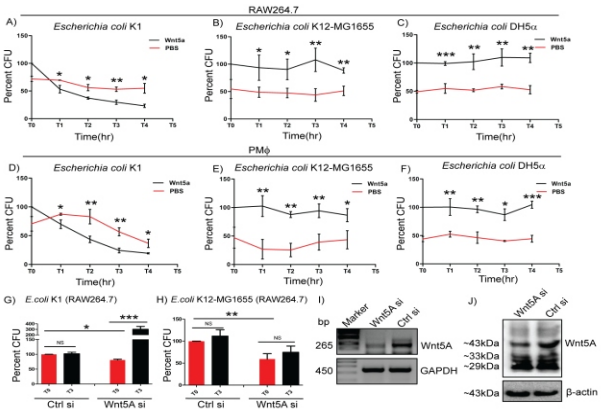


Figure 1 :
Wnt5A signaling facilitates killing of pathogenic but not non-pathogenic E.coli. rWnt5A promotes intracellular killing of pathogenic bacterial strain E.coli K1 in both RAW264.7 (A) and peritoneal macrophages:PMØ (D) as estimated by Colony Forming Units (CFU) (n=3) at different time points (T1-T4), 1hr after infection (T0) at MOI: 10, as compared to corresponding control (PBS). rWnt5A did not promote killing of non-pathogenic bacterial strains E.coli K12-MG1655 (B, E) (n=3) and E.coli DH5α (C, F) (n=3) as observed in both RAW264.7 and PmØ in comparison to corresponding control. Wnt5A siRNA mediated decrease in endogenous Wnt5A expression resulted in decreased uptake of both E.coli K1 and E.coli K12-MG1655, and promoted intracellular proliferation of pathogenic E.coli K1 (n=3) but not non-pathogenic E.coli K12-MG1655 (n=3) as depicted from CFU at T0 and T3 (G, H). Depletion of Wnt5A expression by siRNA was confirmed by RT-PCR (I) and immunoblot analysis (J) in RAW264.7 cells. Data represented as mean ± SEM; *p ≤ 0.05, **p ≤ 0.005, ***p ≤ 0.0005, NS; Not Significant. Wnt5Asi: Wnt5A siRNA, Crtlsi: Control siRNA. Marker: DNA ladder

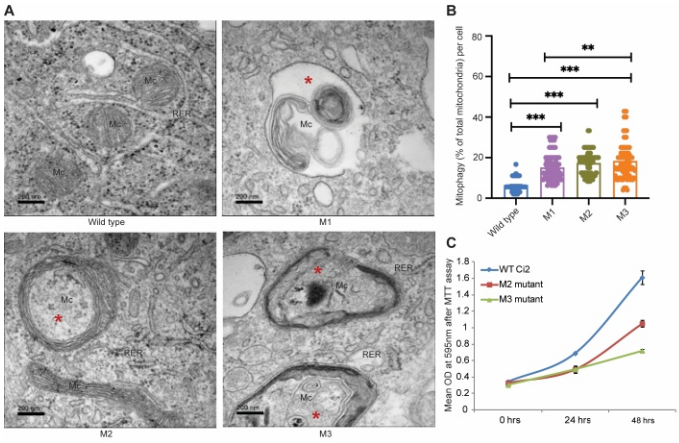


Figure 2 :
Mutations in CCN6 induce accumulation of damaged mitochondria and loss of cell viability. A) Transmission electron micrographs of CCN6 mutant cells showing damaged/abnormal mitochondrial morphology. Mc indicates mitochondria and * (Red asterisks) indicates damaged/abnormal mitochondria. Scale bar: 200 nm. B) Distribution plot with mean value showing percent of damaged mitochondria per cell in mutants and wild type cells. Scoring was done by counting more than 100 cells for each set. Data were analysed by one-way ANOVA followed by multiple comparison test (**p< 0.01, ***p< 0.001). C) MTT assay showing less viability of CCN6 mutant lines as compared to wild type. Data are plotted as Mean + SE of 8 replicates.

PUBLICATIONS

1. Padhan, D. K., Sengupta, A., Patra, M., Ganguly, A., Mahata, S.K., and Sen, M. CCN6 Regulates Mitochondrial Respiratory Complex Assembly and Activity. FASEB J. 2020, doi: 10.1096/fj.202000405RR
2. Blumenthal, A., Martin-Orozco, E., McBride, J.W., Carson, D.A., and Sen, M. Editorial: Wnt Signaling in Immune Cell Regulation during Microbial Infection and Cancer. Front Immunol. 2020; 11: 1133
3. Jati, S., & Sen, M. (2019). Wnt Signaling Regulates Macrophage Mediated Immune Response to Pathogens. In Macrophage at the Crossroads of Innate and Adaptive Immunity. IntechOpen.
4. Chakraborty, A., Maity, S., & Sen, M. (2019). Wnt5A Signaling Antagonizes Leishmania donovani Infection. In Leishmaniasis-from Basic Research to the Field. Intech Open.
5. Jati, S., Sarraf, T. R., Naskar, D., & Sen, M. (2019). Wnt Signaling: Pathogen Incursion and Immune Defense. Frontiers in immunology, 10, 2551.

EXTRAMURAL FUNDING

Grants: (i) Evaluating CCN6 and promoting societal benefit in the context of PPRD (Progressive Pseudo Rheumatoid Dysplasia), a debilitating genetic disorder. Agency: DBT, Govt. of India.
(ii) Role of Wnt5A signaling in bacterial infection. Agency DBT, Govt of India
(iii) Evaluating CCN6 in the context of PPRD using zebrafish as a model organism. Agency SERB, Govt.of India



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

Participants

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Ranit D'Rozario, UGC-JRF
Md. Asmaul Hoque,UGC-JRF
Dr. Bishnu Prasad SInha, ICMR-SRF
Dr. Jayasri Rouy Mandal, Postdoctoral Fellow

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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

Work Achieved

- Development of novel small molecule antagonists for toll-like receptor 9 and 7, promising therapeutic targets in systemic autoimmune diseases as they inhibit activation of plasmacytoid dendritic cell activation and type I IFN induction. [Mukherjee A et al., J Med Chem, 2020; Pal S et al., Eur J Med Chem, 2020.]

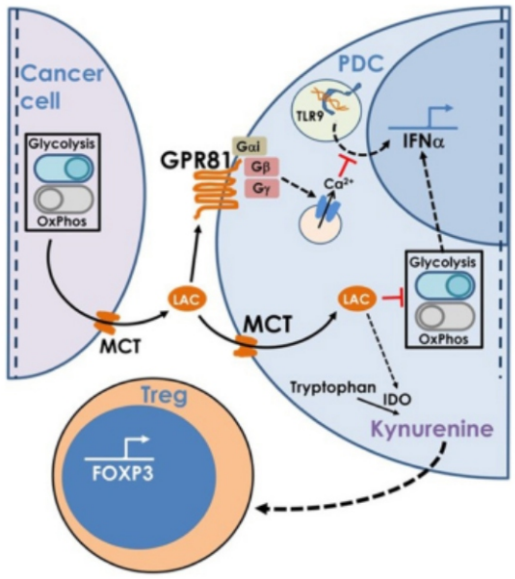
- Discovery of hitherto unknown pro-tumor reprogramming of tumor-infiltrating plasmacytoid dendritic cells driven by lactate released by tumor cells [Raychaudhuri D et al., Front Immunol, 2019].

- Exploration of host immune response in COVID-19 and clinical trial on convalescent plasma therapy in severe COVID-19. [Shah VK et al., Front Immunol, 2020; Bandopadhyay P et al., medRxiv, 2020].

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 dysregulation of tumor-infiltrating plasma cytoid dendritic cells in resonse a oncometabolite. (Raychaudhuri D et al., Front Immunol, 2020)



PUBLICATIONS

1. Pal S, Paul B, Bandopadhyay P, Preethy N, Sarkar D, Rahaman O, Roy S, Ganguly D*, Talukdar A*. Synthesis and Characterization of New Potent TLR7 Antagonists Based on Analysis of the Binding Mode using Biomolecular Simulations. European Journal of Medicinal Chemistry. 2020. In press.

2. Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S*. Overview of Immune Response During SARS-CoV-2 Infection: Lessons From the Past. Frontiers in Immunology. 2020 Aug 7;11:1949.

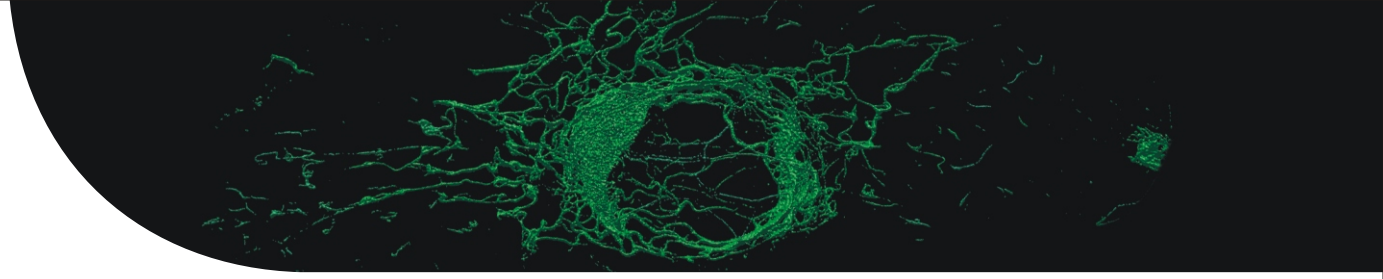
3. Mukherjee A#, Raychaudhuri D#, Sinha BP#, Kundu B, Mitra M, Paul B, Bandopadhyay P, Ganguly D*, Talukdar A*. A chemical switch for transforming a purine agonist for toll-like receptor 7 to a clinically relevant antagonist. Journal of Medicinal Chemistry. 2020 May 14;63(9):4776-4789.

4. Roy Chattopadhyay N, Chatterjee K, Tiwari N, Chakrabarti S, Sahu SK, Roy SD, Ghosh A, Reddy R, Das P, Mal S, Karnar BB, Das AK, Tsering S, Riba K, Puii Z, Zomawia E, Singh YI, Suryawanshi AR, Kumar A, Ganguly D, Goswami C, Choudhuri T*. TLR9 Polymorphisms Might Contribute to the Ethnicity Bias for EBV-Infected Nasopharyngeal Carcinoma. iScience. 2020 March 27; 23(3):100937. doi: 10.1016/j.isci.2020.100937.

5. Raychaudhuri D*, Duttagupta P, Liu CSC, Sarif J, Ghosh AR, Rahaman O, Ganguly D*. Role of Ca2+ in toll-like receptor 9 activation in human plasmacytoid dendritic cells. Cytokine. 2019 Aug 27;125:154822. doi: 10.1016/j.cyto.2019.154822.

EXTRAMURAL FUNDING

No.	Title	Funded by	PI/Co-PI	Amount (Lakh INR)	Brief description
1	Indo-Australia Collaboratve Research on Neglected Tropical Disease	DBT	Co-PI	140.0 (3 years, 2017-2020)	Development of novel small molecule antileishmanial compounds
2	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
3	National Bioscience Award	DBT	PI	15.0 (3 years, 2018-2021	
4	Indo-French Collaborative Project	CEFIPRA	PI	80.0 (3 years, 2019-2022)	Role of DNAse1L3 in metabolic syndrome



6. Raychaudhuri D, Bhattacharya R, Sinha BP, Liu CSC, Ghosh AR, Rahaman O, Bandopadhyay P, Sarif J, D'Rozario R, Paul S, Das A, Sarkar DK, Chattopadhyay S, Ganguly D*. Lactate Induces Pro-tumor Reprogramming in Intratumoral Plasmacytoid Dendritic Cells. Frontiers in Immunology. 2019 Aug 7;10:1878. doi: 10.3389/fimmu.2019.01878.

AWARDS / HONOURS / MEMBERSHIPS

2019- CDRI Award for Excellence in Drug Research
2019- Merck Young Scientist, Award

TALKS BY CSIR-IICB FACULTY

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.

June, 2019: Pre-conception meeting of the National Alliance for Translational Research in Autoimmune Diseases, CSIR-Indian Institute of Chemical Biology, Kolkata, West Bengal.
August, 2019: Ind-CEPI Networking Meeting, invited by Department of Biotechnology, SCOPE complex, New Delhi.



Dr. Amitava Sengupta

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Acute myeloid leukemia pathogenesis, targeted therapy & hematopoiesis

Participants

Liberalis Debraj Boila, CSIR-SRF, SPM Fellow
Sayan Chakraborty, UGC-SRF
Sayantani Sinha, CSIR-SRF (to join postdoc at Fred Hutch Cancer Center, Seattle, USA) Shankha Subhra Chatterjee, PhD (currently postdoc at Weill Cornell Medical Center, NY, USA) Mayukh Biswas, PhD (currently postdoc at Columbia Univ Medical Cemter, NY, USA)

Collaborator(s)

Dr. John E. Dick, FRS, Princess Margaret Cancer Centre, UHN, Toronto, Canada
Dr. Tsvee Lapidot, Weizmann Institute of Science, Israel
Dr. Michael Milyavsky, Tel Aviv University, Israel
Dr. Sanjay Kumar, Centre for Stem Cell Research, CMC Vellore
Dr. Debojyoti Chakraborty, CSIR-IGIB, New Delhi
Dr. Arindam Talukdar, CSIR-IICB, Kolkata
Dr. Debasis Banerjee, Ramakrishna Mission Seva Pratisthan, Kolkata
Dr. Dipti Jain, GMC, Nagpur
Dr. Prantar Chakraborty, NRS Medical College & Hospital

Background

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 are 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. 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

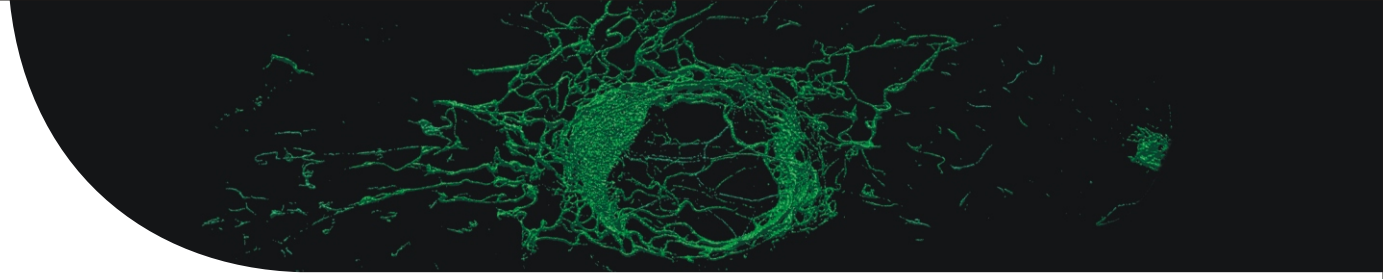
i) Investigate AML epigenetic regulation in pathogenesis and targeted therapy
ii) Leverage immune-microenvironment in hematopoiesis, cancer & immunotherapy
iii) CRISPR/Cas guided gene editing of sickle cell anemia hematopoietic stem cells

Work Achieved

Bone morphogenic protein (BMP/TGF-β) signaling determines mesenchymal-stromal-cell (MSC) osteolineage commitment and tissue identity. However, molecular integration of developmental signaling with MSC-intrinsic chromatin regulation remains incompletely understood. SWI/SNF-(BAF) is an ATP-dependent chromatin remodeler implicated in multi-cellular development. Recently we have identified that BMPs and long-term osteogenic signals in MSCs selectively induce expression of polybromo BAF (PBAF) components Pbrm1, Arid2, and Brd7. Loss of Pbrm1/Arid2/Brd7 profoundly impairs osteolineage gene expression and osteogenesis without compromising adipogenesis. Pbrm1 loss attenuates MSC in vivo ossification. Mechanistically, Pbrm1/PBAF deficiency impairs Smad1/5/8 activation through locus-specific epi-genomic remodeling, involving Pbrm1 bromodomains, along with transcriptional downregulation of Bmpr/TgfβrII affecting BMP-early-responsive gene expression. Gain of function of BmprIβ, TgfβrII in PBAF-deficient MSCs partly restores Smad1/5/8 activation and osteogenesis. Pbrm1 loss further affects hematopoietic stem/progenitor activity through non-cell-autonomous regulation of microenvironment and niche-factor expression. Together, these findings reveal a link illustrating epi-genomic feedforward control of BMP/TGF-β signaling to transcriptional and cellular plasticity in the mesenchymal microenvironment and account for stromal-SWI/SNF in hematopoiesis.

Future Research Plans

We aim to functionally dissect contributions of chromatin remodelers and epigenetic modifying-enzymes in HSPC



transformation in myeloid leukemia. Under the ambit of CSIR Mission we would also interrogate CRISPR/Cas9-guided gene editing for sickle cell HSPCs.

PUBLICATIONS

- Sinha S, Biswas M, Chatterjee SS, Kumar S, Sengupta A. Pbrm1 steers mesenchymal stromal cell osteolineage differentiation by integrating PBAF-dependent chromatin remodeling and BMP/TGF-β signaling. Cell Reports 2020: 31, 107570.
- Boila LD, Sengupta A. Evolving insights on histone methylome regulation in human acute myeloid leukemia pathogenesis and targeted therapy. Experimental Hematology 2020: S0301-472X(20)30554-3.
- Sinha S, Chakraborty S, Sengupta A. Establishment of a long-term co-culture assay for mesenchymal stromal cells and hematopoietic stem/progenitors. STAR Protocols 2020 Cell Press (in press)
- Chakraborty S1, Sinha S1, Sengupta A. Emerging trends in chromatin remodeler plasticity in mesenchymal stromal cell function. FASEB J 2020 (in revision)

AWARDS/HONOURS/MEMBERSHIPS

10/2019 ICMR-DHR International Fellowship for Indian Biomedical Scientists

09/2019 Keystone Symposia Global Health Travel Award

EXTRAMURAL FUNDING

Deciphering epigenetic dysregulation in hematopoietic stem cell transformation in human myelogenous leukemia, PI, 05/2017-12/2020, DBT, Govt. of India.

Targeted hematopoietic stem cell engineering for sickle cell anemia, PI & Nodal Sct., 10/2017-03/2023, CSIR Sickle Cell Anemia Mission, Govt. of India.

INVITED LECTURE

01/2020 Ups & downs of UTX in human AML pathophysiology & targeted therapy. Princess Margaret Cancer Center, University Health Network, Univ. Toronto, Canada.

11/2019 Chromatin remodelers & transcriptional dependencies in human AML targeted therapy. Montreal Clinical Research Institute, McGill Univ/U Montreal, Canada.



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Unraveling the role of ER stress induced URP signaling in regulating the functionality of CD8 T cells in cancer

Participants

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

Collaborator(s) from IICB

Dr. Sandip Paul

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.

T cells in the tumor microenvironment encounter diverse metabolic insults (nutrient deprivation, hypoxia, redox imbalance etc,) which can converge upon ER to induce ER stress. The notion is supported by the recent observations that T cells from the tumor site exhibit elevated expression of proteins involved in the unfolded protein response (UPR) pathways, which gets activated by ER stress. Recent studies have shown that tumor infiltrating T cells (TILs) with heightened expression of IRE1 α-XBP1 axis, an important mediator of UPR pathway failed to mount durable anti-tumor response owing to their defect in oxidative metabolism. Although, the study unraveled the pivotal role of ER stress induced IRE1 XBP1 axis in affecting the metabolic fitness of T cells, its role in regulating the effector response of T cells is still obscure. In the present study we wanted to investigate the role of IRE1 α-XBP1 axis in regulating the functionality of T cells in the tumor milieu. We hypothesized that sustained expression of IRE1 α and XBP1 in T cells curtail their effector response through reinforcing gene programs associated with T cell dysfunction.

Aims and Objectives

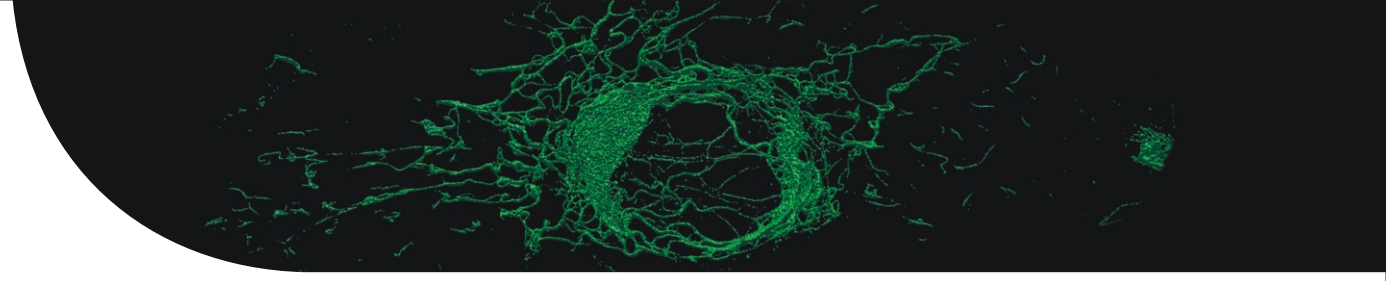
- Determine the precise role of IRE1 α- XBP1axis in regulating the effector function of CD8 T cells at the tumor site.
- Elucidate the role of IRE1 α- XBP1axis in regulating the metabolic fitness of CD8 T cells at the tumor site. Determine the therapeutic potential of targeting IRE1 α-XBP1axis to improve the anti-tumor potential of CD8 T cells.
- Evaluate the combinatorial approach of targeting IRE1 α-XBP1 axis along with anti-PD1 to improve the efficacy of the anti-PD1 therapy.

Work Achieved

CD8 T cells from ovarian tumor site exhibit increased expression of UPR pathway proteins. Since, tumor microenvironment is deprived of essential nutrients which can induce ER stress that in turn triggers the activation of UPR, we sought to determine the expression of various UPR sensors in TILs. Flow cytometric analysis revealed that CD8+ TILs derived from the ID8-VEGF ovarian tumor exhibited increased expression of pPERK, pIRE1α and sXBP1 as compared to splenic CD8 T cells from same mice (Fig 1).

Pharmacological inhibition of IRE1a-XBP1 axis restore the effector function of CD8 T cells exposed to tumor conditioned media. In order to mimic the tumor microenvironment, T cells were cultured in cell free ascitic fluid obtained from mice intraperitoneally injected with ID8-VEGF ovarian tumor. Purified T cells were cultured for 3 days in presence of ovarian cancer ascitic fluid and either in presence or absence of specific inhibitor of IRE1 α (4μ8c). After 72h of activation, cells were re-stimulated with anti-CD3 and anti-CD28 to check their effector cytokine production. As we expected, CD8 T cells cultured in ascitic fluidexhibited 2-4 fold decrease in the level of IFNγ when compared to CD8 T cells that were activated in complete media. However, it was observed that pharmacological inhibition of IRE-1 α using 4 8c restored the IFNγ production in T cells cultured in ovarian cancer ascitic fluid (Fig 2A and 2B).

Restoration of cytokine production in CD8 T cells by inhibition of IRE1a is dependent on cholesterol enrichment of plasma membrane. Having that shown inhibition of IRE1 α restores



IFNγproduction by CD8 T cells following TCR mediated stimulation with anti-CD3, we next wanted to investigate whether the effect could be in part due to modulation of plasma membrane composition which in turn affects the TCR clustering and further downstream signalling. In order to test our hypothesis, T cells were cultured in ID8-VEGF tumor derived ascitic fluid either in presence or absence of 4μ8c. After 72 hours of activation, cells were washed and re-stimulated in presence of very low dose of anti-CD3(1μg/ml) and anti-CD28(1μg/ml). Before re-stimulation with anti-CD3, 4μ8c treated CD8 T cells were either kept untreated or subjected to cholesterol depletion from plasma membrane by brief treatment with 1mM Methyl-β-cyclodextrin(25mins). Interestingly, we found that depletion of plasma membrane cholesterol abrogated the effect of IRE1α inhibition mediated restoration of IFNγ production by CD8 T cells. To further confirm the role of cholesterol in regulating cytokine production by dysfunctional T cells, we repleted membrane cholesterol of ovarian ascitic fluid cultured CD8 T cells by briefly treating the cells with 10μg/ml of cholesterol immediately before re-stimulating with anti-CD3. Our data suggest that repletion of membrane cholesterol helped the ascitic fluid treated cells to regain their IFNγ production potential. This observations suggest that ER stress induced IRE1α- XBP1 axis could modulate plasma cholesterol level in the CD8 T cells and hence dampen the effector cytokine production by CD8 T cells (Fig 3A and 3B).

Future Research Plans

1. Determine the underlying mechanism of how IRE1α-XBP1 axis regulate the membrane cholesterol level in CD8 T cells

2. Determine the therapeutic potential of targeting IRE1α-XBP1 axis on TILs to improve the anti-tumor T cells.

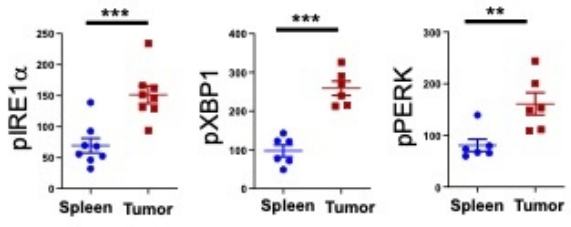


Figure 1. CD8 T cells from ovarian tumor site exhibit increased expression of UPR sensors.(A) Flow cytometry analysis of the expression of pIRE1α, pPERK and sXBP1in CD8 T cells from either ovarian tumor site or spleen from mice bearing ID8-VEGF. Scatter plots represent the cumulative data of mean fluorescence intensity (MFI). ***p<0.005, **p<0.01.

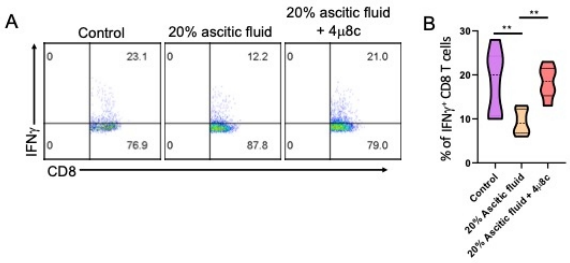


Figure 2. Pharmacological inhibition of IRE1a-XBP1 axis restore the effector function of CD8 T cells. CD8 T cells were cultured in ascitic fluid either in presence or absence of IRE1α inhibitor 4μ8c for 3 days and were stimulated with anti-CD3 (1 μg/ml) + anti CD28 (1 μg/ml) for 6h in presence of Golgi block and intracellular cytokine was assessed using flow cytometry. (A) Dot plot represents frequency of cells secreting IFN-γ by CD8 T cells. (B) scatter plots represent cumulative data with statistical analysis of percentage of cells secreting IFNγ. ***p<0.005, **p<0.01 and *p<0.05.

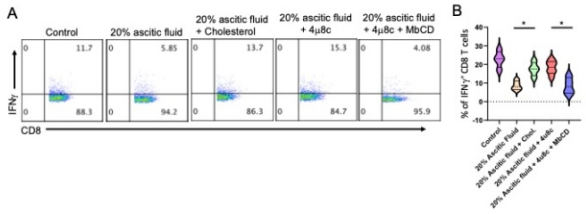
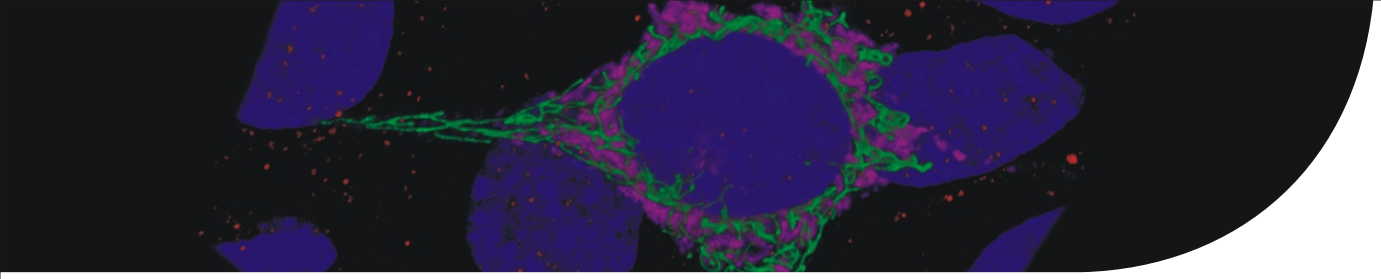


Figure 3. Plasma membrane cholesterol depletion reversed IRE1 α inhibition mediated the increased cytokine production by CD8 T cells. CD8 T cells were cultured in ascitic fluid either in presence or absence of IRE1 α inhibitor 4μ8c for 3 days. Before re-stimulation with anti-CD3 and anti-CD28, T cells were either subjected to cholesterol depletion using MbCD or cholesterol enrichment using brief cholesterol treatment. Intracellular cytokine was assessed using flow cytometry. (A) Dot plot represents frequency of cells secreting IFN-γ by CD8 T cells. (B) scatter plots represent cumulative data with statistical analysis of percentage of cells secreting IFNγ. ***p<0.005, **p<0.01 and *p<0.05.



EXTRAMURAL FUNDING

1. Role of endoplasmic reticulum (ER) stress induced UPR signaling inregulating the metabolic fitness and functionality of CD8+ T cells in cancer. Start year: 2020, Duration: 5 years
   Agency: India Alliance DBT Wellcome.

2. Mechanistic exploration of the role of shingosine-1-phosphate receptor 1 (S1PR1) in regulating the functional fate of tumor infiltrating CD8 T cells.
   Start year: 2020; Duration: 3 years
   Agency: SERB, India



Dr. Siddik Sarkar

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Therapy resistance and heterogeneity in breast and ovarian cancer

Participants

JRF : Sourabrata Chakraborty, Riddhi Pal, Debleena Basu

External Collaborator(s)

Dr. (Professor) Mahitosh Mandal, IIT Kharagpur
Dr. Sachin Kumar, AIIMS

Background

Meta analyses of RNASeq (transcriptomics) data using R/RStudio/Bioconductor packages reveal quiescence, cell dedifferentiation and transmembrane receptor signaling pathways in intratumor heterogeneity, therapy resistance and cancer relapse in ovarian and breast cancer. Our initial studies showed a relation between quiescence and residual tumor that evades conventional chemo-therapy induced cell killing (Fig. 1). These quiescent cells are undifferentiated stem cells responsible for heterogeneity of ovarian and breast cancer. Our laboratory also focusses in designing various targeted therapy to kill both differentiated and undifferentiated stem cells in an anticipation to overcome chemo-resistance and improved the overall survival of cancer patients.

Aims and Objectives:

- Role of 'malefactor quiescent cancer initiator/stem cells' to evade therapy and intra-tumor heterogeneity in breast and ovarian cancer.
- Novel therapeutics and combinatorial approach to effectively kill both differentiated and dedifferentiated cancer stem cells.
- Developing/ synthesizing aptamer targeting CXCR4 and their theranostic implications in triple negative breast cancer.

Work Achieved

Role of cancer quiescent stem cells in chemo-resistance in breast and ovarian cancer

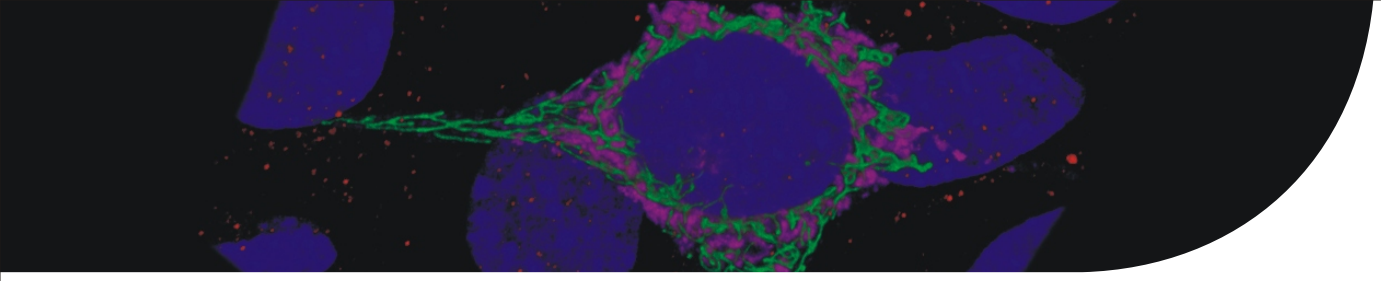
RNA sequencing analysis of public databases of Breast and Ovarian cancer studies reveal that therapy resistance residual cancer cells are quiescent in nature and exhibit high expression of quiescent related genes such as CDKN1B, CDKN1A, CDKN2A. We also found enrichment of quiescent cancer cells in therapy resistance both in in-vitro 3D culture and syngenic mouse models (Fig. 2). We also found up-regulation of quiescence regulatory gene CDKN1B in therapy resistance residual breast and ovarian tumor. We also found up-regulation of epigenetic regulator Enhancer of zeste homolog 2 (EZH2) in residual tumor, indicating a possible epigenetic regulation of quiescent therapy resistance cancer cells.

Novel therapeutics and combinatorial approach to effectively kill both differentiated and dedifferentiated cancer stem cells.

Platinum based chemotherapeutics (cisplatin, carboplatin, oxaloplatin) is standard care of treatment for ovarian cancer, but developed chemo-resistance and succumb to death. Previously few compounds of a heavy metal Rhenium (Re) have shown to possess anti-tumor activity and giving a closer look into the capabilities of the compound may take on the metal compounds for clinical trials. Hence, we also used rhenium (Re) to synthesise four novel compounds viz. (i) Rhenium 2-hydroxy thio-benzhydrazide [ReHTBH] (mol. wt. 685), (ii) Rhenium thiophene 2-thiohydrazide [ReTTH] (mol. wt. 655), (iii) Rhenium furane 2-thio-hydrazide [ReFTH] (mol. wt. 639) and (iv) Rhenium tris thio-benzhydrazide [ReTTBH] (mol. wt. 639); which could be used in-vitro and in-vivo and further taken for clinical trials to develop a better alternative against other heavy metal drugs used for drug resistant ovarian cancer. The four novel compounds were assessed for their antitumor cytotoxic effect using MTT assay on human ovarian and breast cancer cell lines; and Rhenium 2-hydroxy thio-benzhydrazide [ReHTBH] was seen to be the most cytotoxic. The effect of REHTBH in inducing cell death is most likely through mitochondrial damage resulting in necrosis of cancer cells. The microscopic images stained with mitotracker Red and DAPI indicated the role of REHTBH in inducing mitochondrial damages. There is also an indication of reactive oxygen species (ROS) generation as evident from flowcytometric analyses after staining the cells with ROS indicator H2D-CFDA. Further we have evaluated that the cell death is induced most likely by necrosis (Fig. 3).

Developing/ synthesizing aptamer targeting CXCR4 and their theranostic implications in triple negative breast cancer.

Aptamer or sometimes called chemical antibody has been developed as diagnostic and therapeutic tool due to its size,



stability, chemical modification, low cost and ease of synthesis. We have decided to develop novel aptamer targeting CXCR4 which is highly expressed in different cancers. Our aim is to ectopically express 6His tagged target protein in mammalian cell line (HEK293T) to isolate and purify it by Ni-NTA column, for which we have cloned three different fragments of the entire CXCR4 including its ligand binding site (fragment 1) and total protein sequence. We have successfully cloned three different construct namely CXCR4_fragment1 (114bp) CXCR4_fragment2 (906bp) and CXCR4_total (1056bp) into pcDNA 4 his-myc A backbone. We have confirmed the result by restriction digestion from multiple clones.

Future Research Plans

- Gene expression changes that occurred prior to and post treatment and after recurrence in-vitro and in-vivo ovarian/breast cancer models in relation to quiescent cancer stem cell.
- Exploring epigenetic regulation in quiescent cancer cells responsible for chemo-resistance.
- Understanding the molecular mechanism of cell mediated killing (necrosis) of Rhenium 2-hydroxy thio-benzhydrazide [ReHTBH]
- Screening a novel aptamer that specifically binds to CXCR4, scaling up and evaluating its binding kinetics in-vitro system

Figures legends

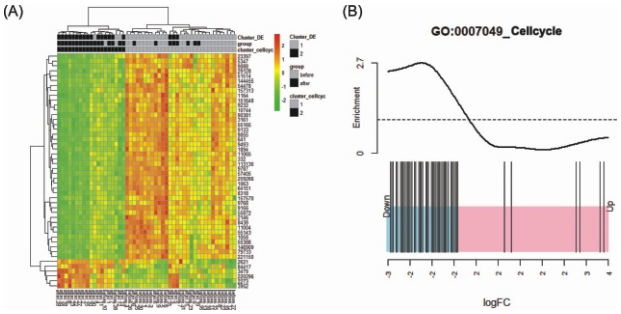


Fig. 1: Cell cycle signalling network is downregulated in residual tumor. Hierarchical clustering of differential genes (FDR >0.05 and FC=2) between untreated vs treated residual tumor; A. Gene enrichment analysis showing enrichment of downregulation of cell cycle genes; B.

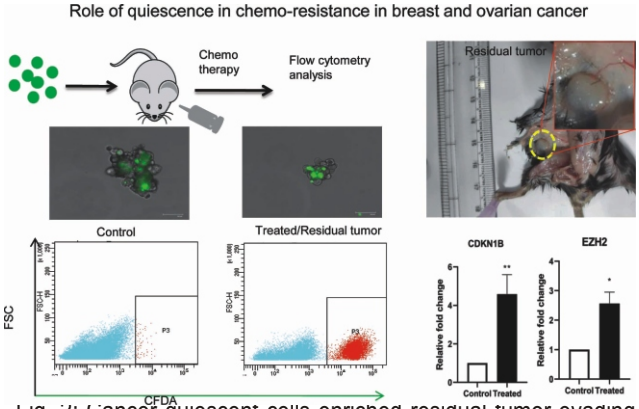
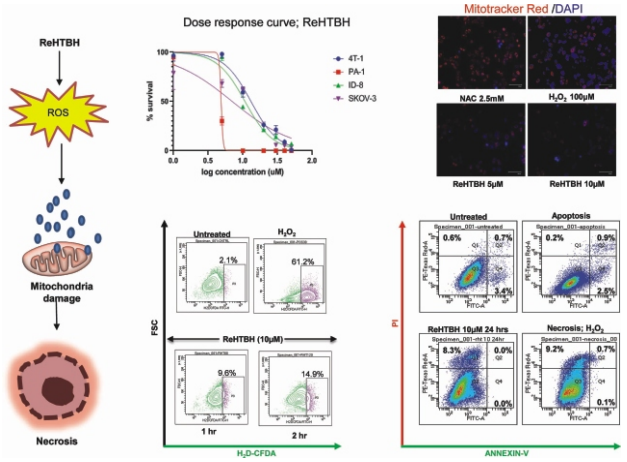


Fig. 2: Cancer quiescent cells enriched residual tumor evading chemotherapy. Both in-vitro 3D tumorspheroid as well as in-vivo allograft (syngenic mouse) model showed enrichment of quiescent cells in treated residual tumor.

Fig 3: Rhenium compounds induced necrosis mediated cell death

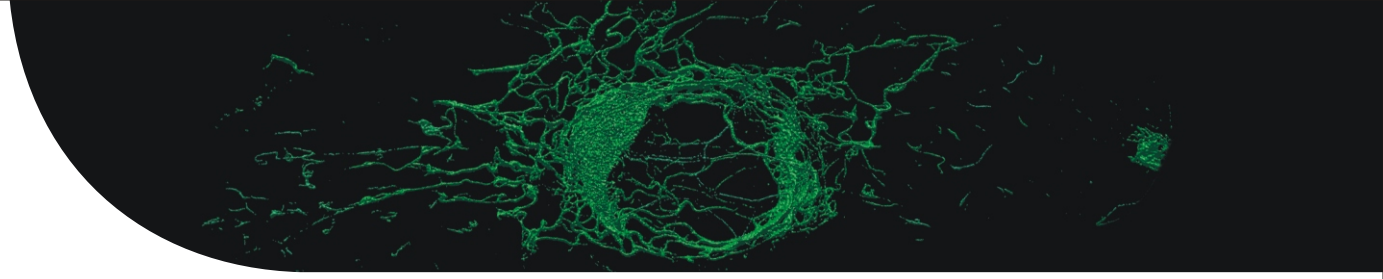


in ovarian and breast cancers.

PUBLICATIONS

Gaur V, Chaudhary S, Tyagi A, Agarwal S, Sharawat SK, Sarkar S, Singh H, Bakhshi S, Sharma P, Kumar S. Dysregulation of miRNA expression and their prognostic significance in paediatric cytogenetically normal acute myeloid leukaemia. Br J Haematol. 2020 Mar; 188(6):e90-e94. PubMed PMID: 32077100.

Malekshah OM, Sarkar S, Nomani A, Patel N, Javidian P, Goedken M, Polunas M, Louro P, Hatefi A. Bioengineered adipose-derived stem cells for targeted enzyme-prodrug therapy of ovarian cancer intraperitoneal metastasis. J Control Release. 2019 Oct;311-312:273-287. PubMed PMID: 31499084.



AWARDS / HONOURS / MEMBERSHIPS:

Students Lab team headed by PhD student Debleena Basu was awarded the prize money (1st prize) from IDEA EXPOSITION organized by BIRAC Regional Innovation Center (BRIC), in collaboration with IKP Knowledge Park, CSIR-IICB, on September 20 & 21, 2019.

EXTRAMURAL FUNDING

Suicidal genetherapy using engineered secretory carboxylesterase-2/Camptothecin-11 targeting chemoresistant ovarian serous adenocarcinoma, Start-Up-Grant Nov 2019- Nov 2021; DST/SERB

CONFERENCES AND WORKSHOPS:
No. 1

INVITED TALKS:

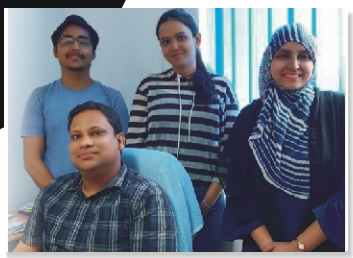
Invited talk on Cancer Biology and molecular imaging in monthly lecture series 'Bio-Illumanati' at Aliah University, BioSciences Dept., Newtown, Kolkata on Sept 19, 2019.

Invited talk on the role of autophagy and cancer stem cell in the workshop cum symposium entitled "Techniques to Understand Autophagic Processes in Mammalian Systems (TUAPMS)" from 26th February-1st March 2020 organized by the Department of Life Science, National Institute of Technology Rourkela.



Dr. Amit Kumar Srivastava

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Understanding and targeting translesion DNA synthesis in lung adenocarcinoma

Participants

RA : Dr. Priyanka Saha

JRF : Devendra Shukla, Tanima Mandal, Bilash Chatterjee, Subhankar Bose

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
Prof. Ramesh Ganju, The Ohio State University, USA

Name of collaborator within CSIR-IICB
Dr. Deepak Kumar
Dr. Prem Prakash Tripathi

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 facilitate eradication of CSCs 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 (CSLCs) in lung cancer. We have isolated and characterized the CSLCs (CD133+) from human lung cancer cell line A549 (Fig 1). CD133+ and CD133- cells were isolated 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 CD133- cells. These findings suggest that CD133+ cells have CSCs like properties. To understand the TLS status in CSLCs, we analyzed the expression levels of various TLS Pols in the CSLCs isolated from A549 cells. Among all tested TLS Pols, POLH mRNA (encoding Pol η) and POLI levels were shown to be highly expressed in CD133+ cells as

compared to CD133- cells. Further, we noticed that the co-transfection of siPOLH and siPOLI sensitizes more CSLCs to cisplatin treatment compared to siPOLH or siPOLI alone.

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

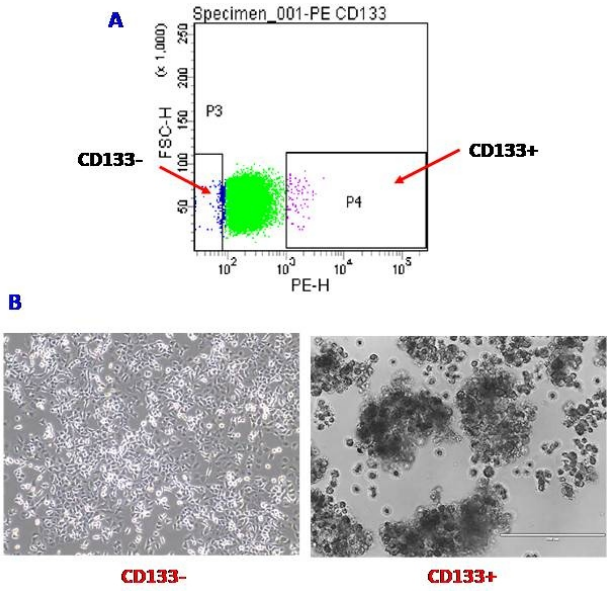


Fig. 1: Isolation and culture of CD133- and CD133+ cells. (A) Photographs of CD133+ and CD133- cells. (B) CD133- and CD133+ cells were sorted from A549 cells using FACS. (C) The percentage of CD133+ cells was determined in A549 (D) Reactive oxygen species (ROS) analysis using flow cytometry.

PUBLICATIONS

Chandra S, Alam T, Dey J, Chakrapani P, Srivastava AK, Gandhi S and Tripathi PP Healthy gut, healthy brain: The gut microbiome in neurodegenerative disorders. Current Topics in Medicinal Chemistry. 20(13):1142-1153.

Book Chapters

Yatham P, Dahat H, Khan P, Baishya R, Srivastava AK, Kumar D. Saponin Stabilized Emulsion as Sustainable Drug Delivery System: Current Status and Future Prospects. Nanopharmaceutical Advanced Delivery systems. Scrivener Publishing Wiley, USA, 2020 (In press)

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)

Understanding the role of translesion DNA synthesis in chemoresistance of lung adenocarcinoma. (Indian Council of Medical Research, New Delhi, 3 years, 2020)

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 Ca^{2+} 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 Ca^{2+} 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

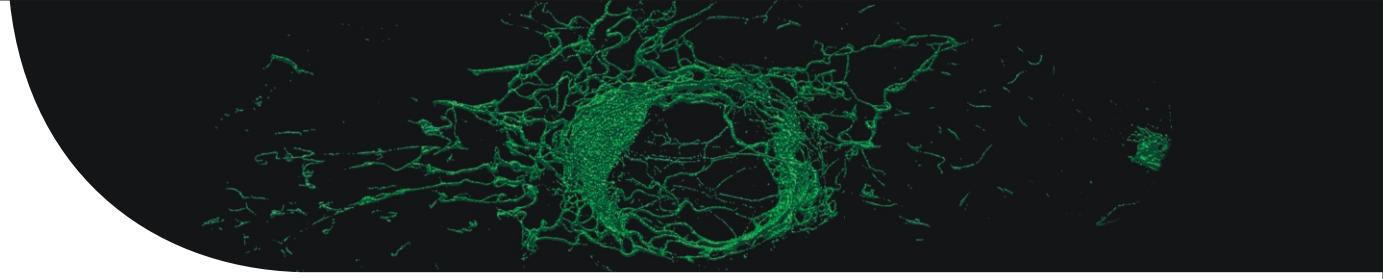
Investigation of modulation of phytohormons like Auxin, Cytokinine by phytosphingosine Investigate the role of phytosphingosine in plant cell growth and plant cell death

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 Ca^{2+} indicator YC3.6 we have observed phytosphingosine induced calcium signals in the nuclei of root cells of Arabidopsis.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 Ca^{2+} 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.

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

Hazak O, Manon E, Lavy M, Sterberg H, Behona S, Schmit2-Tha I, Bloch D, Denentive O, Gretnan I, Danziger T, Schwarz N, Abuzeih A, Mocktails K, Estelle M, Hinsch J, Kudle J, Yalovsky S, A novel Ca2f binding protein that can rapidly transoluce aurin responses during real growth. PLOS Bialogy, 2019, 17(7) e 3000085.



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Role of sialylation in modulating outcomes of infectious diseases, cancer and development of potent phytopharmaceuticals against cancer

Participants:

Ranjita Das, (CSIR project RA)
Eswara Murali Satyavarapu (Thesis submitted)
Shalini Nath (Thesis submitted)
Kaustuv Mukherjee (Thesis submission ongoing)
Joyshree Karmakar (Thesis submitted)

Background

Sialic acids are acidic sugar molecules commonly found terminally in the glycan chains of glycoproteins and glycolipids. Sialylation status is maintained on the basis of competing activities of sialidases and sialyltransferases in the cell. Sialyltransferases catalyze the addition of sialic acids to glycan chains while sialidases remove sialic acid residues. Currently, four mammalian sialidases have been identified - Lysosomal Neu1, cytosolic Neu2, membrane-bound Neu3 and luminal Neu4.

Sialylation of proteins affect their function, alters their association with other interacting proteins, thereby modulating their role in signaling pathways. Study of altered sialylation of cellular components, receptors and signaling proteins with respect to their role in diseased states is of vital interest. In the context of infectious diseases, we have investigated role of sialylation in protozoan (Leishmania donovani) and bacterial (Pseudomonas aeruginosa) pathogenesis. Toll-like receptor 4 (TLR4), is an important cell surface pattern recognition receptor (PRR) of innate immune system. TLR4 is highly sialylated with predominantly α2, 3-linked sialic acids. L. donovani infection leads to deactivation of TLR4-mediated immune response by macrophages. In this context, we have investigated if there is any connection between TLR4-sialylation and activation during such infection. Another group of cellular receptors - siglecs (sialic acid specific immunoglobulin type lectins) recognize and bind sialic acids. Several siglecs are known to be inhibitory receptors, which are targeted by sialylated pathogens to suppress activation of immune cells.

Pseudomonas aeruginosa (PA) is commonly associated with nosocomial and chronic infections of lungs, where it encounters pulmonary macrophages. Role of sialic acids on PA and its possible interactions with macrophages was explored next. Cancer stem cells (CSCs) are a population of cancer cells showing self-renewal and multipotency abilities leading to tumor progression, tumor cell survival and recurrence. CSCs exhibit aberrant activation of various pathways, including Hedgehog (Hh). Sialylation status is also linked with aggressiveness in CSCs. We have previously observed that sialidase Neu2 expression is lower in different pancreatic cancer cell lines and patient tissues which may explain the sialylation status of these cancerous cells. We have investigated if sialidase Neu2 regulates stemness-like properties of representative cancer stem-like cells (pancreatic cancer sphere-forming cells, PCS) and also modulate the Hedgehog (Hh) pathway through its desialylating activity.

Murraya koenigii is an Indian medicinal herb that is well documented in the ancient medical text "Charaka Samhita." We have previously reported that Mahanine, a carbazole alkaloid isolated from this plant, exhibited potent anticancer activity. We have now investigated how seasonal and geographical variations influence medicinal property and carbazole alkaloids composition in this plant. Furthermore, optimization of the method for preparation of a Mahanine enriched fraction (MEF) was also performed. Activity, pH/temperature stability, chronic toxicity studies of MEF as well as its in vivo efficacy against breast cancer was checked.

AIMS AND OBJECTIVES:

1. Role of sialidases, sialylation during Leishmania donovani and Pseudomonas aeruginosa (PA) infection.
2. Sialoglycobiology of cancer stem cells (CSCs)
3. Development of redox manipulating therapeutics against cancers and infectious diseases

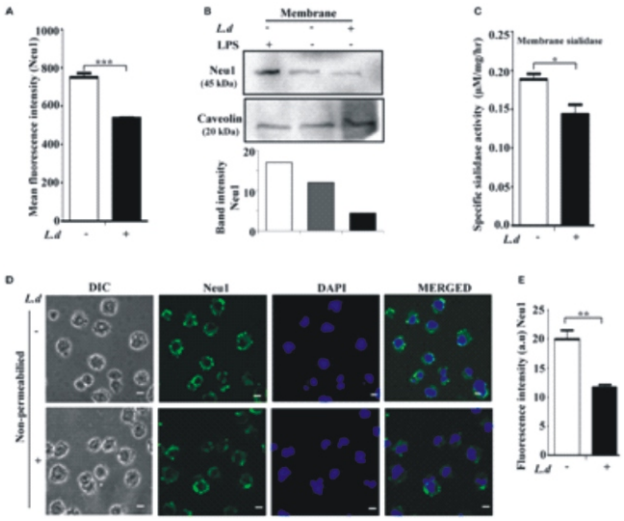
WORK ACHIEVED:

Downregulation of cytosolic Neu1 translocation to the membrane of L. donovani-infected macrophages and its activity resulted in enhanced sialylation of TLR4 (Fig 1). Conversely, Neu1 over expression lead to enhanced association of TLR4 with Neu1 and TLR4 desialylation. Desialylated TLR4 showed increased association with downstream adaptor protein, MyD88, which resulted in activation of MAP kinase signaling pathway, enhanced nuclear translocation of NFκB. Consequently, expression of Th1 cytokines, nitric oxide secretion and elimination of parasite burden in macrophages was enhanced. Neu1 silencing in infected macrophages reversed this situation, confirming its role in regulating TLR4 activation through modulation of TLR4 sialylation (Karmakar

et.al. 2019). We have also reported that PA+Sia utilizes sialic acids (in Pseudomonas aeruginosa) to interact with siglec-E (in macrophages) for higher binding and increased phagocytosis. Such interaction activates siglec-E, leading to recruitment of SHP-2 phosphatases that causes suppression of respiratory burst, pro-inflammatory cytokines secretion. PA+Sia phagocytosis is also associated with lowered intracellular calcium ion concentrations and altered calcium-dependent signaling that negatively affects phagosome maturation. Silencing of siglec-E in macrophages results in improved bactericidal response against PA+Sia. Sialic acid-siglec-E interactions were found to be beneficial for P. aeruginosa as it enhances bacterial internalization but impaired bacterial killing, allowing for persistence of PA in macrophages (Mukherjee et.al. 2020). The status of CD133/CD44/surface-sialylation in pancreatic cancer sphere-forming cells (PCS) was checked by flow cytometry. PCS showed reduced

Figure 1. Cell surface Neu1 is reduced during Leishmania donovani infection.

(A) Uninfected or infected J774.A1 cells were stained with anti-Neu1 antibody, followed by Alexa Fluor 488 conjugated secondary antibody. Representative bar graph indicated reduced mean fluorescence intensity (MFI) on the cell surface of infected compared to uninfected cells.



(B) Status of membrane-bound Neu1 protein in the membrane fractions of uninfected and L. donovani infected as well as LPS stimulated J774.A1 cells.

(C) Decreased sialidase activity of membrane protein on the surface of L. donovani infected macrophages.

(D) The images of uninfected or infected J774.A1 cells was visualized exhibiting reduced fluorescence of Neu1 on the surface of L. donovani infected macrophages.

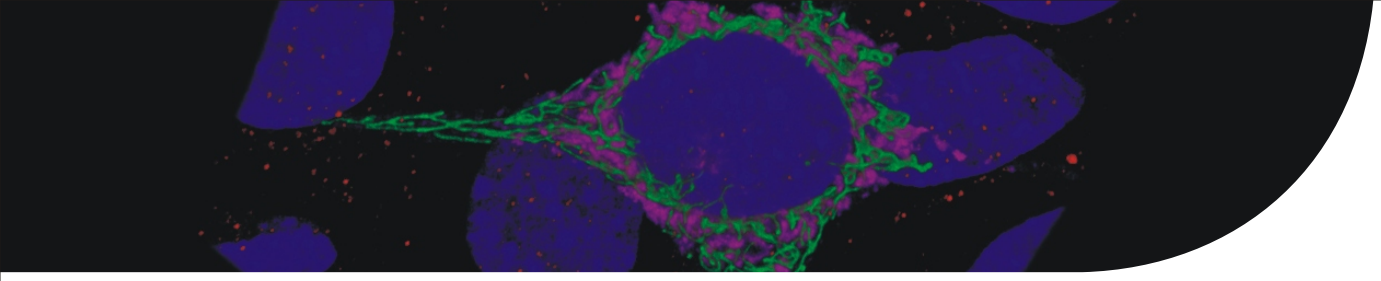
levels of cytosolic-sialidase (Neu2), with enhanced sialylation and high Hedgehog (Hh) pathway activity. Overexpression of Neu2 leads to desialylation of Shh thereby reducing Shh-Patched1 association. This reduced Hh-pathway activity and lowered the expression of Snail/Slug/CyclinD1, leading to reduction of stemness-like properties. Neu2-overexpression also induced apoptosis in PCS and reduced mTORC2 formation and inhibitory-phosphorylation of Gsk3β. In a xenograft model, tumors overexpressing Neu2 also showed reduction in tumor mass with downregulation of stem cell markers/Shh/mTOR. Thus, Neu2 expression levels were found to regulate activation of the Hh pathway and the stemness of CSCs (Nath et.al. 2020). Leaflets of M. koenigii plant were collected from different places at different seasons for three years. A mahanine-enriched fraction (MEF) was prepared. Concentration of identified markers (mahanine, mahanimbine, and koenimbine) was estimated. We have successfully demonstrated that marker content in leaflets is highly dependent on location/season. MEF prepared from leaves of tropical zone exhibited highest mahanine content than subtropical zone. Further studies revealed that MEF showed excellent in vitro antiproliferative activity against sixteen cancer cell lines from nine different origins as evaluated from MTT assay, annexin V-/PI-staining, DNA fragmentation. It significantly reduced tumor mass in lung and ovarian cancer xenograft models and syngeneic mice models in ovarian and breast cancers. Its biological activity remained unchanged at a wide pH (1-10) and temperature ranges. Comparative pharmacokinetics in rats revealed good bioavailability of mahanine in MEF-fed rats. Sub acute, sub chronic, chronic toxicity studies demonstrated that mice fed with MEF did not show any significant clinical signs of toxicity, behavioral changes, mortality, organ weights, serum biochemistry, and hematological parameters indicating no/minimum toxicity for up to 180 days (Satyavarapu et.al. 2020).

FUTURE RESEARCH PLANS:

We plan to further explore if sialylated TLR4 is recognized by any siglecs in L. donovani infected macrophages. Interplay between an immune-activatory (TLR4) and inhibitory (siglec) receptors will be important in determining the outcome of infections.

We also plan to investigate other sialylated bacterial proteins and to determine the effect of sialic acids on its function.

Most importantly, the results from the preclinical study on mahanine



enriched fraction have encouraged us to proceed further for approval of phase 1-2 clinical study.

PUBLICATIONS:

1. Shalini Nath, Susmita Mondal, Ramesh Butt, Vinoth Prasanna Gunasekaran, Gopal C. Kundu , Uttara Chatterjee , Aniket Halderand Chitra Mandal (2020) Desialylation of Sonic-Hedgehog by Neu2 Inhibits Its Association With Patched1 Reducing Stemness-like Properties in Pancreatic Cancer Sphere-forming Cells. Cells 2020, 9(6), 1512. doi: 10.3390/cells9061512
2. Mukherjee, K., Khatua, B., & Mandal, Chitra (2020) Sialic Acid-Siglec-E Interactions During Pseudomonas aeruginosa Infection of Macrophages Interferes With Phagosome Maturation by Altering Intracellular Calcium Concentrations. Frontiers in immunology, 11, 332. Https://doi.org/10.3389/fimmu.2020.00332
3. Eswara Murali Satyavarapu, Prasun Kumar Sinha and Chitra Mandal (2020) Influence of Geographical and Seasonal Variations on Carbazole Alkaloids Distribution in Murraya koenigii: Deciding Factor of Its In Vitro and In Vivo Efficacies against Cancer Cells. BioMed Research International, Volume, Article ID 7821913, 12 pages. Https://doi.org/10.1155/2020/7821913
4. Joyshree Karmakar, Saptarshi Roy, and Chitra Mandal (2019) Modulation of TLR4 Sialylation Mediated by a Sialidase Neu1 and Impairment of Its Signaling in Leishmania donovani Infected Macrophages. Frontier in Immunol.10: 2360. doi: 10.3389/fimmu.2019.02360
5. G. Aditya Kumar, Joyshree Karmakar, Chitra Mandal& Amitabha Chattopadhyay (2019) Leishmania donovani Internalizes into Host Cells via Caveolin-mediated Endocytosis. Scientific Reports, 9, Article number: 12636. Https://doi.org/10.1038/s41598-019-49007-1
6. Arup Bag, Sapan Mandloi, Chhabinath Mandal, Peter Walden, Saikat Chakrabarti, Chitra Mandal (2019) Connecting signalling and metabolic pathways in EGF receptor-mediated oncogenesis of Glioblastoma. PLOS ComputationalBiology15(8) e1007090. doi: 10.1371/journal.pcbi.1007090

AWARDS/HONOURS/MEMBERSHIPS:
SERB Distinguished Fellow

EXTRAMURAL FUNDING: SERB Distinguished Fellowship

INVITED TALKS:

1. "A Potential Edible plant for management of Cancer and cancer stem like cells" in the Refresher Course on Emerging areas in Life Sciences at Dept. of Life Science and Biotechnology, Jadavpur University on January 27th February 2020
2. "Pre-independence endeavours in Biology and contribution of Edavalath Kakkat Janaki Ammal" in the National seminar on "Role of Women Scientists in Developing Science and Society in India" at Asiatic Society, Kolkata in collaboration with All India People's Science Net work, 13-14th January 2020
3. A Potential Therapeutic Lead from Edible plant: Hope for targeting Cancer and cancer stem cells in the Refresher Course UGC-HRDC at the Department of Botany, Ballygunge Science College on January 7th 2020
4. Two Lectures on Burkitt and Hodgkin lymphoma at NIPER, Kolkata, 25th Oct, 2019

5-6. Two lectures on i) Phytopharmaceuticals:Preclinical Studies for commercialization of Herbal product on 21st September 2019 (ii) Publication or Patent? Choosing the right one Science Academies' Lecture Workshop on Medicinal Chemistry and Natural Products: Approaches towards New Drug Discovery, Department of Chemistry, Rajiv Gandhi University, Arunachal Pradesh, September 22nd Sept, 2019

7. Popular lecture on Exploration of Indian herbal source for management of diseases at Vivekananda science Circle, Ramakrishna Mission Inst, Culture Research Dept., Golpark, Kolkata on 22nd August 2019
8. Chairing a session in conference "Bridging Chemistry and Biology for Human Health and Diseases" organized by Society of Biological Chemists (SBC) Kolkata Chapter on 21st Sept. 2019 at CSIR-IICB
9. Meeting as an expert at Saroj Gupta cancer Research on 23rd August 2019

Organized and delivered lectures on Science awareness program at different schools as a Secretary on NASI activity, Kolkata Chapter

1. 'Water pollution and cancer risks' at Sarat Chandra Sur Institution, Kolkata, March 29, 2019
2. "Environmental pollution and Cancer" at Bagnan Girl's H. S., Howrah on June 5, 2019.
3. Science awareness program at Barasat Girls High School, Barasat, Kolkata on July 10, 2019
4. "Scientists journey to fight against Neglected Tropical Diseases" at Bhagabati Devi Balika Vidyalaya, Salt Lake, Kolkata on January 9, 2020
6. National Science Day "Contribution of Women in Science" at Dum Dum Road Govt. Sponsor High School for Girls, Kolkata on February 28, 2020



Dr. Krishna Das Saha

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Exploration of antileishmanial activity and molecular mechanism of a natural triterpenoid and a redox-responsive nanocomposite

Participants

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

Collaborator(s)

Name of collaborator outside CSIR-IICB
Dr. Asim Bhowmik, IACS, 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

collaborator within CSIR-IICB
Dr. Parasuraman Jaisankar
Dr. Biswadip Banerji
Dr. Krishnananda Chattopadhaya

Background:

The protozoan parasites of genus Leishmania after its entry into macrophages dampen signalling cascades leading to immunostimulation and ROS/NO production and manage to survive and proliferate in phagolysosome by preventing recruitment of lysosomal maturation markers (Rab5, Rab7, Rab9, CathepsinD, LAMP1) that leads to inhibition of phagolysosome maturation responsible for microbicidal activity.

Objectives:

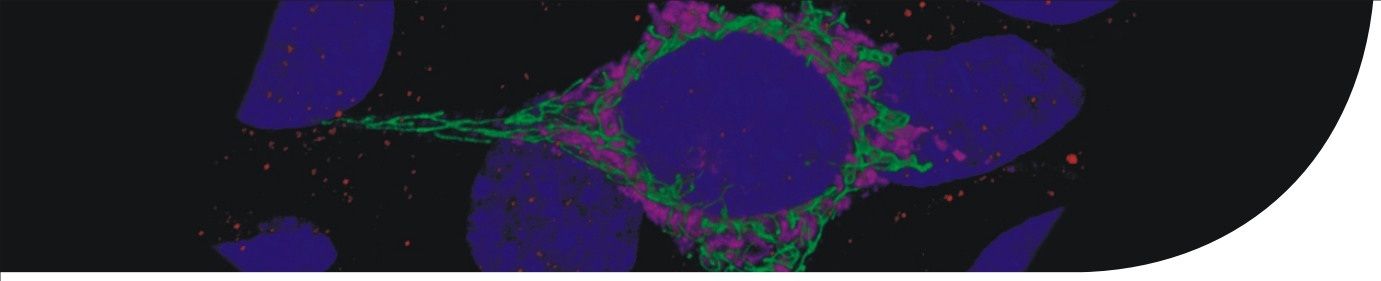
- Texamine the antileishmanial efficacy of spergilin A (SpA), a triterpenoid isolated from Glinus oppositifolius

1. To explore the role of P2X7R in SpA induced antileishmanial activity
2. To study the leishmanicidal potencial of a GSH-sensitive biodegradable polymeric nanoparticles of the antileishmanial drug, miltefosine.
3. Evaluation of phagolysosome maturation status.

Work achieved:

Spergulin A (SpA), a triterpenoid isolated from Glinus oppositifolius enhances leishmanicidal activity of macrophages by triggering ROS and NO release, stimulating proinflammatory cytokines (TNF-α, IL-1β and IL-6) production by macrophages through activation of MAPK signalling and NF-kB pathway. Interestingly, antileishmanial activity of SpA was found to be dependent on activation of purinergic receptors, P2X7R (Figure 1) and presence of BB-G, an inhibitor of P2X7R revive the effect of SpA.

GSH-sensitive biodegradable polymeric nanoparticles of antileishmanial drug, miltefosine (MNC) prepared by our Collaborator showed higher leishmanicidal effect than free miltefosine (Figure 2A and 2B). Miltefosine nanoparticles, MNC strongly activated the recruitment of phagolysosomal maturation proteins (Rab5, rab7, Rab9, and Cathepsin D) in pathogenic leishmania infected macrophages as revealed in Confocal microscope imaging of L. donovani infected RAW 264.7 macrophages incubated for 24hrs after its infection with leishmania for 4hrs (Figure 2C and 2D). Level of Rab7 is low in leishmania infected macrophages as seen in row (b) of Figure 2C compared to the uninfected macrophages, row (a) of Figure 2C. Macrophages pretreated with (c) 8 µg/mL of Miltefosine, (d) 5 ng/mL MNCs for 1hr before infection with leishmania showed significant parasite load whereas (e) 40 ng/mL of MNCs did not show any parasite load and Rab7 level was of reverse order of leishmanial load. Similarly, MNC pretreated leishmania infected macrophages expressed higher level of rab5, Rab9, and Cathepsin D compared to the drug untreated leishmania infected macrophages (row a, b, c, d. and e of Figure 2D).



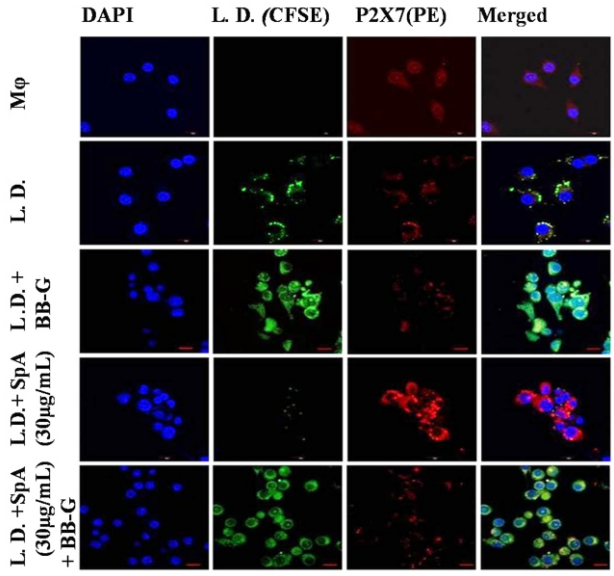
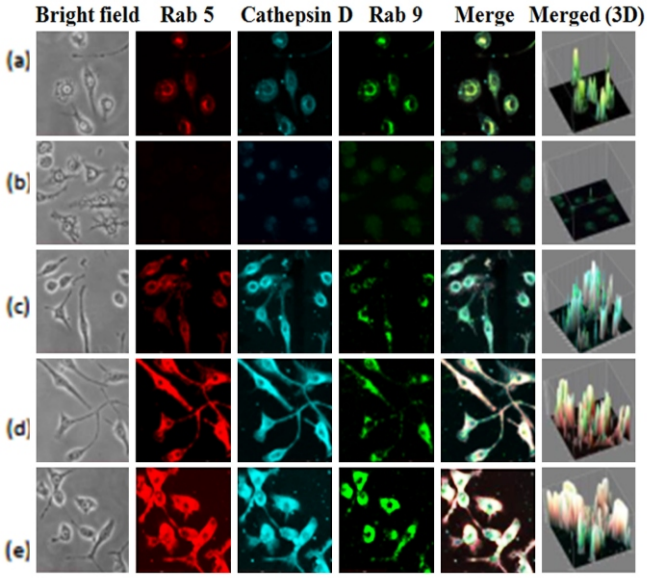


Figure 1: Spergulin A (SpA) mediated antileishmanial activity is triggered through purinergic receptors, P2X7R



C: Effect of MNC on phagolysosomal Rab5 level in pathogenic leishmania infected macrophages.

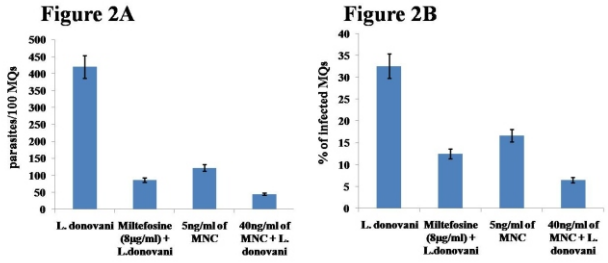
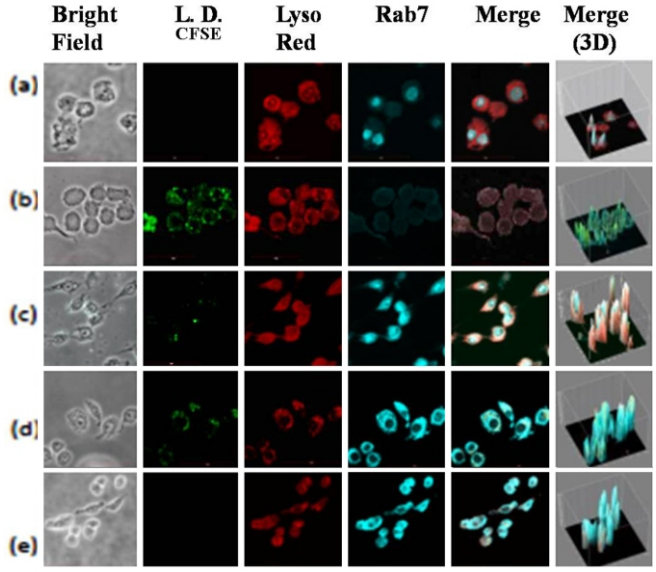
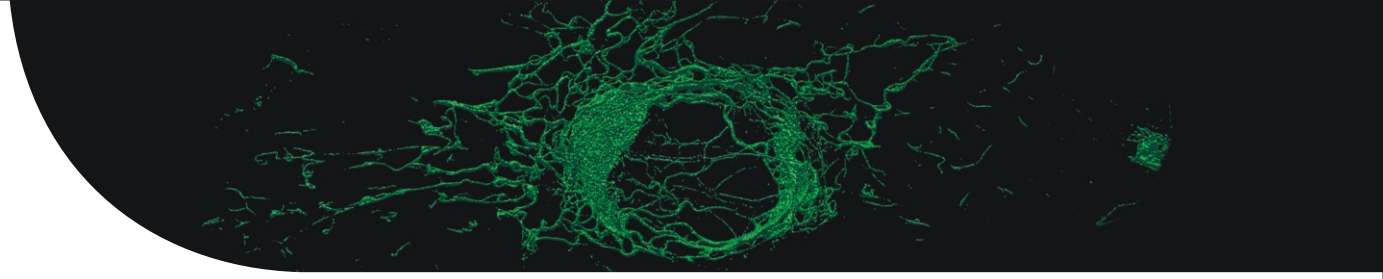


Figure 2: A and B: Antileishmanial activity of miltefosine nanoparticles (MNC)



D: Effect of MNC on phagolysosomal Rab57, Rab9 and cathepsin D level in pathogenic leishmania infected macrophages.



Future Research Plans:

- Management of allergic asthma, liver toxicity and obesity by natural compounds and/or nanoparticles.
- Designing of multi-functional and multi-targeted nanoparticles for improved delivery of anticancer drugs.

Publications:

1. Tannic acid and vitamin E loaded PLGA nanoparticles ameliorate hepatic injury in a chronic alcoholic liver damage model via EGFR-AKT-STAT3 pathway. S Nag, K Manna, M Saha, K D Saha. Nanomedicine 15 (3), 235-257

2. Biological promiscuity of a binuclear Cu (ii) complex of aminoguanidine Schiff base: DNA binding, anticancer activity and histidine sensing ability of the complex. A Mondal, C Das, M Corbella, A Bauzá, A Frontera, M Saha, S Mondal, K. D. Saha and S.K. Chattopadhya. New Journal of Chemistry 44 (18), 7319-7328

3. Designing of novel zinc (II) Schiff base complexes having acyl hydrazone linkage: study of phosphatase and anti-cancer activities. S Dasgupta, S Karim, S Banerjee, M Saha, K. D. Saha, D Das. Dalton Transactions 49 (4), 1232-1240

4. Therapeutic potential of andrographolide-loaded nanoparticles on a murine asthma model. S Chakraborty, I Ehsan, B Mukherjee, L Mondal, S Roy, K D Saha, B Paul, M.C.Debnath, T Bera. Nanomedicine: Nanotechnology, Biology and Medicine 20, 102006

5. Intracellular anti-leishmanial effect of Spergulin-A, a triterpenoid saponin of Glinus oppositifolius. S Banerjee, N Mukherjee, RL Gajbhiye, S Mishra, P Jaisankar, S Datta, K. D. Saha. Infection and Drug Resistance 12, 2933

6. Inhibition of TGF-β induced lipid droplets switches M2 macrophages to M1 phenotype. D Bose, S Banerjee, N Chatterjee, S Das, M Saha, K D Saha. Toxicology in Vitro 58, 207-214.

7. Semisynthetic Quercetin Derivatives with Potent Antitumor Activity in Colon Carcinoma. A Mukherjee, S Mishra, NK Kotla, K Manna, S Roy, B Kundu, D Bhattacharya, K D saha and A Talukdar. ACS Omega 4 (4), 7285-7298

EXTRAMURAL FUNDING

1. 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 (2018-2021)

2. 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. (2019-2022) . DBT-NER, India.

3. Utilization of promegranate for development of functional medical ingredients. (2016-2019) NMPB-AYUSH, India

4. 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. (2016-2019) DBT- NER, India.

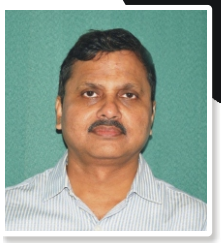
Cell Biology and Physiology Division

Members :

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

This division deals with systems and cell & molecular biology, investigating the functions of subcellular organelles and intracellular signaling events in normal physiology as well in the diseased condition. For the disease-related studies, the investigators utilize human patients' samples, preclinical animal models, and different primary cultures as well as cell lines. These investigations further adhere to molecular events at the subcellular organelles, intracellular signalling events and finally the different regulatory aspects of gene expression. The research endeavours of different groups of this division also have strong translatable objectives towards the development of novel therapeutic targets, diagnostics and therapeutic leads. Additionally, the research group of this division has strong intra-division collaborations, collaborations with other divisions including the scientists from the chemistry divisionand other Institutes. Major interests of the investigators of this division are in the area of metabolic diseases, including cardiometabolic diseases, diabetes, and cancer; neurological diseases, reproductive diseases, and lung disorders and parasitic diseases.





Dr. Sib Sankar Roy

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Understanding the molecular mechanism and pathophysiology of metabolic disorders

Participants

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

JRF: Sekh Eashayan Tanbir, Suman Pakhira

Collaborator(s)
Name of collaborator outside CSIR-IICB

1. Dr. Satinath Mukhopadhyay, SSKM Hospital, Kolkata
2. Dr. Ashima Mukherjee, Chittaranjan National Cancer Institute, Kolkata

Name of collaborator withinCSIR-IICB

1. Dr. Saikat Chakraborty

Background

Metabolic disorder is an immensely complicated area of research and among the different metabolic diseases, cancer has emerged as one of the most deadly disease extensively characterized by metabolic alterations, Late diagnosis, high metastatis, recurrence post chemotherapy and therapy resistance are some of the key features that contribute to thealaringly high mortality associated with the disease, Cancer stem cells play a major role in cancer chemoresistance and subsequent disease recurrence. Recent findings suggest that glutamine plays an important role in cancer cell proliferation, Glutaminase inhibitors are in clinical trials for combating cancer growth. But the impact of glutamine starvation on cancer cells remains poorly understood and the underlying mechanisms remain elusive. Although, transcription factors proto-oncogenic proteins like PITX2 and Ets1 are also emerging as metabolic regulator alongside inducing stemness, chemoresistance and various other aspects of cancer progression, the detailed mechanisms of the same remain majorly fairly unknown. Modulating the function of transcription factors could thus prove to be a promising strategy for countering cancer progression. In this context, DAXX plays an important role as an endegenous Ets1 inhibitor. Thus, detailed investigation of Ets1-DAXX protein-protein interaction will pave ways to an opportunistic domain for cancer treatment.

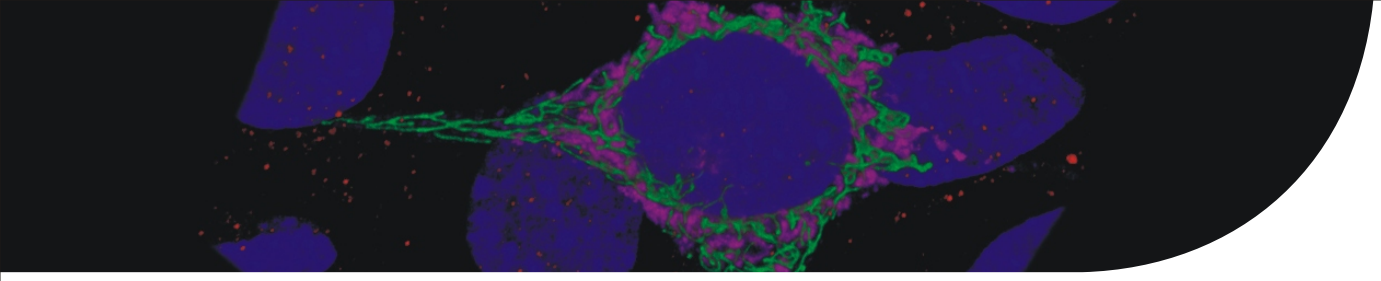
Insulin Resistance (IR) and its adverse consequences often lead to several metabolic disorders including obesity and Type 2 Diabetes (T2DM). Further IR is found to be critically linked to impaired Retinoid Metabolism. Lecithin: Retinol Acyl Transferase (LRAT), a Retinol esterifying enzyme, reported to serve a crucial role in maintaining Retinoid Homeostasis. The study of this group shows how LRAT regulates the function of PPARa in regulating obesity-linked mitochondrial dysfunction in hepatic cells.

Aims and Objectives

- To interpret the glutamine dependency of cancer cells and how targeting glutamine metabolism can be useful for the management of oncogenesis.
- To study the molecular mechanism behind the mitochondrial fragmentation and stemness.
- To establish the role of PITX2A/B in cancer stem cell induction and deciphering the mechanism behind this phenomenon.
- Deciphering the role of Ets1 in metabolic rewiring and in-depth analysis of protein-protein interaction with DAXX.
- To address the role of LRAT in obesity-linked inflammation in hepatocyte.

Work Achieved

Glutamine is essential for maintaining the tri-carboxylic acid (TCA) cycle in cancer cells yet they undergo glutamine starvation in the core of tumors. Cancer stem cells (CSCs), responsible for tumor recurrence are often found in the nutrient limiting cores. Our study uncovers the molecular basis and cellular links between glutamine deprivation and stemness in the cancer cells. Production of reactive ROS in glutamine limiting condition induces MAPK-ERK1/2 signaling pathway to phosphorylate dynamin-related protein-1(DRP1) at Ser616. Moreover, p-DRP1 promotes mitochondrial fragmentation, perinuclear localization and enhances numbers of CD44 and CD117/CD45 positive CSCs. Treatment with glutaminase inhibitor mimics the effects of glutamine starvation without altering cell survival. Interestingly, combinatorial treatment of with DRP1 inhibitor reduces stem cell population as well (Fig. 1).



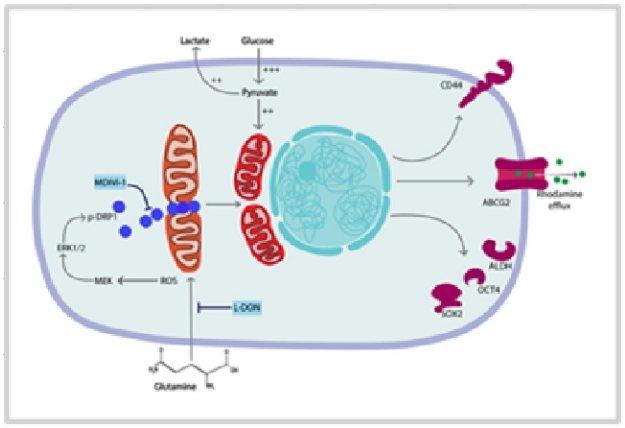


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Fig. 1: Glutamine starvation induces ROS mediated ERK1/2 activation, that phosphorylates the DRP1 leading to mitochondrial fragmentation. Further, mitochondrial fragmentation is involved with increased stemness and chemo-resistance.

Alteration in signaling pathways in cancer cells can impart chemoresistance/stemness, providing a major survival advantage. In the tumor microenvironment TGFβ signaling is most abundant signaling pathway which regulates cancer proliferation, EMT, stemness and chemoresistance. We investigated that TGFβ1 regulate expression of homeobox transcription factor PITX2A/B in both SMAD and non-SMAD signaling pathways. These isoforms promote stem-like characteristics along with chemoresistance, by transactivating ABCB1. PITX2 associated stemness induce low glycolytic and mitochondrial oxygen consumption in these cancer stem cells (Fig. 2).

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. We focus on how glutamine is involved in EMT and metastasis of cancer cells. How glutamine starvation is modulating the cancer metabolism is another important area we are dealing with. Further research is being pursued to develop drug combinations for targeting both tumor growth and cancer stemness. The role of the oncogenes on regulating the oncogenesis and metabolic alterations leading to chemoresistance and stemness will be studied.

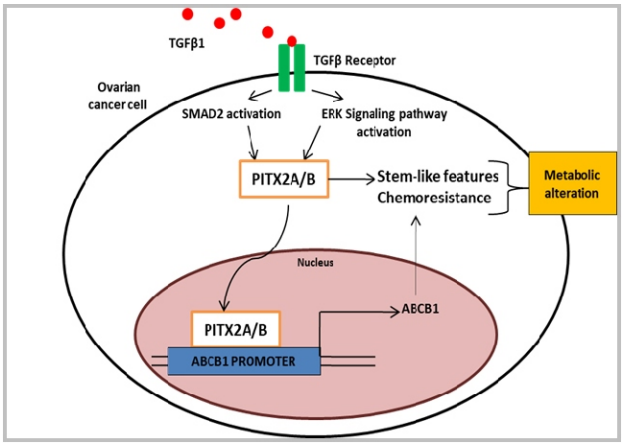


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Fig. 2: TGFβ induces stem-like features and chemoresistance in cancer cells through PITX2A/B activation. PITX2A/B binds to ABCG1 promoter and increases ABCB1 protein expression.

Ets1 have been primely linked with ovarian cancer growth and progression. Ets1 proto-oncoprotein shows an increase in response to epidermal growth factor (EGF), a TME derived cue. Ets1 induces pronounced glycolysis and compromised OXPHOS (Warburg effect). Further, DAXX represses Ets1 expression at both transcript and protein levels. Subsequently, Ets1 transcriptional activity is also regulated. Thus, our work establishes Ets1 as an important metabolic sensor to TME derived cues, alongside emphasizing on the role of DAXX mediated Ets1 regulation in combating OC progression.

PUBLICATIONS

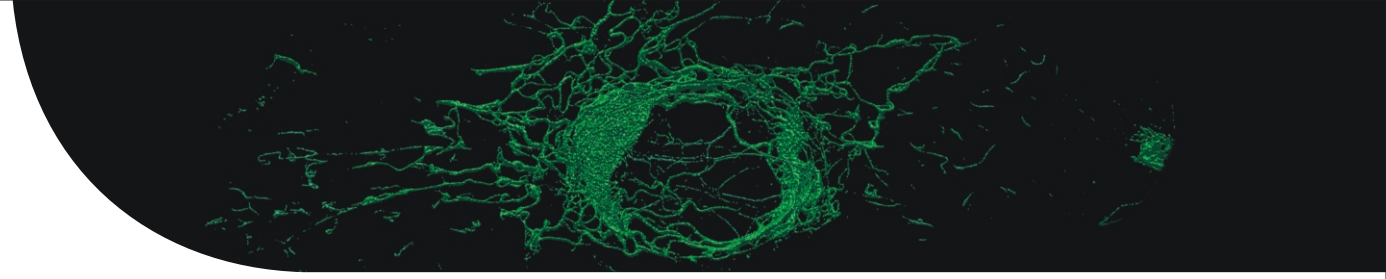
- STRICTLY according to the 'general instructions' given above format as sample only
- DO NOT number - only leave a space between 2 publications
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AWARDS / HONOURS / MEMBERSHIPS

Students

Shreya Bandopadhyay

Best Oral presentation in Life Science in Asia Pacific Microscopy Conference (APMC 2020), held at Hyderabad, during 03-07 February, 2020.



Parash Prasad/Sampurna Ghosh
3rd prize for poster presentation in India International Science Festival (IISF 2019) in the Wellness Conclave (Category- Swasth Bharat)

EXTRAMURAL FUNDING

Sib Sankar Roy (PI) and Aditya Konar (CO-PI)
'Mechanism of Ets-1 transcription factor-mediated metabolic reprogramming and tumorigenesis in ovarian cancer.' EMR/2016/002578 As PI. Sanctioned fund Rs. 39.048 laks; 24.03.2017 to 23.03.2020 (DST, SERB, Govt of India).

Sib Sankar Roy (PI) and Prof Satinath Mukhopadhyay, SSKM Hospital (Co-PI)
"To evaluate the effect of black tea intake on chronic anovulation and insulin resistance in polycystic ovarian syndrome (PCOS)". Code NTRF:207/2018; Sanctioned Fund Rs. 34.45 lakhs, 24/04/2019 to 23/4/2022 (National Tea Research Foundation, NTRF);

CONFERENCES / WORKSHOPS
8

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB
Name of event; Start date – End date, Year; Venue; CSIR-IICB Organizing Committee

Organized the 'Face to Face' program of India International Science Festival-2019 (IISF-2019) as Coordinator, held at Science City Kolkata during November 5-8, 2019.

Organized One-day symposium of Society of Biological Chemists (I), Kolkata Chapter, held at CSIR-IICB on 21st September, 2019.

INVITED TALKS BY CSIR-IICB FACULTY

Roy SS

Roy SS: "Metabolic switching in tumour cells promotes adaptation, survivability and oncogenesis", Invited talk at Indian Science Congress January 03-07, 2020, at Agricultural University, Bangalore, India.

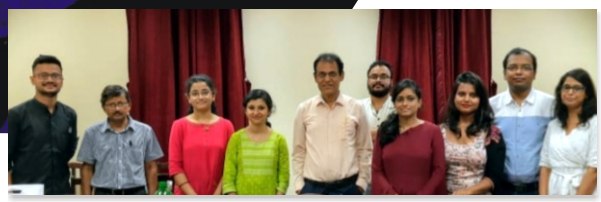
Roy SS: "Ovarian Cancer: Challenges and Future Strategies" Invited talk at refresher course for College and University faculties, held at Jadavpur University, on January 29, 2020.

Roy SS: Metabolic reprogramming favors adaptation, survivability and oncogenesis in tumor cells Plenary Lecture; National Seminar on Advancement of Biology on 21st Century, held at Visva Bharati, during February 28-29, 2020



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Understanding Molecular Mechanism of Compromised Inflammation-resolution and Reverse Cholesterol Transport in Coronary Artery Disease

Participants

Dr. Kamalika Roy Choudhury, RA
Apabrita Ayan Das, SRF
Devasmita Chakravarty, SRF
Aleepta Guha Ray, SRF
Dr. Vivek Chander, RA

Lab members

Dr. Kamalika Roy Choudhury, RA
Dibyanti Mukherjee, SRF
Apabrita Ayan Das, SRF
Devasmita Chakravarty, SRF
Aleepta Guha Ray, SRF
Ritu Kumari, SRF
Swapan Mandal, Technician

Collaborator(s)

Name of collaborator outside

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Apollo Gleneagles Hospital, Kolkata.

Background:

Cholesterol is a vital component of the cell and its homeostasis is one of the critically regulated processes. It is primarily synthesized in the liver and transported to peripheral tissues via formation of low-density lipoproteins (LDLs). Excess cholesterol is transported back to the liver for breakdown and excretion via high-density lipoproteins (HDLs), a process termed as Reverse Cholesterol Transport (RCT). RCT is primarily mediated by ATP-binding cassette transporter protein ABCA1, whose role lies in lipidation of ApoA1 molecules to form nascent HDL molecules, which can then accept excess cholesterol from various cells. Cholesterol efflux in macrophages is mediated by ABCA1 to apoA-I, while ABCG1 and SR-BI unload to mature HDL. Cholesterol laden HDL then reaches to the liver where cholesterol is removed for excretion and the HDL is re-circulated. Thus, ABCA1 plays a vital role in removing intracellular free cholesterol which otherwise might be toxic to cells. Although Reverse cholesterol transport (RCT) plays a critical role in removing cholesterol from the arterial wall very few reports directly relate chronic inflammation and RCT with atherosclerosis.

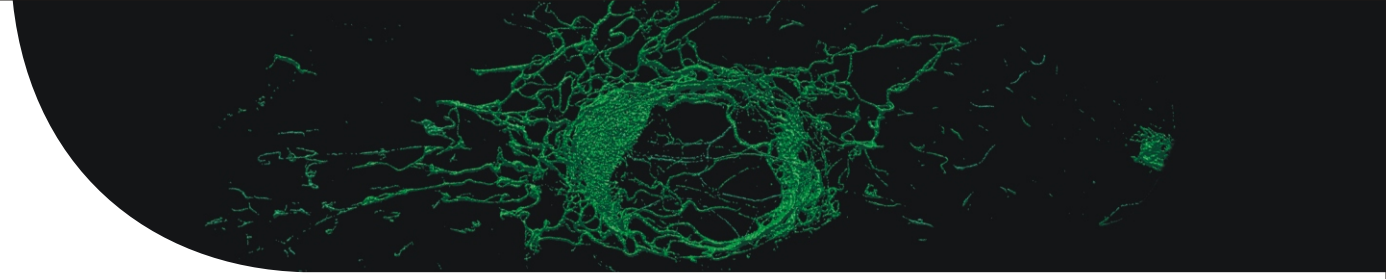
Aims and Objectives

(i) Identification of proteins clinically correlated with the atherosclerosis and acute coronary artery disease.
(Ii) Finding signature profile responsible for impaired RCT and chronic inflammation leading to atherothrombosis and myocardial infarction.
(iii) Understanding the interplay between efflux and influx pathway in relation to cholesterol mobilization in the progression of atherosclerosis.

Work Achieved

Using a case-control design, more than 2500 proteins in both myocardial infarction and healthy control subjects were identified by Orbitrap mass spectrometer. Pathway enrichment analyses indicated that most of the identified proteins were related to chronic inflammation, atherosclerosis and RCT such as AZGP1, ABCA5, Calicin, PGLYRP2, HAVCR2 and C17ORF57. Pathophysiological significance was studied using macrophage derived foam cell for their critical role in RCT which indicated the imbalance of RCT via the interaction of AZGP1 with CD36 (Figure 1).

Cholesterol homeostasis results from a delicate interplay between influx and efflux of free cholesterol primarily mediated by ABCA1. We observed the down-regulation of ABCA1 in hyper-cholesterol conditions in macrophages, which might be responsible for compromised reverse cholesterol transport (RCT) and hyperlipidemia. Surprisingly, this is countered by the upregulation of a lesser known family member ABCA5 to maintain cholesterol efflux. We established ABCA5 as the primary efflux mediator under high cholesterol load. These observations were correlated to cholesterol load in circulation in-vivo and which revealed inverse expression profile between ABCA1 and ABCA5 in mice models of atherosclerosis (ApoE-/-) and hyperlipidemia (PPARα-/-) in response to high cholesterol diet. Simulation studies



revealed a unique conformation of ABCA5 proposing a favoured route for cholesterol loading onto HDLs for reverse cholesterol transport (Figure 2).

Thus, a combination of shotgun and quantitative proteomics followed by in-vitro validations demonstrates a biochemical basis for compromised reverse cholesterol transport in the local milieu of the luminal wall of the artery which are critical for plaque build-up and atherosclerosis.

PUBLICATIONS

1. Das AA, Chakravarty D, Bhunia D, Ghosh S, Mandal PC, Siddiqui KN and Bandyopadhyay A. Elevated level of circulatory sTLT1 induces inflammation through SYK/MEK/ERK signaling in coronary artery disease. Clin Science, 2019, 133 (22), 2283-2299.
2. Das AA, Roychoudhury K, Jagadeeshaprasad M G, Kulkarni MJ, Mondal PC and Bandyopadhyay A. Proteomic Analysis Detects Dysregulated Reverse Cholesterol Transport in Human Subjects with ST-Segment Elevation Myocardial Infarction. J Proteomics. 2020, 30,103796.
3. Guha Ray A, Roy Choudhury K, Chakraborty S, Chakravarty D, Chander V, Jana B, Siddiqui KN and Bandyopadhyay A. Novel Mechanism of Cholesterol Transport by ABCA5 in Macrophages and Its Role in Dyslipidemia. J Mol Biol, 2020, 432,4922-4941.

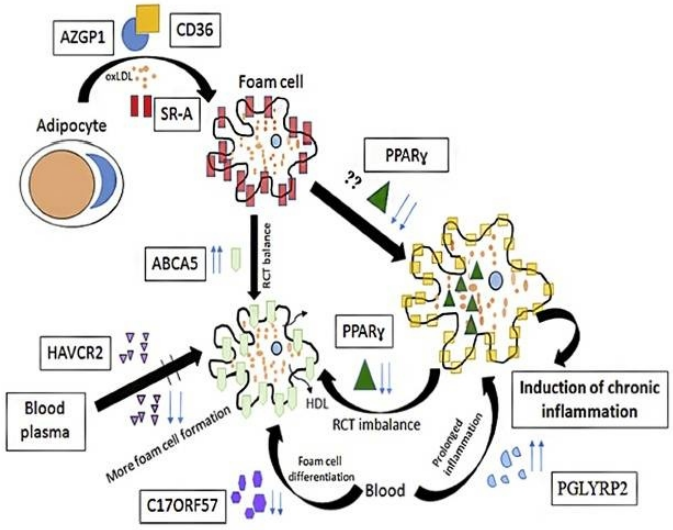


Figure 1. Diagrammatic representation showing the contribution of validated proteins in chronic inflammation, RCT and atherosclerosis
Upward blue arrows indicate an increased level of the protein whereas downward blue arrows indicate a decreased level of the protein as found in the study.

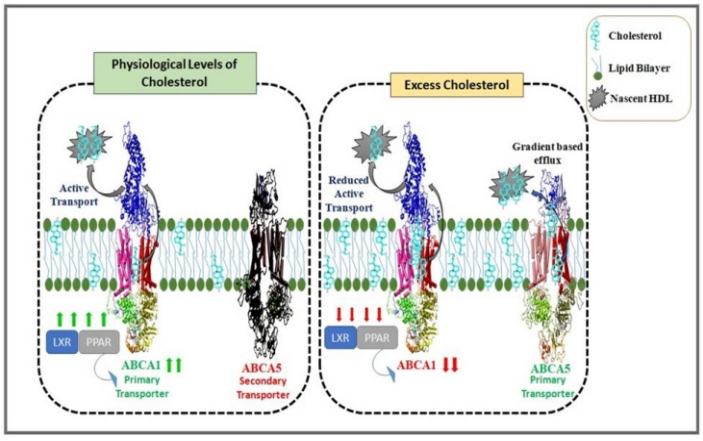


Figure 2. Novel Mechanism of Cholesterol Transport by ABCA5 in Macrophages and Its Role in Dyslipidemia. Under physiological doses of cholesterol, ABCA1 is the primary efflux mediator via an energy dependent process while ABCA5 acts as the secondary transporter. Under excess cholesterol, down-regulation of lipid metabolism results in reduced role of energy dependent ABCA1 for cholesterol efflux thereby promoting ABCA5 as the primary mediator whereby it adapts to a gradient based efflux mechanism via a conformational change.



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Regulation of trophoblast stem cell self-renewal, differentiation, spiral artery remodeling at the feto-maternal interface.

Participants

Madhurima Paul, DBT-RA
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Sarbani Saha, Project-RA
Trishita Basak, CSIR-SRF
Sonali Das, CSIR-SRF

Rumela Bose, CSIR-JRF
Shipra Jena, UGC-JRF
Tamal Gope, CSIR-JRF
Swarnali Dey, UGC-JRF

Collaborator(s)

Dr. Sandip Paul,
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Dr. TK Maity,
Regional Centre for Biotechnology, NCR-Delhi, India
Dr. Agnihotri Bhattacharyay,
Calcutta National Medical College, Kolkata, India.

Background

Central to placental morphogenesis 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 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.

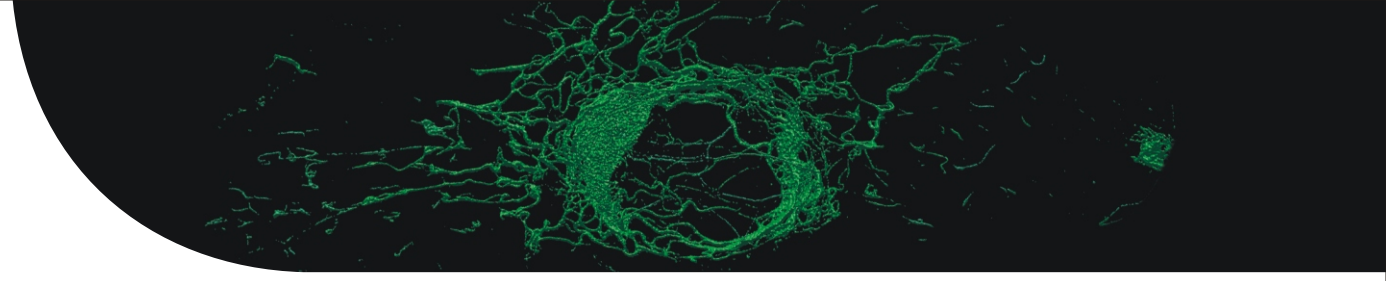
Aims and Objectives

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.

Work Achieved:

- We illustrated that Angimotin (AMOT) interactome in trophoblast cells and demonstrated using bioinformatics and biochemical approach that AMOT interacts with eIF4A leading to curtailment of global protein synthesis [Fig.1, (Basak et al., 2020)].

- We established that post-transcriptional regulation of CDX2 and cell cycle genes by miR-290 and miR-322 clusters along with transactivation of miR-290 cluster and CYCLIN D1 by CDX2 equipoise trophoblast stem cell self-renewal and differentiation (Saha and Ain, 2020).



- We demonstrated that autophagy is a necessary prelude in commitment of trophoblast differentiationfrom the multipotent TS cells probably by regulating protein turnover at the onset of differentiation (Chakraborty et al., 2020)..
- We unravelled the mechanism of trophoblast directed de-differentiation of vascular smooth muscle cells at the maternal-fetal interface (Nandy and Ain, 2020).

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 colorectal carcinogenesis.

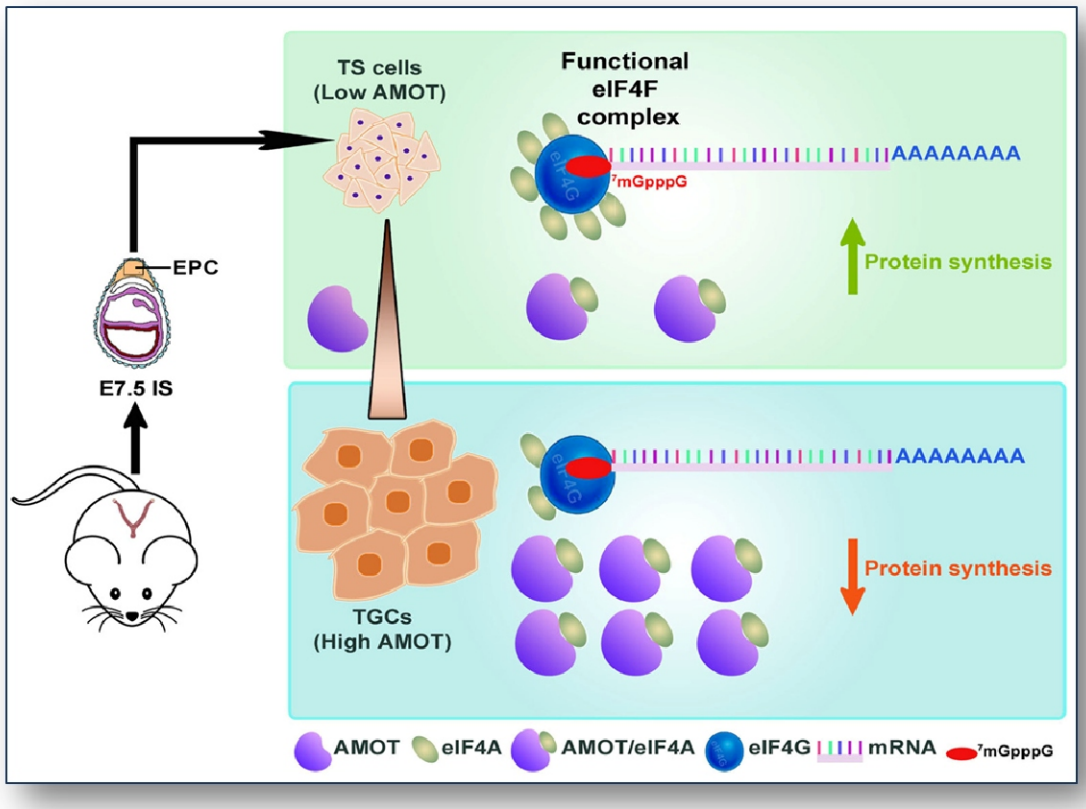


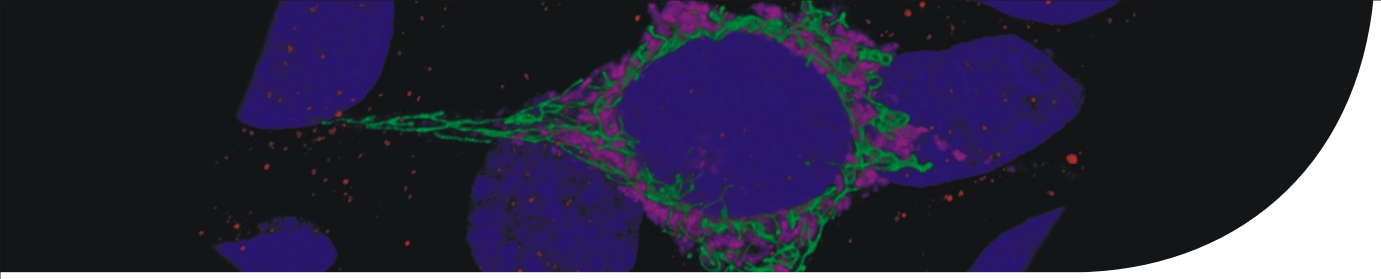
Fig 1: Schematic representation of AMOT function during trophoblast cell development (Basak et al., 2020).

PUBLICATIONS

1) Basak T and Ain R (2020) Sequestration of eIF4A by Angiomotin: a novel mechanism to restrict global protein synthesis in trophoblast cells. Stem Cells. DOI : 10.1002 / Stem. 3305.
2) Saha S and Ain R (2020) MicroRNA regulation of trophoblast stem cell self-renewal and differentiation. Life Science Alliance. 3 (11): e202000674. doi: 10.26 508/lsa.202000674.
3) Chakraborty S, Bose R, Islam S, Das S and Ain R (2020) Harnessing the autophagic network is essential for trophoblast stem cell differentiation. Stem Cells and Development. 29 (11),682-694.
4) Nandy D, Das S, Islam S and Ain R (2020) Trophoblast cells regulate phenotypic switching of vascular smooth muscle cells at the uteroplacental interface. Placenta. 93, 64-73.

AWARDS / HONOURS / MEMBERSHIPS

Life member, Indian Society for Study of Reproduction and Fertility
Life member, International Federation of Placenta Association
Member, Indian Society of Developmental Biology
Life Member, Society of Biological Chemists, India.



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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Pathophysiology and therapeutic potential of astrocytes in Alzheimer's disease

Participants

RA: Kusumika Garami (DST Women Scientist), Paidi Ramesh Kumar (Project RA)

SRF: Hrishita Das, Subhalaksmi Guha, Pallabi Bhattacharyya, Akash Saha, Anoy Kumar Das, Sukanya Sarkar

JRF: Soumita Goswami, Diptesh Roy, Naqiya Ambareen

Collaborator(s)

Outside CSIR-IICB

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Within CSIR-IICB

Suvendra N Bhattacharyya
Molecular Genetics division

Krishnananda Chattopadhyay
Structural Biology and Bioinformatics division

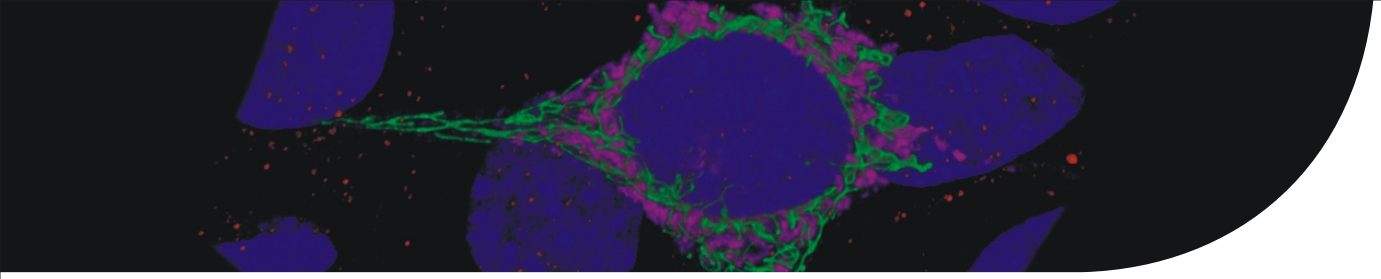
Biswajit Banerjee, R Natarajan, Ranjan Jana
Organic and Medicinal Chemistry division

Background

Alzheimer's disease (AD) is an age-related neurodegenerative disorder associated with impairment of synaptic plasticity, neuronal apoptosis and severe loss of cognition and memory. Pathologically AD is characterized by the presence of two core lesions: extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs).

Astrocytes are the integral components of healthy CNS and demonstrate a vital role in pathogenesis of various neurodegenerative diseases including AD. Recently, a continuum of reactive astrocytes with either protective or detrimental properties and characteristic cytokine profiles has been identified. Astrocyte reaction to a CNS insult involves a set of morphological, biochemical, molecular and functional alterations. The major hallmark of Aβ, extracellular Aβ plaque has been found to be surrounded by reactive astrocytes. Along with proliferation and migration upon exposure to insults, cytokines secretion by reactive astrocytes is one of the major responses to the pathological signals in AD brain. While it is well known that continued CNS insult leads to secretion of pro-inflammatory agents resulting in degeneration and death of neurons, much recent evidence indicates that during the early phase of disease, astrocytes play a critical neuroprotective role limiting apoptosis and providing trophic support to neurons. The impact of secreted cytokines on neuron health is diverse ranging from cell survival to cell death. Current emergence of studies indicates that cytokines are having cell free therapeutic potential in tissue repair and regenerative medicine.

We have found a significant neuroprotective and Aβ clearing role of tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) and Intracellular adhesion molecule-1 (ICAM-1), cytokines secreted from reactive astrocytes in response to Aβ at early time. TIMP-1 is secreted from astrocytes in the early phase of inflammation and found to be increased in CSF of AD patient. It is upregulated at protein level in many neuroinflammatory diseases. In acute and chronic inflammatory conditions, the respective rise and fall of TIMP-1/MMP-β ratio is a strong indication of neuroprotective attempt by TIMP-1 in the early phase of the disease. Intracellular adhesion molecule-1 (ICAM-1) is another cytokine that has been found to be elevated in microglia and astrocytes in CNS pathogenesis. Soluble form of ICAM-1 (sICAM-1) is generated through proteolytic cleavage and/or alternative splicing of mICAM-1 messenger RNA and it has been found to be present in different body fluids including CSF. Post-mortem AD tissues showed that the astrocytes surrounding the Aβ plaques are associated with an increased level of ICAM-1. Importantly a higher level of CSF sICAM-1 is strongly correlated with the higher risk of developing dementia. In a recent study, it has been demonstrated that sICAM-1 secreted from human umbilical cord blood derived mesenchymal stem cell (hUCB-MSC) can reduce Aβ loads in an AD mouse.



Aims and Objectives

To study the kinetics of Aβ-induced activation of astrocyte in culture.

To determine whether Astrocyte conditioned medium (ACM) from Aβ-treated astrocyte cultures display neuroprotective properties.

To study if TIMP-1 and ICAM-1 offers neuroprotection against Aβ-mediated neurotoxicity.

To investigate the mechanism of TIMP-1 and ICAM-1 mediated neuroprotection.

To check whether TIMP-1 and ICAM-1 improve cognitive behaviours in AD animal models.

Work Achieved

The different states of reactive astrocytes which determine their beneficial or detrimental roles in CNS are a major focus of our study. In this study, we investigated the beneficial roles of astrocyte-secreted protein, TIMP-1 and ICAM-1 in Aβ-treated primary cultures of neurons, Aβ-infused rats and 5xFAD mouse (a transgenic AD model). A number of our experimental observations suggest that TIMP-1 and ICAM-1 is rapidly secreted from astrocytes in response to Aβ treatment and promotes neuronal survival by activation of Akt pathway and inhibition of NF-κβ respectively and improves cognitive functions such as learning and memory of Aβ-infused rats and 5xFAD mouse by reducing Aβ load and apoptosis. First, we demonstrate that ACM from primary cultures of 6 h Aβ-treated astrocytes protected cortical neurons significantly from Aβ-induced death. Second, TIMP-1 and ICAM-1 secretion from astrocytes is greatly increased within 6 h of Aβ treatment. Third, TIMP-1 and ICAM-1 render the neuroprotective efficacy of Aβ-treated ACM since neutralization of TIMP-1 or ICAM-1 with specific antibodies diminishes the effect. Fourth, recombinant TIMP-1 and ICAM-1 protect neurons by blocking Aβ-induced inhibition of Akt and activation of NF-κβ respectively. Fifth, TIMP-1 or ICAM-1 injection in rat and mouse brain reduces Aβ-load and apoptosis in the vicinity of Aβ-infusion site. Finally a battery of behavioural studies indicates that TIMP-1 and ICAM-1 restores learning, memory and other cognitive deficits of Aβ-infused rat and 5xFAD mouse. These observations were further supported by the fact that TIMP-1 restores the expression of pre- and post-synaptic proteins, markers of synaptic integrity, in Aβ-infused rat brain. Moreover, NF-κB inhibitor PDTC ameliorates anxiety like behavior and cognitive deficits in 5xFAD mice.

In short, we have identified two cytokines, TIMP-1 and ICAM-1 those are rapidly secreted from reactive astrocytes in response to Aβ. TIMP-1 and ICAM-1 render neuroprotection and ameliorate cognitive deficits in Aβ-infused rat and AD mice probably by reducing Aβ load and by activating Akt pathway and inhibiting pro-apoptotic signaling of NF-κB respectively. Thus our study identifies TIMP-1 and ICAM-1 as major candidates in cytokine-mediated therapy of AD.

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 mechanisms of identified cytokines that promote neuronal survival and ameliorate cognitive behaviours in 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.

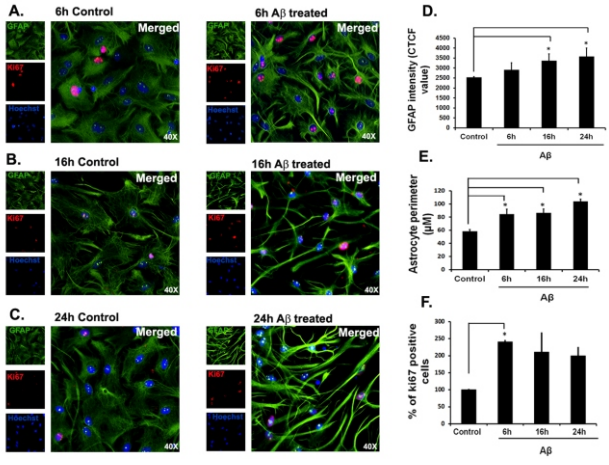
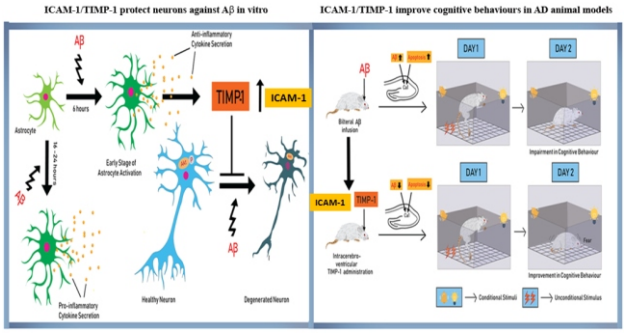


Figure 1: Kinetics of morphological changes and cell proliferation upon Aβ treatment of cortical astrocytes. Astrocytes (14 DIV), treated with 1.5 μM Aβ for 6 h (A), 16 h (B), or 24 h (C), were subjected to immunocytochemical staining with GFAP and Ki67 antibody followed by nuclear staining with Hoechst. Images were taken at a magnification of 40x. Both control and treated

conditionsin (A),(B),(C) figures represent a vertical panel of GFAP, Ki67 and Hoechst and the corresponding merged images (right of the vertical panel). (D), (E), (F) Bar diagrams represent quantitative analysis of GFAP intensity expressed as corrected total cell fluorescence (CTCF), astrocyte perimeter in μM and % of Ki67+ nuclei respectively at different time points of Aβ treatment. Values are expressed as Mean ±SEM of three independent



experiments. *p≤0.05.

Figure 2: A schematic showing the cascade for ICAM-1/TIMP-1 mediated neuronal survival and behavioural recovery in AD models in vitro and in vivo.

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1. Mahapatra A, Sarkar S, Biswas SC, Chattopadhyay K (2020). Modulation of α-Synuclein Fibrillation by Ultra-small and Biocompatible Gold Nanoclusters. ACS Chem Neurosci. Accepted.
2. Bhattacharyya P, Biswas SC. (2020). Small non-coding RNAs: do they encode answers for controlling SARS-CoV-2 in the future? Front. Microbiol. 18 September 2020 (Epub) https://doi.org/10.3389/fmicb.2020.571553
3. Saha P, Guha S, Biswas SC. (2020). P38K and JNK pathways are induced byamyloid-β in astrocyte: implication of MAPK pathways in astrogliosis in Alzheimer's disease. Mol Cell Neurosci. 108:103551.
4. Biswas S, Das H, Das U, Sengupta A, Dey Sharma R, Biswas SC, Dey S. (2020). Smokeless tobacco induces toxicity and apoptosis in neuronal cells: a mechanistic evaluation. Free Radic Res. 54:477-496.
5. Mukherjee C, Saleem S, DAS S, Biswas SC, Bhattacharyya D. (2020). Human placental laminin: Role in neuronal differentiation, cell adhesion and proliferation. J Biosci. 45:93.
6. Lahiri D, Mondal R, Deb S, Bandyopadhyay D, Shome G, Sarkar S, Biswas SC. (2020). Neuroinvasive potential of a primary respiratory pathogen SARS-CoV2: Exploring the underrecognized. Diabetes Metab Syndr. 14:1053-1060.
7. Mondal R, Lahiri D, Deb S, Bandyopadhyay D, Shome G, Sarkar S, Paria SR, Thakurta TG, Singla P, Biswas SC. (2020). COVID-19: Are we dealing with a multisystem vasculopathy in disguise of a viral infection? J Thromb Thrombolysis. 5:1-13.
8. Saha P, Sarkar S, Kumar PR, Biswas SC. (2020). TIMP-1: a key cytokine released from activated astrocytes protects neurons and ameliorates cognitive behaviours in a rodent model of Alzheimer's disease. Brain Behav Immun. 87:804-819.
9. Sanphui P, Das A, Biswas SC. (2020). Forkhead Box O3a requires BAF57, a subunit of chromatin remodeler SWI/SNF complex for induction of p53 up-regulated modulator of apoptosis (Puma) in a model of Parkinson's disease. J Neurochem. 154:547-561.
10. Gharami K, Biswas SC. (2020). Glutamate treatment mimics LTP- and LTD-like biochemical activity in viable synaptososme preparation. Neurochem Int. 134:104655.

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)

CONFERENCES / WORKSHOPS

Number of Abstracts in National/International Conference: 6
Number of Abstracts in International (Overseas) Conference: 1

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

NeuroUpdate; Nov 30, 2019; IICB, Kolkata

INVITED TALK

Astrocytes as therapeutic targets for Alzheimer's disease; 26th Foundation day of Central Calcutta Society for Advancement of Human Development and Research and INSA, 22nd July 2019, Bose Institute, Kolkata.



Dr. Partha Chakrabarti

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

Participants

SRF : Jit Sarkar, Debajyoti Das, Saheli Chowdhury, Ankita Sarkar

JRF : Pratiti Mandal, Tanusree Das, Abhishek Sen

Collaborator(s)

Dr Abhijit Chowdhury,
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 Sanjay Dutta

Background

Nonalcoholic 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 ubiquitinylated, 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

- Deciphering the molecular basis of liver injury in proteasomal inhibition and in NAFLD and NASH
- Development of first-in-class E3 ubiquitin ligase COP1 inhibitor for treatment of NAFLD

Work Achieved

- ASK1 and PPARγ reciprocally weigh the outcome of proteotoxic injury. We have shown that acute inhibition of proteasomal activity leads to profound hepatic injury and dysfunction, effects that are associated with reactive oxygen species (ROS) accumulation that in turn promotes ASK1-JNK dependent hepatocellular death with concomitant failure in surmounting an effective anti-oxidant response through PPARγ-Nrf2 pathway. Thus co-treatment with ASK1 inhibitor and PPARγ activator potently reverse hepatic proteotoxicity and extends survival in acute proteasome inhibition and ameliorates NASH in mice.
- Discovery of small molecule COP1 inhibitor for treatment of NAFLD. We aim to create small molecules with the potential to hinder COP1's ability to ubiquitinate ATGL which in turn would augment hepatic ATGL level restricting hepatic lipid accumulation. We have carried out structure-activity relationship (SAR) studies for over 120 compounds with quinazolinone scaffold by immunoblot, in vivo ubiquitination assay and confocal microscopy both in cultured and in murine primary hepatocytes. The small molecules could increase ATGL protein level, reduce ATGL ubiquitination and decrease lipid droplet count upon oleate induction without significant

alteration in the ATGL gene expression. The compounds could even enhance ATGL level in a background of COP1 overexpression in HepG2 cells. Moreover, we have identified UbcH6 as the bona fide E2 ubiquitin conjugating enzyme of COP1-ATGL axis. Furthermore reconstituting the in vitro ubiquitination with the inhibitor molecules, we have corroborated their specificity and potency. Adipose explant culture, however, were resistant to the effect of the compounds. Our study thus unveils novel small molecules as potential inhibitors of COP1 to ameliorate NAFLD. This study has been carried out in collaboration with Dr Arindam Talukdar.

Future Research Plans

- Developing a novel combination therapeutic regimen for proteotoxic hepatic injury in NAFLD
- Identifying key deubiquitinases (DUB) that have significant impact on proteotoxic hepatic injury
- Developing COP1 inhibitors up to the pre-clinical studies

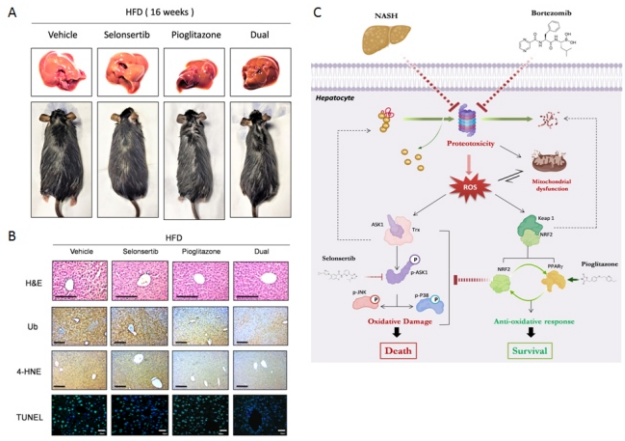


Fig. 1: Combinations of ASK1 inhibitor seloncertib and PPARg agonist pioglitazone reversed NAFLD/NASH in mice. (A) Gross examination of liver and the mice fed with high fat diet (HFD) for 16 weeks and treated with combination drugs for last four weeks. (B) Histology, immunohistochemistry (IHC) and TUNEL assay in liver sections of four groups of mice. (C) Proposed mechanistic model for proteasomal inhibition and NAFLD/NASH.

PUBLICATIONS

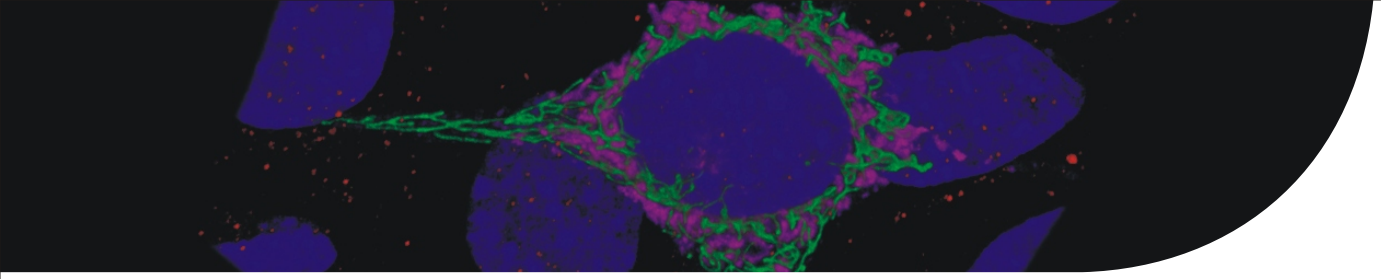
- Basu S, Barad M, Yadav D, Nandy A, Mukherjee B, Sarkar J, Chakrabarti P, Mukhopadhyay S, Biswas D. DBC1, p300, HDAC3, and Siah1 coordinately regulate ELL stability and function for expression of its target genes. Proc Natl Acad Sci U S A. 2020 Mar 24;117(12):6509-6520. doi: 10.1073/pnas.1912375117
- Sarkar J, Maity SK, Sen A, Nargis T, Ray D, Chakrabarti P*. (2019) Impaired compensatory hyperinsulinaemia among non-obese Type 2 Diabetes patients: A cross-sectional study. Ther Adv Endocrinol Metab.10:2042018819889024. doi: https://doi.org/10.1177/2042018819889024
- Sarkar J, Nargis T, Tantia O, Ghosh S, Chakrabarti P*. (2019) Increased Plasma Dipeptidyl Peptidase-4 (DPP4) Activity is an Obesity-independent Parameter for Glycemic Deregulation in Type 2 Diabetes Patients. Frontiers in Endocrinology, 10:505. doi: 10.3389/fendo.2019.00505. eCollection 2019.
- Niyogi, S., Ghosh, M., Adak, M., Chakrabarti, P. (2019) PEDF Promotes Nuclear Degradation of ATGL through COP1. Biochem Biophy Res Commun 512, 806-811

AWARDS / HONOURS / MEMBERSHIPS

Faculty
Scientist's Name : Partha Chakrabarti

Memberships

- Member, SERB Programme Advisory Committee on Health Science (PAC-HS) (2019-21).



EXTRAMURAL FUNDING

Name : Partha Chakrabarti

- Adipose tissue-β cell axis in the pathophysiology of Non-obese Type 2 Diabetes: Role of Adipokines. 2020-23. (ICMR, India)
- Non-alcoholic Fatty Liver Disease (NAFLD): Novel Pathogenetic mechanism and therapeutic development. 2020-25. (CSIR, India)
- Impact of tryptophan derived bacterial metabolites on metaflammation. 2019-22 (DST-SERB, India)

INVITED TALKS BY CSIR-IICB FACULTY

Name Surname: Partha Chakrabarti

- Pathophysiological Characterization of non-obese type 2 diabetes. Global AI summit, 23rd Dec, 2019
- Food, Environment and Diabetes. IISF, Kolkata, 6th Nov, 2019
- Creation of a Research Niche in Metabolic Syndrome. Medinipur College, 12th March, 2020



Dr. Ulaganathan Mabalirajan

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Role of Ku70/80 in the prevention of allergic airway inflammation

Participants

SRF : Ashish Jaiswal

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

Background

Asthma is a chronic inflammatory disease of airways affecting 1 in 6 persons in developed countries, and its incidence is increasing worldwide. Pathologically, asthma is characterized by profound allergic airway inflammation resulting in increased mucus production, airway remodeling, and bronchospasm. Recently, multiple studies have demonstrated the role of primary airway epithelial dysfunction as a key etiologic factor driving airway inflammation in asthma, rather than inflammation-induced airway remodeling. Indeed, innate immune responses of airway epithelia lead to downstream effects on adaptive immunity, and insufficiency in these responses have been linked to acute exaerbations in asthma. Airway epithelia exposed to various insults such as airborne allergens, foreign particles, and oxidants demonstrate increased stress response and accentuate asthma-like responses. In this context, our lab and others have demonstrated that mitochondrial dysfunction and ER stress in airway epithelia are prominent features of the stress response in human asthma. In addition, downregulation of epithelial stress responses in vivo has been shown to attenuate asthma-like features in mouse models of allergic airway inflammation via mesenchymal stem cell-mediated mitochondrial donation. These findings suggest that maintenance of organelle homeostasis in airway epithelial cells may be protective against the allergic inflammatory response that develops in asthmatic patients. This accords with a large body of recent work that has highlighted the importance of organelles such as mitochondria in the pathogenesis of airway diseases.

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 Ku70 and Ku80 in asthma
2. Detailed role of Ku70 and Ku80 in asthma pathogenesis

Work Achieved

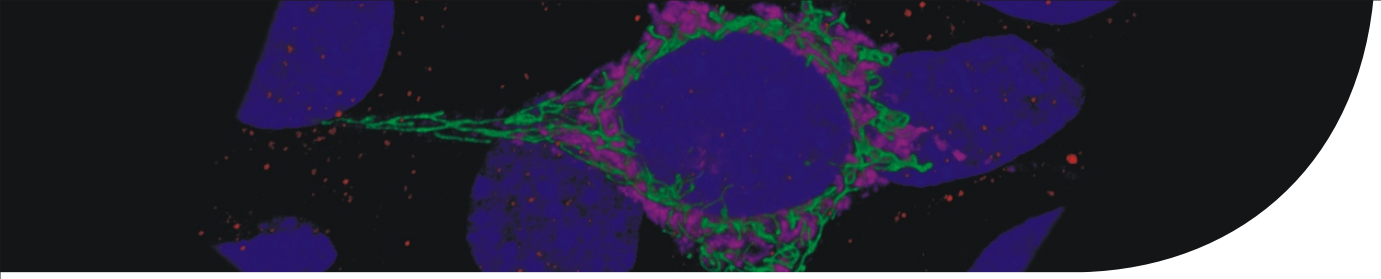
1. We first determined that airway epithelial cells derived from both asthmatic lungs and murine asthma models demonstrate increased expression of 8-hydroxy-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage. Ku protein expression was dramatically reduced in the bronchial epithelium of patients with asthma, as well as in human bronchial epithelial cells exposed to oxidative stress.

2. Knockdown of Ku70 or Ku80 in naïve mice elicited mitochondrial collapse or ER stress, leading to bronchial epithelial cell apoptosis and spontaneous development of asthma-like features including airway hyperresponsiveness, airway inflammation, and sub-epithelial fibrosis.

3. These findings demonstrate an essential non-canonical role for Ku proteins in asthma pathogenesis, likely via maintenance of organelle homeostasis. This novel function of Ku proteins may also be important in other disease processes associated with organelle stress.

Future Plans:

1. Role of Ku70 and Ku80 overexpression in asthma therapy
2. Identification of small molecules that can increase Ku70 and Ku80 expression.



PUBLICATIONS in last one year:

1. Rakhshinda Rehman, Vijay Elakkya Vijayakumar, Ashish Jaiswal, Vaibhav Jain, Shravani Mukherjee, Shamsudheen K. Vellarikkal, Paul B. Dieffenbach, Laura E. Fredenburgh, Y. S. Prakash, Balaram Ghosh, Anurag Agrawal, Ulaganathan Mabalirajan* Non-canonical role for Ku70/80 in the prevention of allergic airway inflammation via maintenance of airway epithelial cell organelle homeostasis. Am J Physiol Lung Cell Mol Physiol. 2020 Sep 2. doi: 10.1152/ajplung.00522.2019. Epub ahead of print. PMID: 32877223.

2. Archita Ray, Ashish Jaiswal, Joytri Dutta, Sabita Singh, Ulaganathan Mabalirajan* A looming role of mitochondrial calcium in dictating the lung epithelial integrity and pathophysiology of lung diseases. Mitochondrion. 2020 Sep 21:S1567-7249(20)30190-2. doi: 10.1016/j.mito.2020.09.004.

3. Mahesh Padukudru Anand, Kjell Larsson, Gunnar Johanson, Harish C. Phuleria, Ravindra PV, Lena Ernstgård, Ulaganathan Mabalirajan, Murali Krishna, Lena Palmberg, Krystal J. Godri Pollitt, Swapna Upadhyay and Koustav Ganguly. Clinical, epidemiological and experimental approaches to assess adverse health outcomes of indoor biomass smoke exposure: Conclusions from an Indo-Swedish workshop in Mysuru, January 2020. Toxics. 2020 Sep 5;8(3):E68. doi: 10.3390/toxics8030068. PMID: 32899560.

4. Sabita Singh, Ulaganathan Mabalirajan*. Mitochondrial calcium in command of juggling myriads of cellular functions. Accepted in principle in Mitochondrion, Accepted in Mitochondrion Sep 2020.

AWARDS / HONOURS / MEMBERSHIPS

1. Dr Mabalirajan delivered an invited Lecture titled “Airway epithelia: A natural borderline security force of lungs for wellness of lungs !!!” at 5th India International Science Festival (IISF), that was conducted from 5-8 November 2019.

2. Dr Mabalirajan delivered an invited lecture titled “In Vivo models to study environmental lung diseases” at "Indo-Swedish conference on Clinical, epidemiological and experimental approaches to assess air pollution-related chronic health effects" on 7th January 2020 at JSS Medical College, JSS Academy of Higher Education & Research, Mysuru, Karnataka.

3. Dr Mabalirajan delivered Dr. P. Kutumbiah Lectureship Award lecure at Dr. ALM. P.G. Institute of Basic Medical Sciences, University of Madras, Chennai on 24th February 2020.



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:

i) KA cause hippocampal neuron cell death: We have examined neuronal cell death in the KA 30 mg/kg treated mice using TUNEL and immunofluorescence staining. In the KA-treated mice, TUNEL positive cells were observed in the CA1 and CA3 region of the hippocampus, 3 days after KA treatment (Fig. 1). TUNEL-positive cells were also seen in the CA1 and CA3 region of hippocampus 5 days after KA treatment. No TUNEL-positive cells were seen in the hippocampus of control mice (Fig 1).

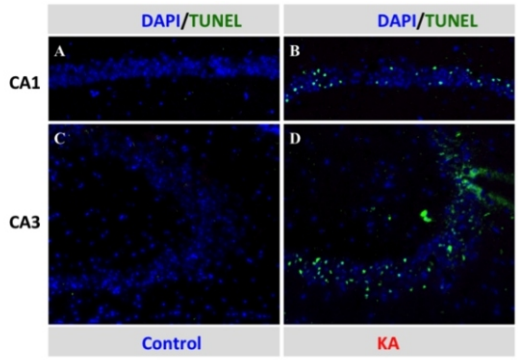


Fig 1: KA cause hippocampal neuron cell death

ii) Increased proliferation following KA induced cell death: In order to check the effect of KA on adult neurogenesis, we have injected KA 30mg/kg in P28 mice to induce neurogenesis and behavioral seizure score was observed (Racine 1972). New-born neurons were marked by acute intraperitoneal injection of BrdU. We have observed approximate increased in neurogenesis marked by BrdU+ cells in SGZ of hippocampus (Fig 2A). Quantitative analysis of BrdU+ cell in the SGZ of dentate gyrus of the hippocampus was performed. Every 10thsection of hippocampus was analyzed from rostral to caudal. Quantification data confirmed that BrdU+ cells were increase four fold in KA treated mice in comparison to control animals (Fig. 2B).

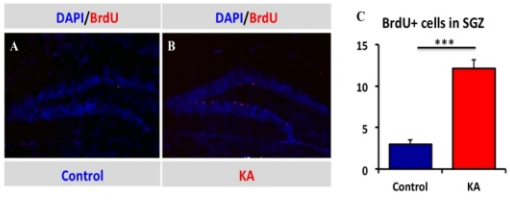
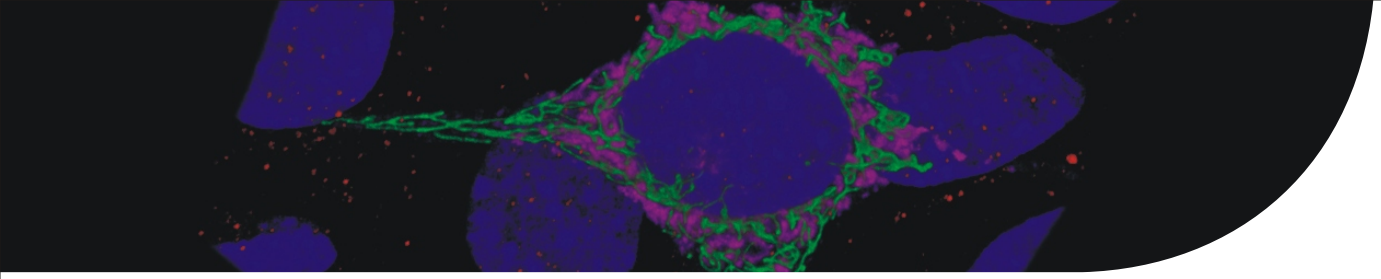


Fig 2: Increased proliferation following KA induced cell death



Future research plan:

We aim to further confirm that Brdu+ cells migrate to the injury site, we will injected KA, allowed the degeneration to happens for three days followed by BrdU for injections for seven consecutive days to follow the migration of newly generated neuronal progenitors. We will check if BrdU+ neuronal progenitors are increased at the DG and there are significantly higher number of Brdu+ new born cells to the CA1 and CA3 region of the hippocampus which was prone to KA induced injury/cell death. This will highlight that increased neurogenesis at DG regions of the hippocampus and their migration to the site of injury that may be further differentiated to integrate into the circuitry.

Publications:

1) Dey J, Alam MT, Chandra S, Gandhi S, Tripathi PP*. Recalibrating the Existence of New Neurons in Adult Brain. ACS Chemical Neuroscience 2019(corresponding) (IF- 4.5)
2) Chandra S, Alam MT, Dey J, Chakrapani P S B, Ray U, Srivastava AK, Tripathi PP. Healthy Gut, Healthy Brain: The Gut Microbiome in Neurodegenerative Disorders. Curr Top Med Chem. 2020.(corresponding) (IF- 3.1)
3) Roberts A, Tripathi PP, Gandhi S. Graphenenanosheets as an electric mediator for ultrafast sensing of urokinase plasminogen activator receptor-A biomarker of cancer. BiosensBioelectron. 2019 Sep 15;141:111398 (IF- 10.2)

Extramural Funding:

1) Role of endogenous intermediate progenitors in neurogenesis following neurodegeneration. Start year: 2018, End year 2021, Agency: DST, Govt of India
2) Electrochemical nanosensor of BACE-1 for early detection for Alzheimer disease. Start year: 2019, End year 2022, Agency: ICMR, Govt of India

Conferences/Workshops

Organizing committee member of IISF:India International Science Festival. Organized Engineering Science Expo (organized and handles stage/ anchoring).



Dr. Joy Chakraborty

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Understanding basic mechanisms of mitophagy in neurodegenerative disorders.

Participants

JRF:
Moumita Roy
Rupsha Mondal
Chayan Banerjee

Project fellow:
Sumangal Nandi

Collaborator outside CSIR-IICB
Dr. Luca Scorrano
University of Padova, Padova, Italy

Collaborators within CSIR-IICB
Dr. Deepak Kumar
Dr. Partha Chakraborty
Dr. Subhas C. Biswas
Dr. Krishnananda Chattopadhyay

Background and origin of the research plan

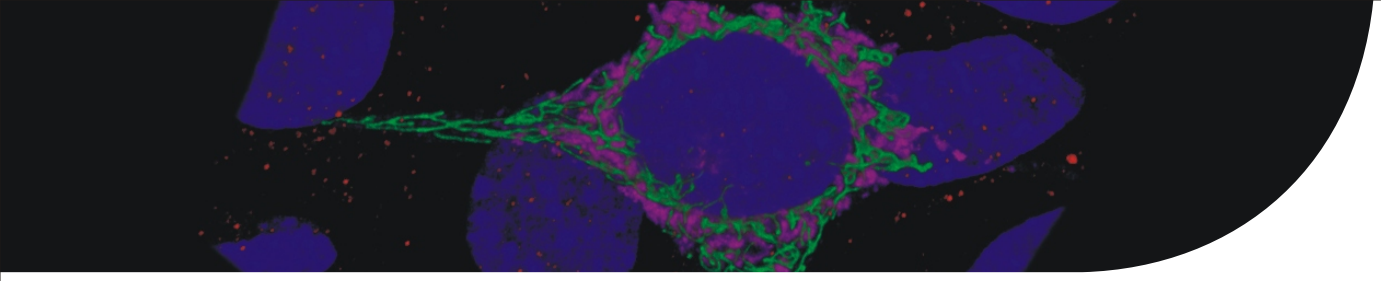
In a cell, defective mitochondria are sorted out and degraded by autophagy machinery (mitophagy)to avoid oxidative stress and apoptosis. Mitochondrial clearance depends on three differentprerequisites: shape (for optimal size), ubiquitin proteasome system (UPS) activation (for membranerupture) and autophagic engulfment (through autophagic vesicle-mitochondria adaptor proteins).Though it is a well-established fact that UPS and autophagy are interdependent for propermitophagy, how these two systems communicate and orchestrate mitochondrial clearance is mostlyunknown. For instance, it remains unknown whether outer mitochondrial membrane (OMM)proteins responsible for membrane rupture, remain in close proximity with the inner mitochondrialmembrane (IMM) autophagy receptor; or IMM mitophagy receptor exposure is a random process.

To add to the mystery, it is not properly understood why some areas of brain are more vulnerable when mitophagy is interrupted. For example, hindrance in mitophagy process due to mutation in PINK1 or Parkin (two key players in mitophagy process) leads to Parkinson's disease (PD) where the dopaminergic neuronal population in substantianigra region of brain degenerates progressively. There are few theories which partially explain the site specificity of neurodegeneration in PD. One of the most plausible hypotheses is dopamine (DA) metabolite mediated toxicity which is exerted mainly via oxidative stress due to breakdown by Monoamine oxidases (MAO). It remains unanswered whether DA supplementation therapy, the only therapy available for the ailment, can actually accelerate degeneration or not. A proper comparison of dopaminergic neuron loss between PD patients with/ without dopamine supplementation therapy is still missing in literature. Also, literature does not provide any characterization of mitochondrial population in dopaminergic neuronal terminals during PD progression or aging.

With the central hypothesis that variations in mitochondrial clearance holds the key to differential vulnerability of neurons at different brain regions, during aging and neurodegeneration, our main objective is to characterize the proximity between OMM and IMM protein (individually or in complex) responsible for tagging mitochondria for proteasome invasion and engulfment by autophagic machinery. To address DA mediated neuronal damage we are characterizing how MAO mediated oxidative stress affects mitophagy process.

Aims and objective:

- Characterization of the outer and inner mitochondrial membrane protein interaction during mitochondrial membrane rupture and autophagic vesicle attachment. Quantification of mitophagy receptor exposure level in relation to IMM-OMM protein interaction in different brain regions, during aging and progression of Parkinson's disease. Investigating the effect of autophagy and proteasome activity enhancement on mitophagy receptor exposure during Parkinson's disease progression.
- Determining the role of dopamine or enhanced MAO activity on mitochondrial clearance and how it can affect specific neuronal populations.
- Quantification of mitochondrial distribution and aberration in mitophagy during Parkinson's disease progression, in presence or absence of dopamine supplementation. As an extension of the central objectives and to explore the therapeutic aspects, we will also determine whether enhancement of mitophagy or inhibition of MAO can halt the disease progression in presence / absence of L-DOPA therapy.



Work achieved so far

- We have identified that some of the best known substrates of Parkin oligomerize during mitochondrial depolarization, which is accompanied by PHB2. While the oligomerization of OMM channel forming proteinsare mediated through Cysteine sulfhydryl groups, PHB2 reorganization is yet to be characterized. Inhibition of this OMMoligomerization leads to decreased mitophagy. Further we also found that PINK1 and Parkin mutation affects the oligomerization state of these proteins differently, in vivo.
- We have characterized the effect of MAO activation and DA treatment on mitochondrial morphology and cell survival. We found that mito-fragmentation is mediated by both Calcineurin-DRP1 axis and breakdown of OPA1 long forms.
- We have screened 50 different compounds / fractions isolated from natural sources and identified 7 potent MAO inhibitors which might have therapeutic values against neurodegeneration during PD development. The initial toxicity screening and in vivo validation is underway.

Publications

- Banerjee C, Roy M, Mondal R, Chakraborty J. USP14 as a Therapeutic Target Against Neurodegeneration: A Rat Brain Perspective. Front Cell Dev Biol. 8:727, 2020.
- Chakraborty J, Caicci F, Roy M, Ziviani E. Investigating mitochondrial autophagy by routine transmission electron microscopy: Seeing is believing? Pharmacol Res. 160:105097, 2020.
- Chakraborty J, Ziviani E. Deubiquitinating Enzymes in Parkinson's Disease. Front Physiol. 11:535, 2020.
- 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 MB, Szabo I, Whitworth AJ, Scorrano L, Ziviani E. Inhibition of the deubiquitinase USP8 corrects a Drosophila PINK1 model of mitochondria dysfunction. Life Sci Alliance, 2, 2019.

Awards

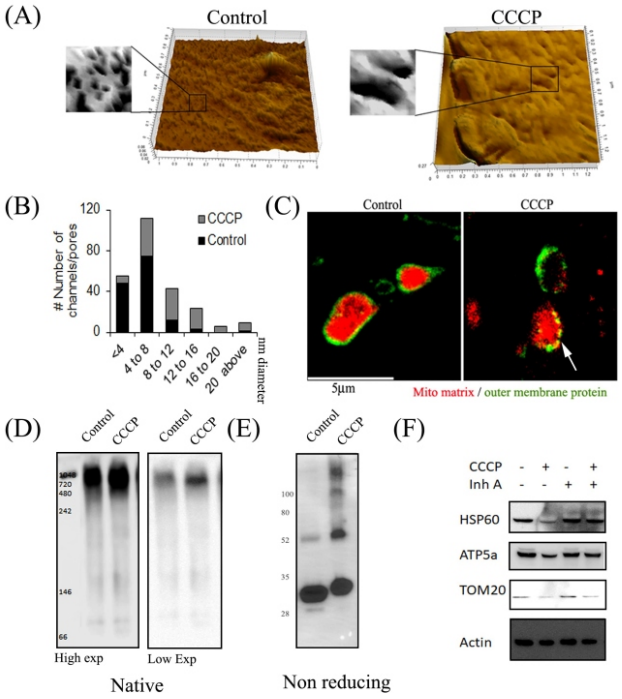
- Young IBRO Regions Connecting Award. International Brain Research Organization.

Extramural funding

Mitochondrial clearance in aging brain: therapeutic approach against differential neurodegeneration in Parkinson's disease.ECR/2018/000833 01-11-2019 to 31-10-2022 (DST-SERB, Govt. of India).

Managing mitochondria from dopamine: halting Parkinson's disease progression2019-0142/F1 02-09-2019 to 01-09-2021 (ICMR, Govt. of India).

Figure legend: (A) Atomic force microscopic images of isolated rat brain mitochondria after vehicle or CCCP (mitochondrial



depolarizer) treatment. (B) Quantification of pore / channel numbers present on mitochondrial outer surface after depolarization, based on their diameter. (C) Super resolution confocal images of a mitochondrial protein (green) on mitochondrial surface after vehicle or CCCP treatment (mitochondrial matrix : red). (D and E) Oligomerization state of a mitochondrial surface protein after CCCP treatment, in native and non-reducing conditions. (F) Inhibition of oligomerization by pharmacological inhibitor (Inh A) leads to reduced mitophagy in response to CCCP treatment. Mitochondrial mass was monitored bymeasuring mitochondrial marker proteins.

Infectious Diseases and Immunology Division

Members:
Dr. Snehasikta Swarnakar (Head), Dr. Subhajit Biswas, Dr. Sujoy K Das, Dr. Upasana Ray, Dr. Sudipta Das (Ramalingaswami Fellow), Dr. Rupak K. Bhadra

At the Infectious Diseases and Immunology Division of CSIR-IICB, the faculties and fellows are involved in various research works including basic science, application science related to the prevention and control of cholera, leishmaniasis, malaria, gastric ulcer and viral diseases like dengue, chikungunya, herpes and hepatitis B. Work is also being carried out on endometriosis. The other interest lies on wound healing 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 matrix metalloproteases in determining clinical outcome of *H. pylori* infection. Malaria and gastropathy work is focused on (i) characterization of *Plasmodium falciparum* vaculor protein sorting, (ii) development of anti-malarial small molecule therapeutics, (iii) a novel gastroprotective mechanism independent of gastric acid suppression, but dependent on matrix metalloproteases activity, (iv) demonstration of the effects of curcumin and melatonin on protease: antiprotease stochiometry, (v) preparation and use of tamaraxitin derivatives in gastropathy. Work on leishmaniasis is comprisesd 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 antileishmanial 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) Very 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. LesihmaniaLeishmania 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 towardsmay allow in 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, (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 herpes virus clinical isolates including their sensitivity to antivirals and (v) dengue virus diagnostics.(vi) Elucidating the “Dengue Covid-19 conundrum” based on CSIR-IICB’s discovery that dengue anti bodies can cross react with SARS-CoV-2.





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MATRIX METALLOPROTEASES (MMPS) AND DISEASES

Participants

SRF: Nilanjana Deb, Anuradha Pandit, Yasmin Begam
Project SRF: Preety Choudhary
JRF: Sudipta Mallick, Abhishek Chatterjee, Susmita Saha, Rahul Gupta
RA: Dr. Vineet Kumar Mishra
SERB-NPDF: Dr. Tapasi Roy
Senior Technician (2): Anirban Manna

BACKGROUND:

We study the pathogenesis of different diseases including gastric ulcer, gastric cancer, neurodegenerative disorders, endometriosis and ovarian cancer. We address different causative factors and their mechanism of actions behind pathogenesis of several diseases. 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 major focus area of my research. My laboratory is interested in understanding the role of matrix metalloproteinases (MMPs), a group of zinc containing calcium dependantendopeptidases, which are involved in the degradation of different extra-cellular matrix proteins in different disease progression. Several studies have identified altered expression of MMP-9, -3, -7 in ovarian and gastric cancer. In addition to promoting cellular migration and invasion, certain MMPs are involved in specific regulation of other cellular responses as well. The association of MMP-13 promoter polymorphism and studies on hormonal regulation of endometriosis and role of MMPs and dopamine in the progression of neurodegenerative disorders are currently under progression.

AIMS AND OBJECTIVES:

1. To understand the specific role of MMPs in the pathogenesis of endometriosis and neurodegenerative diseases. To study the hormonal regulation of endometriosis and crosstalk with MMPs.
2. To understand the association of MMP-13 promoter polymorphism to endometriosis progression.
3. Searching for some potent molecules that can inhibit MMPs and thereby reduce the neuronal cell damage

WORK ACHIEVED:

Interleukin-1β induced c-fos factor differentially binds to MMP13 -77 promoter site varient and is associated to endometriosis severity.

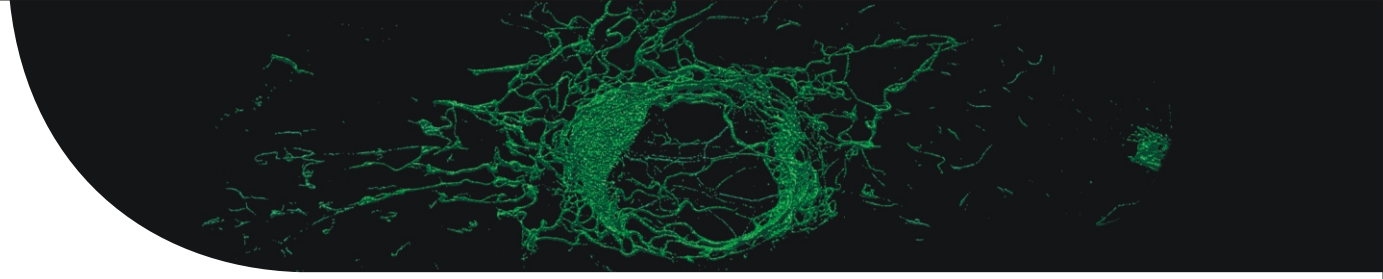
Endometriosis is a benign gynecological disease characterized by increased inflammation, invasion and metastasis. Elevated expression of MMP13 has been reported to play an important role in cellular invasion and disease progression. Till date, role of MMP13 in the development of endometriosis has not been reported. From our study, the -77 A/G polymorphism of MMP13 promoter has been implicated to regulate gene expression and subsequent susceptibility to endometriosis. Activity and expression of MMP13 was significantly higher in AA individuals. A-containing genotype was predisposed to endometriosis risk compared to G-genotype. In support, MMP13 promoter-reporter assays showed greater transcriptional activity toward G to A transition under basal/Il1β-induced/c-Fos overexpressed conditions in endometrial epithelial cells. Altogether, specific binding of phosphorylated c-Fos to A allele-carrying promoter enhances MMP13 gene expression that is further augmented by IL1β due to increased c-Fos phosphorylation and thereby increases the risk for endometriosis (Fig.1 A-F).

Investigating co-localization of MMP-9 and alpha synuclein in neuronal cells:

To study sub-cellular localization and interaction among the neighboring proteins; untreated and treated neuronal cells were cultured on confocal dishes, microscopic analysis was performed using a high resolution Stimulated Emission Depletion Microscopy (STED) (Leica TCS SP8) in randomly selected fields. Localization of proteins inside a cell and/or in its different compartments is of great interest for interaction studies. DA treated and untreated neuronal cells revealed that both MMP-9 (green for FITC) and alpha synuclein (red for Texas Red) are located in the cytoplasm of the cell (Fig. 2A &2B).

In Silico approach to study the interaction of MMP-9 with alpha synuclein in the presence and absence of dopamine

The computational model of the interaction between alpha



synuclein and MMP9 in the presence or absence of DA was carried out using online protein-protein dock server, Hex 8.0.0. The amino acid sequences of human alpha synuclein (PDBID: 1XQ8) and MMP9 (abinitio model) were downloaded from the NCBI website, and uploaded to the server. The final image of the model was downloaded and visualized by Discovery Studio Visualizer 4.0 (BIOVIA, San Diego, CA, USA).

The result showed that MMP-9 and alpha synuclein interacts with each other at numerous amino acid positions. During bond formation with MMP-9, alpha synuclein interacts at Lysine10 & 80, Threonine 81 and Valine 70, while MMP-9 uses Lysine 286, Proline 287, Glycine 73 & 281, Aspartic acid 309 & 321, Arginine 307 and Tyrosine 320 for the bond formation with alpha synuclein (Fig. 2C.). When DA is introduced in the system interaction becomes more complex. Alpha synuclein now interacts with MMP-9 at lysine 32 & 60 along with lysine 10 & 80 and Isoleucine 88; however MMP-9 uses Asparagine282, Aspartic acid 138 & 266 and Threonine 264 to interact with alpha synuclein. Further, alpha synuclein connects itself with DA molecule by Threonine 92 residue, and MMP-9 connects by Glycine 238 residue (Fig. 2D).

FUTURE RESEARCH PLANS:

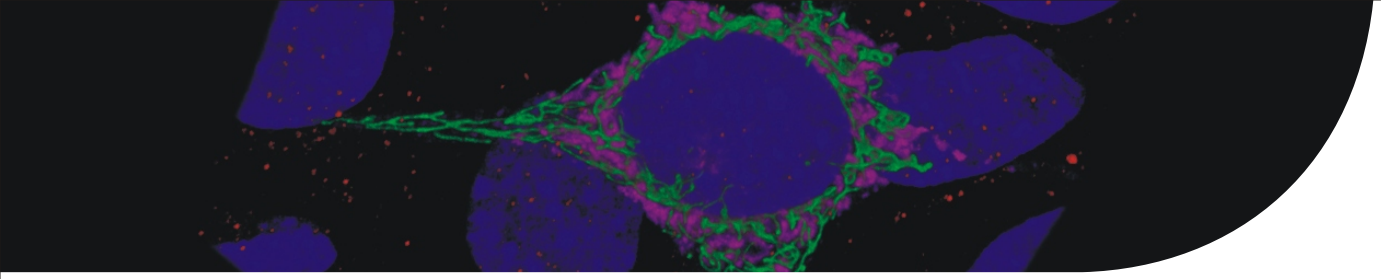
- To develop a non-invasive technique for the identification of a biomarker using MMP13 indicating the early detection of endometriosis.
- Investigating the crosstalk between MMPs to find a specific target to abrogate MMP activity against endometriosis disease progression.
- Studying the interaction between MMP-9 and other proteins which are involved in neurodegenerative disorders to establish the probable link of MMPs in such diseases.

PUBLICATIONS:

1. **Swarnakar S**, Bhattacharya P, Banerjee S & Chatterjee K. (2020) Green Synthesis of Zinc Oxide Nanoparticles via Algal Route and its Action on Cancerous Cells and Pathogenic Microbes. DOI: 10.21467/anr.3.1.15-27
2. Bhattacharyaa P, Mukherjee, D, Deb N, **Swarnakar S** & Banerjee, S. (2020) Application of green synthesized ZnO nanoparticle coated ceramic ultrafiltration membrane for remediation of pharmaceutical components from synthetic water: Reusability assay of treated water on seed germination. J Env. Chem. Eng. 8(3): 103803.
3. Bhattacharjee P, Chatterjee S, Achari A, Saha A, Nandi D, Acharya C, Chatterjee K, Ghosh S, **Swarnakar S** & Jaisankar P. (2020) A bis-indole/carbazole based C5-curcuminoid fluorescent probe with large Stokes shift for selective detection of biothiols and application to live cell imaging. Analyst 45(4): 1184-1189..
4. Subramanian L, Maghajothi S, Singh M, Kesh K, Kalyani A, Sharma S, Khullar M, Victor SM, **Swarnakar S**, Asthana S, Mullasari AS & Mahapatra NR. (2019) A Common Tag Nucleotide Variant in MMP7 Promoter Increases Risk for Hypertension via Enhanced Interactions With CREB (Cyclic AMP Response Element-Binding Protein) Transcription Factor. Hypertension 74(6): 1448-1459.
5. Subhramanian L, Maghajothi S, Singh M, Kesh K, Anantamohan K, **Sharma S**, Khullar M, Victor SM, Swarnakar S, Asthana S, Mullasari A & Mahapatra NR. (2019) A common tag nucleotide variant in MMP7 promoter increases risk for hypertension via enhanced interactions with CREB transcription factor. Bio Rxiv DOI: 10.1101/568774.
6. Bhattacharyaa P, **Swarnakar** S, Ghosh S, Majumdar S & Banerjee S. (2019) Disinfection of drinking water via algae mediated green synthesized copper oxide nanoparticles and its toxicity evaluation. J Env. Chem. Eng 7: 102867.
7. Pramanik SK, Pal U, Choudhary P, Singh H, Reiter RJ, Ethirajan A, **Swarnakar S** & Das A (2019) Stimuli-Responsive Nanocapsules for the Spatiotemporal Release of Melatonin: Protection against Gastric Inflammation. ACS Appl. Bio Mater. Https://doi.org/10.1021/acsabm.9b00236.
8. Raychaudhuri S, Ghosh S, Roy A & **Swarnakar S** (2019) Protective Role of Black Tea Flavonoids Against Ethanol-Induced Gastropathy via Matrix Metalloproteinase Pathway. Ind J. of Clin. Biochem. 34(4): 379-394

BOOK CHAPTERS:

1. Roy T, Mishra V, Mallick S and Swarnakar S. Functional regulation between matrix metalloproteases and cell junction proteins in gastric cancer in the book handbook of oxidative stress in cancer (2020).
2. Deb N, Mallick S, Jaiswal A, Manna A, Mabalirajan U and Swarnakar S. Chapter: Role of matrix metalloproteinase and oxidants in lung diseases. Oxidative stress in lung diseases. Springer (2019).



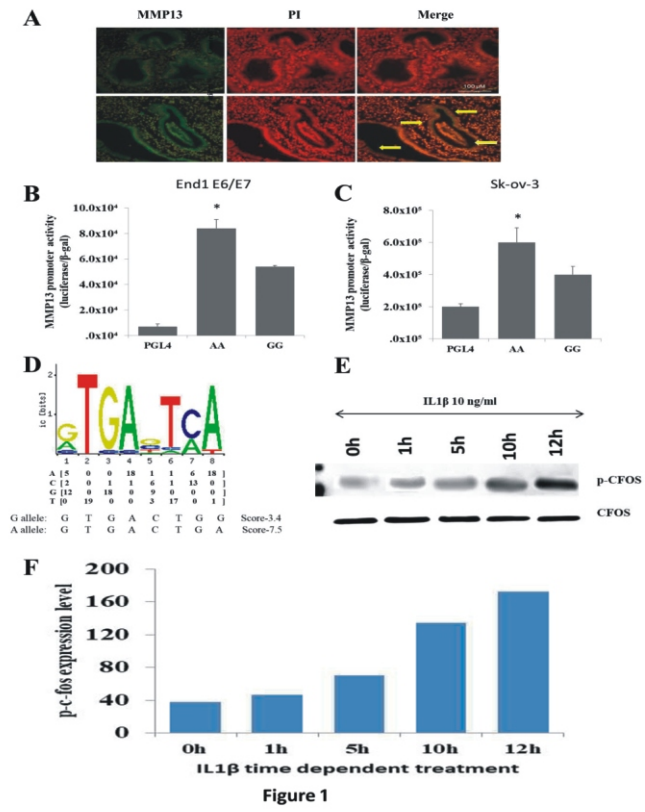


Figure 1

Figure 1. (A) Immunofluorescence staining of endometriotic tissue (B-C) Luciferase assay from cells transfected with A or G allele promoter constructs (D) Propensity of C-fos binding to MMP13 promoter -77 region (E-F) Phosphorylation of c-fos by IL1β induction.

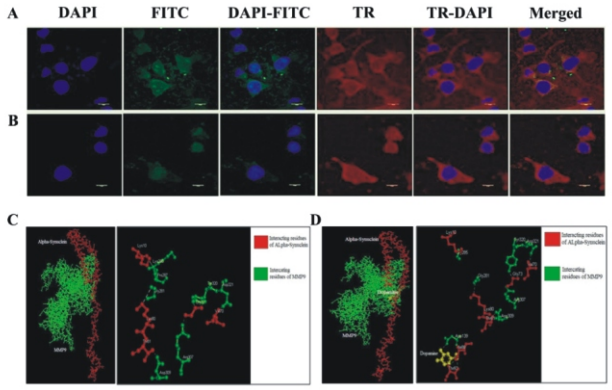
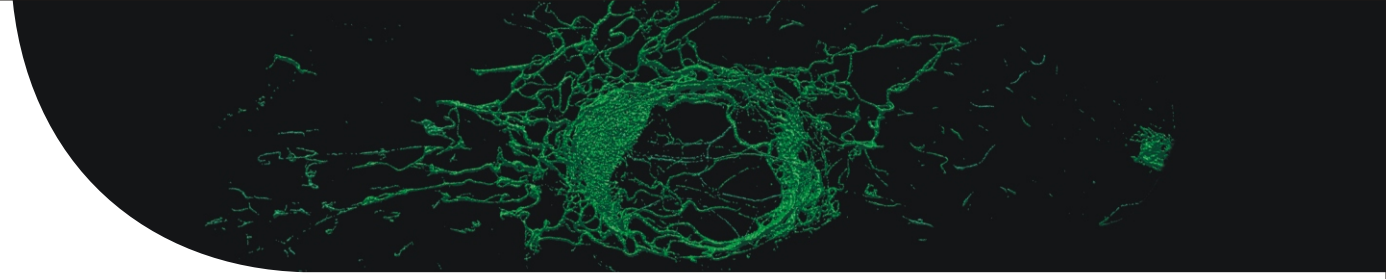


Figure 2

Figure 2. Studying co-localization and interaction of MMP-9 with alpha-synuclein. Localization of alpha synuclein and MMP-9 was analyzed by Confocal microscopy. Cells were treated without (A) or with dopamine (B) for 24 hrs. before imaging alpha synuclein and MMP-9 were probed after primary antibody treatment with Texas red (red) and FITC (green) conjugated secondary antibody respectively. Nuclei were stained with DAPI (blue). (C) Interaction between alpha synuclein and MMP-9 (D) Interaction between alpha synuclein and MMP-9 in presence of dopamine.

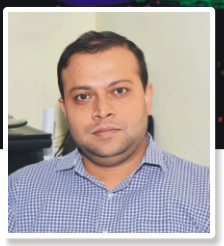


INVITED LECTURES:

1.	**Anti-inflammatory mechanism of a novel flavonoid from neem leaf**	National Conference on drug discovery at Gupta college, Asansol, 6th Apr 2019	Guest lecture & Chairing session
2.	**Orientation of Fulbright scholar for 2018-2019**	Grand Hotel, Kolkata, 11th June 2019	Panel Discussion
3.	**MMP13 polymorphism and endometriosis severity**	JNM Medical College, Kalyani, WB, 21 st June 2019	Invited talk
4.	**Recent advancement and perspective in cancer biology**	Annual Retreat of IICB, 25th June 2019	Panel discussion
5.	**Management of Cystic fibrosis disease**	NIPER- Kolkata, 23rd July 2019	Panel discussion
6.	**Science in everyday life:**	Kendriya Vidyalay, Ballygunge, Kolkata, August 2019	Popular lecture
7.	**An overview of scientific achievement in the journey of own career**	Nehru Yuba Centre, Krishnagar, West Bengal, 5th Sep 2019	Guest Lecture
8.	**Open house program for college students**	CSIR-IICB, Kolkata, 25th September 2019	Popular talk
9.	**Role of protease and gastric inflammation**	Pachunga College, Mizoram, 21st October, 2019	Guest Lecture
10.	**Women Scientists and Enterprieneurs**	5th India International Science Festival, Kolkata, 5-9 Nov 2019	Co-ordinater
11.	**Gene regulation and endometriosis**	Endometriosis meet, Durgapur, 23rd Nov 2019	Chairperson
12.	**Neem leaf extract prevent gastric ulcer: Inhibition of MMP-9 activity**	Indo-US meet, Andaman, 2-8th Dec 2019	Invited Speaker
13.	**Scientific awareness and benefit**	Majdia School, Krishnagar, 10th Jan 20202	Guest lecture
14.	**Therapeutic target for neurodegenerative disease**	NIPER-Bidhan nagar College, Kolkata, 21-22 Jan 2020	Chairing
15.	**Matrix metalloprotease as driver for stress induced gastric ulcer**	SFRR International meet of redox-biology, BARC, Feb 2020	Invited Speaker and chair
16.	**Matrix metalloprotease-7 as key regulator for metastasis in gastric cancer**	International symposium on Cancer, Tezpur, 17th Feb 2020	Invited Speaker and chair
17.	**Matrix metalloproteae-7 driven metastasis**	Advance in Biology 21st Century, Viswa Bharati Univ, 28th Feb '20	Invited Speaker

PRESENTATIONS AT NATIONAL AND INTERNATIONAL SYMPOSIUMS:

1. Diospyros melanoxylon bark extract inhibits leukemic cell growth through mitochondria-mediated apoptosis and MMP regulation. Present Scenario, challenges & Future perspective of Drug discovery & Smart delivery system development". Swarnakar S., et. al. Organized by Gupta College of Technological Sciences, Asansol on 6th April 2019.
2. Immunomodulatory effect of Shorea robusta Resin extract on Raw 264.7 cells. Swarnakar S., et. al. Organized by Gupta College of Technological Sciences, Asansol on 6th April 2019.
3. Dynamics of Macrophage phenotypes in diabetes and heart disease: role of dietary fat. Swarnakar S., et. al. NIPER, Kolkata.



Dr Subhajit Biswas

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

Participants

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

Project Assistant
Tathagata Kayal

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 RNA viruses like dengue virus (DENV).
2. 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

Research had been conducted in connection to a highly competitive and multi-institutional CSIR-Mission Mode Project (MMP) entitled "Nano-Biosensors and Microfluidics for Healthcare". This MMP enabled us to do research and development about the much coveted "Label free, affordable and easy-to-use point of care system for detection of Dengue virus infections in patient sample." We optimized the protocol for the pan-dengue detection in DENV-infected serum samples with pan-dengue probes (p-DENV probe) immobilized on magnetic beads and provisionally e-filed our patent application in India covering this system.

Advantages of our method:

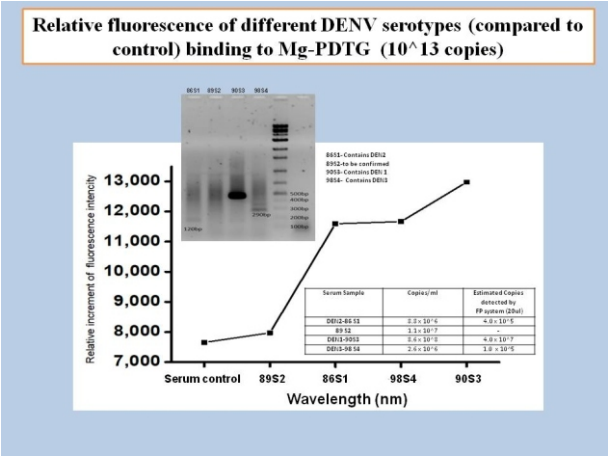
1. Faster than qRT-PCR as no nucleic acid amplification step is involved and it is still semi-quantitative.
2. More adaptable than ELISA as probe sequence can be changed more easily based on changing target (eg. evolving DV strains over seasons) but the same is not so easy for ELISA where antibodies are used for capture and detection.
3. Combination of probes can be used to target different virus/serotypes in a given sample at the same time.
4. Our "molecular probe-based" sensor platform will be an unique approach of nucleic acid hybridization based user -friendly technique. It will be cheaper (currently Rs 400/test), less time consuming and easy to detect the target pathogens.

Future Research Plans

Few DENV-infected sera samples with pre-determined viral load (by qRT-PCR) had been tested using the pan-DENV probe and it was found that the virus RNA load corroborated with the level of fluorescence-based detection. Larger numbers of samples are required to be tested for further clinical validation.

Being the sole virologist in this multi-institutional MMP, I served as the key expert in designing the dengue virus probes (eg. serotype-specific/ pan-dengue etc). I extended 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 have executed all aspects that involved handling and testing of dengue virus samples.

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 RNA viruses like dengue virus (DENV).
2. 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.
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5. Screening of kala-azar samples for the presence of protozoan viruses like LRVs and LepseyNLV1.

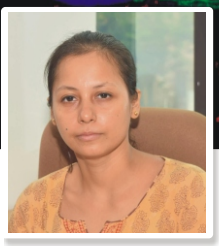
Work Achieved

Research had been conducted in connection to a highly competitive and multi-institutional CSIR-Mission Mode Project (MMP) entitled "Nano-Biosensors and Microfluidics for Healthcare". This MMP enabled us to do research and development about the much coveted "Label free, affordable and easy-to-use point of care system for detection of Dengue virus infections in patient sample." We optimized the protocol for the pan-dengue detection in DENV-infected serum samples with pan-dengue probes (p-DENV probe) immobilized on magnetic beads and provisionally e-filed our patent application in India covering this system.

Advantages of our method:

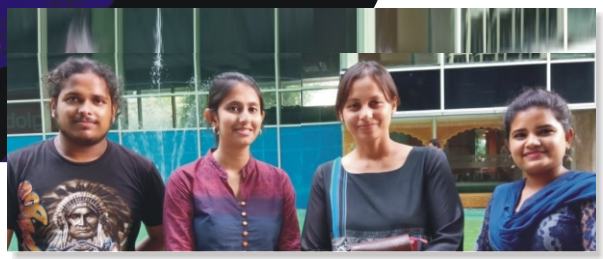
1. Faster than qRT-PCR as no nucleic acid amplification step is involved and it is still semi-quantitative.
2. More adaptable than ELISA as probe sequence can be changed more easily based on changing target (eg. evolving DV strains over seasons) but the same is not so easy for ELISA where antibodies are used for capture and detection.
3. Combination of probes can be used to target different virus/serotypes in a given sample at the same time.
4. Our "molecular probe-based" sensor platform will be an unique approach of nucleic acid hybridization based user -friendly technique. It will be cheaper (currently Rs 400/test), less time consuming and easy to detect the target pathogens.

Future Research Plans



Dr. Upasana Ray

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Understanding the host-virus interactions of Dengue virus structural proteins and non-structural protein NS1

Participants

JRF : Debica Mukherjee, Feroza Begum, Sandeepan Das, Dluya Samuel Thagriki

Aims and Objectives

Cloning expression of Dengue virus NS1 gene of serotypes 1, 2, 3 and 4 in mammalian expression vector.

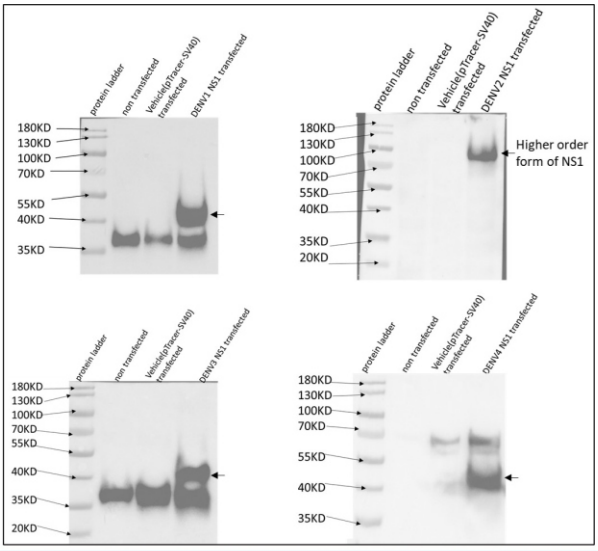
Standardization and verification of expression of NS1 proteins of the four Dengue serotypes in mammalian cell line using western blot and immunofluorescence.

Work Achieved

We cloned Dengue virus NS1 genes with respect to the four serotypes, 1, 2, 3 and 4 in a mammalian expression plasmid pTracer-SV40. The clones were confirmed by PCR and restriction digestions. After validation of all the clones, expression of the clones was checked in mammalian cell line Huh7. For Serotypes 1, 3 and 4 we obtained bands at a molecular weight corresponding to the monomeric form of Dengue NS1 protein (Figure 1). However, for serotype 2 we have observed the multimeric form of NS1. Expression of NS1, serotype 2 could be verified by immune-fluorescence as well as using anti-NS1 antibody (Figure 2).

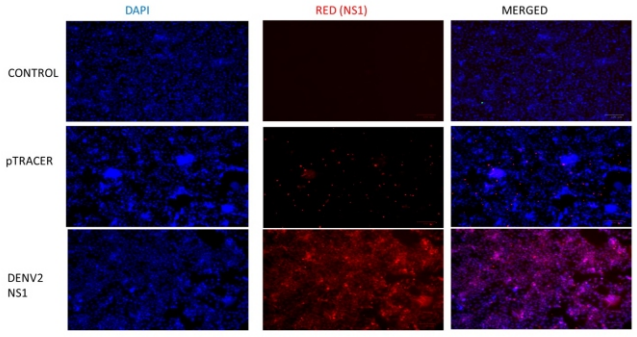
Future Research Plans

In future effect of NS1 on host cell protein expression and cellular transcriptome will be checked. We will check the interaction of NS1 protein with host cell membrane proteins using human endothelial cells and correlate with endothelial leakage. We are also carrying our transcriptomics and mi-RNA sequencing using NGS platform to understand how NS1 regulated the host cell environment.



Western blot to check expression of NS1 of Dengue virus serotypes 1, 2, 3 and in Huh7 cells

Figure 1



Immunofluorescence to check expression of NS1 of Dengue virus serotype 2

Figure 2

Fig. 1: Western blot to check expression of NS1 of serotypes 1, 2, 3 and 4 in Huh7 cells

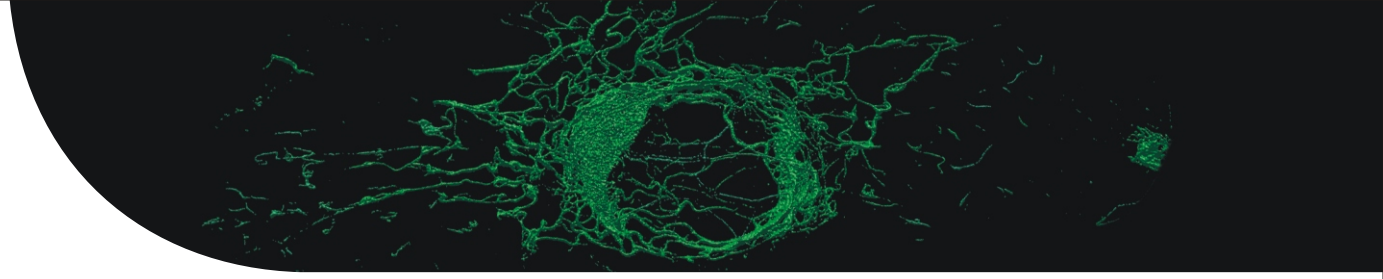
Fig. 2: Immuno-fluorescence study to check expression of NS1 of serotype 2

AWARDS / HONOURS / MEMBERSHIPS

1. **SERB Women Excellence award**, SERB, 2019.
2. **ILDC-AMP Women excellence award**, International Leadership Development Council, March 2020

EXTRAMURAL FUNDING

1. 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)

2. Scanning through the molecular interactome of Dengue virus NS1 protein and host cell factors (miRNA, mRNA and proteins) to identify potential targets for anti-Dengue antivirals. 2019-2022 (Funding Agency: SERB)

CONFERENCES / WORKSHOPS

Organizing committee member of IISF: India International Science Festival. Organized Engineering Science Expo (organized and handles stage/ anchoring) and Wellness Conclave and Expo (6.11.2019-7.11.2019) (Scientific Discussion management team). Managed and performed stage anchoring for all the days for the Engineering Science Expo at IICB-TRUE campus, Salt Lake.



Dr. Sujoy K Das

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Biofabrication strategies to construct 3D scaffold for bacterial infection control and tissue engineering application

Participants

JRF : Ms. Somashree Bose, Ms. Chandrika Boddety

Background:

Uncontrolled hemorrhage is the leading cause of death due to excessive loss of blood. Bacterial infection at the wound sites often delayed wound repair and even leading to life-threatening sepsis. Full thickness skin injuries including road traffic injuries are a major source of mortality and morbidity for civilians with an estimated 7 million people died globally every year. Therefore, effective hemorrhage control, infection prevention and rapid wound closure plays a vital role in prevention of hypertrophic scarring and saving the life of millions of people.

Biofabrication techniques have opened new windows and perspectives in tissue engineering and regenerative medicine (TERM) applications. Our research group is actively involved in designing of nanobiomaterial based advanced 3D hydrogel scaffold through biofabrication concept for hemorrhage control and wound healing application.

Aims and Objective:

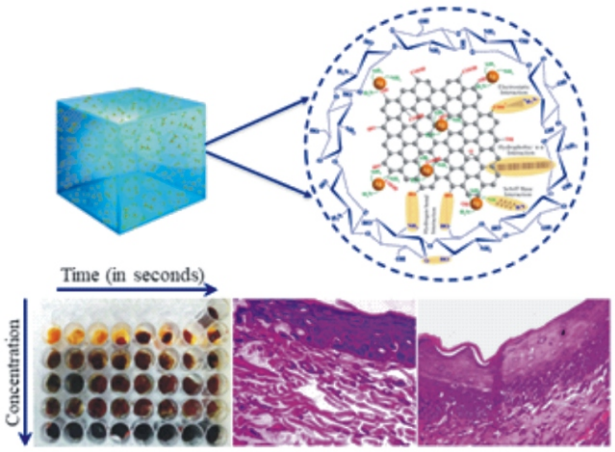
Development of nanobiomaterial based biofabricated 3D hydrogel scaffold using safe-by-design approach.

Understanding the microstructure, physicochemical properties including mechanical behavior, and cell viability.

Applications of the 3D hydrogel scaffold in blood clotting, bacterial infection control, and wound healing management.

Work Achieved:

Biomaterial reinforced multifunctional graphene nanocomposite based hydrogel scaffolds have been prepared through in-situ gelling process adopting safe-by-design concept. The nanobiocomposite scaffolds exhibited excellent mechanical strength, porosity, and fluid absorption capacity.The nanobiocomposite scaffold stops bleeding within 60 s. Further, the



nanobiocomposite scaffold demonstrated profound antibacterial activity against Gram negative and Gram positive bacteria. The reactive oxygen species (ROS) generation and electrostatic interaction of nanocomposite scaffold with bacterial cells caused the physical disruption of the cells.The in vivo results showed skin contraction, and the histological examination revealed the regeneration of skin tissue. The obtained information provided a novel safe-by-design concept for fabrication of nanobiocomposite scaffolds and demonstrated potential development of antibacterial hemostatic and wound dressing in traumacare management

This work has been published in ACS Biomater. Sci. Eng. 2020,6,5911-5929 (I.F. 4.49).

Future Research Plans:

Nanomaterial based delivery of antimicrobial peptide to prevent bacterial infection

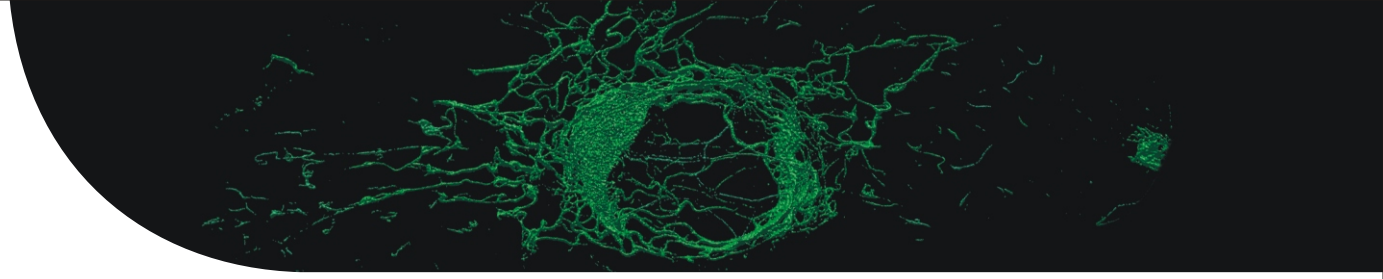
Photothermal therapy for infected wound management

PUBLICATIONS

Choudhary, P., Ramalingam, B. **Das, S. K*.** Fabrication of chitosan-reinforced multifunctional graphene nanocomposite as antibacterial scaffolds for hemorrhage control and wound-healing application. ACS Biomater. Sci. Eng. 2020, 6,6599-5929 (I.F. 4.49).

Book Chapters / Invited Reviews:

Parandhaman, T., Dey, M. D., **Das, S. K***.Biofabrication of supported metal nanoparticles: exploring the bioinspiration strategy to mitigate the environmental challenges. Green



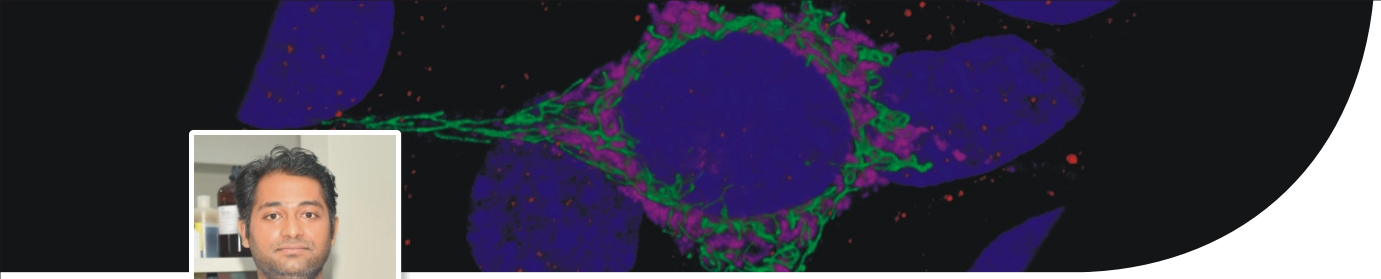
Chemistry 2019, 21, 5469-5500 (I.F. 9.48)

AWARDS / HONOURS / MEMBERSHIPS
Faculty
Scientist's Name Surname: Sujoy K Das

Awards / Honours
Editorial Board: Enzyme and Microbial Technology (Elsevier Journal, I.F. 3.448)

MEMBERSHIPS:
Royal Society of Chemistry (MRSC)
Royal Society of Biology (MRSB)
American Chemical Society

EXTRAMURAL FUNDING
Principle Investigator: Sujoy K Das
Funding Agency: SERB, Govt. of India





Dr. Sudipta Das

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Role of ribosomal P-proteins in the asymmetric nuclear division of Plasmodium falciparum: A potential therapeutic intervention.

Participants

Dr. Sudipta Das

Students

Mr. Bhaskar Roy
Mr. Saswata Chakraborty

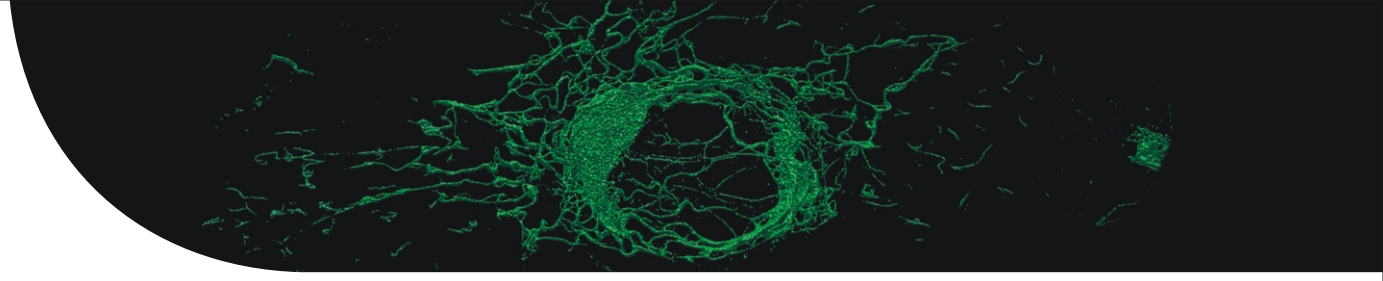
Introduction

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 (1). 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 (13), 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 (13), (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 (15). Palmitic and oleic acids depleted serum did not support parasite growth and that resulted into the arrest of cell division (15). 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. 2 Disha 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. (16, 17, 18). 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 (19, 20). 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 intraerythrocytic development. 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.

Publication

Non-ribosomal insights of ribosomal P proteins in Apicomplexan parasites. Bhaskar Roy, Saswata Chakraborty & Sudipta Das# (# Correspondence) (Under revision)

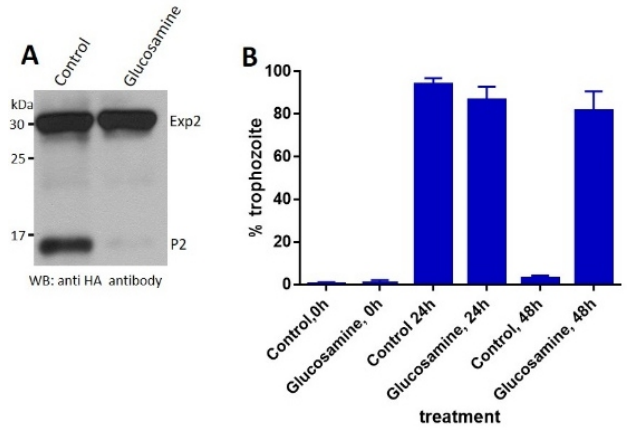


Fig. 1 (A) P2-HA-Ribozyme transfected transgenic parasite was treated with 5mM glucosamine in cRPMI for 24h (ring to trophozoite). Parasites were harvested by gentle saponin lysis. SDS-PAGE and Immunoblot was probed with HA antibody. Exp2 was used as a loading control. (B) Quantitation of arrested trophozoite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

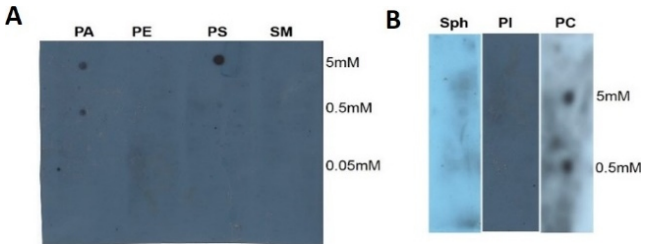


Fig.2 (A&B) Three different concentration of Phosphatidic acid (PA), Phosphatidyl ethanolamine (PE), Phosphatidyl serine (PS), Sphingomyelin (SM), Sphingosine (Sph), Phosphatidyl inositol (PI), Phosphatidyl choline (PC) were blotted and incubated with recombinant P2 protein. Subsequently, P2 protein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

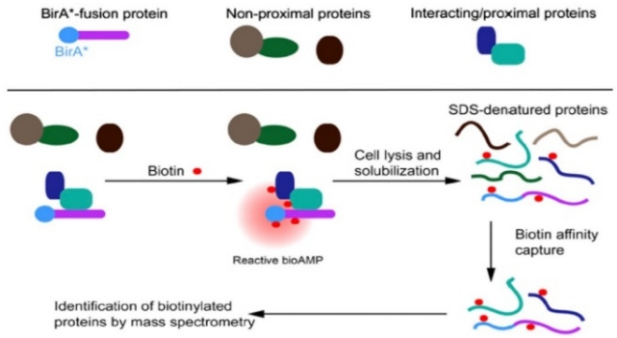


Fig. 3 Schematic of proximity-biotinylation method. In a cell expressing a protein fused with BirA*, biotin addition results in its activation and biotinylation of interacting and proximal proteins while non-proximal proteins are not labeled. Affinity capture of biotinylated proteins can be followed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



Dr. H. K. Majumder
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Targeting DNA topoisomerases in kinetoplastid parasites as key players in DNA metabolism and inducing cell death by inhibitors of DNA topoisomerases.

Background and work achieved

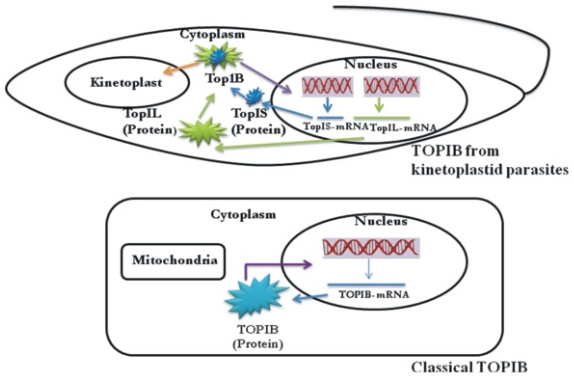
Topoisomerases are a group of enzymes that resolve DNA topological problems and aid in different DNA transaction processes viz. replication, transcription, recombination, etc. inside cells. These proteins accomplish their feats by steps of DNA strand(s) scission, strand passage or rotation and subsequent rejoining activities. All organisms, including unicellular pathogens, compulsorily possess DNA topoisomerases for successful nucleic acid metabolism. But particular subtypes of topoisomerases exist, in all prokaryotes and in some unicellular eukaryotes, that are absent in higher eukaryotes. Moreover, topoisomerases from pathogenic members of a niche possess some unique molecular architecture and functionalities completely distinct from their nonpathogenic colleagues. Topoisomerases of kinetoplastid parasites have been extensively studied because of their unusual features. The unique presence of heterodimeric Type 1B topoisomerase and prokaryotic 'TopA homologue' Type 1A topoisomerase in kinetoplastids still generate immense interest among scientists. Moreover, because of their structural dissimilarity with the host enzymes, topoisomerases of kinetoplastid parasites are attractive targets for chemotherapeutic interventions to kill these deadly parasites.

This group of parasites have been found to possess a structurally “unique” topoisomerase, the “unusual bi-subunit” type 1B topoisomerase (LdTOP1B). In all other organisms, this subtype of topoisomerase is a single-subunit enzyme. This structural distinction has made this trypanosomatid enzyme an excellent target for investigation. Structural and functional dissection of this unusual enzyme from Leishmania spp. and Trypanosoma spp. have strongly helped drug development research to move forward. Along with this bi-subunit enzyme, our laboratory has been engaged for last three decades in characterizing different other topoisomerases present in Leishmania donovani, a member of trypanosomatid protozoa family. We have also been identifying and validating molecules, both from synthetic and natural origins, that target different DNA topoisomerases of L. donovani. Many of such molecules have been found to exert strong antileishmanial activity in experimental mice model of visceral leishmaniasis. Some of them are potent against Trypanosoma spp. in vitro. A number of synthetic and natural compounds have been identified as eukaryotic topoisomerase inhibitors. Some of them target human topoisomerase whereas few have been established as inhibitors of Leishmania donovani topoisomerases. The compounds tested from our lab which inhibit type 1B topoisomerase of L. donovani (LdTOP1B) are (i) Voacamine, an indole alkaloid isolated from plant Tabernaemontana coronaria(SR Chowdhury et. al., 2017), and (iii) Cadambine (SR Chowdhury et. al., submitted). An isobenzofuranone compound JVPH3, inhibitor of type 2 topoisomerase of L. donovani (LdTOP2) (SR Chowdhury et. al., 2018) also had been successfully tested in our laboratory. Additionally, through collaboration with the laboratory of Prof. Wanderley De Souza, Universidade Federal Do Rio De Janeiro, Brazil, we have evaluated the cytotoxicity and ultrastructural alterations caused by Voacamine, Cadambine and JVPH3 in two Brazilian parasites L. amazonensis and T. cruzi.

Future Research Plan

Detailed mechanism of action of the topoisomerase inhibitor molecules and phenotypic changes occurring in the parasites need to be extensively investigated.

Figure 1. Basic Structural Differences between Type 1B Topoisomerases from Kinetoplastid Protozoa and All Other Organisms. Kinetoplastid parasites encode two different subunits (large and small) from two different chromosomes, which interact with each other in the cytoplasm giving rise to the active heterodimeric enzyme. This, in turn, localises both to the nucleus and mitochondria. All other organisms encode a single subunit enzyme (referred to as classical Top1B), which localises solely to the nucleus. Top1B, Type 1B topoisomerase.



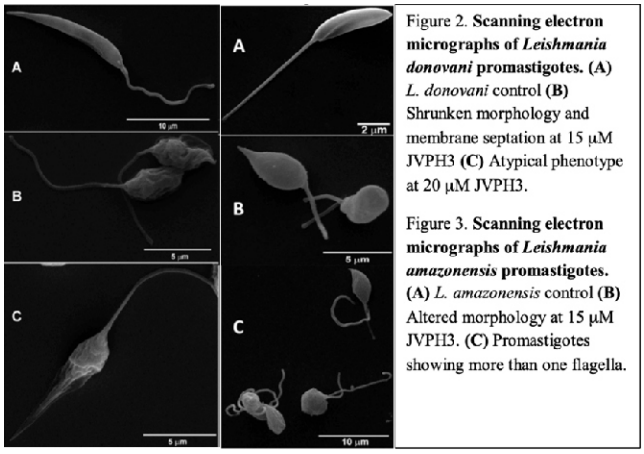


Figure 2. **Scanning electron micrographs of *Leishmania donovani* promastigotes. (A)** *L. donovani* control **(B)** Shrunken morphology and membrane septation at 15 μM JVPH3 **(C)** Atypical phenotype at 20 μM JVPH3.

Figure 3. **Scanning electron micrographs of *Leishmania amazonensis* promastigotes. (A)** *L. amazonensis* control **(B)** Altered morphology at 15 μM JVPH3. **(C)** Promastigotes showing more than one flagella.

PUBLICATIONS (2019-2020)

Karunakaran, J., Moorthy, N. D., Chowdhury, S. R., Iqbal, S., Majumder, H. K., Gunasekaran, K., Vellaichamy, E., Mohanakrishnan, A. K. (2019) Divergent Synthesis and Evaluation of the in vitro Cytotoxicity Profiles of 3,4-Ethylenedioxythiophenyl-2-propen-1-one Analogues. ChemMedChem 14(15), 1418-1430.

BOOK CHAPTERS & REVIEWS (2019-2020)

Saha, S., Chowdhury, S. R., Majumder, H. K. (2019) DNA Topoisomerases of Kinetoplastid Parasites: Brief Overview and Recent Perspectives. Curr Issues Mol Med 31, 45-62.

Chowdhury, S. R., Majumder, H. K. (2019) DNA Topoisomerases in Unicellular Pathogens: Structure, Function, and Druggability. Trends Biochem Sci 44(5),415-432.

Chowdhury, S. R., Gupta, V. K., Majumder, H. K. (2020) Chapter 11 - Targeting DNA topoisomerases in parasitic protozoa by natural products: Chemical and biological perspectives. Studies in Natural Product Chemistry 67, 389-410.

Ph.D Degree Awarded

Somenath Roy Chowdhury was awarded Ph.D on 23/3/2019

AWARDS

Faculty

- Chancellor's Nominee for the Court of Kalyani University
- Member of the Board of Studies in Department of Microbiology, Lady Brabourne College, Kolkata
- Honorary Director, The Advanced Research Centre, Department of Microbiology, Lady Brabourne College, Kolkata
- Adjunct Professor, Department of Biophysics, Molecular Biology & Bioinformatics, University of Calcutta
- Sir C. V. Raman Birth Centenary Award (2019) by Indian Science Congress Association at 106th Indian Science Congress, Lovely Professional University, Jalandhar, January 3 – 7 , 2019.
- President, NASI Local Chapter, Kolkata.
- Selected as Council Member, Indian National Science Academy (INSA), New Delhi.
- Convener INSA Local Chapter, Kolkata.

Students

Somenath Roy Chowdhury

- European Molecular Biology Organization (EMBO) TRAVEL GRANT of 500 EURO for attending EMBO Workshop on DNA Topology & Topoisomerases in Genome Dynamics, Les Diablerets, Switzerland, September 16 – 20, 2019 (2019)
- Shortlisted for Indian National Science Academy (INSA)-MEDAL FOR YOUNG SCIENTISTS 2019 in ANIMAL SCIENCES (Among TOP 7 shortlisted candidates across India) (2019)• BEST ORAL PRESENTATION AWARD in 7th-International Symposium on Current Trends in Drug Discovery Research (CTDDR) organized by February 20-23, 2019 at CSIR-Central Drug Research Institute, Lucknow (2019)
- Professional Enhancement Grant worth Rs. 80,000/- INR by TATA EDUCATION & DEVELOPMENT TRUST to Somenath Roy Chowdhury, September 2019 for attending.



Dr. Nahid Ali

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Background and work achieved:

Visceral leishmaniasis (VL) is one of the leading infectious diseases affecting developing countries. We have holistically tried to target for eventual elimination of Leishmaniasis by working for its diagnosis, therapeutics, vaccine strategy, understanding the host-pathogen mechanism and the changes in immunological parameters in diseases and treated conditions for almost three decades.

We have previously reported the diagnostic potential of leishmanial antigen in the diagnosis of the diseases from Serum and Urine samples of patients. A recent study was designed to validate a serum-based dipstick test in eight centers of six countries, India, Nepal, Sri Lanka, Brazil, Ethiopia and Spain with archived and fresh sera from 1003 subjects. The overall sensitivity and specificity of the test with 95% confidence intervals were found to be 97.10% and 93.44%, respectively. The test showed good sensitivity and specificity in the Indian subcontinent (>95%). In Brazil, Ethiopia, and Spain the sensitivity and specificity of the dipstick test (83.78-100% and 79.06-100%) were better as compared to the earlier reports of the performance of rK39 rapid test in these regions. Interestingly, less cross-reactivity was found with the cutaneous form of the disease in Spain, Brazil, and Sri Lanka demonstrating 91.58% specificity. This dipstick test can therefore be a useful tool for diagnosing VL from other symptomatically similar diseases and against cutaneous form of leishmaniasis.

Chronic visceral leishmaniasis is manifested with severe immunosuppression. Role of immunosuppressive cytokines and precise cellular sources during progressive VL is still not completely understood. Along with IL-10 and TGF-β, we investigated a newly discovered IL-12 family cytokines, IL-35.These revealed a progressive elevation during infection of Leishmania donovani in BALB/c mice. These cytokines were mainly secreted from Treg cells and have been associated with down-regulation of immuno-protective cytokines like IFN-γ and TNF-α response in advanced disease. Neutralization of EBI-3 subunit of IL-35 along with TGF-β is pre-requisite in suppression of host anti-leishmanial immunity.

Future Plans:

1. Identification of leads for structure based drug designing for Leishmaniasis.

2. Identification of essential virulence factors of L. donovani and L. infantum as potent drug targets in parasitic diseases in India and Brazil.

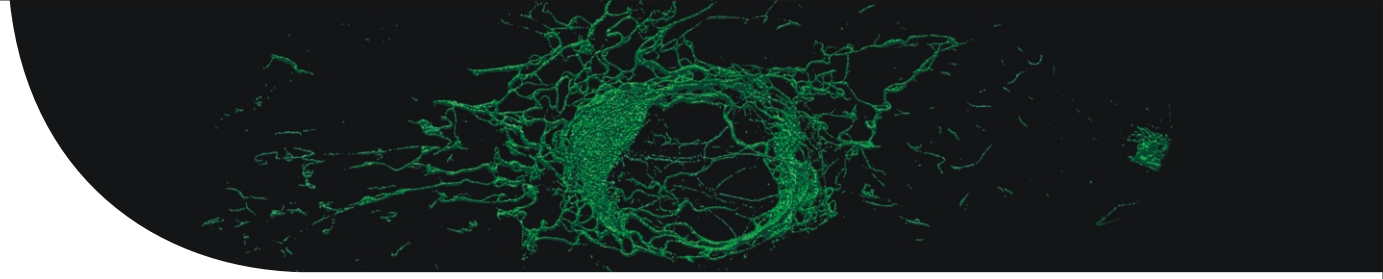
3. Investigating the effects of novel cationic liposome mediated immunotherapy on checkpoint blockade in cancer.

Publications:

1. Sadab, M., Das, S., Banerjee, A., Sinha, R., Asad, M., Kamran, M., Maji, M., Jha, B., Deepthi, m., 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. Frontires in Cellular and Infection Microbiology (9) 1-19.
2. Asad, M., Sabur, A., shadab, M., Das, S., kamran, M., Didwania, N., Ali, N. 2019. EB-I chain of IL-35 along with TGF-B synergistically regulate anti-leishmania Immunity. Frontiers in Immunology (10) 1-12
3. Ejazi, S., Ghosh, S., Saha, S., Thakur Choudhury, S., Bhattacharyya.A., Chatterjee, M., Pandey, K., Das,V.N.R., Das, P., Rahaman, M., ProsadGoswami, R., Rai, R., Khanal, B., Bhattarai, N., Deepachandi, B., Siriwardana, Y., Karunaweera, N. D., deBrito, M. E. F., MirandaGomes, Y. D., Nakazawa, M., Costa, C.H.N., Adem, E., Yeshanew, A., Melkamu, R., Fikre, H., Hurissa, Z., Diro, E., Carrillo, E., Moreno, J. & Ali.N. 2019. A multicentric evaluation of dipstick test for serodiagnosis of visceral leishmaniasis in India, Nepal, Sri Lanka, Brazil, Ethiopia and Spain. Scientific Reports. 9:9932 1-7.

PhD Awarded

Abdus Sabur, 2019 Genetic and Chemical validation of post-translational enzymes of Leishmania donavani. (GCRF)



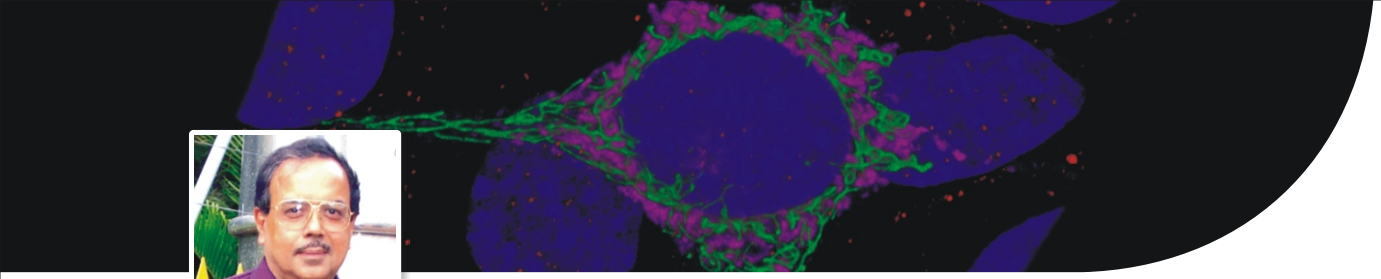
Invited talks

1. Topic: A global network for Neglected Tropical Disease (NTD); Chagas and Leishmania Research : India Hub
   Venue: NTD Network Annual General Meeting 2019 Institut Pasteur de Montevideo,Montevideo, Uruguay, 31st March to 5th April, 2019.
2. Topic: Delivered two lectures on "Leishmania" to NIBMG Graduate Students
   Venue: National Institute of Biomedical Genomics Kalyani, 11th July, 2019.
3. Topic: Challenges in the management of visceral leishmaniasis with an emphasis on diagnosis.
   Venue: National Seminar "Interface of Microbiology and Medicine" at Adamas University West Bengal India, 23rd August, 2019.
4. Topic: Delivered lecture on "Anti-parasitic immune response Leishmania" to CSIR-IICB Phd Students.
   Venue: CSIR-IICB, Kolkata, 22th August, 2019.
5. Topic: "Animal models for infectious diseases" seminar to CSIR-IICB Phd Students
   Venue: CSIR-IICB, Kolkata, 19th September, 2019.

Funding and Ongoing Projects:

1. Received MRC-Global Challenge Research Fund (GCRF) of amount 10,000 GBP (Rs.8,89,600/-) for procurement of Research Instrument under instrument head of pump priming project title " A genomics platform for drug target identification & validation in Leishmania." 2019.
2. Received MRC-Global Challenge Research Fund (GCRF) of amount 10,000 GBP under consumable head and 5,000 GBP under travel head for pump priming project 'Prospects of a liposomal multivalent vaccine formulation against visceral leishmaniasis-Building a Kolkata-Rio de Janerio link into the Global NTD Network'. 2019.
3. Received MRC-Global Challenge Research Fund (GCRF) of amount 37,280 GBP for call-off order for proof of concept funding under work package title "Genetic and chemical validation of post-translational enzymes of Leishmania donovani." 2019.

Researcher name	Position (PhD, PDRA etc)	Title
Sarfaraz Ahmad Ejazi	PDRA	Genetic and Chemical validation of post-translational enzymes of Leishmania donavani
Anand Kumar Gupta	PDRA	Screening and functional characterization of important leishmanial virulence and immunomodulatory factors as putative drug targets – part A
Nicky Didwania	PhD	Development and evaluation of protective efficacy of recombinant multiantigenic liposomal vaccine formulation against experimental visceral leishmaniasis
Mohd Kamran	PhD	Role of Leishmania donovani in exploiting various cellular signaling network and immune mechanism of host for its survival and propagation.
Sonali Das	PhD	Characterization of parasite & host derived immune modulations for regulating macrophage plasticity in VL
Sneha Ghosh	PhD	Investigation of anticancer potentials of immunotherapy directed at PD-1 pathway blockade.
Amrita Das	PDRA	Coupling CTLA-4 vaccine induced immune checkpoint blockade with a potent anti-tumour agent: a novel approach towards cancer immunotherapy.





Dr. Pijush K. Das
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The thorough and sustained research in my laboratory mainly addressed fundamental issues pertaining to macrophage biology especially the robust host defense mechanisms using leishmaniasis as model intra-macrophage disease.Earlier we showed that Leishmania induces differential regulation of programmed cell death 1 receptor (PD-1)in early and late phase of infection. We aimed to address the precise underlying mechanism of how PD-1 activationexploits anti-inflammatory responses to curb host-protective responses. We observed that PD-1 agonist-mediated increased PD-1 signaling negatively impacts the phosphorylation of JNK and STAT1 involving PD-1/SHP axis. Concurrently, the involvements of PD-1/SHP/JNK and PD-1/SHP/STAT1 axes in execution of anti-inflammatory response were also corroborated in the context ofL. donovani infection. Blockade of infection-induced PD-1 pathway also led to activation of ELK1 followed by cFos induction, which again was a downstream consequence of blockade-mediated JNK activation and played a role in clearance of parasite burden, further documenting that PD-1 pathway activation has a detrimental influence on downstream effectors of JNK signaling cascade during late infection which plays an instrumental role in favoring disease progression.All these work have great potential in formulating robust intervention strategies. We also identified key regulatory molecules along with their underlying mechanisms exploited by Leishmaniaincluding A20, UCP2, TRAF3 and SOCS. Earlier we showed that UCP2 (uncoupling protein 2), an inner mitochondrial membrane protein, was up-regulated by Leishmaniato neutralize the harmful effects of ROS generated by host macrophage. Therefore initially we wanted to evaluate and characterize the therapeutic effect of genipin, (aglycone derivative from Gardenia jasminoides), a specific inhibitor of UCP2 against visceral leishmaniasis. Detailed studies using in vitro culture modelas well as in vivo animal model of visceral leishmaniasis showed genipin to be highly effective antileishmanial agent. Co-treatment of genipin along with sub-lethal doses of the frontline anti-leishmanial drug, sodium antimony gluconate (SAG) showed marked reduction in spleen and liver parasite burden suggesting potential synergistic use of genipin with marketed anti-leishmanial drugs as effective therapeutic approach against visceral leishmaniasis.

Papers published:

1. Roy, S., Saha, S., Gupta, P., Ukil, A. and Das, P.K. (2019) Crosstalk of PD-1 signaling with the SIRT1/FOXO-1 axis during the progression of visceral leishmaniasis. J. Cell Sci. May 2; 132(9):JCS226274, doi: 10.1242/jcs.226274 [E-Pub ahead of print].

2. Basu, M. and Das P.K. (2019) Role of reactive oxygen species in infection by the intracellular Leishmaniaparasites in Oxidative Stress in Microbial Diseases Eds. Chakraborti, S., Chakraborti, T., Chattopadhyaya, D.J. and Shaha, C. pp 297-314Springer Nature Publications. ISBN 978-981-13-8762-3; ISBN 978-981-13-8763-0 (eBook); https://doi.org/10.1007/978-981-13-8763-0

3. Biswas, A., Bhattacharjee, A. and Das, P.K. (2019). Role of cAMP homeostasis in intra-macrophage survival and infectivity of unicellular parasites like Leishmania in: "Vector-Borne Diseases – Recent Developments in Epidemiology and Control" ISBN: 978-1-83880-022-2. InTechOpen Limited. UK.

4. Gupta, A.K., Roy, S. and Das, P.K. (2020). Anti-leishmanial effect of the natural immunomodulatorgenepin through suppression of host negative regulatory protein UCP2. J. Antimirobial. Chemother. …https:doi.org/10.1093/jac/dkaa406.(in press).

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 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 study the molecular basis of genetic disease and 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 : Debduti Dutta
SRF : Bartika Ghoshal, Avijit Goswami, Dipayan De, Satarupa Ganguly, Saikat Banerjee, Susanta Chatterjee, Diptankar Banerjee

JRF : Syamantak Ghosh, Sourav Homchoudhury, Ishani Bannerjee, Shreya Bhattacharya, Shreemoyee Chakraborty, Sritama Roy

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.

Aims and Objectives

Maintaining inflammatory homeostasis is an important event in immune cells. Macrophages, that act as first line defence against any invading pathogens, need to show balanced immune response to safeguard themselves from self-destruction at the time of pathogen killing. Parasites like Leishmania have developed clever strategy to evade the immune sentinels and continue to propagate within macrophages. Sodium stibogluconate (SSG)-resistant clinical isolates are of serious clinical concern as they shifted the immune balance of the infected macrophage more towards a strong anti-inflammatory one. How to stimulate the infected macrophage to a pro-inflammatory setting to clear the residing drug-resistant pathogens is a major challenge from the clinical point of view.

Work Achieved

We have identified two major players HuR, a miRNA depressor protein, and PP2A, a phosphatase that favours the pro or anti-inflammatory responses, respectively. During Ld infection, the parasite reciprocally modulates HuR and PP2A which ensure parasite survival

within the macrophage. Although HuR overexpression could successfully control the drug-sensitive strain of Leishmania (LdS), it was not sufficient alone to clear the resistant form (LdR). HuR restoration along with PP2A inhibition however effectively counters the strong antiinflammatory response induced by LdR. Interestingly, both the factors work by influencing the phosphorylation of miRNA effector protein Ago2 to regulate miRNA activity against target cytokines. Our data suggest intricate regulation of inflammatory response by PP2A and HuR that works primarily by modulating Ago2 phosphorylation during infection and inflammation. This might hold true for any disease that involves alteration of inflammatory homeostasis. Therefore, HuR and PP2A would be new drug targets not only to treat inflammatory diseases but also to affect anti-inflammatory responses during invasion of host cells by pathogens like Leishmania or mycobacterium

Future Research Plans

Interestingly, a new role of miRNA exporter HuR in inflammatory

process has been resolved here. Therefore, HuR and PP2A would be new drug targets not only to treat inflammatory diseases but also to affect anti-inflammatory responses during invasion of host cells by pathogens like Leishmania or mycobacterium. We are Eager to find how mechanistically the cross talk between HuR, miRNA and other regulatory proteins occours. We also aims to develop anti-HuR chemical to be susued as modulator of miRNA function in immune cells.

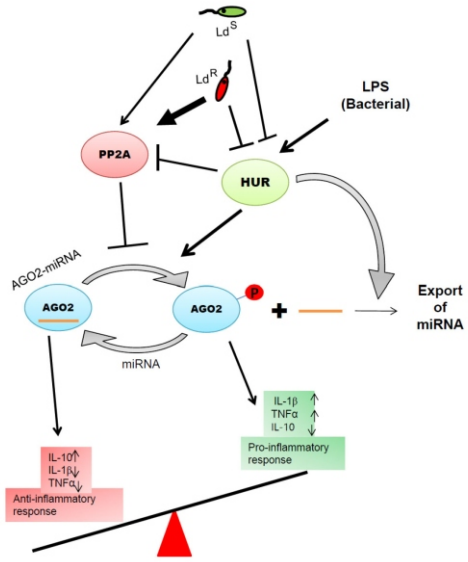


Fig. 1: The model depicts inter-regulatory balance between PP2A and HuR in controlling pro-inflammatory and anti-inflammatory response by altering Ago2 phosphorylation–dephosphorylation cycle and exosomal export of miRNAs in mammalian macrophage cells. Left half of the model shows lipopolysaccharide (LPS)-induced PP2A upregulation via TLR4 pathway during late hours of treatment which results in Ago2 dephosphorylation. Right half of the scheme represents Leishmania-induced PP2A increase mediated by membrane glycolipid lipophosphoglycan (LPG). Interestingly, the RNA binding protein HuR plays a central role in both the contexts. Inhibitory effect of HuR on PP2A ensures phosphorylated form of Ago2 to dominate which in turn facilitates miRNA unbinding to Ago2 and miRNA export via exosome thereby promoting pro-inflammatory cytokine response. On the contrary, Ld induced downregulation of HuR via a zinc-metalloprotease, GP63 which results in PP2A upregulation that facilitates anti-inflammatory response necessary for the parasite survival and proliferation.

PUBLICATIONS

Research papers

1. Goswami A, Mukherjee K, Mazumder A, Ganguly S, Mukherjee I, Chakrabarti S, RoyS, Sundar S, Chattopadhyay K, Bhattacharyya SN. MicroRNA exporter HuR clears the internalized pathogens by promoting pro-inflammatory response in infected macrophages(2020) EMBO Mol Med. Feb 7:e11011. IF:11.0;
2. Bose M, Chatterjee S, Chakrabarty Y, Barman B, Bhattacharyya SN. Retrograde trafficking of Argonaute 2 acts as a rate-limiting step for de novo miRNP formation on endoplasmic reticulum-attached polysomes in mammalian cells(2020) Life Sci Alliance. 3(2)pii: e201800161.

AWARDS / HONOURS / MEMBERSHIPS

Khosla Anational Award in Science by IIT Roorkee

CONFERENCES / WORKSHOPS

Presented an selected talk in the Annual Meeting of International Society of Extracellular Vesicles in Kyoto Japan 24-29th April, 2019

Chaired a session in the Annual Meeting of International Society of Extracellular Vesicles in Kyoto Japan 24-29th April, 2019

INVITED TALKS BY CSIR-IICB FACULTY

Presented an invited talk in INSPIRE camp in JBNSTS Science Orientation Workshop (May 29-31, 2019).

Presented a talk in the scheme evaluation meeting for the 'Basic Research In Modern Biology' programme on 16th July'2019 at Dept of Biotech Govt of India

Presented the Prof. G. K. Manna Memorial Lecture at the 19th All India Congress of Genetics and Genomics (formerly known at All India Congress of Cytology and Genetics) and a Special International Symposium on “Air Pollution and Its Impact on Human Health” which will be held from December 2-4, 2019 at the CSIR-Indian Institute of Chemical Biology, Kolkata-700032.

Presented the Khoshla National Award Lecture presented at IIT Roorkee on 19th February 2020.

Presented an Lecture in CSIR-IIP Dehradun on 20th February 2020



Dr. Debabrata Biswas

dbiswas@iicb.res.in



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

Participants

JRF: Prathama Talukdar, Sushrita Roymuhury, Avik Ghosh, Arnab Ghosh
SRF: Sujay Pal, Arijit Nandy, Subham Basu, Nidhi Kumari, Dheerendra Pratap Mall, Md. Abul Hassan

Collaborator(s)

Name of collaborator outside CSIR-IICB

Dr. Benubrata Das
IACS, Kolkata

Dr. Shweta Tyagi
CDFD, Hyderabad

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.

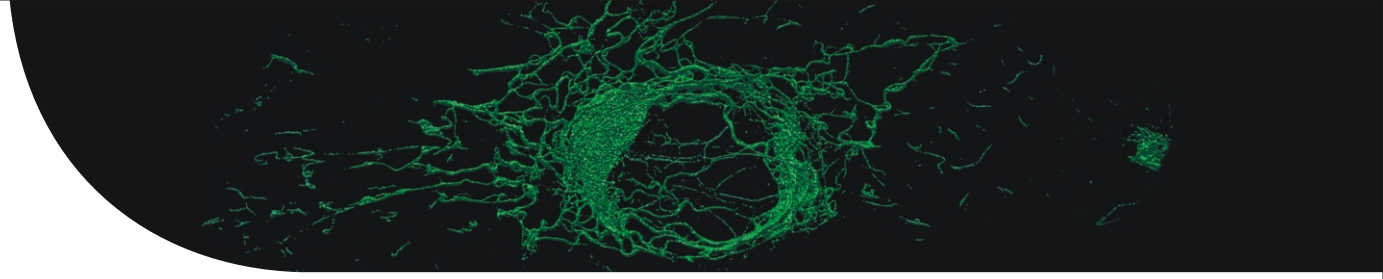
Aims and Objectives

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
Temporal regulation of functions of SEC through post-translational modification of AFF1

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 of the Super Elongation Complex (SEC) components, ELL1 (also known as ELL) is the only bona fide elongation factor that directly stimulates transcription elongation by RNA polymerase II. However, the mechanism(s) of functional regulation of ELL1 (referred to as ELL hereafter), through its stabilization, is completely unknown. Here, we report a function of human DBC1 in regulating ELL stability involving HDAC3, p300, and Siah1. Mechanistically, we show that p300-mediated site-specific acetylation increases, whereas HDAC3-mediated deacetylation decreases, ELL stability through polyubiquitylation by the E3 ubiquitin ligase Siah1. DBC1 competes with HDAC3 for the same binding sites on ELL and thus increases its acetylation and stability. Knockdown of DBC1 reduces ELL levels and expression of a significant number of genes, including those involved in glucose metabolism. Consistently, Type 2 diabetes patient-derived peripheral blood mononuclear cells show reduced expression of DBC1 and ELL and associated key target genes required for glucose homeostasis. Thus, we describe a pathway of regulating stability and functions of key elongation factor ELL for expression of diverse sets of genes, including ones that are linked to Type 2 diabetes pathogenesis (Fig. 3).

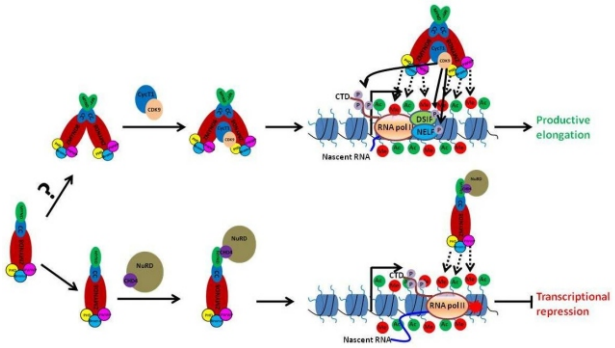
AFF1 acetylation by p300 temporally inhibits transcription during genotoxic stress response

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.

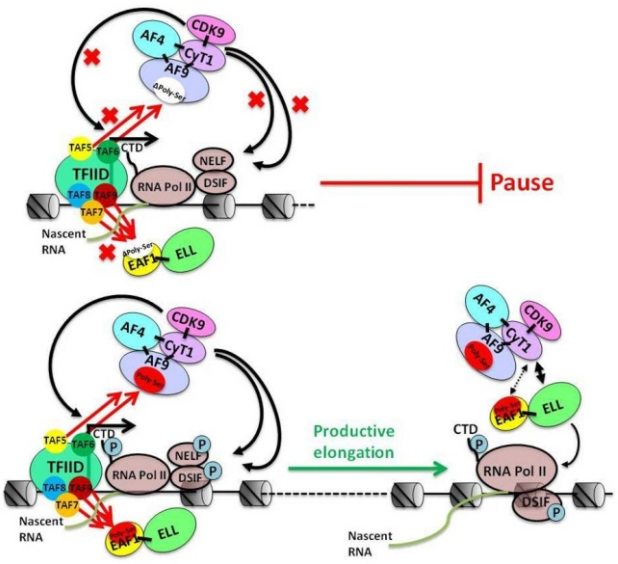
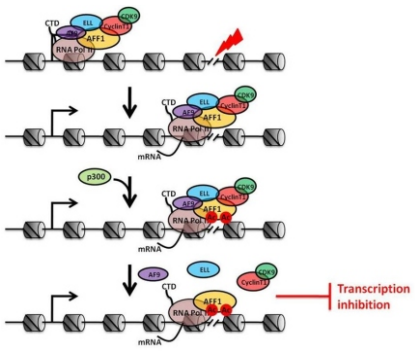


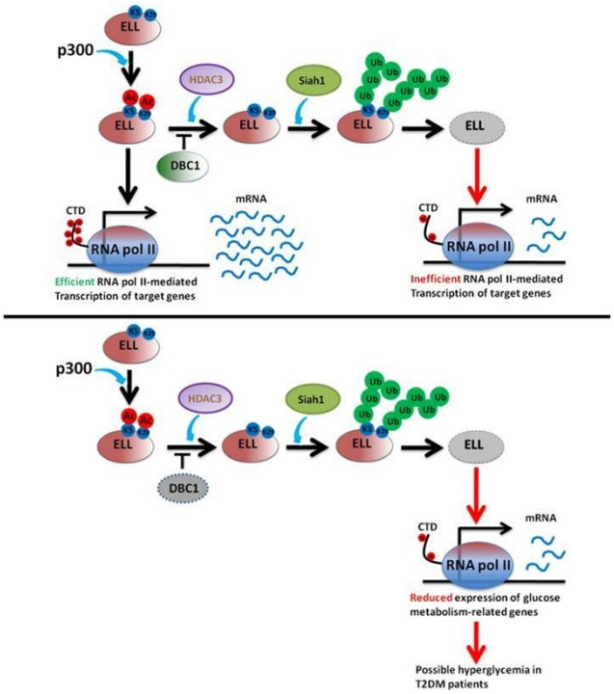
Fig. 3: Cartoon diagram showing the overall model of the role of p300-mediated acetylation, DBC1-mediated acetylation protection, HDAC3-mediated deacetylation and subsequent Siah1-mediated degradation in maintaining ELL level for proper expression of target genes that are strongly associated with glucose homeostasis in healthy individuals. A down-regulation of upstream DBC1 in these processes, lead to decreased ELL level through HDAC3-mediated degradation and thus possibly lead to decreased expression of key genes required for glucose homeostasis



in healthy individuals, and thus indicating a possible involvement of this mechanism of hyperglycemia in Type 2 diabetes patients.

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.

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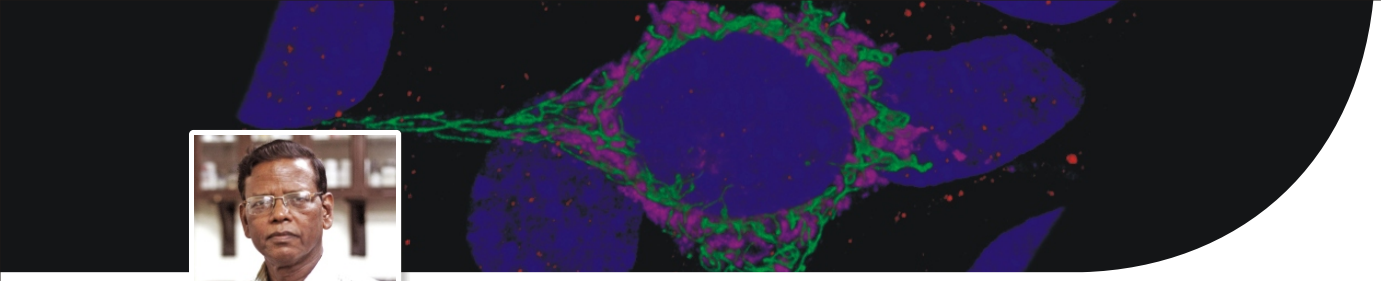
Arijit Nandy, Subham Basu, Mahesh K. Barad, and Debabrata Biswas: Critical role for ELL-associated factor 1 and 2 in regulating SEC abundance and functions through regulation of ELL stability (Manuscript under preparation).

Extramural Funding:

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

CONFERENCES / WORKSHOPS

1. DBC1, p300, HDAC3 and Siah1 coordinately regulate ELL stability and function for expression of Type 2 diabetes-linked genes: AOGCR - Institute of Mathematical Sciences, Chennai - Jan 2020





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Role of WNT and WISP in Health and Disease.

Participants

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1. Identification of miRNAs contributing to arsenic induced skin lesions and skin cancer and other diseases.

More than 60 million people in 7 states of India are affected by the ground water arsenic contamination. Arsenic is an exclusive human carcinogen and not induced cancer in animal model. For this reason the mechanism of arsenic induced cancer is still unknown. It is assumed that epigenetic dis-regulation plays an important role in arsenic induced carcinogenesis. Previously we have reported that miR21 has a significant role in arsenic induced skin lesions and non dermatological effects like respiratory diseases. We have also reported that up-regulation of miR-29a was closely associated with arsenic induced peripheral neuropathy via the beta-catenin axis. In this study our aim was to identify whether microRNAs (miRNA) have any role to play in causing such arsenic susceptibility.

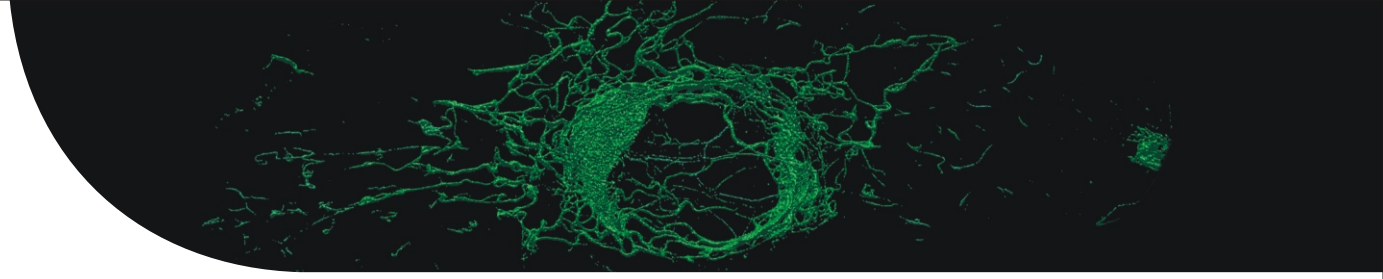
Global plasma miRNA profiling was done in 12 arsenic exposed individuals with skin lesions and 12 exposed individuals without skin lesions. 202 miRNAs were found to be differentially regulated between the two study groups. The results were validated by quantitative real time PCR in 30 exposed subjects from each of the groups, which showed that among others, miR-21, miR-23a, miR-27a, miR-122, miR-124, miR-126, miR-619, and miR-3613 and were significantly up regulated and miR-1282 and miR-4530 were downregulated in the skin lesion group compared to the no skin lesion group. Bioinformatic analyses predicted that these altered miRNAs have targets in 7 different biochemical pathways, including Glycerophospholipid metabolism, Colorectal cancer, Glycosphingolipid biosynthesis, T cell receptor signaling and Neurotrophin signaling pathways; Glycerophospholipid metabolism pathway being the most enriched pathway. Association study show that, these microRNAs contribute significantly to the increased prevalence of other non-dermatological health effects like conjunctival irritations of the eyes and respiratory distress in the study subjects (Banerjee et al. 2019).

2. Epigenetic regulations in alternative telomere lengthening:

Telomere integrity is considered to be one of the important cause of malignancy. We have explored the role of epigenetic deregulationin alternative lengthening of telomeres (ALT) in arsenic-exposed skin cancer tissues and corresponding non-tumor tissues. The relative telomere length (RTL) was analyzed by qRT-PCR using 2–DDCt method. The role of constitutive heterochromatin histone marks in the regulation of telomere length(TL) was analyzed by targeted ELISA. A 2-fold increase of relative telomere length in 85% of the arsenic induced skin cancer tissues was observed. Among the four chromosomes, subtelomere of XpYp was foundto be hypermethylated ($p < 0.001$) where as 18p was hypomethylated ($p < 0.01$). Additionally, the level of H4K20me3, a heterochromatic mark was found to be significantly down-regulated ($p < 0.0003$), and inversely correlated with telomere length indicating loss of heterochromatinization of telomeric DNA.These observations highlight the novel role of epigenetic regulation in the maintenance of constitutive heterochromatin structure at telomere. Alteration in subtelomeric DNA methylation patterns and depletion of H4K20me3might lead to loss of heterochromatinization resulting in arsenic-induced telomericelongation. These data indicating possible alternative determinants of telomere elongationthrough epigenetic modifications and coud be used asearly 'epimarkers' in the near future. The findings provide new insights about the mechanism of arsenic inducedcar cinogenesis (Bhattacharjee et al. 2020).

3. Is Hydroxychloroquine (HCQ) and Chloroquine (CQ) are safe to use as prophylactic drug against COVID-19?

Hydroxychloroquine (HCQ) and Chloroquine (CQ) are two anti-malarial drugs that are now being extensively used by front-line healthcare workers and other common people as a prophylactic drug against the Corona Virus Disease− 19 (COVID-19) in India and as well as in many parts of the world. To date, there are no clinical studies that have established any clinical efficacy of these drugs as a prophylactic. These drugs are commonly used for the treatment of Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) because of its immunomodulatory effects. Thus, we recognize the need to critically review the mutagenic, genotoxic, and immunomodulatory effects of these drugs, to find



out whether it is safe to use as a prophylactic drug against COVID-19. Existing literature suggests that CQ can induce mutagenic and genotoxic effects in multiple test systems and both the drugs have immunomodulatory effects. Both HCQ and CQ are immunomodulatory drugs and have the potential to suppress normal immune system activation. This review is written with the sole objective that the reader will be able to recognize the adverse effects of these drugs when consumed by healthy individuals as a prophylactic. Current literature indicates that healthy individuals should refrain from the use of these drugs until further investigation (Giri et al. 2020).

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1. Giri, A., Das, A., Sarkar, A. K. and Giri, A. K. (2020). Mutagenic, Genotoxic and Immunomodulatory Effects of Hydroxychloroquine and Chloroquine: a Review to Evaluate its Potential to Use as a Prophylactic Drug Against COVID-19, Genes and Environment. 42: 25, https://doi.org/10.1186/s41021-020-00164-0.
2. Bhattacharjee, P., Das, A., Giri, A. K., and Bhattacharjee, P (2020). Epigenetic regulations in alternative telomere lengthening: Understanding the mechanistic insight in arsenic-induced skin cancer patients. Science of the Total Environment, 704: 135388. Doi:10.1016/j.scitotenv.2019.135388.
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Organic & Medicinal Chemistry Division

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The organic and medicinal chemistry division is the major backbone of the institute, wherein the chemical molecules, for required function, are made and isolated at will. The divisional scientists have expertise in diverse fields of chemistry. The major and innovative research activities include (1) isolation of bioactive natural products, (2) development of new synthetic methodologies for biologically important therapeutic molecules, (3) development of medicinally important therapeutic lead molecules towards drugs, (4) development of functional molecules to probe biological events and (5) development of synthetic supramolecular receptors with biological relevance and functions among others.

The divisional scientists take part in major research programs of CSIR, such as focused basic research (FBR) and fast-track translation (FTT), under the Healthcare, Chemicals, and Agri, Nutrition & Biotech themes, among others. The scientists have developed cost effective synthetic methods for the manufacture of crucial drug molecules and agrochemicals. The short preamble paves way for the descriptions of the research activities of the divisional scientists in the following pages.





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Development of natural product inspired, potential lead molecular scaffolds and investigation of their biological applications

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Background

Our group is engaged in the development of fluorescent probes for plausible application to live cell imaging. Another aspect of our work involves the development of lead molecules having anti-cancer, anti-leishmanial, anti-bacterial and anti-ulcer properties. Our investigations towards the 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 by inhibition of quorum sensing inhibition in Pseudomonas aeruginosa. We are also engaged in purifying enzymes from edible sources and utilizing them as catalysts in organic reactions to synthesize specific epigenetic enzyme inhibitors by understanding the molecular targets as well as in the synthesis of precursors to pharmaceutically active compounds. Apart from these we also investigate asymmetric organic transformations by using chiral ligands/catalysts to synthesize bioactive scaffolds. Introduction of stable atropisomerismis another field that our group explores. Atropisomerism which gives optically rich compounds, is responsible for target selectivity of a promiscuous scaffold. This approach is dependent on the ability to incorporate steric bulk adjacent to the axis in order to make it more rigid.

Aims and Objectives

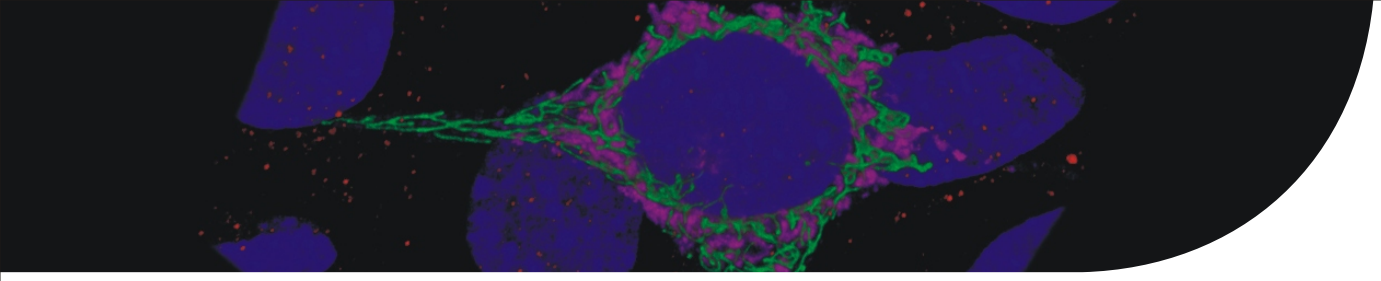
- Our research revolves around the development of fluorescent probes with plausible application in cell imaging.
- Performing asymmetric reactions by using chiral catalysts.
- Development of lead molecules of natural origins with specific targets against various diseases.

Work Achieved

A C5-curcuminoid based fluorescent probe for selective detection of biothiols and its application to live cell imaging

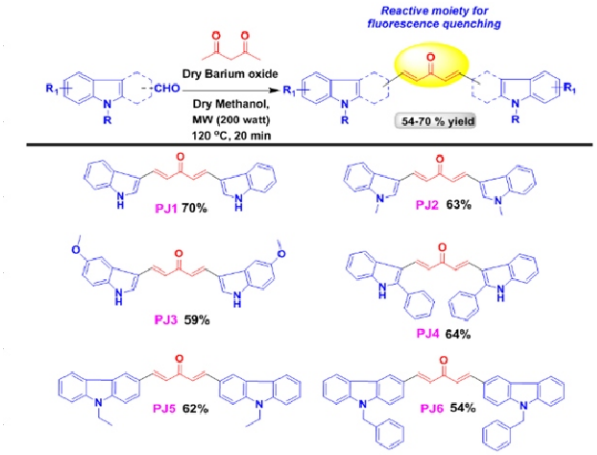
Biological thiols such as cysteine (Cys), homocysteine (Hcy) and glutathione (GSH) play significant roles in maintaining the appropriate redox status in physiological processes.Abnormal levels of these thiols are responsible for diseases e.g. cancer, AIDS, and neuronal disorder. Abnormal levels of Cys are associated with slow growth, hair depigmentation, edema, lethargy, liver damage, loss of muscle and many pathological disorders. In a recent study, it has been found that Hcy is a risk factor for disorders including cardiovascular and Alzheimer's diseases, folate and cobalamin deficiency coronary disease, whereas the plasma total Hcy(tHcy) concentration is inextricably related to birth defects and cognitiveimpairment in the elderly. GSH is usually found to regulate many cellular functions which include maintenance of intracellular redox activities, intracellular signal transduction and gene regulation.

To discriminate different sulfhydryl-containing amino acids is of great interest in terms of early diagnosis of biological thiol associated diseases and evaluation of disease progression. Techniques like HPLC, capillary electrophoresis, UV–vis absorption spectrophotometry, FTIR spectroscopy, mass



spectrometry and enzyme-linked immunosorbent assays usually suffered from several drawbacks including complex sample pretreatment, costly equipment handling and the need for well-trained operators. In contrast, for detecting biothiols, fluorescent probes have been widely employed owing to the merits of fluorescence techniques including high sensitivity, simplicity for implementation, quick-response, noninvasive and realtimedetection for biosamples.

Fluorescent probes having large Stokes shift (≥ 80 nm) can minimize severe spectralcross-talk for cellular imaging with an enhanced signal-to noise ratio and prevent photobleaching. On the other hand, highly photo-stable fluorescent probes are advantageous for noninvasive long-term cellular imaging, which is of great significance for investigating pathological pathways, cellular processes, and therapeutic effects over long time spans. Therefore, large Stokes shift and high photo-stability are the primary criteria for the development of an efficient fluorescent probe towards biological application.Recent literature suggests that bis(arylmethylidene) acetones, C5-curcumin analogues bearing a reactive cross-conjugated dienone structure have multiple applications in molecular fluorescence markers of diseased cells, field effect transistors (FFTs), hole-transporting layers, and organic light-emitting diodes (OLEDs).Quadrupolar electronic distribution (D–π-A–π-D motif) has been extensively found to possess nonlinear optical properties (NLO) due to ICT transition which can be utilized especially in the field of bioimaging as well as in polarity and voltage sensing purpose. Many lines of evidence have been accrued justifying that α ,β -unsaturated ketones are excellent thiol alkylators via the Michael addition reaction.Therefore, our main focus is to design a novel protocol to synthesize indole/carbazole based C5-curcuminoids within a short period of time and utilize them as fluorescent sensors for cell imaging and thiol sensing.With this scenario in mind, we have rationally constructed a new class of bis(arylmethylidene)acetone based C5-curcuminoid fluorescent probes (PJ1– PJ6) having possible advantages of high Stokes shift and utilized towards cell imaging and thiol detection in living cells (Scheme 1).



Scheme 1: Substrate scope microwave assisted synthesis of C5-curcuminoids.

To the best of our knowledge heterocyclic bis-indole/carbazole C5-curcuminoids have not been synthesized yet by deacetylation under microwave irradiation because the efficient removal of the acetyl group from acetoacetates is rare and no reports have been found to possess selective biothiol sensing properties of these series of compounds (Fig. 1).

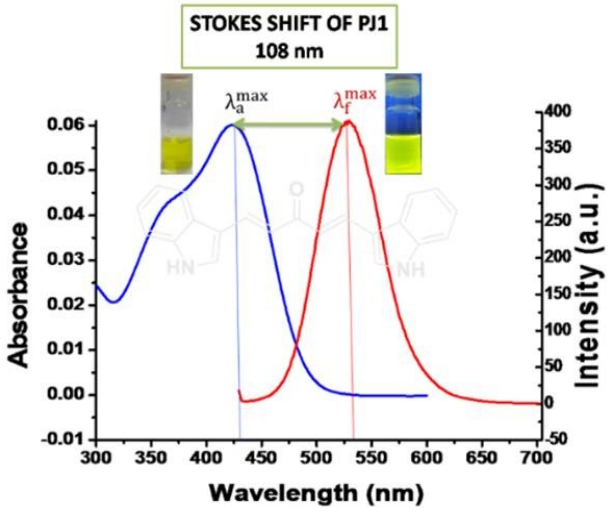


Fig. 1 (a) UV-vis and fluorescence spectra of PJ1 (3.2 μM) with a large Stokes shift.

The absorption and emission spectra of PJ1 in solvents of varying polarities are obtained for the solvatochromismstudy.The absorbance and emission spectrum of the probe PJ1(3.2 × 10−3M)

exhibited the most intense peak at 428 nm (ε_{max} 26 907 mol^{-1} cm^{-1}) and 536 nm in a 3 : 7 CH_3CN/H_2O solvent system. The large Stokes shift was obtained for these synthesized compounds PJ1–PJ6 (Δλ = 104–173 nm) as compared to the commercially available fluorescent dyes. In order to determine the sensing efficacy of these synthesized compounds, the detection of biothiols was monitored colorimetrically. Due to the structural similarity of all the synthesized probes we have chosen the simplest unsubstituted indole based probe PJ1 as an exemplar for performing further kinetic experiments. In order to confirm our hypothesized selective responses of probe PJ1 to biological thiols, the effect of thiols on the absorbance of PJ1 was evaluated. The addition of biothiols (Cys, Hcyand GSH) at 37 °C to solutions of PJ1 separately resulted in noticeable colour changes from yellow to colourless within 24 h for Cys and Hcy. The prominent optical change was observed by the naked eye. However, when treated with GSH, a very slow decrease of colour intensity was observed without complete decolourization within two days.

To investigate the potential bio-analytical application of the probe PJ1, we studied the emission responses of PJ1 (3.2 μM) in the presence of various natural amino acids including Cys, Hcy and GSH in acetonitrile–water (3 : 7, v/v) solution after 24 h of incubation at 37 °C (Fig. 2). Expectedly, the probe PJ1 showed a strong fluorescence but the fluorescence maximum intensity of the probe was dramatically decreased with the addition of Cys and Hcy whereas interestingly no significant decrease of fluorescence was observed with the addition of non-thiol amino acids.

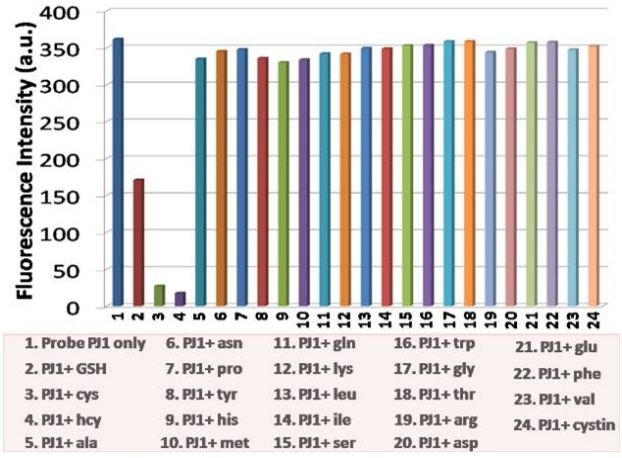


Fig. 2Fluorescence responses of PJ1 (3.2 μM) with various amino acids (200 equiv.) in acetonitrile–water (v/v = 3 : 7, pH = 7.2) solution at 37 °C.

For the determination of the interaction between PJ1 and Hcy and Cys, fluorescence titrations were conducted using probe PJ1 in acetonitrile–water (3: 7). Upon the addition of Hcy/Cys to the solution, a significant decrease of the fluorescence emission band centered at 536 nm was observed. Kinetic studies of the response of Hcy and Cys to probe PJ1 were performed and the rate constant (kobs) was estimated to be 4.60 × 10–5 s−1 and 5.54 × 10–5 s−1 respectively by fitting the initial fluorescence intensity changes according to a pseudo-first-order kinetics equation. The fluorescence quantum yield (Φ) of PJ1 was found to be 0.47 and the detection limit (LOD) of Hcy and Cys was measured by fluorescence titration experiment and it was found to be 5.12 μM and 5.8 μM respectively. For the determination of the fluorescence life time of the probe PJ1, time-correlated single-photon counting (TCSPC) was performed. The profile was fitted with bi-exponential decay profile fitting and the average lifetime has been estimated to be 135.88 ps. The higher fluorescence lifetime favors its potential biological fluorescence imaging applications over an appreciable time span (Fig. 3).

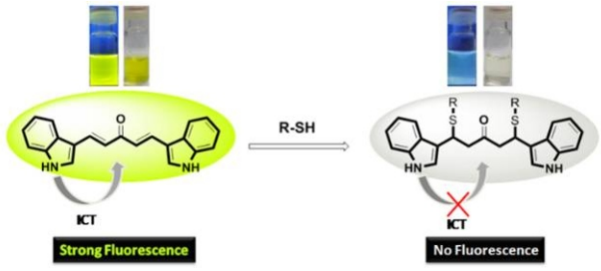


Fig. 3: The transformation of fluorescent compound PJ1 to a non-fluorescent product in the presence of biological thiols.

The possible detection mechanism involves a nucleophilic attack of Hcy/Cys to the electron-deficient α,β-unsaturated ketone in PJ1. Expectedly, the nucleophilic attack of a thiol will break the conjugation in probe PJ1 and induce color fading.To gain insight into the plausible mechanism in detail, 2-mercaptoethanol (ME), which has a similar structure to Hcy/Cys, was selected for the mechanism study with the probe PJ1. To confirm this reaction event, ESI-MS analysis of the reaction mixture PJ1 + ME was carried out. The identification of stable products in the ESI-MS analysis made it possible to propose the signaling mechanism. To

rationalize the fluorescence quenching of molecular probe PJ1, the interaction with thiols was verified by HPLC analysis. The addition of 200 equivalents of 2-mercaptoethanol (ME) (600 μM) to probe PJ1 (3.2 μM) resulted in a gradual decrease of the HPLC signal area for PJ1 followed by the complete disappearance of the PJ1 peak. This observation suggested that the interaction of biothiols with probe PJ1 resulted in fluorescence quenching. Upon the addition of Cys or Hcy to the solution of PJ1 in acetonitrile–water (3: 7, v/v) at 37 °C and at varying pH values of 5 to 9 did not change its fluorescence intensity and its colour indicating a high molecular stability of probe PJ1 in a wide pH range which is really advantageous for practical sensing application. We have also performed quenching PJ1 with Hcy in a pH range of 5 to 9 which showed a colour change from bright yellow to colourless within the aforesaid time period.

As the probe PJ1 possessed a significant sensitivity and reactivity towards biothiols, bioimaging study with this probe is ideal. In order to investigate the intracellular detection of thiol containing amino acids in the living cells by the probe PJ1, we have studied the fluorescence imaging in vitro.Probe PJ1 could provide a sophisticated tool in terms of fluorescence imaging to detect thiol containing proteins and discriminate healthy cells from apoptotic cells. The in vitro fluorescence imaging activity of the probe has been investigated for thiol enriched human melanoma(A375) and apoptosis in human gastric adeno-carcinoma (AGS) cell lines respectively. It is evident that the probe PJ1 can penetrate the A375 cell membrane when the cell was treated with PJ1 for 4h and imaged under a fluorescence microscope after 6 h, 12 h and 24 h respectively. Initially, strong green fluorescence was observed from the cell after 6h suggesting that the probe PJ1 easily crossed the plasma membrane barrier of the A375 cell. Interestingly, the green fluorescence intensity gradually decreased over time and no significant fluorescence was observed after 24 h. This interesting result demonstrated that the probe PJ1 could be useful for the imaging of biothiols present in melanoma cells (Fig. 4).

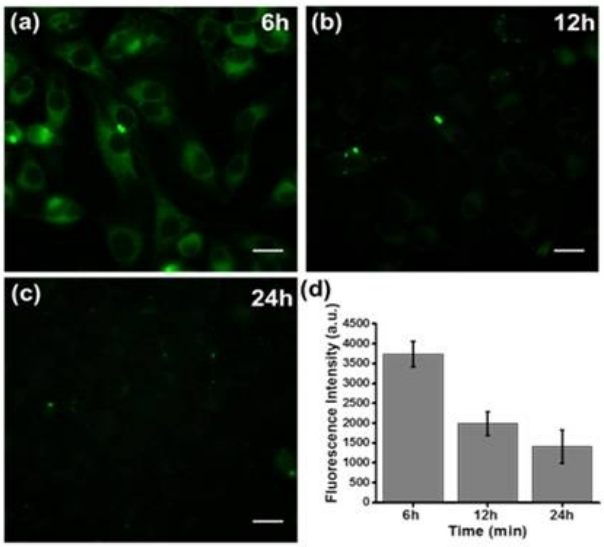


Fig. 4: Bio-imaging of live cell: Degradation of fluorescence intensity of PJ1 with time in Hcy rich A375 cell. Images of A375 cell (a) 6 h after incubation, (b) 12 h after incubation (c) 24 h after incubation. (d) Bar diagram indicates the degradation of fluorescence signal with time. Scale bars correspond to 20 μM.

Hence the fluorescence quenching response of this molecular probe PJ1 can be utilized as a selective indicator for Cys, Hcy and GSH in various cell lines depending on the cellular thiol content. On the other hand, the incubation of the probe PJ1 with the AGS cell line showed the decrease of green fluorescence under stressed conditions (Fig. 5).

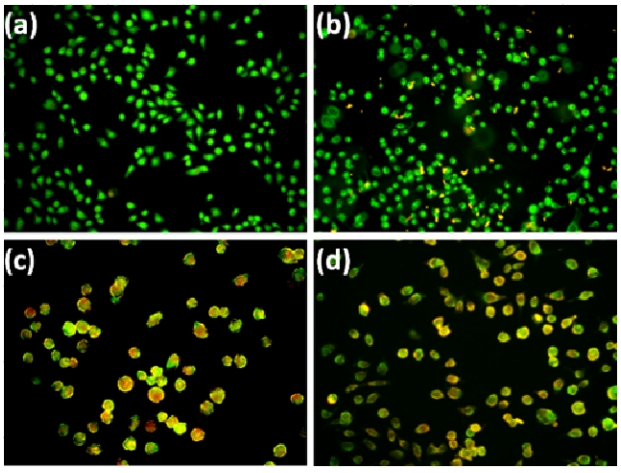
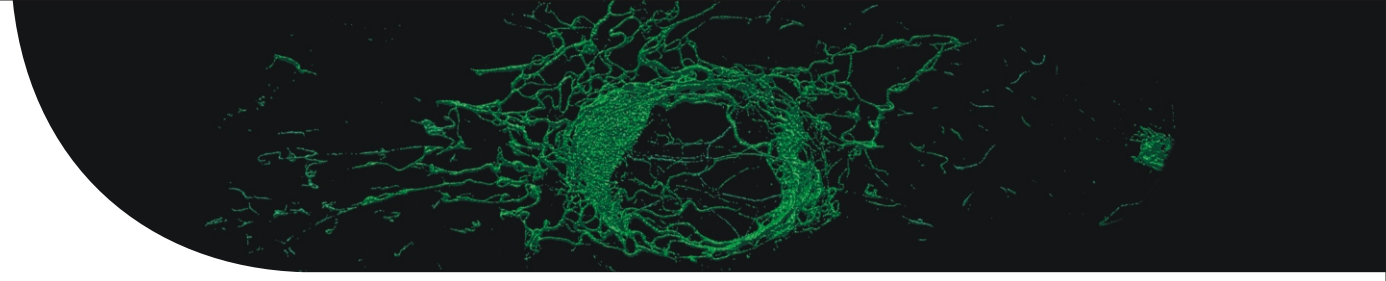


Fig. 5: Evaluation of cellular death by probe PJ1/EB in comparison to staining by AO/EB with healthy 60% confluent AGS cells: (a)



stained with AO/EB, (b) stained with probe PJ1/EB (c) AGS cells were treated with 2.5% ethanol for 30 mins and stained with AO/EB. (d) AGS cells were treated with 2.5% ethanol for 30 mins and stained with probe PJ1/EB.

Therefore, a newly developed probe can also be used to quantify the status of percentage of cellular dead cells. Hence this probe could be useful for understanding the oxidative stress of cells.
In summary, we have developed new fluorescent imaging probes PJ1–PJ6 with large Stokes shift for the selective detection of Cys, Hcy and GSH under optimized conditions. The large Stokes shift led to their practical application in live cell imaging to detect cellular thiols over a recordable time span. The sensing properties were ascribed to the strong affinity between the mercapto groups of the biothiols and the probe PJ1. The in vitro cell imaging efficacy of this newly developed fluorescent probe PJ1 could be utilized to explore and understand cellular apoptosis. This probe is highly selective towards Cys, Hcy & GSH and capable of detecting homocysteine localized live human melanoma cells (A375) under fluorescence microscopy.

Future Research Plans

- The development of new fluorescent, indole based heteroaryl derivativesare currently being pursued in our laboratory.
- Synthesis of new lead compounds of natural product origin having furan/indole/isobenzofuran core and their analogues having various biological activities,with special focus on anticancer, anti-microbial, anti-leishmanialand anti-inflammatory compounds are on-going.
- Extraction, isolation and purification of compounds and evaluation of their biological activities from medicinal plants are also on-going.

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Ricinuscommunis L. fruit extract inhibits migration/invasion, induces apoptosis in breast cancer cells and arrests tumor progression in vivo: M. Majumder, S. Debnath, R. Gajbhiye, R. Saikia, B. Gogoi, S. Kr. Samanta. D. Das, K. Biswas, P. Jaisankar, R. Mukhopadhyay, Sci Rep (2019), 9 , 14493.
Intracellular anti-leishmanial effect of Spergulin-A, a triterpenoid saponin of Glinusoppositifolius: S. Banerjee, N. Mukherjee, R. L. Gajbhiye, S. Mishra, P. Jaisankar, S. Datta, K. D. Saha, Infection and Drug Resistance(2019), 12, 2933–2942.
Euryhalinemamangrovii gen. nov., sp. nov. and Leptoelongatuslitoralis gen. nov., sp. nov. (Leptolyngbyaceae) isolated from an Indian mangrove forest: Sandeep Chakraborty, V. Maruthanayagam, A. Achari, R. Mahansaria, A. Pramanik, P. Jaisankar, J. Mukherjee, Phytotaxa, (2019),422, 1, 058–074.

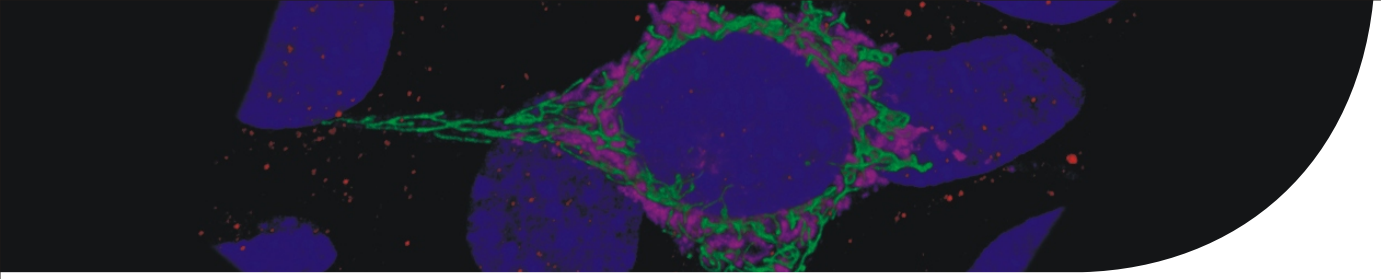
Book Chapters / Invited Reviews
Parasuraman Jaisankar
(US10590116B2)3-Indolyl furanoids as inhibitors of matrix metalloproteinase-9 for prevention of gastric ulcer and other inflammatory diseases(2020):US Patent Appl. No.: US15/897688,Filing date: 15.02.2018;Publication Number: US10590116B2,Publication Date: 17.03.2020;Status: Active
Co-inventors:
Snehasikta Swarnakar: CSIR- Indian Institute of Chemical Biology
Sourav Chatterjee: CSIR- Indian Institute of Chemical Biology
SugreevVerma:CSIR- Indian Institute of Chemical Biology
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
Awards / Honours

Awarded Fulbright-Nehru Academic and Professional Excellence Fellowship (2020-2021)



Joined as the Global Chair of the "Membership-Outreach-Services-Committee" of the International Chemical Biology Society.

Memberships

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.

Mission Mode Project(CSIR)

Indu Bhusan Deb, Parasuraman Jaisankar, Ranjan Jana

Development of processes for active pharmaceutical ingredients towards COVID-19. July 2020-March 2021; Council of Scientific and Industrial Research.

CONFERENCES / WORKSHOPS

ParasuramanJaisankar
Webinar on "Post Covid-19: Resurgence of Indian Industry and R & D," organised by SRM University- AP, 15th May 2020.

Webinar on "Prior-art Searching with Google Patents," organised by Turnip Innovations Pvt. Ltd., 26th June 2020.

Session on "Patent Prosecution Challenges and Strategies in India," organised by The Frontiers Legal and Turnip Innovations, 25th July 2020.

Live Session on "Innovation Commercialisation for Atmanirbhar Bharat" by Dr. H. Purushotham Chairman & Managing Director National Research Development Organisation conducted by Turnip Innovations Pvt. Ltd., 14th August 2020.

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 "An Overview of Asymmetric Synthesis of natural products" in a webinar titled "Chirality in drug development," organised by National Institute of Pharmaceutical Education and Research, Kolkata, on 10th Sep 2020. Chirality on Drug Development.

Delivered an Invited Lecture on "Modern NMR spectroscopic techniques driving natural products research" in a Webinar series titled "Advances in pure and applied chemistry" organised by Presidency College, Chennai on 6-7th August 2020



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.

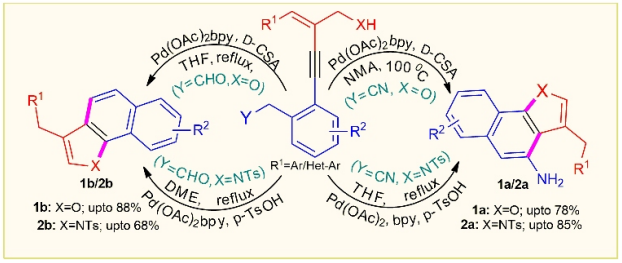
In addition, fused heterocycles are of great importance because of their broad applications in different areas. Among these compounds, 6H-dibenzo[c,h]chromenes are considered as privileged scaffolds and important substructures in modern drug discovery. Besides, benzo[c]phenanthridines and its 5,6-dihydro 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.

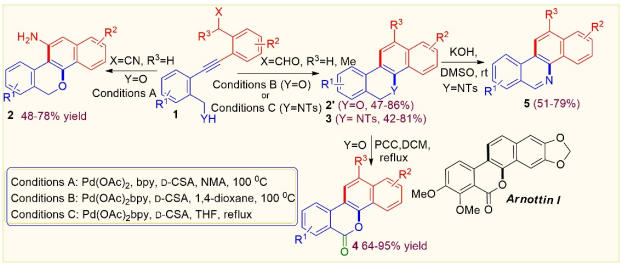
Work Achieved:

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. Biswadip Banerji

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Transition-Metal Catalyzed Synthesis of Novel N-Fused Heterocycle Rings via C-H Activation Reaction and Study Their Biological Efficacies

Participants

SRF : Debabrata Sarkar, Ravuri Srinath, Leena Mazumder, Saswati Ghosh, Saswati Adhikary

Collaborators (within IICB)

Dr.N.C. Maiti (Structural Biology & Bioinformatics)
Dr. SibSankar Roy (Cancer Biology & Inflamatory Disorder)
Dr. Chitra Mandal (Cancer Biology & Inflamatory Disorder)
Dr. Shbhajit Biswas (Infectious Disease & Immunology)

Background

Our lab is engaged in designing and synthesizing new N-fused heterocyclic molecules starting from easily synthesizing/ available starting materials using transition metal catalyzed C-H activation reaction. Strategically we have used mainly quinozolinone or Indole rings etc as our starting materials in our designs which are bioactive in nature having potential therapeutic importance. Following these methodologies, new N-fused heterocycles are formed, by stitching different bonds. These heterocycle are first of all, differently fused inernally, resulting novel heterocyclic structures.

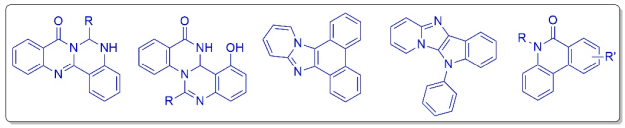


Figure 1: Representative structures of Structures of some synthesized N-Fused Heterocycles.

Interestingly, they are usually highly fluorescence active and show important biological propeties. Hence structurally important these scaffolds can be well used as biomarkers utilizing their strong fluorescence properties as well as therapeutic agents. We have thus further investigated these molecules against different cancer cells and tried to develop new therapeutic agents. These works are ongoing in the lab. Apart from Synthetic Organic Chemistry, and Medicinal Chemistry, our laboratory is also engaged in synthesizing small peptide fragments which formed beautiful nano structures and studying their different bio-physical properties. In adiition we also work on anion/ molecular sensors having biological relevances. The followings are few examples of our recently published works.

Aims & Objectives:

- To develop novel methodologies to synthesize N-fused heterocyclic scaffolds with important Biological efficacies.
- To screen the new molecules against different cancer cell lines to find their therapeutic importance
- Synthesis & Biophysical propertiy studies of Small synthetic peptide based nano structures and their applications
- Design, synthesis and photophysical studies of different anion as well as molecular sensors (Biomarkers).

Work Achieved (Some Representative works):

(a) Cu-Catalyzed Direct Diversification of Quinazolinone Derivatives (Organic Synthesis):

A modular strategy to obtain three different products from a single substrate was developed. The present protocol unveils a new step-economical and cost-efficient route to access diverse fused quinazolinoquinazolinone derivatives, which are not prevalent in literature. Owing to the importance of quinazolinones in therapeutics, quick access to the arena of these scaffolds could be a valuable addition to the scientific domain of heterocyclic chemistry.

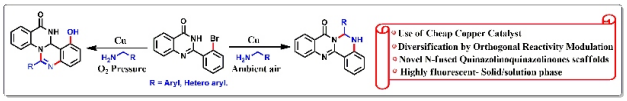


Fig. 2: Quinazolino-quinazolinone Synthesis1

(b) Solvent-Assisted Tyrosine Based Dipeptide from low-Mol Weight Gel: Synthesis & its Application in Dye Removal and Oil Spillage separation from water (Nano Materials):

Low-molecular weight gelators (supramolecular or simply molcular gels) are highly important scaffolds because of their potential application in drug delivery, catalysis, pollutant removal, sensing materials and so forth. Herein, a small dipeptide composed of N-(tert-butoxycarbonyl)-pentafluoro-L-phenylalanine and O-benzyl-L-tyrosine methyl ester was synthesized, and its gelation ability was investigated in different

solvent systems. It was found that the dipeptide was unable to form gel with a single solvent, but a mixture of solvent systems was found to be suitable for the gelation of this dipeptide. Interestingly, water was found to be essential for gelation with the polar protic solvent and long-chain hydrocarbon units such as, petroleum ether, kerosine, and diesel, were important for gelation with aromatic solvents.

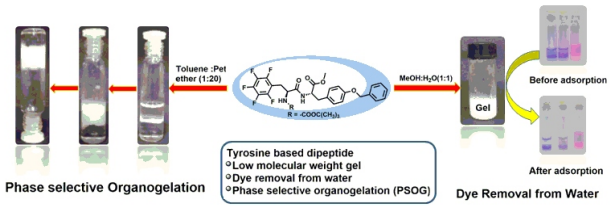


Fig 3: Nano Structure from Tyrosine based dipeptide and its applications2

The structural insights of these gels were characterized by field-emission scanning electronic microscopy, atomic force microscopy, Fourier transform IR analysis and X-ray diffraction studies and their mechanical strengths were characterized by Rheology expteriments. Both of the gels obtained from these two solvent systems were thermoreversible in nature and these translucent gels had potential application for the treatment of waste water. The gel obtained from dipeptides with methanol-water was used to remove toxic dyes (crystal violet, Eriochrome Black T and rhodamine B) from water. Furthermore, the gel obtained from dipeptide with assistance from toluene-petroleum ether was used as a phase-selective gelator for oil-spill recovery.

(c) Design and Synthesis of Natural Product Inspired Scaffolds as Hsp70 inhibitors Targeting Chaperone Activity on Cancer Cells (Medicinal Chemstry):

Heat shock proteins (Hsps) are overexpressed and help cancer cells survive through proper protein-folding. We have designed a simple heterocycle-based scaffold by ring-truncation strategy on a natural product. A small library of these scaffolds was synthesized and explored for Hsp-inhibition. Among the library, the lead compound showed cytotoxicity in cervical, ovarian, pancreatic, colon, oral and lung cancers with no cytotoxicity against normal cell. It enhances programed cell death by up-regulating pro-apoptotic and down-regulating anti-apoptotic proteins in two representative ovarian and pancreatic cancer cells. It inhibits Hsp70/Hsp40 leading to the down-regulation of client proteins (Akt/B-raf/Stat3) confirming its role in apoptosis. Binding of the lead molecule with Hsp70 was additionally validated by molecular-modelling. Taken together, this scaffold is a potent Hsp70 inhibitor and its client proteins and therefore, may be considered for the management of cancer.

PUBLICATIONS (Ref.) :

1. Cu-Catalyzed Direct Diversification of 2-(2-Bromophenyl)quinazolin-4(3H)-ones through Orthogonal Reactivity Modulation; Satadru Chatterjee, Ravuri Srinath, Suvankar Bera, Krishnendu Khamaru, Afifa Rahman, **Biswadip Banerji* Organic. Letters**; 2019, 21, 22, 9028-9032. (Organic Synthesis)
2. Solvent-Assisted Tyrosine-Based Dipeptide Forms Low-Molecular Weight Gel: Preparation and Its Potential Use in Dye Removal and Oil Spillage Separation from Water; Leena Majumder, Moumita Chatterjee, Kaushik Bera, Nakul Chandra Maiti, **Biswadip Banerji*; ACS Omega**, 2019, 4, 11, 14411-14419. (Nano Materials)
3. Rh(III)CatalyzedDecarboxylative o-Acylation of Arenes Bearing an Oxidizing Directing Group; Suvankar Bera, K. Chandrasekhar, SatadruChatterjee,Sunil Kumar Killi, Debabrata Sarkar, **Biswadip Banerji*, European Journal of Organic Chemistry,** 2019, 24, 3877-3881.(Organic Synthesis)
4. 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. (Sensors)
5. A Green Synthetic Approach towards PolyarylatedOxazoles via Iodine-Catalyzed One-Pot sp3 C−H Functionalization in Water: From Natural Product Synthesis To Photophysical Studies; **Biswadip Banerji*,** Saswati Adhikary, Leena Majumder, Saswati Ghosh; **Asian Journal of Organic Chemistry**; 2019, 24, (Organic Synthesis)



Dr. Ranjan Jana

rjana@iicb.res.in



Molecular Diversity through Cascade C-H Activation

Participants

Kartic Manna, SRF
Hasina Mamataj Begam, SRF
Pritha Das, SRF
Shantanu Nandi, SRF
Varalaxmi Kasarla, SRF (NIPERK)

Subhodeep Das, JRF
Shuvam Mondal, SRF
Souryaban Choudhury, JRF

Collaborator(s)

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. Recently, we have initiated a research program for the utilization of CO_2, SO_2 etc. which are feedstock chemicals for the production of value-added products.

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 (Fig 1 & Fig 2).

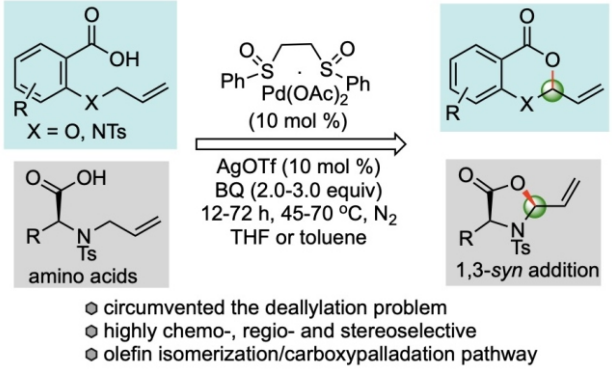


Fig 1. Allylic C-H activation.

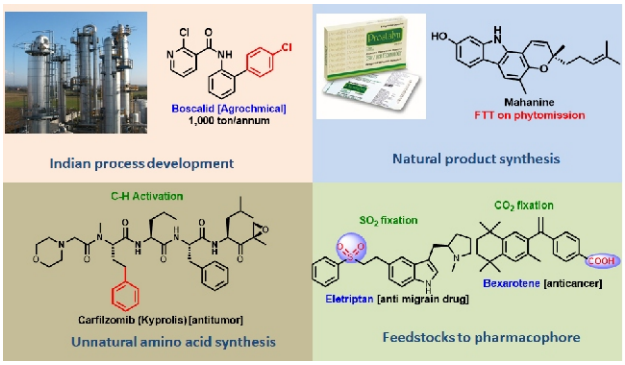


FIG 2. Research Activities.

PUBLICATIONS

Bhunia, S. K.; Das, P.; Nanda, S.; Jana, R. (2019) Carboxylation of Aryl Triflates with CO_2 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 $C(sp^2)$-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."

Das, P.; Begam, H. M.; Bhunia, S. K.; Jana, R. (2019) Photoredox-Catalyzed Tandem Demethylation of N,N-Dimethyl Anilines Followed by Amidation with α Keto or Alkynyl Carboxylic Acids, Adv. Synth. Catal. 361, 4048-4054.

Manna, K.; Begam, H. M.; Samanta, K.; Jana, R. (2020) Overcoming the Deallylation Problem: Palladium(II)-Catalyzed Chemo-, Regio-, and Stereoselective Allylic Oxidation of Aryl Allyl Ether, Amine, and Amino Acids, Org. Lett. 22, 7443-7449.

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

Phytomission (HCP-10), CSIR

INPROTICS (HCP-11), CSIR

Agrochemical Mission (HCP-21), CSIR

COVID-19 Mission (HCP-29)

CONFERENCES / WORKSHOPS

- Invited lecture at University of Calcutta, Heritage Institute of Technology, ICCHD.
- Invited lecture at IITKGP.
- Invited lecture at JIS university.
- Invited lecture at Surendranath College.
- Invited lecture at BITS-Hyderabad.
- Popular Science Lecture 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. HCV infection is endemic in many countries, particularly in certain countries such as Egypt almost 10% of the population is infected with HCV. HCV mainly effects liver, pathophysiological symptoms associated with this disease is liver cirrhosis, liver failure and hepatocellular carcinoma. 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. Rapid mutations in protein envelop and drug resistances are great concerns and targeting viral conserved region is more imperative strategy to deal with this issue.

Work Achieved:

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. We have synthesized a series of novel quinoxaline small molecules based on the crystal structure of 2-amino-benzimidazole bound to HCV IRES RNA. The quinoxaline derivatives inhibit the viral protein translation in a Dual Luciferase reporter based assay containing the HCV IRES in low micromolar range. Mutagenesis studies of HCV IRES show that the compounds can target the domain IIa of HCV IRES RNA. FRET assay, molecular dynamics and docking study further confirm that the quinoxaline derivatives target the domain IIa. Our studies provide potential leads for the development of antiviral therapy against HCV. These compounds have also shown to decrease viral translation and replication in virus as done in the laboratory of our collaborator Prof Saumitra Das at IISc, Bangalore. (Published in Chem. Commun., 2019, 55, 14027, DOI: 10.1039/c9cc06531h).

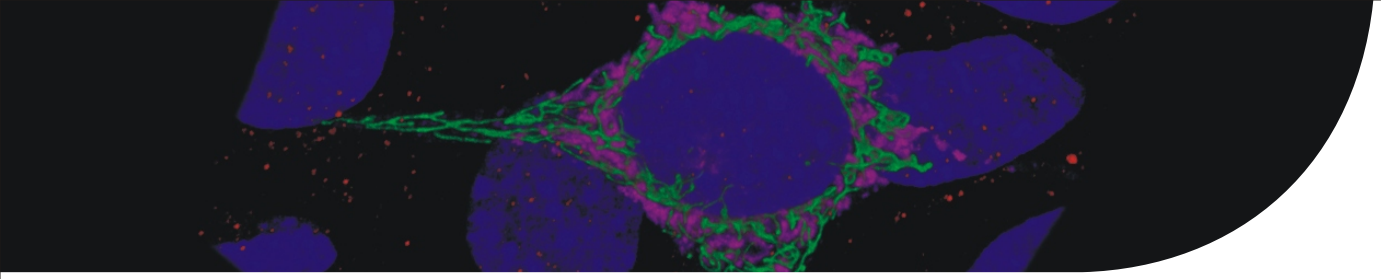
Developments of Antibacterials:

Abstract: Structural integrity of the bacterial genome plays an important role in bacterial survival. Cellular consequences of an intolerable amount of change in the DNA structure are not well understood in bacteria. Here we have stated that binding of synthetic 6-nitroquinoxaline derivatives with DNA led to change in its global structure, subsequently culminating with over-supercoiled form through in-path intermediates. This structural change results in induction of programmed cell death like physiological hallmarks, which is dependent on substitution driven structural modulation properties of the sca□old. A sub-lethal dose of a representative derivative, 3a, significantly inhibits DNA synthesis, produces fragmented nucleoids, and alters membrane architecture. We have also shown that exposure to the compound changes the native morphology of Staphylococcus aureus cells and significantly disrupts preformed biofilms. Thus, our study gives new insight into bacterial responses to local or global DNA structural changes induced by 6-nitroquinoxaline small molecules. (Published in J. Med. Chem., 2019, 62, 17, 7840-7856, DOI: 10.1021/acs.jmedchem.9b00599.)

Title of the project: Interaction of aloe active compounds with calf thymus DNA

Participants: Dr. Abhi Das (DST Women Scientist), Dr. Gopinatha Suresh Kumar

Abstract: Natural anthraquinone compounds have emerged as potent anticancer chemotherapeutic agents because of their promising DNA - binding properties. Aloe vera is among one of the very well□known medicinal plants, and the anthraquinone derivatives like aloe emodin (ALM), aloins (ALN), and aloe emodin-8-glucoside (ALMG) are known



to have immense biological activities. Here, we have used biophysical methods to elucidate the comparative DNA - binding abilities of these three molecules. Steady state fluorescence study indicated complexation between calf thymus DNA (ctDNA) and both the molecules ALM and ALMG whereas ALN showed very weak interaction with DNA. Displacement assays with ctDNA-bound intercalator (ethidium bromide) and a groove binder (Hoechst 33258) indicated preferential binding of both ALM and ALMG to minor groove of DNA. Isothermal titration calorimetric (ITC) data suggested spontaneous exothermic single binding mode of both the molecules: ALM and ALMG. Entropy is the most important factor which contributed to the standard molar Gibbs energy associated with relatively small favorable enthalpic contribution. The equilibrium constants of binding to ctDNA were $(6.02 \pm 0.10) \times 10^4\ M^{-1}$ and $(4.90 \pm 0.11) \times 10^4\ M^{-1}$ at 298.15 K, for ALM and ALMG, respectively. The enthalpy vs temperature plot yielded negative standard molar heat capacity value, and a strong negative correlation between enthalpy and entropy terms was observed which indicates the enthalpy entropy compensation behavior in both systems. All these thermodynamic phenomena indicate that hydrophobic force is the key factor which is involved in the binding process. Moreover, the enhancement of thermal stability of DNA helix by ALM and ALMG fully agreed to the complexation of these molecules with DNA. (Published in J Mol Recognit. 2019, e2786, 1-9, doi/10.1002/jmr.2786)

Future Research Plans

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

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

Inivited Lectures

1) Delivered an invited lecture at BARC, Mumbai, India, at SBCI, on 1st November 2019.

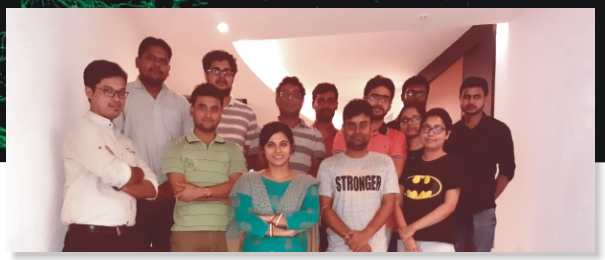
Publications

1. Jeet Chakravarty, Ajay Kanungo, Tridib Mahata, Krishna Kumar, Geetika Sharma, Ritesh Pal, Khondakar Sayef Ahammed, Dipendu Patra, Bhim Majhi, Saikat Chakrabarti, Saumitra Das and Sanjay Dutta* "Quinoxaline derivatives disrupt the base stacking of Hepatitis C Virus Internal Ribosome Entry Site RNA: reduce translation and replication" Chem. Commun., 2019, 55, 14027, DOI: 10.1039/c9cc06531h.
2. Khondakar Sayef Ahammed, Ritesh Pal, Jeet Chakraborty, Ajay Kanungo, Polnati Sravani Purnima, and Sanjay Dutta* "DNA Structural Alteration Leading to Antibacterial Property of 6-Nitroquinoxaline Derivatives" J. Med. Chem., 2019, 62, 17, 7840-7856, DOI: 10.1021/acs.jmedchem.9b00599.
3. Abhi Das*, Gopinatha Suresh Kumar and Sanjay Dutta* "Interaction of aloe active compounds with calf thymus DNA" J Mol Recognit. 2019, e2786, 1-9, doi/10.1002/jmr.2786



Dr. Arindam Talukdar

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Target Based Design, Synthesis, Development and Validation of Novel Small Molecules Inhibitors/ Modulators against Auto Immune Disorders, Anti Cancer Therapeutics and Neglected Tropical Diseases.

Participants

Biswajit Kundu, SRF
Sourav Pal, SRF
Debomita Bhattacharya, SRF
Dipayan Sarkar, SRF
Sunny Goon, JRF
Dipika Sarkar, JRF
Nirmal Das, JRF

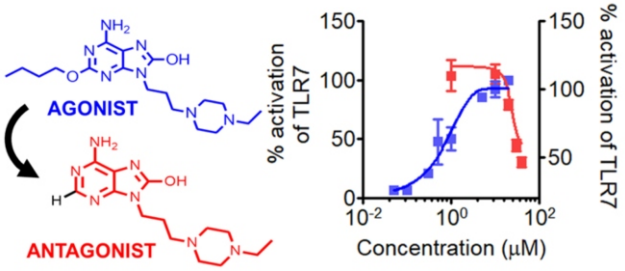
Collaborator(s)

Name of collaborator within CSIR-IICB:

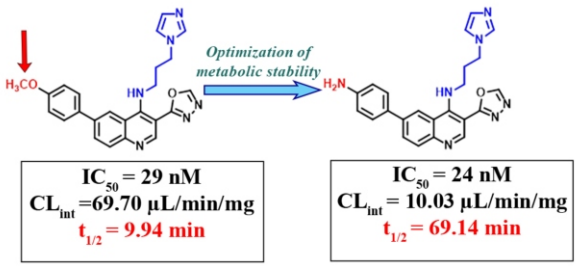
Dr. Dipyaman Ganguly,
Principal Scientist, Cancer Biology & Inflammatory Disorder.
Dr. Partha Chakrabarti,
Principal Scientist, Cell Biology & Physiology
Dr. Shilpak Chatterjee,
Senior Scientist, Cancer Biology & Inflammatory Disorder
Dr. Amitava Sengupta,
Principal Scientist, Cancer Biology & Inflammatory Disorder

BACKGROUND

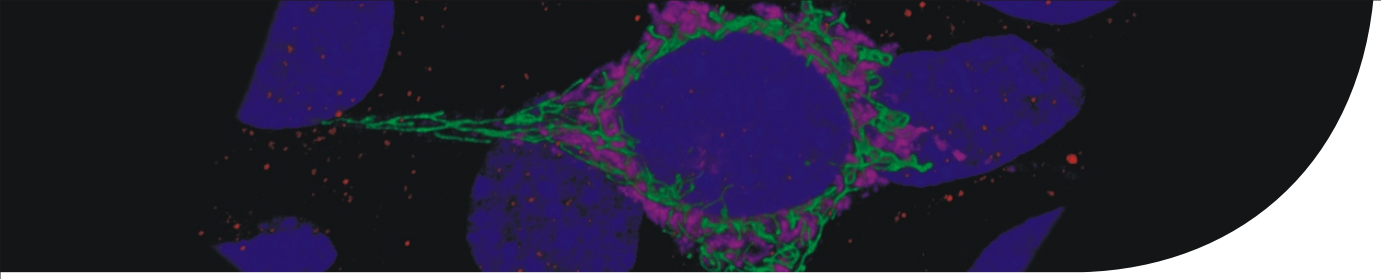
1. **Probing Endosomal Toll-like Receptors (TLRs):** TLRs are the members of the larger family of evolutionary conserved pattern recognition receptors (PRRs) which plays critical and important role in first line of defence for self-nonself discrimination by the host immune response. Aberrant endosomal TLR activation is implicated in auto-reactive inflammation in different autoimmune diseases. Herein, we report a purine scaffold TLR7 antagonist, first-of-its-kind to our knowledge, which was developed by rationally dissecting the structural requirements for TLR7-targeted activity for a purine scaffold. Specifically, we identified a singular chemical switch at C-2 that could make a potent purine scaffold TLR7 agonist to lose agonism and acquire antagonist activity. To further validate the in vivo applicability of this novel TLR7 antagonist, we demonstrated its excellent efficacy in preventing TLR7-induced pathology in a preclinical murine model of psoriasis.



2. **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. This topological problem is solved by topoisomerase enzyme 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. During optimization, that it has been observed that our previously reported lead compound suffers from high intrinsic clearance in human liver microsomes. To overcome the metabolic instability of compound, we strategically designed and made of new metabolically stable Top1 poison. Newly identified Top1 poison exhibits t1/2 (half life) of 69.1 min in human liver microsomes in comparison to parent compound with t1/2 (half life) of 9.9 min.



3. **Designing of Development of Novel Small molecules ameliorating Non alcoholic Steatohepatitis (NASH)**



Nonalcoholic fatty liver disease (NAFLD) is the most chronic liver disease in which >5 % steatosis has been occurred in absence of significant alcohol consumption, monogenic hereditary disorders, and steatogenic medications. Also it is strongly associated with type 2 diabetis and obesity. NAFLD is subdivided into two classes based on histological outcome. Nonalcoholic steatohepatitis (NASH) is the invasive progression of NAFLD where extracellular matrix proteins, notably collagen fibres, accumulate in the liver encircling hepatocytes and forming scar tissue resulting in irreversible hepatocellular damage (ballooning) and inflammation occurs. Nonalcoholic fatty liver (NAFL) is the pre sign of NASH, usually considered as benign (accumulation of fat). NASH progression leads to fibrosis, cirrhosis, liver failure and finally hepatocellular carcinoma (HCC). There is no current therapeutics to prevent NASH. So our lab is mainly focusing on novel small molecules curing NASH in a rational way.

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 and dual/selective TLR9 and TLR7 antagonists and filled two patents to protect the IP. Two patents are now in pipieline in filing in US.We also published four articles in various reputed journal. Three in European Journal of Medicinal Chemistry (Elsevier), One in Journal of Medicinal Chemistry (ACS) 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. We filed provisional as well as PCT/WO to protect our IP. We published three articles; one in Journal of Medicinal Chemistry (ACS), European Journal of Medicinal Chemistry (Elsevier), and another in Computational and Structural Biotechnology Journal.

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 recently filed provisional patent in NASH. Application no: 0186NF2019

We'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 Research Plans:

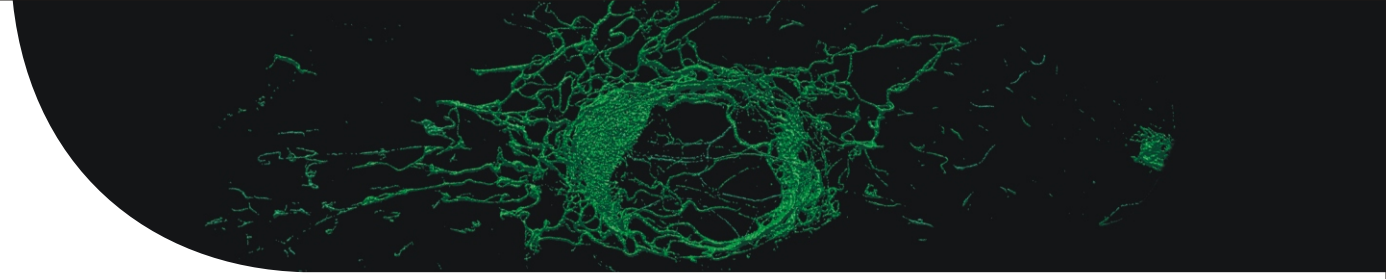
Preclinical development of rationally designed inhibitors for the nucleic acid-recognizing Toll-like receptors (TLRs) for which two patent has been filed. In vivo validation of our novel Topoisomerase 1 (Top1) poisons as anticancer agents.

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. Development of a metabolically stable topoisomerase I poison as anticancer agent. Biswajit Kundu, Dipayan Sarkar, Srijita



Paul Chowdhuri, Sourav Pal, Subhendu K. Das, Benu Brata Das, Arindam Talukdar. European Journal of Medicinal Chemistry. 2020, 202, 112551. DOI: 10.1016/j.ejmech.2020.112551.

2. Chemical switch for transforming a purine agonist for Toll-like receptor 7 to a clinically relevant antagonist. Ayan Mukherjee, Deblina Raychaudhuri, Bishnu Prasad Sinha, Biswajit Kundu, Mousumi Mitra, Barnali Paul, Purbita Bandopadhyay, Dipyaman Ganguly, Arindam Talukdar. Journal of Medicinal Chemistry, 2020, 63, 4776−4789. DOI:10.1021/acs.jmedchem.0c00011.
3. Protective role of ACE inhibitors and ARBs in hypertensive patients suffering from COVID-19. Arindam Talukdar*, Dipayan Sarkar, Subhasis Roy Chowdhury, Dipyaman Ganguly. 2020. Preprint authorea.com. DOI: 10.22541/au.158955396.63298622.
4. Emergence of multiple variants of SARS-CoV-2 with signature structural changes. Debaleena Bhowmik, Sourav Pal, Abhishake Lahiri, Arindam Talukdar, Sandip Paul. 2020. bioRxiv preprint. DOI: 10.1101/2020.04.26.062471.
5. Compilation of Potential Protein Targets for SARS-CoV-2: Preparation of Homology Model and Active Site Determination for Future Rational Antiviral Design. Sourav Pal, Arindam Talukdar. 2020. ChemRxiv. DOI: 10.26434/chemrxiv.12084468.

Patent:

No.	Title	Country	Filed on (Date)	Names of the inventors
1	Bicycle Topoisomerase I Inhibiting Compounds, Process For Preparation And Use Thereof	PCT	PCT/IN2019 /050410 Date of filing: 24.05.2019	**ARINDAM TALUKDAR**, B B Das, B Kundu, S K Das, S P Chowdhuri, D Sarkar, S Pal, D Bhattacharya, A Mukherjee, S Roy
2	Purine Based Compounds As Toll-Like Receptor 9 Antagonist.	World and Europe	WO 2019/092739 A1 International Publication date: 16 May 2019	**ARINDAM TALUKDAR** Dipyaman Ganguly, Ayan Mukherjee Barnali Paul, Swarnali Roy Amrit Raj GHOSH, Roopkatha Bhattacharya, Oindrilla Rahaman Deblina Raychaudhuri

Memberships :
Life member of Chemical Biology society

EXTRAMURAL FUNDING

1. Design and Development of Selective inhibitors of protein arginine methyltransferase 1 involved in epigenetic modifications. Core Research Grant. SERB. February 2020. CRG/2019/000853.

2. Development of new drugs for leishmania- an australia-indian partnershipAustralia-India Strategic Research Fund (AISRF): Start Year: June 2017. End Year: June 2020. Agency: DBT, Gov. of India.

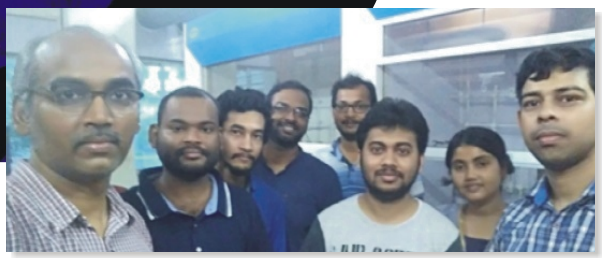
3. Probing endosomal toll-like receptor 9 biology using novel small molecule antagonists. Start Year: September 2016. End Year: March 2019. Agency: EMR/2015/000117. Agency: DST-SERB, Gov. of India.

4. 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.



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 : Shovan Kumar Sen, Krishanu Samanta

JRF : Raju Biswas, Suman Maji, Sandipan Gorai, Bhaswati Paul

Collaborator(s)

Dr. P. S. Subramanian, CSIR-CSMCRI, Bhavanagar, and Dr. P. Murugesapandiyan, Bharathiyar University, Coimbatore.

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 receptors for the recognition of biologically relevant molecules through specific intermolecular interactions.

Crystal engineering of organic molecules to develop functional materials and modulating the properties of drugs

Work Achieved

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.



Fig. 1:self-assembly and self-sorting of unsymmetrical chiral ligand and Pd(II) ions to form a single isomer of M2L4 chiral cage

PUBLICATIONS

Sen, S. K.; Natarajan, R. (2019) Influence of Conformational Change and Interligand Hydrogen Bonding in a Chiral Metal–Organic Cage. Inorg. Chem. 58, 7180-7188

Chinnaraja, E.; Arunachalam, R.; Samanta, K.; Natarajan, R.; Subramanian, P. S. (2020) Enantioselective Michael Addition Reaction Catalysed by Enantiopure Binuclear Nickel (II) Close□Ended Helicates. Adv. Synth. Catal. 362, 1144-1155





Dr. Indu Bhusan Deb

indubhusandeb@iicb.res.in

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-SRF
Siddhartha Samanta CSIR-JRF
Shantonu Roy CSIR-JRF
Imtiaz Mondal UGC-JRF
Koushik Naskar UGC-JRF

Collaborator(s)

Name of collaborator within CSIR-IICB: Dr. Subhajit Biswas

Background

The ubiquitousness of Benoxazine, Benzosultam, Oxaziridine, Quinazolines as well as Quinazolinones skeletons in various natural products and pharmaceuticals make them immensely valuable heterocycles. Hence, development of new and efficient method 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 the concept of electrocatalyzed and transition metal catalyzed (Pd, Fe, Co, Ni, Ru, Rh & Ir) C–H/C–X bond activation.

Aims and Objectives

- Development of electro catalyzed and transition metal catalyzed cost effective, affordable and industry friendly C-H activation methodology for the late stage functionalization of pharmacophores such asbenzoxazines, benzosultams, azaindole and quinoline.
- Developemt of process for the synthesis of generic version of FDA approved drug against COVID-19.

Work Achieved:

Diastereoselective Spirocyclization of Benzoxazines with Nitroalkenes via Rhodium-Catalyzed C-H Functionalization / Annulation Cascade under Mild Conditions: We have developed

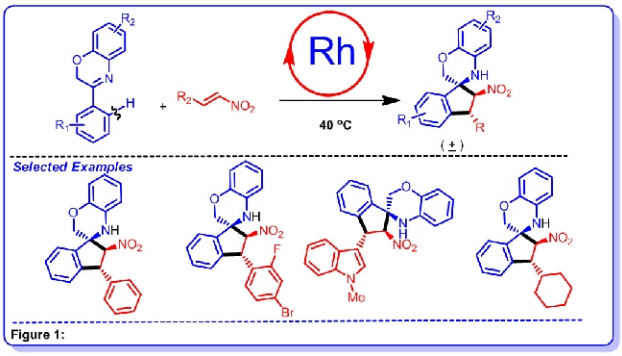


Figure 1:

an efficient, highly regioselective and scalable rhodium-catalyzed ortho aryl C–H activation followed by annulations reaction for the synthesis of a new class of nitro functionalized spirocyclic benzoxazine. The scope of the reaction has been successfull. The products could have potential application in drug discovery programme (Fig. 1). This work has been published in Organic Letters 2020. 22,1340-1344 (IF: 6.555).

Diastereoselective Spirocyclization of Cyclic N-Sulfonyl

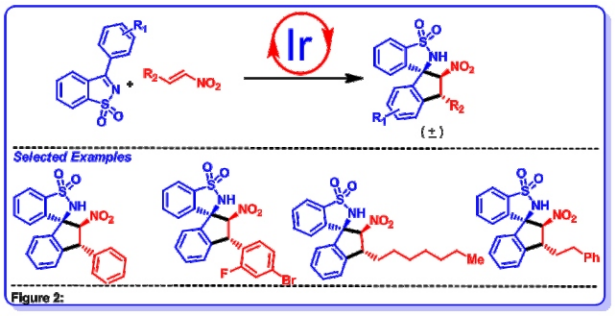


Figure 2:

Ketimines with Nitroalkenes via Iridium-Catalyzed Redox Neutral Cascade: We have achieved an iridium (III)-catalyzed diastereoselcetive redox neutral cascade annulation reaction between weakly co-ordinationg N-sulfonyl ketimines and challenging α, β -unsaturated nitroalkene. The methodology provides an easy access to a broad spectrum of nitro functionalized valuable spirocyclic benzosultams which may find potential applications in the field of medicinal chemistry (Fig. 2). This work has been published in Organic Letters 2019, 21, 2056-2059 (Selected as Cover page). (IF: 6.555)

Iridium-Catalyzed Direct C-H Arylation of Cyclic N-Sulfonyl Ketimines with Arylsiloxanes at Room Temperature: An iridium-catalyzed ortho-selective C–H arylation of cyclic N-sulfonyl

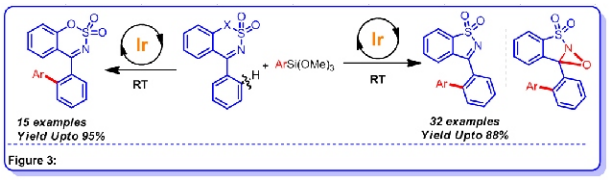


Figure 3:

ketimines has been achieved with environmentally benign aryl siloxanes. The reaction is highly efficient and works at ambient temperature which is the key feature of the methodology considering the weak coordination nature of the substrate as well as sluggish reactivity of siloxanes. A wide array of pharmaceutically relevant novel class of biaryls has been synthesized under operationally simple conditions (Fig. 3).

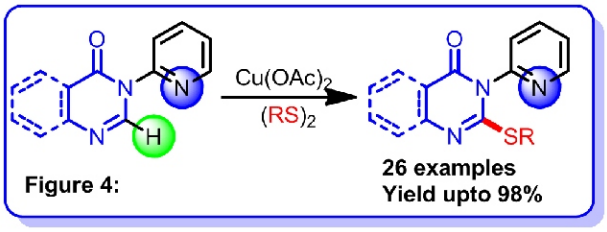


Figure 4:

Copper-Mediated Direct and Selective C-H Thiolation of Quinazolinones: We have developed a cheap and benign copper-mediated direct thiolation of quinazolinones under simple reaction conditions for the synthesis of an array of biologically important thioquinazolinones (Fig. 4). Asian J. Org. Chem.2019, 819-822. (IF: 3.13).

Future Research Plans

Development of process for the synthesis of broad spectrum of pharmaceutically relevant (chiral) molecules employing Electrocatalysis and Metal-catalysis. Boactivity study of newly synthesized molecules will be pursued.

Development of affordable process for generic version of FDA approved API.

PUBLICATIONS

1. Aniket Mishra, Arup Bhowmik , Siddhartha Samanta, Writhabrata Sarkar, Sumit Das, and Indubhusan Deb* "Diastereoselective Spirocyclization of Benzoxazines with Nitroalkenes via Rhodium-Catalyzed C-H Functionalization / Annulation Cascade under Mild Conditions" Org. Lett. 2020, 22, 1340-1344. (IF: 6.555).

2. Aniket Mishra, Upasana Mukherjee, Writhabrata Sarkar, Sudha Lahari Meduri, Arup Bhowmik and Indubhusan Deb* "Diastereoselective Spirocyclization of Cyclic N-Sulfonyl Ketimines with Nitroalkenes via Iridium-Catalyzed Redox Neutral Cascade Reaction" Org. Lett. 2019, 21, 2056-2059 (Selected as Cover page), (IF: 6.555).

3. Writhabrata Sarkar,†Aniket Mishra,† Arup Bhowmik and Indubhusan Deb* "Copper-Mediated Direct and Selective C-H Thiolation of Quinazolinones" Asian J. Org. Chem.2019, 819-822 (†contributed equally), (IF: 3.13).

AWARDS / HONOURS / MEMBERSHIPS

Faculty
Scientist's Name Surname **Indu Bhusan Deb**
Awards / Honours
Bristol Mayer 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. $ 10,000 (BMS-USA), 2019

CONFERENCES / WORKSHOPS

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

TALKS BY CSIR-IICB FACULTY

Japan: The symposium "Naito Conference, Japan" Invited Talk, 2-5th July 2019:





Dr. Indrajit Das

indrajit@iicb.res.in

C3-Thioester/-Ester Substituted Linear Dienones: A Pluripotent Molecular Platform for Diversification

Participants

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

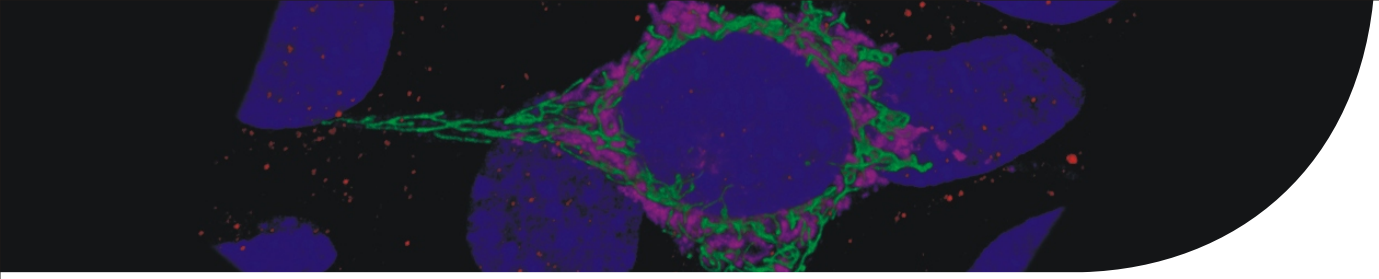
Reagent-based diversity-oriented synthesis that utilizes a densely functionalized substrate (pluripotent molecular platform) with cascade or domino reaction sequences represents a powerful strategy in organic synthesis and can immensely improve the efficiency of a chemical reaction. In this strategy, a common multifunctional substrate is transformed into diverse topologically complex molecular frameworks by using different reactants and reaction conditions. Several well-designed pluripotent molecular platforms have been developed by different research groups. Although substantial progress has been made with the dienals, reagent-based cascade reactions of the corresponding C3-carbonyl substituted dienones have not been reported until recently due to the paucity of methods available to access them. Over the past few years, we have been involved in the development of synthetic methods for cyclopropanated furans, regioselective E $\rightarrow$ Z isomerization of olefins, and butenolides from dienones. Recently, we have reported that neat dienones underwent dimerization due to a substituent-driven acceleration effect via sequential s-trans to s-cis isomerization/regioselective E/Z isomerization/Diels–Alder cycloaddition to provide cyclohexene derivatives under direct excitation of the reactant by visible light absorption. But dienones lacking such substitution did not undergo the transformation. The substituent effect was rationalized based on molecular orbital calculation which supports the contention that the substituent at the C3-position of dienal reduces the activation energy of the process.

Aims and Objectives

C3-thioester/-ester substituted 2,4-dienones are versatile intermediates for generating structural complexity under green and sustainable reaction conditions and this has enabled the invention of a wide variety of novel new bond-forming protocols via a series of activation modes with or without visible light. We successfully utilized 2,4-dienones as starting materials to access cyclopropanated furans and butenolides under mild and metal-free reaction conditions. Further, In the light of the above findings and to convert densely functionalized dienones into diverse scaffolds, we reported their reactivity under thermal conditions to access substituted oxabicyclo derivatives bearing two quaternary carbon centers and five contiguous stereocenters via cascade pericyclic reactions.

Work Achieved

Visible-light excitation of electron-rich dienones in isopropanol solvent under ambient conditions using hexafluoroisopropanol (HFIP) as an additive promotes intramolecular radical cascade cyclization to afford cyclopropanated furans. Molecular dioxygen in the air serves as a redox catalyst in this reaction which is proposed to proceed through a radical cation intermediate generated by single-electron transfer (SET) from a phototransient dienone to oxygen. By changing the solvent from isopropanol to HFIP, exclusive formation of substituted butenolides occurs via ionic cascade cyclization involving E $\rightarrow$ Z isomerization/lactonization/thiolate addition. HFIP is assumed to act as a medium, hydrogen bond donor catalyst, and a Lewis acid substitute as well. This reaction may be conducted even in the absence of light and no catalyst or reagent is required. Substituted oxabicyclo derivatives bearing two quaternary carbon centers and five contiguous stereocenters have been synthesized from C3-thioester/-ester substituted dienones, a simple and linear pluripotent molecular



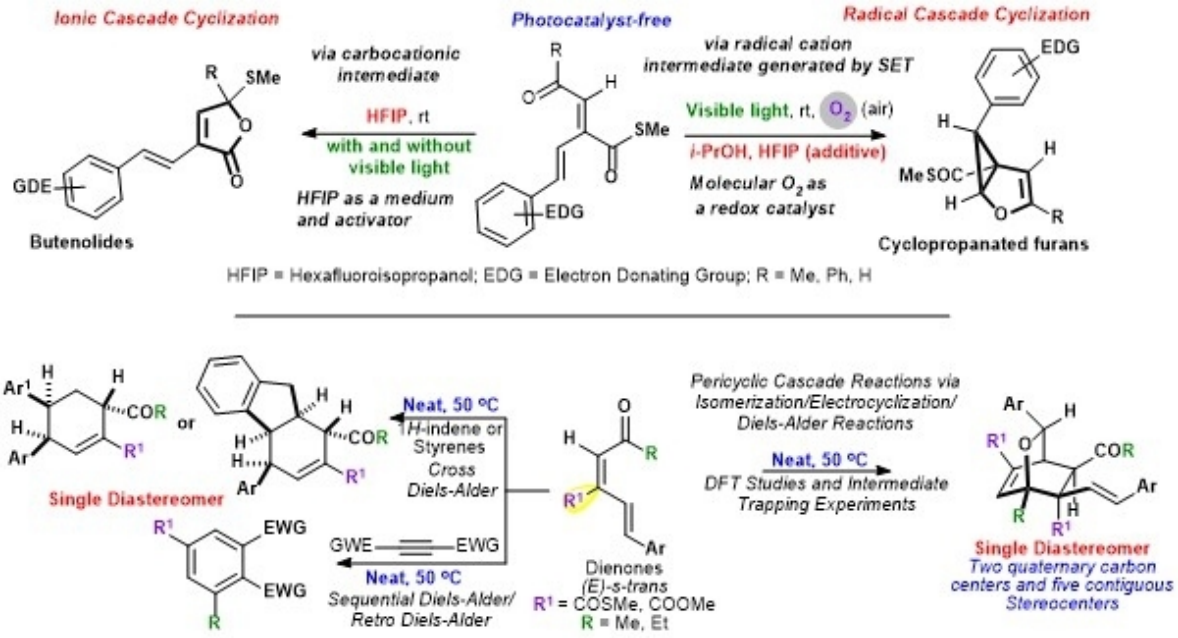


Fig. 1. Divergent Reactivity of Pluripotent Dienones with or without Visible-Light

platform. The conversion proceeds from neat reactants, possibly via a thermally-driven pericyclic cascade manifold involving sequential (E)-s-trans to (E)-s-cis isomerization, oxa-6 π -electrocyclization, and intermolecular, regioselective [4 π + 2 π] cycloaddition. The proposed mechanism has been substantiated by intermediate trapping experiments and DFT studies. Such dienones have also been exploited to effect stereoselective cross Diels-Alder cycloadditions with olefins and sequential Diels-Alder/retro-Diels-Alder reactions with activated alkynes. The reaction is greatly influenced by the substituent effect exerted by the C3-thioester/-ester group (Figure 1).

Future Research Plans

Following our success in C3-thioester/-ester substituted dienones as pluripotent molecular platform in diverse 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.

Publications

Bankura, A., Naskar, S., Chowdhury, S. R., Maity, R., Mishra, S., Das, I. (2020) C3-Thioester/-ester substituted linear dienones: A pluripotent molecular platform for diversification via cascade pericyclic reactions. Adv. Synth. Catal. 362, 3604–3612 Saha, J., Das, I. (2020) Solvent dependent divergent reactivity of electron-rich dienones with and without visible light: Access to cyclopropanated furans and butenolides. Adv. Synth. Catal. 362, 609–617

Extramural Funding



Dr. Deepak Kumar

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Chemical investigation of medicinal plants for potential bioactive leads

Participants

Priyanka Yatham, NIPER JRF
Yogita Dahat, JRF
Chayan Banerjee, JRF (co-guide)

Collaborator(s)

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 cell lines 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 organosulfides, pentacyclic triterpenes and polyphenolic compounds against cancer cell lines.

Isolation and characterization of flavonoids and sesqueterpene as potential MAO inhibitors.

Development of analytical methods for isolation, purification of bioactive compounds and standardization of raw materials/crude extracts.

Work Achieved

We have been successful in isolation and characterization of several compounds belonging to terpene, xanthone, flavonoids, coumarin, and organosulfides class. The isolation of compounds has been achived employing modern chromatographic techniques and integration of several methods. These molecules are being explored for their potential against cancer cell lines and MAO.

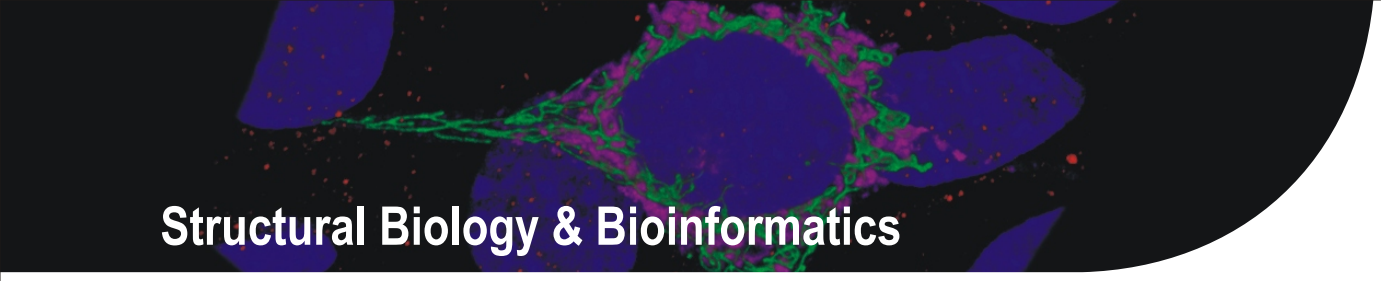
Future Research Plans

- 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.

Extramural funding

Affinity ultrafiltration liquid chromatography (UF-LC) assisted identification and characterization of α-glucosidase and α-amylase inhibitory constituents from Pterocarpus santalinus heartwood. Funding: National Biodiversity Authority, Chennai. 2020-2022, PI

Bio-assay guided isolation of anti-cancer compounds from Pterocarpus santalinus and assessment of cytotoxicity, pharmacokinetics and detailed molecular mechanisms. Funding: National Biodiversity Authority, Chennai. 2020-2022, Co-PI, PI – Dr Amit K Srivastava



Structural Biology & Bioinformatics

With a view to understand cellular function and dysfunction in human health and disease, researchers at the Structural Biology & Bioinformatics Division studies and 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

SRF : Sumangal Roychowdhury, Bidisha Das

Dr. Ramdhan Majhi, Technical Officer

Collaborator(s)

Professor Ujjwal Maulik,
Department 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.

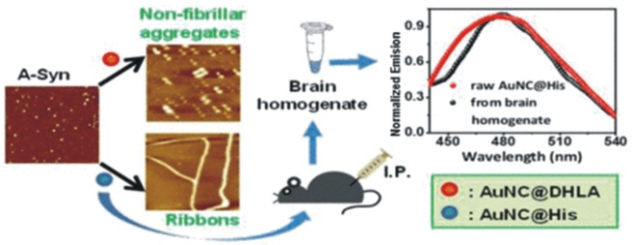
Aims and Objectives

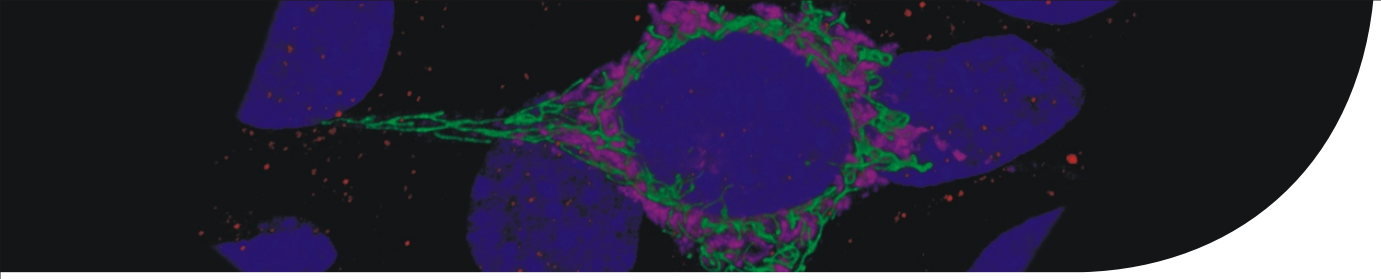
1. To detect, characterize and investigate in details the early folding pathways of proteins involved in different neurodegenerative diseases
2. To study early stages of aggregation of intrinsically disordered proteins (IDPs) in vitro and inside live cells using fluorescence correlation spectroscopy (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

Modulation of α-Synuclein Fibrillation by Ultrasmall and Biocompatible Gold Nanoclusters (Mahaptra et al 2020 ACS Chemical Neuroscience; doi: https://doi.org/10.1021/acschemneuro.0c00550)

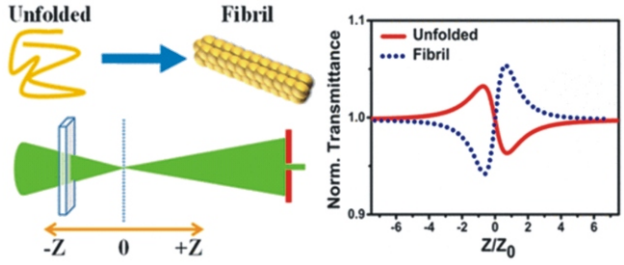
Parkinson's disease (PD) is the second most common neurodegenerative disorder, the pathogenesis of which is closely linked to the misfolding and aggregation of the neuronal protein α-Synuclein (A-Syn). Numerous molecules that inhibit/modulate the pathogenic aggregation of A-Syn in an effort to tackle PD pathogenesis have been reported, but none so far have been successful in treating the disease at the clinic. One major reason for this is the poor blood-brain barrier (BBB) permeability of most of the molecules being used. Therefore, using BBB-permeable (and biocompatible) nanomaterials as fibrillation modulators is gaining importance. In the present work, we show how nontoxic and ultrasmall gold nanoclusters (AuNCs) can systematically modulate the pathogenic fibrillation of A-Syn in vitro, based on the chemical nature of their capping agents, using two reported easily synthesizable AuNCs as models. In addition, we detect the BBB permeability in mice of one of these AuNCs solely by making use of its intrinsic fluorescence. Thus, our work exemplifies how AuNCs can be potential therapeutics against PD; while also acting as fluorescent probes for their own BBB permeability.





A Novel Tool to Investigate the Early and Late Stages of α-Synuclein Aggregation (Ghosh et al 2020 ACS Chemical Neuroscience; doi: https://doi.org/10.1021/acschemneuro.0c00068)

The accumulation of an inherently disordered protein α-synuclein (α-syn) aggregates in brain tissue play a pivotal role in the pathology and etiology of Parkinson's disease. Aggregation of α-syn has been found to be complex and heterogeneous, occurring through multitudes of early- and late-stage intermediates. Because of the inherent complexity and large dynamic range (between a few microseconds to several days under in vitro measurement conditions), it is difficult for the conventional biophysical and biochemical techniques to sample the entire time window of α-syn aggregation. Here, for the first time, we introduced the Z-scan technique as a novel tool to investigate different conformations formed in the early and late stage of temperature and mechanical stress-induced α-syn aggregation, in which different species showed its characteristic nonlinear characteristics. A power-dependent study was also performed to observe the changes in the protein nonlinearity. The perceived nonlinearity was accredited to the thermal-lensing effect. A switch in the sign of the refractive nonlinearity was observed for the first time as a signature of the late oligomeric conformation, a prime suspect that triggers cell death associated with neurodegeneration. We validate Z-scan results using a combination of different techniques, like thioflavin-T fluorescence assay, fluorescence correlation spectroscopy, Fourier-transform infrared spectroscopy, and atomic force microscopy. We believe that this simple, inexpensive, and sensitive method can have potential future applications in detecting/monitoring conformations in other essential peptides/proteins related to different neurodegenerative and other human diseases.

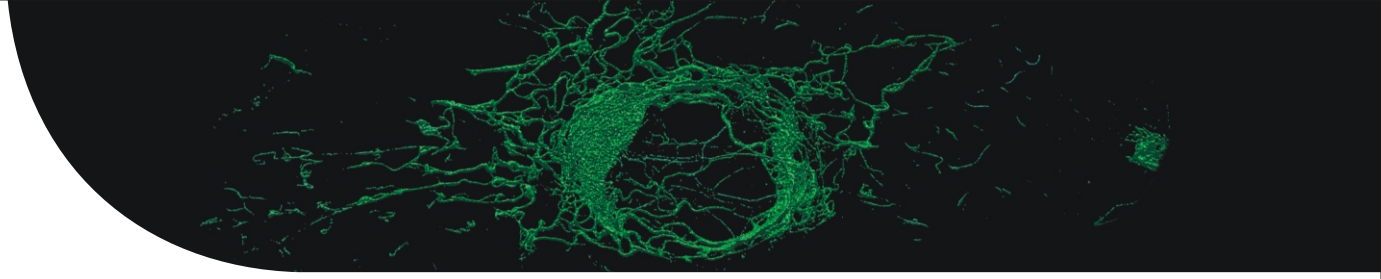


An exploration of the SARS-CoV-2 spike receptor binding domain (RBD) – a complex palette of evolutionary and structural features (Sanyal et al 2020 Biorxiv; doi: https://doi.org/10.1101/2020.05.31.126615)

SARS-CoV-2 spike protein (S) is associated with the entry of virus inside the host cell by recruiting its loop dominant receptor binding domain (RBD) and interacting with the host ACE2 receptor. Our study deploying a two-tier approach encompassing evolutionary and structural analysis provides a comprehensive picture of the RBD, which could be of potential use for better understanding the RBD and address its druggability issues. Resorting to an ensemble of sequence space exploratory tools including co-evolutionary analysis and deep mutational scans we provide a quantitative insight into the evolutionarily constrained subspace of the RBD sequence space. Guided by structure network analysis and Monte Carlo simulation we highlight regions inside the RBD, which are critical for providing structural integrity and conformational flexibility of the binding cleft. We further deployed fuzzy C-means clustering by plugging the evolutionary and structural features of discrete structure blocks of RBD to understand which structure blocks share maximum overlap based on their evolutionary and structural features. Deploying this multi-tier interlinked approach, which essentially distilled the evolutionary and structural features of RBD, we highlight discrete region, which could be a potential druggable pocket thereby destabilizing the structure and addressing evolutionary routes.

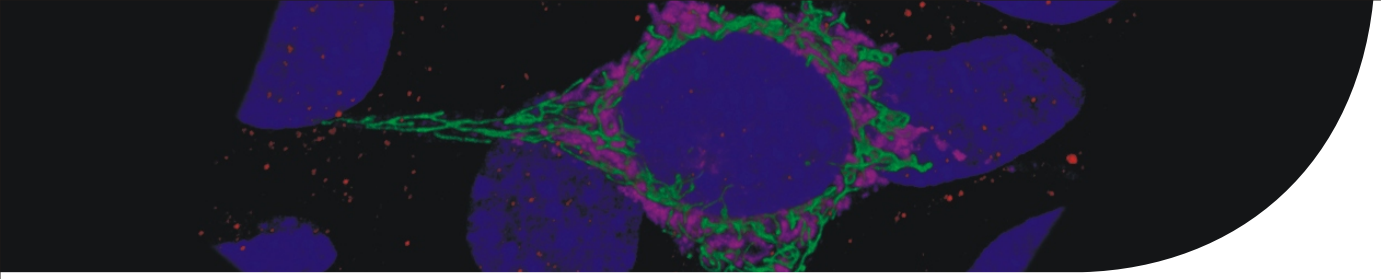
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Book Chapters / Invited Reviews

1. Chakraborty, Ritobrita, and Krishnananda Chattopadhyay. "Protein Folding, Dynamics and Aggregation at Single-Molecule Resolution." Frontiers in Protein Structure, Function, and Dynamics. Springer, Singapore, 2020. 239-258.
2. Basak, Sujit, Sombuddha Sengupta, and Krishnananda Chattopadhyay. "Understanding biochemical processes in the presence of sub-diffusive behavior of biomolecules in solution and living cells." Biophysical reviews (2019): 1-22.

PATENTS FILED / SEALED

AWARDS / HONOURS / MEMBERSHIPS

Krishnananda Chattopadhyay

- Fellow of West Bengal Academy of Science and Technology
- Fellow of the Royal Society of Chemistry

Ritobrita Chakraborty

- International Brain Research Organization (IBRO) International Travel Grant 2020 to speak at the Gordon Research Conference and Seminar on Protein Folding and Dynamics, Galveston, TX, USA, January, 2020.
- International Union of Pure and Applied Biophysics (IUPAB) Bursary to attend the Joint 12th EBSA and 10th ICBP-IUPAP Biophysics Congress, Madrid, Spain, July, 2019. • Department of Science and Technology (Govt. of India) International Travel Grant to attend the Joint 12th EBSA and 10th ICBP-IUPAP Biophysics Congress, Madrid, Spain, July, 2019.
- Best Poster Award, 43rd Indian Biophysical Society Meeting, Indian Institute of Science Education and Research-Kolkata, India, March, 2019.

Dwipanjan Sanyal

- Travel grant for Intrinsically disordered proteins: From molecules to systems; EMBO Workshop (08-13 December 2019; Bengaluru, India).

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
- Understanding the early events of alpha synuclein aggregation and its implications in Parkinson's Disease related neurodegeneration, Department of Biotechnology-NER as a Co-PI

CONFERENCES / WORKSHOPS

EMBO Practical Course on 'Cryo Electron Microscopy and 3D Image Processing of Macromolecular Assemblies and Cellular Tomography' was held at CSIR-IICB, Kolkata in Jan 2020

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

Organized jointly with EMBO Practical Course on 'Cryo Electron Microscopy and 3D Image Processing of Macromolecular Assemblies and Cellular Tomography', which was held at CSIR-IICB, Kolkata in Jan 2020 (20th and 21st Jan held at CSIR-IICB)



Dr. Subrata Adak
adaks@iicb.res.in



New *Leishmania* specific protein: PAS domain containing phosphoglycerate kinase

Participants

SRF : Aditi Mukherjee, Ayan Adhikari, Saroj Biswas, Priya Das, Sumit Das

JRF : Yuthika Dholey, Puja Panja, Gaurab Chowdhury
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. Toxic and 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. Five new parasite specific proteins are PAS domain containing phosphoglycerate kinase, heme containing adenylate cyclase, ascorbate peroxidase, pseudoperoxidase and NAD(P)H cytochrome b5 oxidoreductase. 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. Recently we discover a novel parasite specific protein, PAS domain containing phosphoglycerate kinase (LmPAS-PGK), which shows acidic pH (5.5)-dependent optimum catalytic activity. The PAS domain of LmPAS-PGK is expected to regulate PGK activity during catalysis, but the mechanism of regulation by PAS domain at the molecular level is uncharacterized.

Aims and Objectives

The aim of our goals is the structure and functional characterization of PAS domain containing phosphoglycerate kinase proteins in vitro. In this work, we have utilized the full-length, PAS domain-deleted and mutant enzymes to measure the enzymatic activity in the presence of divalent cation at various pH values. To identify the Mg^{2+} binding residues of the PAS domain, we exploited a systematic mutational analysis of all (four) His residues in the PAS domain for potential divalent cation binding.

Work Achieved

Catalytic activity measurement indicates that Mg^{2+} binding through PAS domain inhibits the PGK activity at pH 7.5, and this inhibition is withdrawn at pH 5.5. Replacement of His-57 with alanine resulted in depression in the presence of Mg^{2+} at pH 7.5, but H71A, H89A, and H111A showed similar characteristics with respect to the wild-type protein. Fluorescence and isothermal titration calorimetry studies revealed that H57 is responsible for Mg^{2+} binding in the absence of substrates. Thus, the protonated form of His57 at acidic pH 5.5 destabilizes the Mg^{2+} binding in the PAS domain, which is an essential requirement in the wild-type LmPAS-PGK for a conformational alteration in the sensor domain that, sequentially, activates the PGK domain, resulting in the synthesis of higher amounts of ATP.

Future Research Plans

Due to the lack of X-ray crystal structure of PAS domain-containing PGK protein from any other organisms in the literature, we have created a modeled structure of LmPAS-PGK, where His57 is located on the long λ5-helix of the regulatory PAS domain of LmPAS-PGK, which locates near hinge region of the catalytic PGK domain. The Mg^{2+} ions are hypothesized to form bridges between the PAS domain and the PGK domain. The X-ray crystal structure of divalent cation-bound PAS-PGK protein will be helpful in elucidating the complete network interaction of metal binding site in LmPAS-PGK in the near future.

PUBLICATIONS

Adhikari A, Biswas S, Mukherjee A, Das S, Adak S. (2019) PAS domain-containing phosphoglycerate kinase deficiency in *Leishmania major* results in increased autophagosome formation and cell death. Biochem J. 476, 1303-1321.

EXTRAMURAL FUNDING

Subrata Adak

Expression, intracellular localization and functional characterization of PAS domain containing phosphoglycerate kinase in *Leishmania*. 2017-2000 (DST, India)



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Bacterial Metabolic Pathway

Participants

SRF : Chittran Roy, Gourab Basu Choudhury, Atanu Pramanik

JRF : Rajeev Kumar,Arkaprabha Choudhury, Bidisha Chakraborty, Angira Saha, Md. Maruf Hossain
Chittran Roy, SRF, ICMR

Background

The metabolism of many microbial pathogens is extraordinarily complex, flexible and adaptive, making identification of suitable metabolic drugs targets challenging. In order to identify effective targets, an improved understanding of metabolic pathways from the structural, regulatory and evolutionary perspective is essential. Pantothenic acid also referred as vitamin B5, is an important metabolic precursor to coenzyme A (CoA), which is indispensable cofactor for nearly 7–13% of all characterized enzymes catalyzing varieties of biochemical reactions, e.g. fatty acid biosythesis. Furthermore, the phosphopantetheinyl portion of CoA is a crucial component of acyl carrier protein (ACP), essential for the biosynthesis of fatty acid, cholesterol and numerous regulatory mechanisms that involves acylation and acetylation. Typically, the pantothenate biosynthesis pathway comprises four enzyme-catalyzed steps in two separate branches. The first branch involves the conversion of α-ketoisovalerate, a common intermediate of valine and leucine biosynthesis pathways, into pantoate via two enzyme catalyzed steps. The initial conversion of α-ketoisovalerate into ketopantoate is catalyzed by 3-methyl-2-oxobutanoate hydroxymethyltransferase encoded by the panB gene. Consequently, in a second step, ketopantoate is reduced to pantoate via NADPH-dependent reduction reaction catalyzed by ketopantoate reductase encoded by panE gene. Separately, in the second branch of the pantothenate biosynthesis pathway, β-alanine is synthesized from L-aspartate by aspartate 1-decarboxylase encoded by panD gene. In the last step, pantothenate synthetase encoded by the panC gene catalyzes the ATP dependent condensation of pantoate and β-alanine to form pantothenate. Although the overall structure of the pantothenate biosynthesis pathway is almost similar in all the organisms, the metabolic sources of β-alanine may vary in some bacterial, fungal and plants species.

Aims and Objectives

In the current investigation, we observe that many bacterial species possess multiple copies of pantothenate biosynthesis pathway (especially panE) genes. Furthermore, as duplication frequencies of ketopantoate reductases (KPR), an enzyme that catalyzes the rate-limiting step in pantothenate biosynthesis pathway was found to be significantly higher than others. To shed light on factors possibly responsible for biased evolutionary selection on ketopantoate reductases, we carried out comparative X-ray crystallographic, steady-state kinetics, and molecular dynamics simulation analysis of P. aeruginosa KPR with orthologs.

Work Achieved

In our current study, we find that many bacterial species have acquired multiple copies of pantothenate biosynthesis pathway genes (Figure 1). As previous studies have shown that, overexpression of pantothenate biosynthesis pathway genes can significantly increase production of pantothenate and CoA. The increased frequencies for multiple copies of pantothenate biosynthesis pathway genes depict the adaptive evolutionary strategies in bacterial species for enhancing the production of pantothenate and CoA. Strikingly, many bacterial species were also found to lack panE and panD gene, and depend on alternative enzymes or metabolic sources such as panG, ilvC, spermidine and uracil degradation pathways. Interestingly, in contrast to pantothenate biosynthesis pathway, downstream CoA biosynthesis pathway genes rarely exist in multiple copies. Thus, suggesting that the production of CoA is more stringently regulated than the production of pantothenate.

Among four genes involved in pantothenate biosynthesis, the frequency of multiple panE gene copies is significantly higher, in fact, 1/3rd of bacterial species possessing all four pantothenate biosynthesis genes possess multiple copies panE genes. From existence of such gene distribution pattern, apparently it seems that the reaction catalyzed by panE is a rate-limiting in pantothenate biosynthesis pathway. Furthermore, to shed light on factors responsible for dynamic evolutionary selections on KPRs,

we carried out the comparative structural analysis of P. aeruginosa KPR with other orthologs (Figure 2). From our analysis of apo and NADP+ bound crystal structures of PaKPR with orthologs, it was observed that the residues involved in interaction with specific phosphate moiety of adenylate of NADP+ are relatively less conserved than other. The cofactor binding interface of PaKPR is more enriched with positively charged residues than EcKPR. Since enriched positive charged interface increases long-range electrostatic interactions for more negatively charged NADPH cofactor than NADH cofactor, PaKPR exhibit higher specificity for NADPH than EcKPR. Additionally, the conformational changes triggered by binding of NADP+ is also significantly different, as the PaKPR exhibits quasi-closed to open conformational transition with significantly lesser shear-like domain motions than observed in EcKPR.

Future Research Plans

To investigate the evolutionary selection of NADPH over NADH as cofactor for KPR.

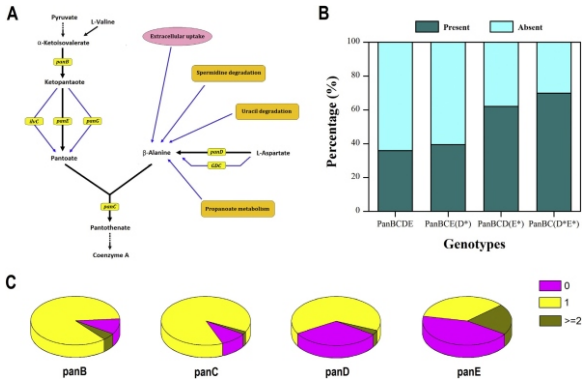


Fig. 1: Dynamic evolutionary trajectories in Vitamin B5 biosynthesis pathways (A) Schematic overview of pantothenate biosynthesis pathways depicting key enzymatic steps (thick black arrow) and alternative metabolic source or promiscuous enzymes/genes catalyzing the particular reactions step (blue arrow). The enzymes/ genes relevant for particular enzyme catalyzed reaction are shown in yellow boxes. (B) Relative abundance of various genotypes responsible for functional pantothenate biosynthesis pathway in bacterial species. Mark (*) indicates consideration for alternative metabolic sources of product or enzymes catalyzing particular reaction step in pantothenate biosynthesis pathway (C) Pie chart graph showing the frequency of bacterial species carrying different copy numbers (i.e. absent (0), single copy (1), multiple copies (≥2)) of key four enzymes/genes associated with pantothenate biosynthesis pathway.

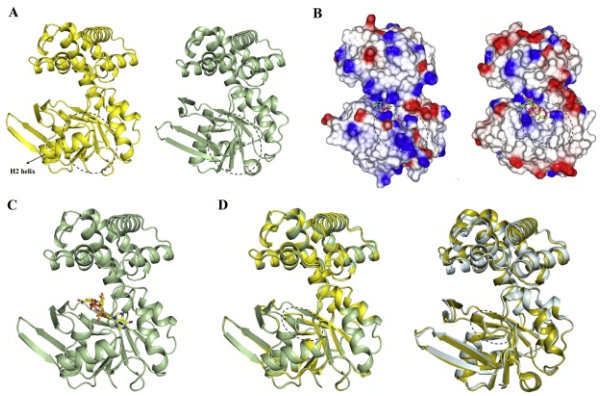


Fig. 2: Comparative structural analysis of apo and NADP+ bound structures of KPRs from P. aeruginosa and E. coli. (A) The depiction of additional H2 helix present in close-milieu of the NADP+ binding interface of PaKPR that is typically absent in EcKPR and other well-characterized KPRs. (B) Surface electrostatic representation showing significant enrichment of positively charged residues in the cofactor binding interface of PaKPR (right) compared to EcKPR (left). The enriched positively charged interface may significantly contribute to increased binding and catalytic proficiency of PaKPR through long-range electrostatic interactions. Red indicates negative potential, blue indicates positive potential. (C) Cartoon representation of crystal structure of PaKPR in complex with NADP+. (D) Comparison of apo and NADP+ conformers of PaKPR (right) with EcKPR (left), we can observe that significant transition of conserved GXGXXG motif from quasi closed-to-open conformation as seen in PaKPR, is absent in EcKPR, as GXGXXG motif exists in open conformer in both apo and NADP+ bound state.

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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Structural elucidations of biomacromolecules to understand their functional mechanisms

Participants

JRF : Mr. Aneek Banerjee, Mr. Krishnamoorthi Srinivasan

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, (Viva voce completed)
Mr. Sandip Dey (Thesis submitted)

Collaborator(s)

Prof. Siddhartha Roy,
Bose Institute, Kolkata

Dr. Chandana Barat,
St. Xavier's College, Kolkata

Dr. Krishnananda Chattopadhyay,
Structural Biology Division, CSIR-IICB, Kolkata

Background

Our group primarily employs cryo-electron microscopy (Cryo-EM) along with various biochemical and biophysical tools to study macromolecular assemblies involved in disease-related crucial cellular functions (e.g. metabolic diseases, neurodegerative diseases, cancer etc.).

Aims and Objectives

Primarily we are a ribosome-research group. 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-resolution 3D cryo-EM.

Besides, we are also interested in structural characterization of molecular interactions involved in different diseases to get insights into the mechanisms of the related cellular processes.

Work Achieved

A. Studies on macromolecules related to neuro-diseases Alzheimer's disease (AD) progression involves amyloid-beta (Aβ) aggregation cascade where intermediate oligomers show prime toxicity. In one of our recent studies we have reported a synthetic peptide (Pactive) identified from a fibrinolytic enzyme, extracted from the roots of A. Indica, a medicinal plant of the Indian subcontinent, which showed noticeable anti-amyloidogenicity against Aβ, sequestering toxic Aβ oligomers and fibrilsinto nontoxic off-pathway oligomeric forms. The interactions of identified peptide with Aβ have been established (Figure 1A,B).

Another recent study was on the G-protein coupled receptor, which is implicated in many psychiatric disorders. We have made a molecular model of the full-length 5-HT2AR in order to understand the structural dynamics of the ligand-free active form of the receptor using theoretical approaches. We also have standardized a novel strategy to purify full-length receptor (5-HT2AR) for further experimental studies (Figure 1C).

Figure 1:

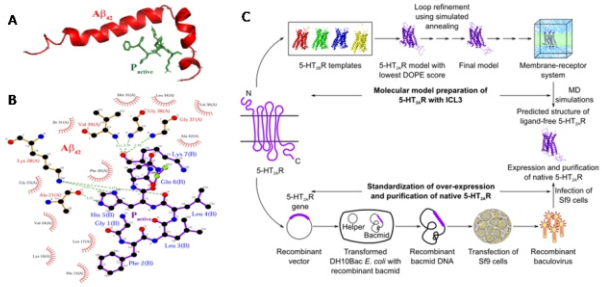


Figure 1: Docking results using Haddock 2.2 Web server show: (A) the pocket of Aβ42 (PDB: 1IYT, Model 1) where Pactive accommodates itself, and (B) the interactions involved. (C) Schematic representation of modeling and purification of 5-HT2A receptor.

B. Research on metabolic disease-related macromolecular assembly

Amyloidogenesis of insulin reduces its bioavailability during long-term storage. Commercially available insulin is formulated with phenolic compounds as excipient, which stabilizes active hexameric form of insulin. To find out a nontoxic substitute of cytotoxic phenolic products we have studied the effects of

naturally occurring polyphenols. Our study found that resveratrol, a natural polyphenolic compound, has the potential to be used as nontoxic insulin stabilizing excipient in commercial formulation. Structural analysis using cryo-EM revealed that resveratrol-stabilized insulin adopts a tri-lobed globular shape resembling native insulin hexamer conformation. In collaboration with Dr. Partha Chakraborti's group, we have also shown that resveratrol-treated insulin retains full biological activities and it exerts no toxicity towards cell lines (Figure 2).

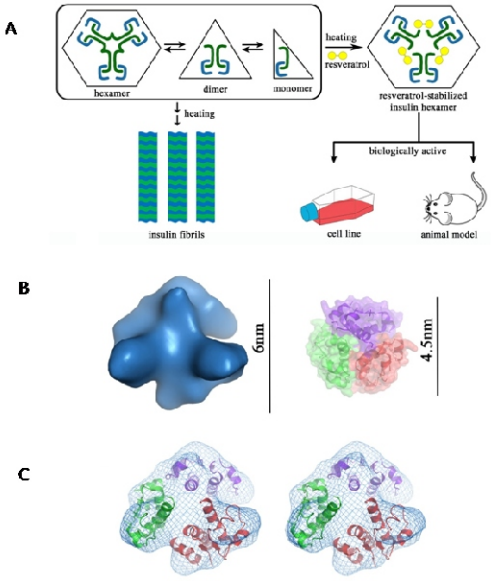


Figure 2: (A) Schematic representation of the proposed model for resveratrol-mediated insulin stabilization. The resveratrol-stabilized insulin oligomers (likely hexamer) are fully bioactive. (B) Cryo-EM 3D density map of insulin in complex with resveratrol shows globular tri-lobed structure (left panel) and crystal structure of the insulin hexamer containing phenolic derivatives (PDB: 1EV6) is shown (righ panel). (C) Stereo view of the density map (blue mesh surface) where atomic structures of three dimers are fitted into the lobes of the density map.

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 correlative approaches in conjunction with high resolution cryo-EM to understand functional role of various macromolecular assemblies that participate in key cellular processes involved in human diseases (thereby potential drug targets).

PUBLICATIONS

1. Bhattacharyya R, Bhattacharjee S, Pathak BK, Sengupta J. (2020) Heptameric Peptide Interferes with Amyloid-β Aggregation by Structural Reorganization of the Toxic Oligomers. ACS Omega, 5(26):16128-16138. doi: 10.1021/acsomega.0c01730.

2. Pathak BK, Das D, Bhakta S, Chakrabarti P, Sengupta J. (2020) Resveratrol as a nontoxic excipient stabilizes insulin in a bioactive hexameric form. J Comput Aided Mol Des., 34(8):915-927. doi: 10.1007/s10822-020-00311-3. Epub 2020 Apr 9.

3. Akbar S, Mozumder S, Sengupta J. (2020) Retrospect and Prospect of Single Particle Cryo-Electron Microscopy: The Class of Integral Membrane Proteins as an Example. J Chem Inf Model., 60(5):2448-2457. doi: 10.1021/acs.jcim.9b01015. Epub 2020 Mar 20.

4. Mozumder S, Bej A, Srinivasan K, Mukherjee S, Sengupta J. (2020) Comprehensive structural modeling and preparation of human 5-HT2A G-protein coupled receptor in functionally active form. Biopolymers, 111(1):e23329. doi: 10.1002/bip.23329.

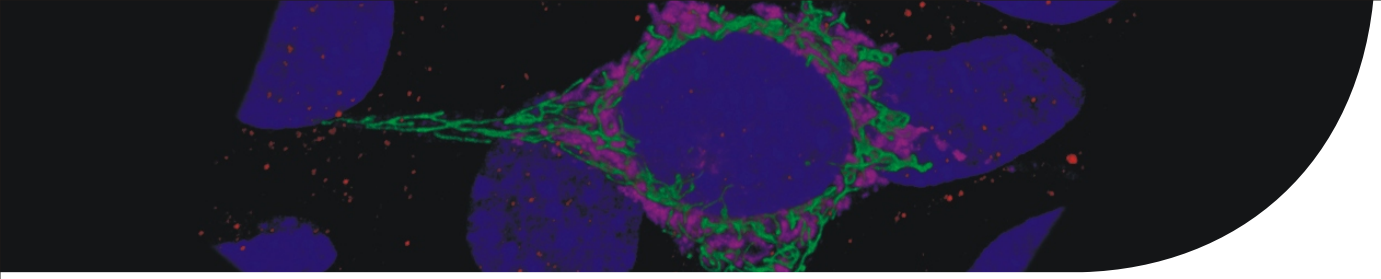
5. Ghosh R, Kaypee S, Shasmal M, Kundu TK, Roy S, Sengupta J. (2019) Tumor Suppressor p53-Mediated Structural Reorganization of the Transcriptional Coactivator p300. Biochemistry, 58(32):3434-3443. doi: 10.1021/acs.biochem.9b00333.

Extramural Funding

SERB (DST) funded project (CRG/2019/001788) entitled 'High-resolution structural descriptions of HflX's interactions with 70S ribosome and ribosomal subunits to decipher its functional role in bacteria under stress'; Sanctioned in February, 2020.

Conference/Workshop

- Organized part of the EMBO Practical Course on 'Cryo Electron Microscopy and 3D Image Processing of Macromolecular Assemblies and Cellular Tomography' at CSIR-IICB, Kolkata in Jan 2020 (20th and 21st Jan held at CSIR-IICB where Prof.



Joachim Frank, Nobel Laureate, Chemistry 2017, delivered lecture)

Invited talks

- Delivered 'Plenary lecture' and chair a session in 12th Asia-Pacific Microscopy Conference (APMC-2020) Hyderabad International Convention Centre, 3-7 February 2020, Hyderabad, India
- Invited lecture at INSA Outreach Programme, Kolkata chapter organized at Bidhannagar College, Kolkata on February 26, 2020



Dr. Sucheta Tripathy

tsucheta@gmail.com/tsucheta@iicb.res.in



Piecing together genomes of microbes for exploring thebiological treasure trove

Participants

RA: Aditya Narayan Sarangi, SRA-CSIR;

SRF: Samrat Ghosh, Deeksha Singh, Mayuri Mukherjee, Shashi Kant,

JRF: Asharani Prusty, Priyashree Bhadra, Aribam Geeta, Subhajeet Dutta Masters students: Ms. Shreya Kothari.

Students Graduated:
Abhishek Das (Oct 2019)
Subhadeep Das (June 2019)
Arijit Panda (March 2019)

Thesis Submitted:
Pijush Das

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

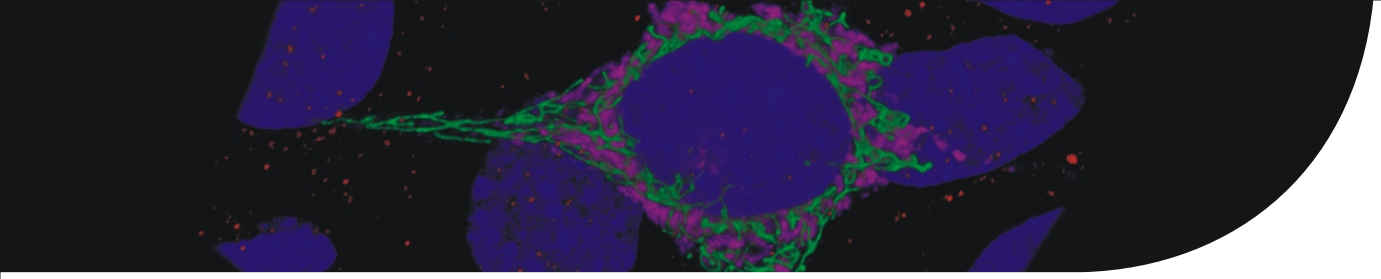
India is a major mega diverse nation with most of its microbial populations lying under explored. We work on a plethora of organisms belonging to different phylogenetic clades towards solving the biological riddles encoded in their genomes and exploiting them for beneficial purposes. We use existing 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.

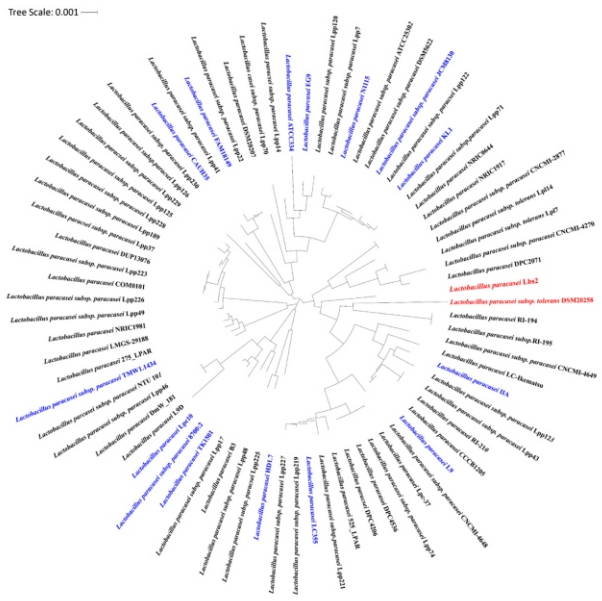
Aims and Objectives

Analyzing complex genomes in understanding the genomic re-arrangements.

Developing biological softwares for data analysis.

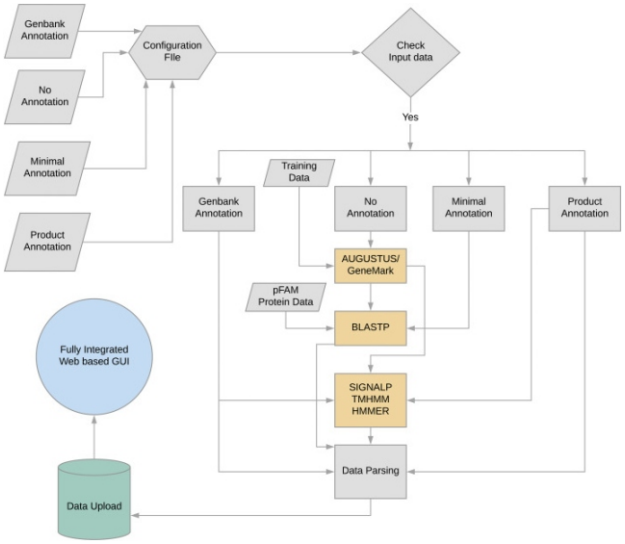
Work Achieved:
We worked on an endophytic fungus isolated from Jaduguda mines (this fungus was isolated by Dr. Anindita Seal, Calcutta University). This endophytic fungus is known to have growth benefits for higher plants in boosting the vegetative and reproductive growth of the host plant. However, it was not known whether this fungus is alone capable of fixing nitrogen for the host. Our genomics work unraveled that there is another diazotrophic bacteria harboring this fungus which in turn fixes nitrogen for the host in a somewhat unknown yet spectacular association involving a tri-partite interaction (Paul et.al., Plant Cell, 2020). This was a collaborative work with Calcultta University, NIPGR, Delhi and IIT Delhi. We have carried out large scale data analysis involving one of the native strains of Lactobacillus casei and ~70 other genomes belonging to the same genus. Our largescale analysis not only established the correct taxonomic position of the native strain from Lactobacillus casei to Lactobacillus paracasei but als corrected taxonomic positions of many other species erroneously identified as a different spacies. We used multiple





algorithms for this purpose including a popular tool based on tetra nucleotide abundance (CheckM). The whole genome phylogenetic trees are represented in Fig-1.

We have created a fully automated genome annotation and visualization tool based on docker called as genome Annotator Light (Panda et. al.; 2020). This containerized version can run on any platform and is independent of third party utility softwares. This package is gaining huge popularity in recent days and is extremely lightweight. The functional workflow is deicted in Fig -2.



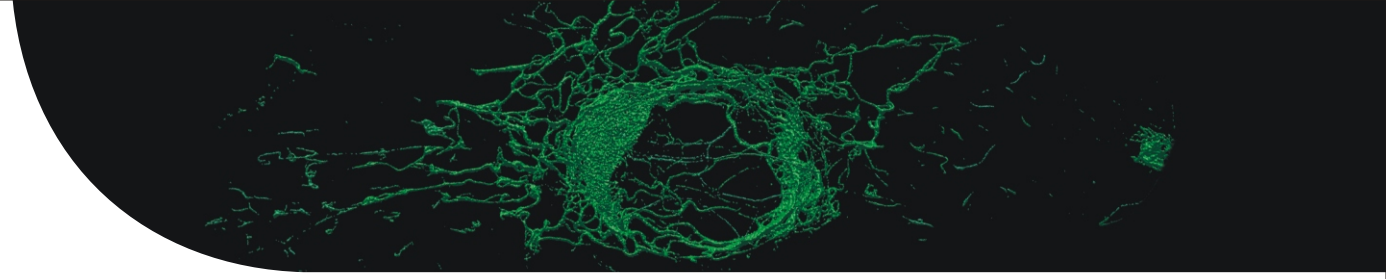
In addition, we worked on multiple collaborative projects and the publications are listed as below.

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. Ghosh S, Sarangi AN, Mukherjee M, Bhowmick S, Tripathy S*. Reanalysis of Lactobacillus paracasei Lbs2 Strain and Large-Scale Comparative Genomics Place Many Strains into Their Correct Taxonomic Position. Microorganisms. 2019 Oct25;7(11). pii: E487. doi: 10.3390/microorganisms7110487. PubMed PMID: 31731444.
2. Prasad S, Gaddam A, Jana A, Kant S, Sinha PK, Tripathy S, Annapurna K, Ferreira JMF, Allu AR, Biswas K. (2019) Structure and Stability of High CaO- and P2O5-Containing Silicate and Borosilicate Bioactive Glasses. J PhysChem B. 2019 Aug 23. doi: 10.1021/acs.jpcb.9b02455.
3. Banerjee, N., Das, S., Tripathy, S. et al. MicroRNAs play an important role in contributing to arsenic susceptibility in the chronically exposed individuals of West Bengal, India Environ SciPollut Res (2019). https://doi.org/10.1007/s11356-019-05980-8
4. Elucidating the effect of CaF2 on structure, biocompatibility and antibacterial properties of S53P4 glass. S Prasad, S Ganisetti, A Jana, S Kant, PK Sinha, S Tripathy, K Illath, Journal of Alloys and Compounds, Volume 831, 5 August 2020, https://doi.org/10.1016/j.jallcom.2020.154704.
5. Paul K, Saha C, Nag M, Mandal D, Naiya H, Sen D, Mitra S, Kumar M, Bose D, Mukherjee G, Naskar N, Lahiri S, Das Ghosh U, Tripathi S, Poddar Sarkar M, Banerjee M, Kleinert A, Valentine A, Tripathy S, Sinharoy S, Seal A. A Tripartite Interaction among the Basidiomycete Rhodotorula mucilaginosa, N2-fixing Endobacteria, and Rice Improves Plant Nitrogen Nutrition. Plant Cell. 2020, Feb. 32(2):486-507. [Epub ahead of print] PubMed PMID: 31757927.
6. 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]

AWARDS / HONOURS / MEMBERSHIPS

Research Advisory board of National Tea Research Foundation (2019-2022)

Associate Editor of Frontiers in Genetics and Microbiology (2019)
Senior Editor for Molecular Plant Microbial Interaction (An American Phytopathological Society Journal)

Students
Deeksha Singh got full travel award from International Association of Cyanophyte and DBT CTEP travel award, 2019 to attend 21st Symposium of the International Association of Cyanophyte/Cyanobacteria Research, University of Queensland, Australia. Title of oral presentation: Genome mining of an environmental cyanobacteria Halomicronema for potential bioremediation and bio-metabolite production

EXTRAMURAL FUNDING

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.

Sucheta Tripathy (Acting PI)
Identification of stress responsive microRNA in Arabidopsis under altered GSH condition, DST(2017-2020).

CONFERENCES / WORKSHOPS : 3

INVITED TALKS BY CSIR-IICB FACULTY

"Taming the genomics big data by horn - A new perspective" at the international conference Recent Trends in Bioinformatics hosted at NEIST, Jorhat, May 2019.



Dr. Saikat Chakrabarti

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Understanding the molecular mechanisms underlying systemic diseases and host-pathogen interactions using systems biology approaches

Participants

SRF : Ishita Mukherjee, Subhangshu Das, Krishna Kumar

JRF : Sarpita Bose, Priyanka Mullick, Izaz Monir Kamal, Priyanka Panigraghi, Aninnita Choudhury

Dr. Nupur Biswas Research Associate

Collaborator(s)

Simanti Datta, IPGMER, Kolkata
Oishee Chakrabarti, SINP, Kolkata
Subhabrata Sen, SNU, Delhi
Koustuv Panda, CU

S N Bhattacharyya, IICB
Partha Chakrabarti, IICB
Dipyaman Ganguly, IICB
Sandip Paul, IICB
Nahid Ali, IICB
Sib Sankar 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. 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

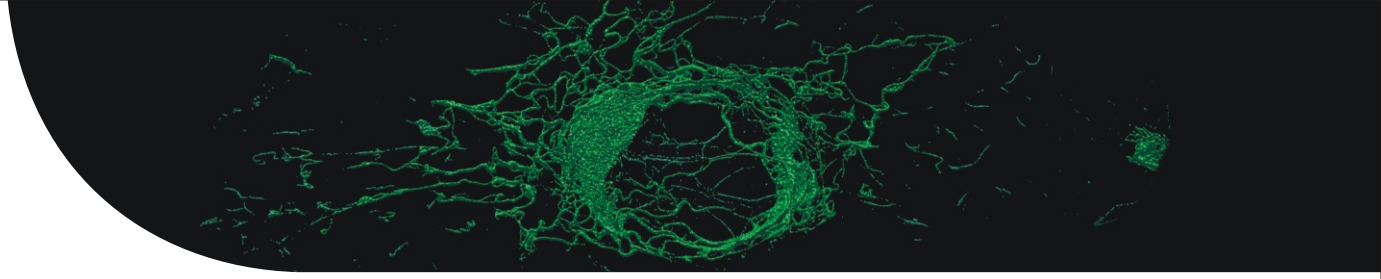
- To understand the hidden properties of systemic disease using network biology and graph theoretical approaches.
- To construct and analyze the protein-protein interactions (PPI) networks of host-pathogen system in order to identify novel targets.
- To validate the importance of the identified important 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 host-pathogen interactions

Network analysis in *Leishmania donovani*: We have studied the human pathogen, *Leishmania donovani* by compiling and analyzing the 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 (HSP78) using the network biology approach and its probable inhibitor using high throughput virtual screening (HTVS) technique(Figure 1 and 2) (1). Expression analysis of this protein belonging to heat shock protein family suggests amastigote specific expression whereas knock-out studies confirmed the importance of this protein in sustaining the infection within mouse bone marrow macrophages infected with *L. donovani*. HTVS study suggested a potential inhibitor (Ap5A) of the target protein which significantly reduced parasite burden in infected mouse bone marrow macrophages when used in dose dependent manner. This work was performed in collaboration with Prof. Nahid Ali's laboratory at IICB.

Identification of bacterial small-RNA sequences and their



targets with probable binding region

Bacterial small-RNA (sRNA) sequences are functional RNAs, which play an important role in regulating the expression of a diverse class of genes. We have developed new tools and techniques to identify sRNA and their targets through an integrated online platform called 'PresRAT'. PresRAT uses the primary and secondary structural attributes to predict sRNA from a given sequence and/or bacterial genome. PresRAT also finds probable target mRNAs of sRNA sequences from a given bacterial chromosome and further identifies the probable sRNA-mRNA binding regions. We have also implemented a protocol to build and refine 3D models of sRNA and sRNA-mRNA duplex regions using this platform (2).

Quantitative image analysis of microscopic images of sub-cellular organelles

We have been developing image processing and analytical tools to inspect microscopic images of sub-cellular organelles to provide more quantitative interpretation of the cell biological data. Z-stacked microscopic (e.g., confocal, STED) images were converted to pixel matrices and various colour channels were processed using MATLAB image processing tool box. 3D models of the cellular substructures were created by combining the z-stack slides and converting the 3D pixel matrix into Cartesian coordinates. Using the Cartesian coordinate representation of the sub-cellular organelles like endoplasmic reticulum (ER), mitochondria, cytoskeletal framework formed by actin filaments, we could estimate quantitative measurements like volume, inter-organeller distance and overlap, mitochondrial shape and size, actin filament length and localization, etc.

We have made a significant technical advancement in our sub-cellular image analyses where by converting the pixels into pseudo-unit length and estimated then eighbourhood analysis between ER and mitochondrial membranes which falls within 20% error range of actual measurement derived by electron microscopy and/or high resolution confocal microscopy. This demonstrated that careful imaging and astute analyses, a substantially significant amount of extra information can be derived from even "diffraction limited" images. Our image analysis efforts have successfully complimented various important cell biological discoveries (3, 4).

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.

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.

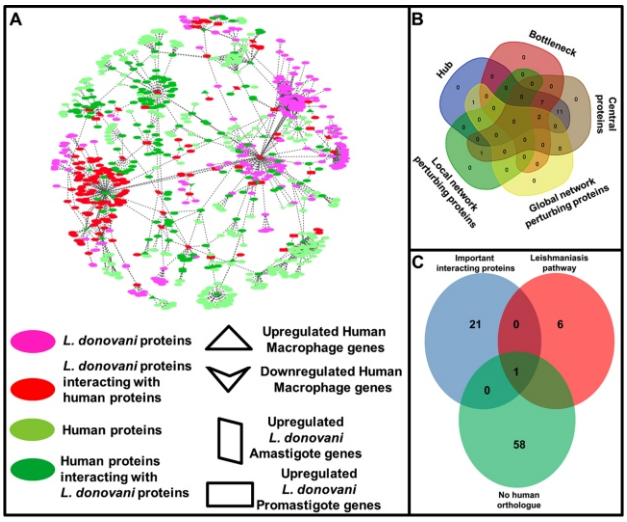


Figure 1: Identification of important interacting proteins (IIPs) from the *Leishmania donovani* – human protein-protein interaction network. Pictorial representation of the protein-protein interaction network between human and *L. donovani (Panel A)*. Total number of IIPs as overlap between important network properties like Hub ness, bottleneck property and network perturbation potential (Panel B). Overlap between IIPs, *L. donovani* proteins that are part of KEGG Leishmaniasis pathway and are non-orthologous to human proteins (Panel C).

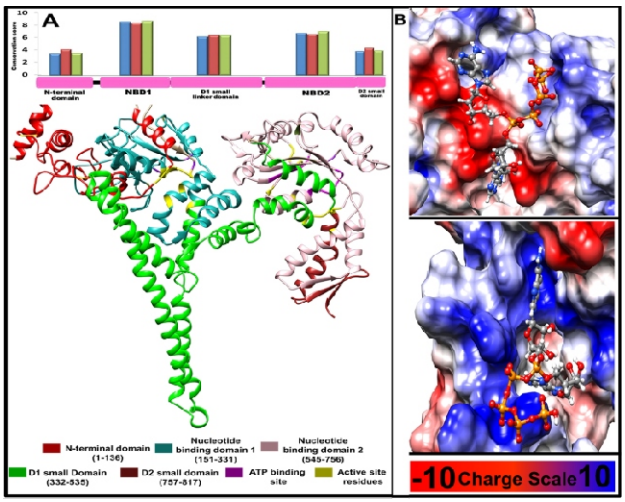


Figure 2: Structural features of *L. donovani* HSP78 protein. (A) Two-dimensional (2D) and three-dimensional (3D) domain organization of *L. donovani* HSP78 protein and their relative conservation. Blue, red and green bars show conservation of individual domain calculated using the representative sequences from all phyla, Euglenozoa and Ascomycota, respectively. Panel B and C show the binding mode and probable interactions of the selected inhibitor, Ap5A, which shows significant binding potential for nucleotide binding domains 1 and 2, respectively.

PUBLICATIONS

1. Das S, Banerjee A, Kamran M, Ejazi SA, Asad M, Ali N, Chakrabarti S*. A chemical inhibitor of heat shock protein 78 (HSP78) from *Leishmania donovani* represents a potential antileishmanial drug candidate. J Biol Chem. 2020 Jul 17;295(29):9934-9947.

2. Kumar K, Chakraborty A, Chakrabarti S*. PresRAT: a server for identification of bacterial small-RNA sequences and their targets with probable binding region.RNA Biol. 2020 Oct 25:1-8.

3. Mookherjee D, Das S, Mukherjee R, Bera M, Jana SC, Chakrabarti S, Chakrabarti O. RETREG1/FAM134B mediated autophagosomal degradation of AMFR/GP78 and OPA1 -a dual organellar turnover mechanism.Autophagy.2020 Jul 1:1-24.

4. Kaul Z, Mookherjee D, Das S, Chatterjee D, Chakrabarti S, Chakrabarti O. Loss of tumor susceptibility gene 101 (TSG101) perturbs endoplasmic reticulum structure and function.BiochimBiophysActaMol Cell Res. 2020 Sep;1867(9):118741.

Book Chapters / Invited Reviews

1.Nupur Biswas* and Saikat Chakrabarti*.Artificial Intelligence (AI)-Based Systems Biology Approaches in Multi-Omics Data Analysis of Cancer.Front. Oncol.2020.

EXTRAMURAL FUNDING

Saikat Chakrabarti (Co-PI)
Platform integration for high Through-put multi omics data analysis and text
processing. 2020 - 2025. (Department of Biotechnology, India).

Genome sequencing of the SARS-CoV2 variants from West Bengal.2020-2021. (CSIR, India).





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Protein Conformation Linked Human Diseases and Nano-Formulation for Cancer Therapy

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Name of collaborator within CSIR-IICB

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Background

The misfolded fibrillar aggregate is directly linked to a large number of human diseases, known as amyloidoses. There is also a growing number of reports of functional amyloids that provide some beneficial role to our cellular systems. In situ measurements also revealed that a great number of proteins failed to maintain their folded native structure under harsh denaturing conditions and, transformed into amyloid-like fibrils. Therefore, now it is thought that amyloid-like protein aggregation is a kind of universal phenomenon and it largely depends on proteins structure, stability and solution conditions. This has a great pathological and physiological implication and databases are made with a huge amount of data linked to amyloid fibril formation and their overall pathological and biochemical implications

Work Achieved

Conformation of Lysozyme in its Oligomeric State by Raman Spectroscopy

We report here both the secondary and tertiary structure intricacy of highly folded hen egg-white lysozyme (HEWL) in its crystalline state, weakly folded oligomer assembly and steric zipped thermodynamically most stable fibrillar structure by Raman spectroscopic method. Lysozyme, like many other well-folded globular proteins, under harsh conditions produces nano-scale oligomer assembly and amyloid-like fibrillar aggregates. Engaging Raman microscopy, we made a critical structural analysis of oligomer and other assembly structures of hen egg-white lysozyme and provided a semiquantitative estimation of protein secondary structure in a different state of its fibrillation. A strong amide I band at 1659 cm-1 and N-Cα-C stretching vibrations bands at ~892 and ~934 cm−1 clearly indicated the presence of a substantial amount of α-helical folds of the protein in the oligomeric assembly state. Raman difference spectrum and the band fitting analysis revealed some increase in β-sheet and PPII like secondary structure in the oligomer form without major loss of α-helical folds found in the monomeric state.

Insulin Fibrillation by NMR and Raman Spectroscopic Analysis

Insulin is an excellent hormonal protein, however, some instability cases its aggregation which has interested many groups in exploring structural and kinetics aspects of its fibrillation. An hydrophobic residue segment of insulin B chain is a key player in insulin fibril formation. However, we established that salt bridge formation between Glu4 in A chain and residuesTyr26 and Lys29 in the C-terminal of B-chain hinder the hydrophobic collapse (and formation of molten globule state) that lead to eventual formation of cross-β-sheet rich amyloid formation. (Both the NMR and Raman spectroscopic analysis, and collaboration with Dr. Anirban Bhunia establish) the atomic detail of the interaction by studying the three types of insulin which are varied in sequence number.

Future Research Plans

(i) Understanding amyloid formation mechanism and its

implication in amyloid diseaes

(ii) Structural implication of protein oligomers in several disease formation

(iii) Nando-biomeicine

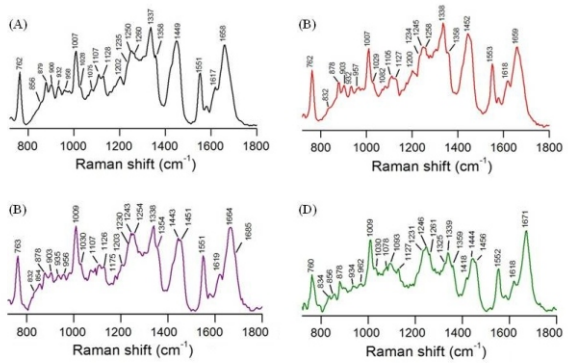


Figure 2: 532 nm excited Raman spectra (500-1800 cm-1) of lysozyme monomer, oligomer, protofiber, and fiber

PUBLICATIONS:

1. Khanppnavar, B; Roy,A.; Chandra, K.; Uversky, V. N.; Maiti, N.C; Datta, S., Deciphering the structural intricacy in virulence effectors for proton-motive force mediated unfolding in type-III protein secretion, International Journal of Biological Macromolecules, 159, 2020, 18–33

2. Bera, K, Mondal, A., Pal, U., and Maiti, N.C., Porphyrin-Armored Gold Nanospheres Modulate the Secondary Structure of α-Synuclein and Arrest Its Fibrillation, J. Phys. Chem. C 2020, 124, 11, 6418-6434

3. Dolui, S., Mondal, A. Roy, A., Pal, U. Das, S., Saha, A. and Maiti, N.C., Order, Disorder, and Reorder State of Lysozyme: Aggregation Mechanism by Raman Spectroscopy, J. Phys. Chem. B, 2020, 124, 50-60

4. Ratha, B. N.; Kar, R.K.; Bednarikova, Z.; Gazova, Z.; Kotler,S.A.; Raha, S.; De, S.; Maiti, N. C and Bhunia, A., Molecular Details of a Salt Bridge and Its Role in Insulin Fibrillationby NMR and Raman Spectroscopic Analysis, J. Phys. Chem. B, 2020, 124, 1125−1136.

5. Chowdhury, T.; Bera, K.; Samanta, D.; Dolui, S.; Maity, S.; Maiti, N. C.; Ghosh, P. K.; and Das, D., Unveiling the binding interaction of zinc (II) complexes of homologous Schiff-base ligands on the surface of BSA protein: A combined experimental and theoretical approach, Appl. Organometal Chem., 2020,34, e5556

6. Majumder, L.; Chatterjee, M.; Bera, K.; Maiti, N. C.; Banerji, B., Solvent-Assisted Tyrosine-Based Dipeptide Forms Low-Molecular Weight Gel: Preparation and Its Potential Use in Dye Removal and Oil Spillage Separation from Water, Acs Omega, 2019, 4, 14411−14419

AWARDS / HONOURS / MEMBERSHIPS

(1) Author with the highest number of publications in the journal, Journal of Proteins and Proteomics in the last 10 years, by Springer Nature

(2) Highest number of Cover Pages and Designed in the journal, Journal of Proteins and Proteomics by an author between 2010 and 2018, by Springer Nature

EXTRAMURAL FUNDING

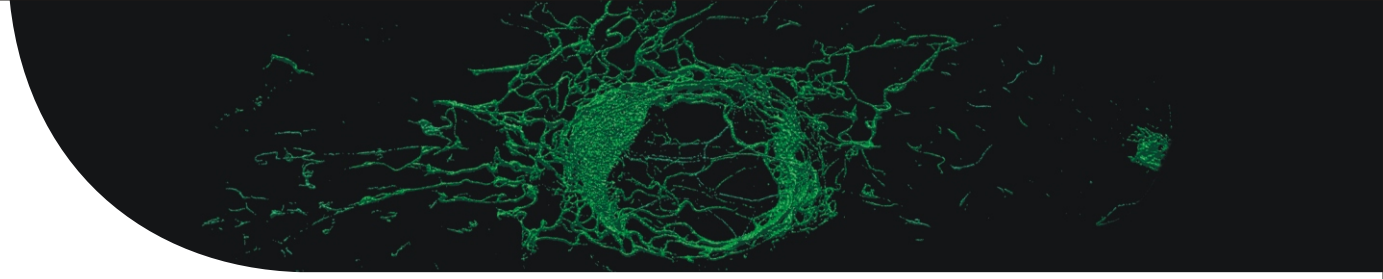
1. Structural Implication of Amyloid Oligomers in Alzheimer's Disease, SERB, DST 2017-2021, 37 lacs, File No: EMR/2016/006322

CONFERENCES / WORKSHOPS

1. Porphyrin Gold Nanomaterial: an Efficient Drug Delivery Systems, , 19th All India Congress of Genetics and Genomics, CSIR-Indian Institute of Chemical Biology, Dec 2-4, 2019
2. Effect of Mutation on Alpha-Synuclein Structure and Aggregation: Molecular detail by Raman and Fluorescence Spectroscopy, National workshop on Fluorescence and Raman Spectroscopy, Tata Institute of Fundamental Research Hyderabad, Dec 17-21

TALKS BY CSIR-IICB FACULTY

1. Structural Intricacy and Raman Signature of Protein Prior to Their Transformation into Amyloid like Fibrillar State, VIII International Conference on Perspectives in Vibrational



Spectroscopy, (VIII ICOPVS-2020) Feb 24-29, 2020

2. Structural organization of protein oligomer: A critical insight of disulfide linkages based on Raman spectroscopic analysis, National Workshop on Fluorescence and Raman Spectroscopy, Tata Institute of Fundamental Research Hyderabad, December 16-21, 2019

3. Finding potentially druggable sites for use in orthosteric and allosteric lead detection in a single virtual screening setup, The 3rd International Symposium On Genomics In Aquaculture - 2020 (ISGA-III), ICAR - CIFA (Central Institute of Freshwater Aquaculture) Bhubaneswar, India., 21 - 23 January, 2020

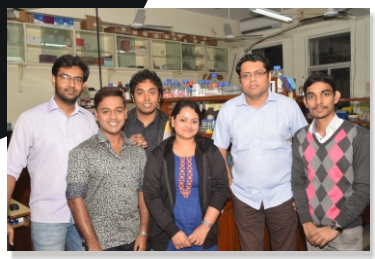
4. 11th Annual Meeting of the Proteomics Society, India (PSI) and the International Conference on Proteomics for System Integrated Bio-Omics, One Health and Food Safety" from 2nd to 4th Dec 2019. ICAR-National Dairy Research Institute, Karnal-132001, Haryana, India (Attended to receive awards).

5. Fourth bi-annual Raman Spectroscopy event - "Inside Raman" Tuesday 9th and Wednesday 10th April 2019. Centre for Research in Nanoscience & Nanotechnology, University of Calcutta, JD-2, Salt Lake City, Kolkata 700098, West Bengal (Attended)



Dr. Siddhartha Roy

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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 structurecontaining nucleosome core particles with 147bp of DNA wrapped around histone octamer. All the DNA-mediated activities, including transcription, replication, recombination, andDNA repair use the concerted efforts of histone chaperone protein that facilitates the assembly anddisassembly of chromatin by deposition or eviction of histones. The NAP(Nucleosome Assembly Protein) family of histone chaperones is conserved from yeast to humanand has been implicated in many biological functions including shuttling histones from the cytosol tothe nucleosome, cell proliferation, cell-cycle regulation, transcription, replication, silencing, andapoptosis. TSPYL1, a new member of the NAP proteinfamily, 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 Nterminalnucleosome assembly protein (NAP) domain. The sequence analysis of the TSPYL genein 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. Asthe loss of NAP domain of TSPYL1 causes the disease in infants, NAP domain of TSPYL may playa role in development by altering regulation of specific developmental genes and contributing toregion-specific chromatin remodeling (Puffenberger et al., 2004). In the present study we aim toelucidate the TSPYL1 NAP domain structure which may shed light on fundamental aspects ofembryogenesis of the human nervous and reproductive systems and may also characterize thefunction through a previously not described epigenetic crosstalk and signaling mechanism ofbrainstem development. More important, studies of TSPYL structure will help in betterunderstanding of its expression and function in the developing brain may provide new insight intothe 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-ray crystallography
- 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 regulatesthe chromatin assembly and altered gene expression?
- Role of TSPYL1 in cell proliferation, metastasis and cancer progression in human.

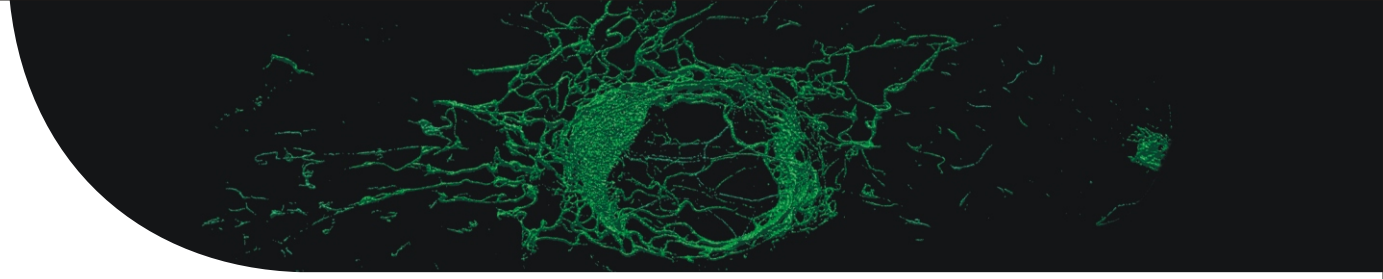
Work Achieved

Cloning

Initially attempts have been made to clone the human TSPYL1 gene from HEK humancell-line cDNA. But after cloning the gene the protein is not expressed with desiredamount. So we opted for synthesis of TSPYL1gene. We cloned the C-terminal histonechaperone domain of NAP1 (residue 162-416) & (residue 198-416) from the codonoptimized TSPYL1 gene in a pGEX 6p1 vector (Gateway Technologies) containing GSTaffinity tags. We also cloned full length TSPYL1 (residue 1-416) in pDEST-15 vectorhaving 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 stockwas maintained. Rossetta P-Lys strain of Escherichia coli were transformed withTSPYL1 clones and plated on LB agar plate containing ampicilin(100µg/ml) andchloramphenicol (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 anOD600nm value between 0.6 and 0.8. Afterwards TSPYL1 expression was



induced for aperiod of 16 hrs by adding 1mM IPTG and shaking at 180rpm @ 20°C. The cells wereharvested 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 wassonicated 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 supernatantwas incubated with pre-equilibrated GST-Agarose beads (equilibrated in lysis bufferwithout adding NP-40) at 4°C for 4 hrs. After incubation, the beads were washed withwash buffer (20mM Tris-Cl pH 7.5, 250mM NaCl, 2mM DTT) thoroughly. The washedbeads were then incubated with precision protease enzyme for 36 hrs @ 4°C to cleave theprotein in precision protease buffer (20mM Tris-Cl pH 7.5, 150mM NaCl and 2mMDTT). All the samples from each step were then analyzed on SDS-PAGE gel. Thecleaved protein was then eluted using the same precision protease buffer and then passedthrough a gel filtration column to remove impurities. After concentrating the protein todesired 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 protocolas given in Trypsin Gold Manual.

Crystallization:
Purified TSPYL1 (162-416) was dialyzed in high salt concentration buffer andconcentrate up to 8-10mg/mL concentrations. Concentrated protein was used to set upseveral crystallization screens using sitting drop method. Initial hits obtained fromselected drops were optimized and a crystal of considerable size was obtained in acrystallization condition containing 100mM Imidazole pH-8.0, 200mM Calcium Acetateand 20% PEG1000 (Figure 2).

Biochemical and Biophysical Characterization
Determination of Oligomer property of TSPYL1 by Analytical Size ExclusionChromatography:

Analytical size exclusion chromatography (aSEC) with a HiLoad Superdex 200 16/600column (GE healthcare) in different ionic strength buffer was used to determinemolecular weights (MWs) in solution by comparison of the protein standards of preciselyknown 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 forcalculation of standard curve since the separation range of the column is from 10 kDa to600 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 affinitychromatography method. Briefly transformed Rosetta P Lys strain of E.coli was growntill log phase followed by induction using 1 mM IPTG and incubation @200rpm @20°Cfor 16 hrs. Post harvesting the cells, lysis was done in 20mM Tris, 200mM NaCl, 2mMDTT. Lysed cells were sonicated and GST-TSPYL1 was affinity purified using GSTSepharoseBeads. 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 beadwas wash with Binding buffer for four times, the protein complex was resolved in SDSPAGE followed by western blotting.Pull down assay also performed with different ionic strength buffers to check the bindingstrength of the TSPYL1 and Histones.

DLS study of oligomer of TSPYL1:
Protein size was determined by dynamic light scattering (DLS) using the Nano ZSMalvern instrument (measurement range of 0.6 nm to 6 µm) using 2 micro molar ofTSPYL1 oligomer protein. This technique measures the time dependent fluctuations inthe intensity of scattered light that occur because particles undergo Brownian motion. Theanalysis of these intensity fluctuations enables the determination of the diffusioncoefficients 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 proteinswere 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.

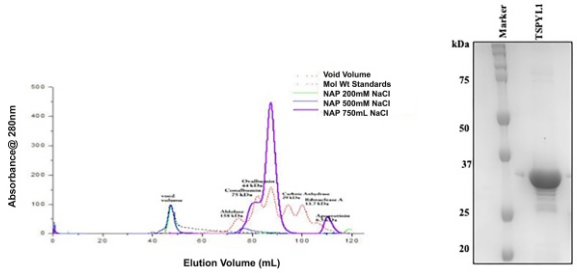


Fig. 1: Elution profiles of TSPYL1 NAP protein (~31kDA) protein and Calibration Kit proteins onHiLoad 16/600 Superdex 200 pg column in different salt strength buffer. Elution volumes (Ve) arefound at maximum peak height of each respective protein.

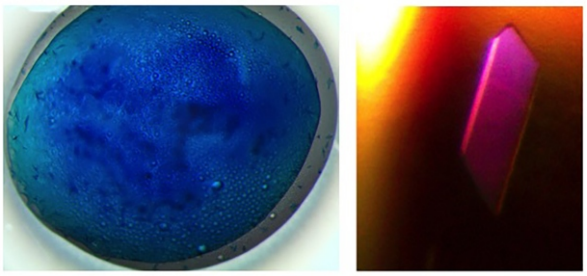


Fig. 2: Crystal of purified TSPYL1 NAP domain.

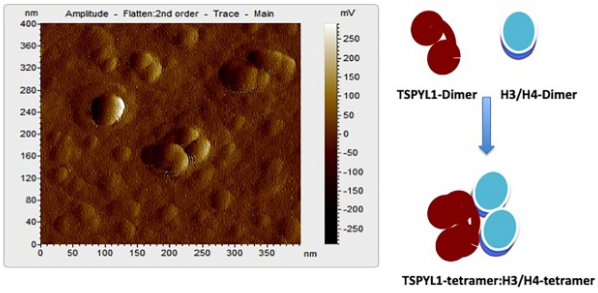


Fig. 3: AFM images in 400nm magnification TSPYL1& H3H4 complex.

PUBLICATIONS

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. Nat Commun. 2019 Mar 28;10(1):1398.

EXTRAMURAL FUNDING

Siddhartha Roy
Grant Title: Structural and functional characterization of TSPYL1, a novel histone chaperone implicated in Sudden infant death with dysgenesis of the testes syndrome (SIDDT) in human. EMR/2016/006233 (2017-2020) (SERB, DST)

Siddhartha Roy
Grant Title: Histone chaperon Asf1 in Plasmodium falciparum: Novel anti-malarialtargets. BT/PR23434/MED/29/1189/2017 (2018-2021) (DBT)



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Identification of common genes, hub genes, and pathways responsible for retinoblastoma

Participants

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Aditi Karmakar, UGC-JRF

Collaborator(s)

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Regional Institute of Ophthalmology, Kolkata

Name of collaborator within CSIR-IICB
Dr. Saikat Chakrabarti, Principal Scientist,
Structural Biology & Bioinformatics division

Background

Retinoblastoma (Rb), a rare form of childhood cancer that occurs in children is below the age of five which impacts the everyday life of the affected child. RB1 gene biallelic mutations are major causative for retinoblastoma. Both heritable (bilateral) and non-heritable (unilateral) form of retinoblastoma were observed. The recent advancement of chemotherapy treatment has shown the promising outcome of the patients although it results in serious side effects. Further, the patients having RB gene mutations are highly prone to the development of second primary cancers however, the exact molecular mechanism by which it develops is still elusive. Many research studies were attempted to identify key genes responsible for the retinoblastoma by profiling the differentially expressed genes or aberrant methylation patterns or miRNAs of the cancer tissues. Considering the huge diversity of sample sources, data collections and analyzing in a few sets of microarray data may skew the results. Hence, integration of multiple microarray data and systematic analysis may help to find out the key genes acting a critical role in retinoblastoma development, functional pathways, and biological processes.

Aims and Objectives

Identification of differentially expressed or methylated genes or miRNAs associated with retinoblastoma

To identify common and hub genes of retinoblastoma by integrative and co-expression analysis

To validate the identified hub genes by using in vitro model.

Work Achieved

We have identified highly significant-top ten genes of each up-regulated and hypomethylated / down-regulated and hypermethylated and miRNAs target genes are associated with retinoblastoma.

By integrative and co-expression analysis we also have identified common genes and hub genes of retinoblastoma

Future Research Plans

Validating the retinoblastoma associated hub genes in retinoblastoma cell lines

Developing an in vitro model for the screening of novel inhibitors for identified hub genes of retinoblastoma

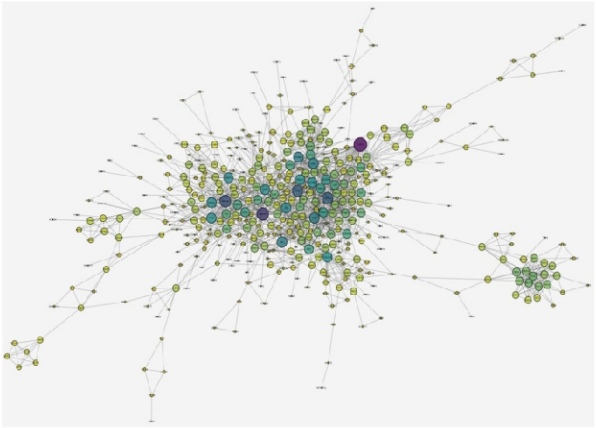
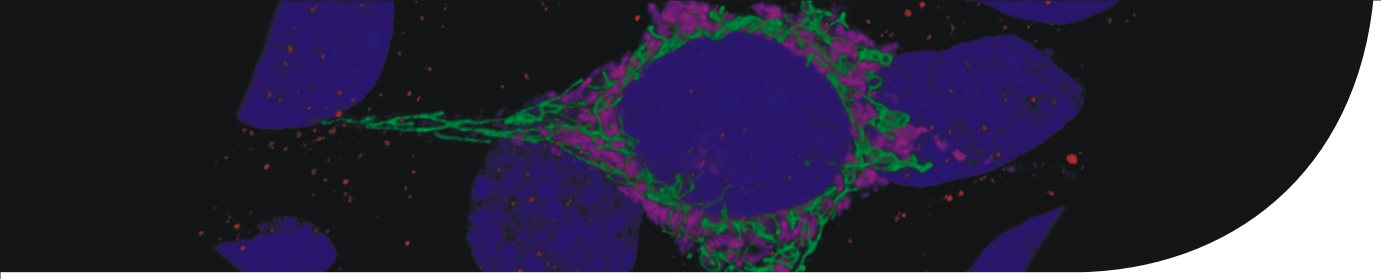


Fig. 1: Common RB intersection network of transcriptome, methylation and miRNAs dataset network

PUBLICATIONS

Kumari N, Karmakar A, Chakrabarti S, Kumar GS. Integrative computational approach revealed crucial genes associated with different stages of diabetic retinopathy. Front. Genet. (2020)| doi: 10.3389/fgene.2020.576442

Ganesan, S.K., Venkatratnam, P., Mahendra, J. et al. Increased mortality of COVID-19 infected diabetes patients: role of furin



proteases. Int J Obes (2020). https://doi.org/10.1038/s41366-020-00670-9

EXTRAMURAL FUNDING

Evaluation of Insulin-Like Growth Factor 2 (IGF2) as a potential epigenetic biomarker and therapeutic target to abolish the metabolic memory in diabetic retinopathy funded by ICMR, Govt of India

CONFERENCES / WORKSHOPS 2

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB
Name of event; Start date – End date, Year; Venue; CSIR-IICB Organizing Committee



Dr. Sandip Paul
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Understanding Human Microbiome in Health and Disease

Participants

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Debaleena Bhowmik, 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 in disease. Human microbiome related studies have revealed intriguing association between specific patters of microbial diversity and several aspects of host health, including autoimmune disorders, diabetes, obesity, inflammatory bowel disease, and even psychiatric conditions.

In order to have a better understanding of the metabolism in microbial community and environment-related metabolic principle and association with disease in human microbiome, our lab focuses towards a rigorous and comprehensive pipeline to build systematic metabolic modeling of human microbiome from metagenomic samples, with special emphasis on the application of metabolic modeling to understand host-microbe interactions in different disease conditions.

Aims and Objectives

1. To create a metagenomic data analysis pipeline for metabolic modeling of microbial community.
2. To understand microbe-microbe and host-microbe metabolic interactions at different body niche.
3. To reveal the alterations in metabolic interactions and its affect on different oral disease states.

Work Achieved

Microbial community maintains its ecological dynamics via metabolites crosstalk. Hence knowledge of the metabolome, alongside its populace, would help us understand the functionality of that community and also predict how it alters in atypical conditions. The metabolic potential of a community signifies the ability to produce or utilize each metabolite and can serve as potential marker of the differentially controlled biochemical pathways among different communities. We developed M2M (Microbiome to Metabolome), a web-based analytical and predictive tool that can describe the microbial diversity and the metabolic potential between two sets of microbial communities from targeted amplicon sequencing data via community level metabolic modeling (http://www.bioinfo.iicb.res.in/m2m/index.html). The machine learning approach implemented in M2M is capable of highlighting significant metabolic features associated with any group in comparison with another along with probable microbial sources.

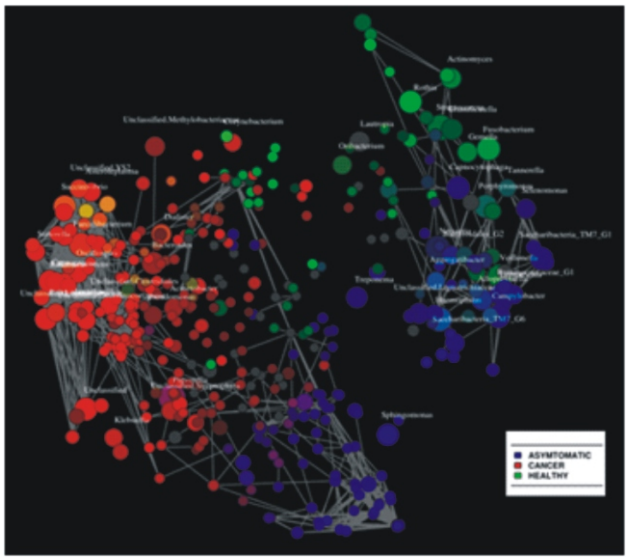
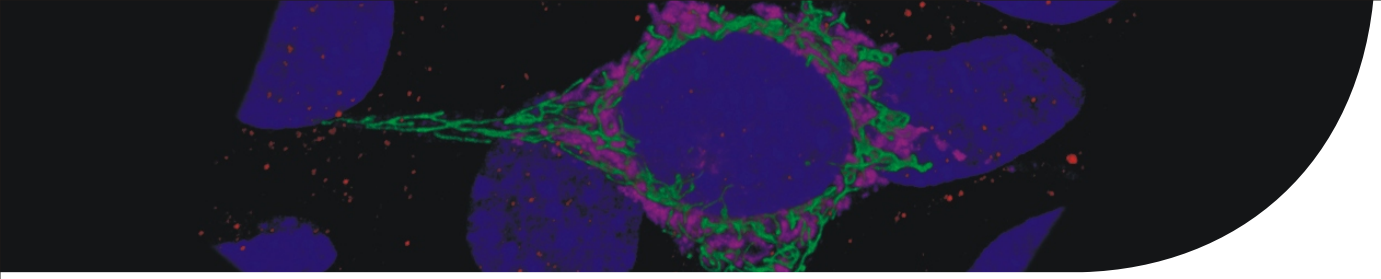


Figure 2 Genus level co-occurrence network of Operational Taxonomic Units (OTUs) from different disease states of oral microbiota

Several studies have indicated that the oral microbiome has a role in the maintenance of oral health and a dysbiosis is associated with disease. In our multi-omics study of the oral metagenomics along with metabolites, we assessed the healthy individuals and patients suffering from oral cancer in the Eastern Indian population. From our analysis of changes in the oral microbiota and the metabolites associated with development of OSCC in individuals in comparison to healthy oral-microbiota, we explored



enrichment of some genera/metabolites in oral cancer patients with while simultaneously several other genera/metabolites were significantly decreased. This pattern of abundance of these genera of bacteria/metabolites can potentially distinguish the oral cancer samples from the healthy ones.

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.

EXTRAMURAL FUNDING

Sandip Paul

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)

CONFERENCES / WORKSHOPS : 2

CONFERENCES / EVENTS ORGANIZED BY CSIR-IICB

Participated in CSIR-IICB Open-house in “Jigyasa” programs for school students and introduced the basic concepts about sequence analysis and protein structure.

Participated as course-member in CSIR-IICB “Skill development program” for the Basic Bioinformatics and Advanced Bioinformatics courses.



Dr. Paulomi Ghosh
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Development of biopolymer-based fibers for healthcare applications

Participants

Ashmita Mukherjee, ICMR-SRF
Shivangi Parhi DBT-JRF
Sreyasi Pal, Project Assistant

Collaborator(s)

Name of collaborator outside CSIR-IICB
Dr. Subhadip Bodhak, CSIR-CGCRI, Kolkata

Name of collaborator within CSIR-IICB
Dr. Indubhusan Deb

Background

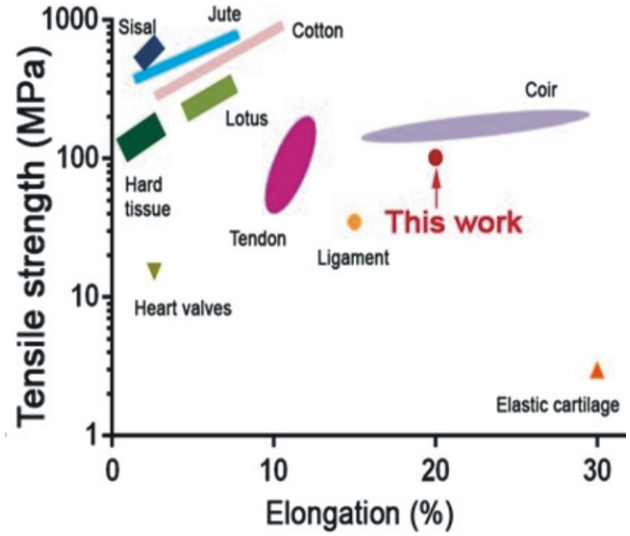
Combination of medical science and textile technology has led to the emergence of medical textile industry. Applications of medical textile include wound dressing/gauze/surgical end-use/artificial ligament/hollow fibers for dialysis, etc. We have extracted keratin protein from Gallus gallus domesticus feathers/human hair/yak hair and characterized it. Thereafter, we have chemically/ionocally crosslinked keratin with other biopolymers to form uniform sized micro/nano fiber. An elaborate comparative study was done to evaluate the effect of the dual crosslinking on tensile strength, elastic modulus, swelling, and thermal properties. Further, surface modification of the fibers is attempted to achieve desired wettability and hydrophilicity. The fibers formed will be used for diverse biomedical applications including skin tissue engineering, hemostatic application and as restorative dental materials.

Aims and Objectives

- To develop micro/nano fiber dressing for hemostatic applications
- To develop antibacterial fiber reinforced resin of high mechanical strength for dental applications

Work Achieved

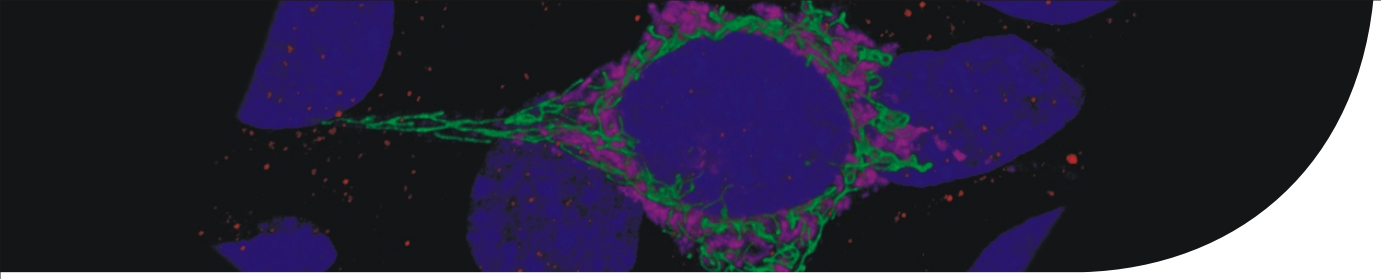
Dual crosslinked keratin-alginate fibers formed via ionic complexation of amide networks with improved toughness for



assembling into braids In this study, keratin was extracted from bio-waste of chicken feathers with a thiol content of 0.172 mM. The extracted keratin was used to prepare dope with alginate at different ratios and N-(3-Dimethylaminopropyl)-N 0 -ethylcarbodiimide hydrochloride via amide linkages. The formation of covalently crosslinked dope was evidenced from FTIR and ninhydrin assay. The dope was then extruded in calcium bath to produce fibers with uniform diameter wherein the calcium ions were used to ion-ically crosslink the covalently crosslinked dope. The resulting dual crosslinked fibers were characterized in terms of chemical composition, surface morphology, mechanical properties, thermal degradation, and swelling. The strength, modulus and toughness of the dual crosslinked fibers were substantially improved by 27%, 20%, and 33% respectively than that of control fiber. The gravimetric toughness of the optimised dual crosslinked fiber (724 J/g) was much higher than the values reported for Kevlar (78 J/g). We further assembled the dual crosslinked fibers into complex braided architectures using the textile techniques, demonstrating the flexibility of the fibers. We believe that this preliminary work of sustainable fiber production could open new insights into eco-friendly organic textile manufacturing and for tissue engineering applications. This work has been published in **Polymer Testing (Elsevier) 2020, 81, 106286. [JIF 3.275]**

Antibacterial fiber reinforced resin of high mechanical strength for dental applications

In this study, we prepared the base resin consisting of 2,2-bis[4-



(20-hydroxy-30-ethacryloyloxypropoxy)phenyl]propane (Bis-GMA), Triethylene glycol dimethacrylate (TEGDMA) making a 50/50 mass ratio of Bis-GMA/TEGDMA, Camphorquinone and a co-initiator/accelerator. The dental resin mixture was then transferred to ultra-violet crosslinker to be photocured. Presently, production of keratin nanofibers is being optimised and modified to incorporate antibacterial properties. In future, these antibacterial nanofibers will be incorporated within dental resin at different mass ratio to obtain fiber reinforced dental products of high mechanical strength.

Future Research Plans

- Development of crosslinked micro/nanofibers with surface modification to increase hydrophilicity of the materials which will help in absorption of wound fluids. Further, the fibers will undergo detailed in vitro and in vivo procedures to demonstrate blood clotting efficacy.
- Incorporation of antibacterial nanofibers in dental resin to develop mechanically robust antiseptic oral healthcare products.

PUBLICATIONS

1. Chia-ying James Lin, Stacey Gruber, Patrick W Whitlock, **Paulomi Ghosh**. Microspheres containing decellularized donor tssue and their use in fabricating polymeric structures. US patent, Application number: 16759380, Publication date: 2020/9/17.
2. Ashmita Mukherjee, Yogesh H. Kabutare, **Paulomi Ghosh***. Dual crosslinked keratin-alginate fibers formed via ionic complexation of amide networks with improved toughness for assembling into braids. Polymer Testing (Elsevier) 2020, 81, 106286. (*Corresponding author) [JIF 3.275].
3. Arun Prabhu Rameshbabu, Kamakshi Bankoti, Sayanti Datta, Elavarasan Subramani, Anupam Apoorva, **Paulomi Ghosh**, Subhodeep Jana, Padmavati Manchikanti, Sabyasachi Roy, Koel Chaudhury, Santanu Dhara. Bioinspired 3D porous human placental derived extracellular matrix/silk fibroin sponges for accelerated bone regeneration. Materials Science and Engineering: C (Elsevier) 2020, 110990 [JIF 5.880].

AWARDS / HONOURS / MEMBERSHIPS
Faculty
Scientist's Name Surname
Paulomi Ghosh

Awards / Honours
DST Inspire Faculty fellowship and grant

Memberships
Society for Biomaterials

EXTRAMURAL FUNDING

Name Surname: Paulomi Ghosh (PI)

Local delivery of microspheres containing decellularized extracellular matrix for neo-cartilage formation and reduction in osteoarthritis inflammation in an animal model. 2017-22. Sponsor: Inspire faculty research award, Department of Science and Technology, Govt. of India, India.

CONFERENCES / WORKSHOPS

1. Ashmita Mukherjee, Paulomi Ghosh* Dual Crosslinked Keratin-Alginate Fibers with Improved Mechanical Properties for Fabricating Braids. Workshop on Recent Trends in Biomedical Engineering (RTBE-2020), January 3-7, 2020, National Institute of Technology, Durgapur, India. Organized by: centre of Biomedical Engineering & Assistive Technology (BEAT). Awarded 3rd prize in poster competition.

2. Ashmita Mukherjee, Paulomi Ghosh*. Keratin Biomaterial from Bio-Waste for Haemostatic Application. International Conference on Smart Materials for Sustainable Technology (SMST-2020), 22nd-25th February, 2020. Organised by Society for Interdisciplinary Research in Materials and Biology

Business Development Intellectual Property Management Group

Members :

Dr. Arindam Talukdar, Head BDG (Principal Scientist) Dr Aparna Laskar, Mr. Arupesh Majumder, Mr. Madan Halder, Mr. Saibal Giri

CSIR-IICB is engaged primarily in research on diseases and certain biological problem of global interest. It is conducting basic research on infectious diseases, cardiovascular disease, autoimmune diseases, and neurodegeration along with the development of technologies for diagnosis immuneprophylaxis, cancer and therapeutic aspects of various diseases.

CSIR-IICB is putting emphasis on quality basic research having applied potential and is looking forward to a successful Industry-Institute liaison towards closer partnership. The Business Development Group is the technology transfer arm of CSIR-IICB facilitating protection of Institute's intellectual property and marketing inventions/knowhow's generated.
The group is maintaining strong relationships with the Industries and innovations arising out of the state of research and development activities.

Major activity of this group involves

1. Liaison with private industries/R&D institutes/academic institutions and other potential clients.
2. Negotiating business plans with industries and corporate sectors and implementing them, and also drawing agreements and memorandum of understandings.
3. Arranging and conducting meetings between institute and industry/corporate clients, induction of new schemes, arrangement of visitors interaction with scientists etc
4. Dealing with Parliamentary and other related matters, responses to parliamentary queries RTI queries and other questions etc.
5. Assistance for Technical support
6. Distribution of royalty earned.
7. Preparation of lists of knowledge base/products developed, dissemination of information on technologies developed etc.
8. Processing of requirement of R&D related services in accordance with Clause No. 1.3 of CSIR Manual of Procurement of Goods 2019.. R&D Services will be processed by BDG. R&D services such as sequencing mechanical testing etc is considered as Non-Consultancy services. . The elaborate work related to R&D related service was looked by BDG.

Intellectual Property Management Cell

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 or 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. 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. This cell provides necessary information on technologies developed, patents filed and granted whenever required; 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

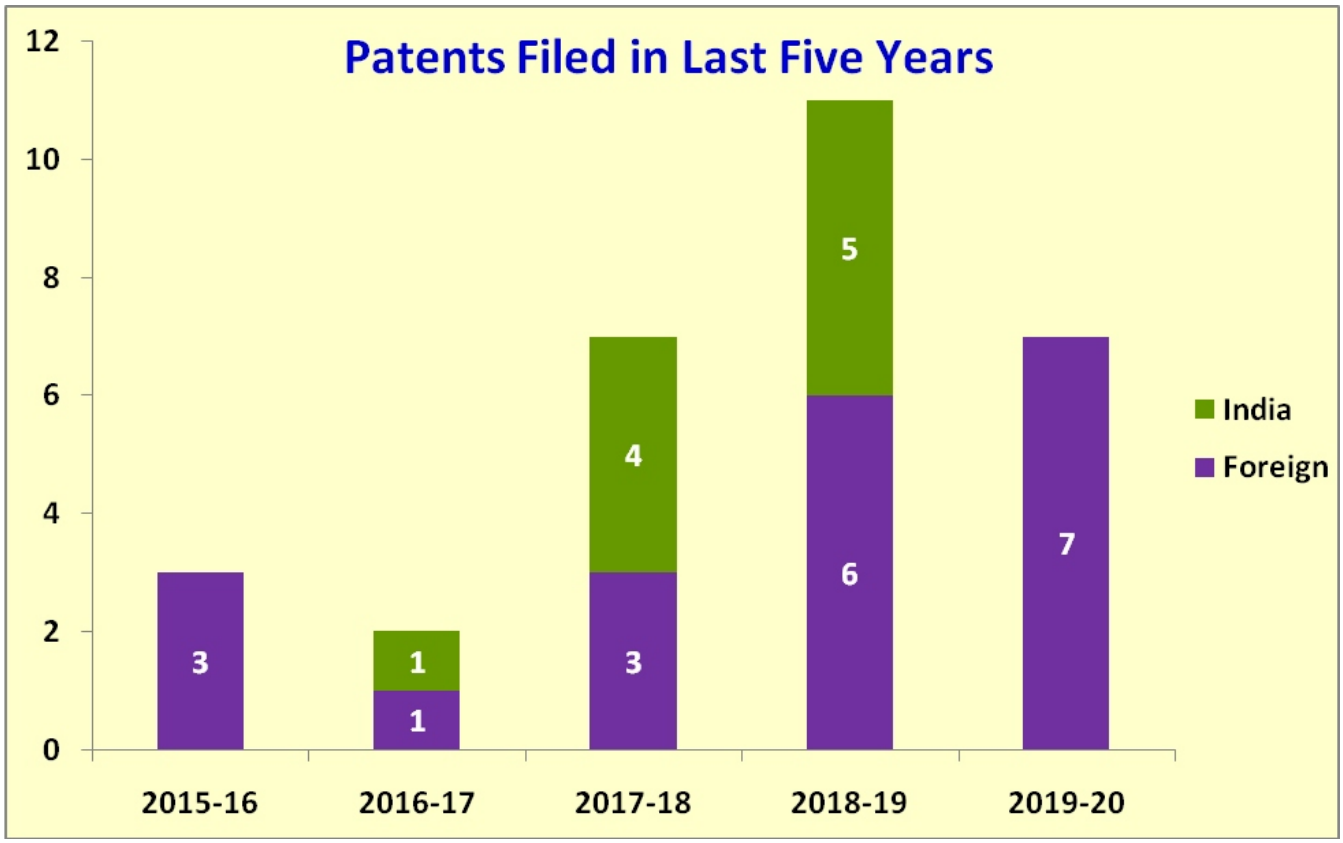
as follows:

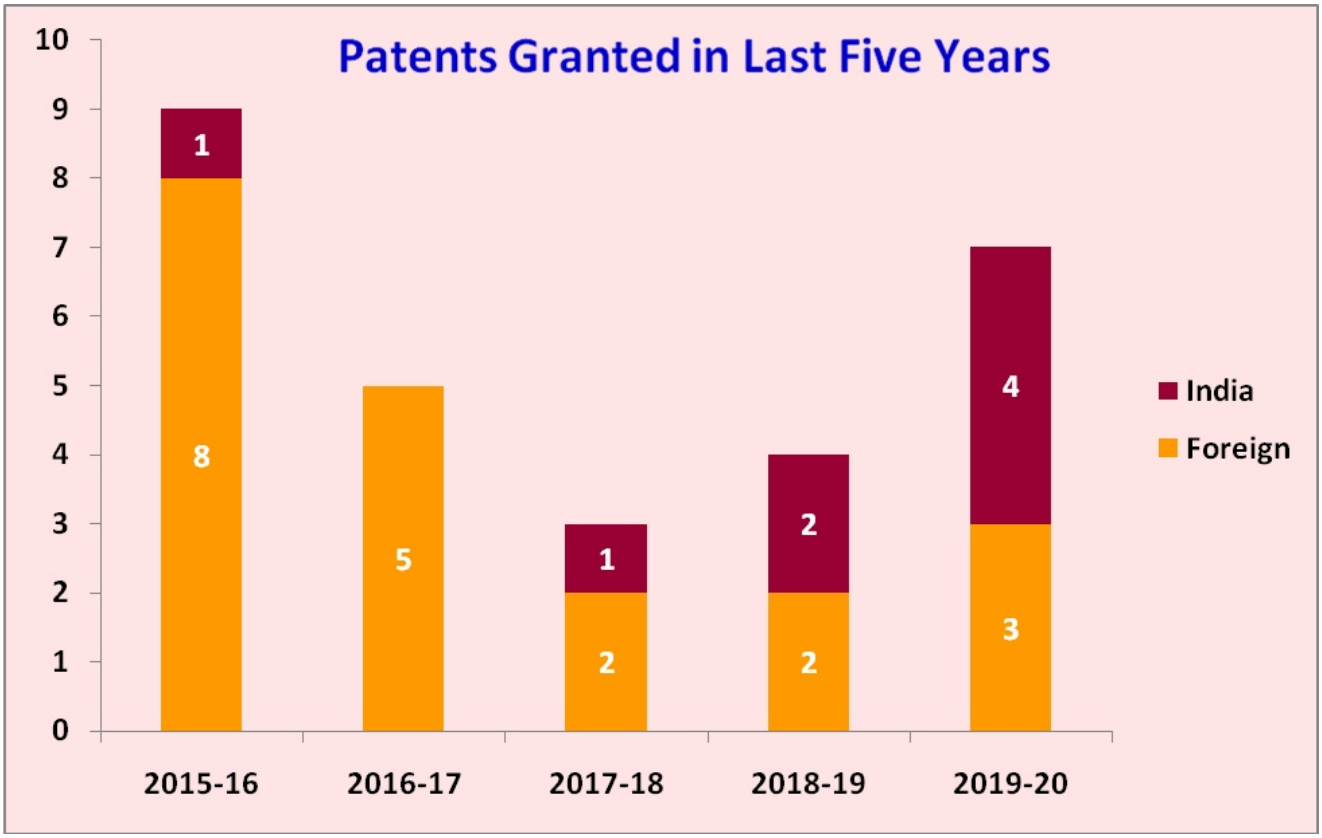
Patents Filed:

Indian Patents Filed:	…	0
International Patents Filed	…	7

Patents Granted:

Indian Patents Granted	…	4
International Patents Granted	…	3




Patents Granted in Last Five Years
10
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8
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6
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1
8
5
1
2
2
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3
India
Foreign
2015-16
2016-17
2017-18
2018-19
2019-20

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. Dipika Roy, Mrs. Banasri Das, Mr. Diptendu Bhattacharya, Mr. Binayak Pal, 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. Santu Paul, Mr. M. Vigneshwaran, 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 provides facilities to the researchers at CSIR-IICB along with different academic and R&D organizations, including Universities and Colleges. The objective of these facilities is to provide accurate experimental data to the researchers. We have about thirty-five high end and sophisticated instruments in our facility. Most of these instruments have well-trained operators, who runs theinstruments properly to get high-quality data and reliable data. This is indeed a pleasure for us to share that a few new types of equipment, like Fluorescence Correlation Spectroscopy (FCS), SEC-MALS - the combination of size-exclusion chromatography with multi-angle light scatteringhas been inducted to the facilities this year. We plan to procure more high-end instruments in the coming years.

Central Instrumentation Facilities organizes special hands-on training sessions in a regular fashion for students and staffs to train them about the principle and application. CIF at IICB has also demonstrated and trained college students about different instruments. For the mandatory course work of PhD students Instrumentation and techniques happen to be a compulsory paper, where theoretical and practical aspects of relevant Instruments for Biology and Chemistry students are imparted 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. As per CSIR guideline booking for the instruments with AnalytiCSIR portal has been initiated. CSIR's objective is to share all major R&D facilities to research community all over India. "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 throughout the country. The process of booking instruments and data collection have been simplified, which allows easy access to these instruments for all.Still there is a lot of scopes to improve the service of CIF and all the staffs of this division are always working on this aspect. We need a sophisticated TEM instrument, confocal microscopes, and some other high-end instruments. CIF is taking care of extending all sorts of support to the recipient students and faculties under the science dissemination and popularization scheme of CSIR-IICB. 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 is really satisfying 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 increasing day by day. Although our objective is to provide satisfactory and accurate 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 capable and firm towards providing instrumental service towards the research fraternity.



Dr. Umesh Prasad Singh

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Discovery of plants based natural products for development of dengue virus inibitor combination-formulations

Participants

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Deethi Jyothi, CSIR-JRF
Ayesha Noor UGC-JRF
Sudesna Das CSIR-JRF

Collaborator(s)

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Name of collaborator within CSIR-IICB
Dr. Snehasikta Swarnakar,
Dr. Krishna Das Saha

Background

Dengue fever (DF) and dengue hemorrhagic fever (DHF) are acute febrile diseases transmitted by mosquitoes (Aedes aegypti, A. albopictus). Nowadays, they are the most rapidly spreading mosquito-borne diseases in the world. About 2.5 billion people, two-fifths of the world's population, are now at risk of infection and 50 million cases of DF are reported worldwide every year.1 In recent decades, these diseases have spread to over more than 100 countries.2 The World Health Organization (WHO) estimates that the annual global incidence of dengue is close to 390 million, a number nearly three times higher than the number of cases estimated by the same organization for 2009.3

The dengue virus particle is about 50 nm in diameter. The 10,723-nucleotide RNA genome encodes an uninterrupted open reading frame (ORF), directing the synthesis of a polyprotein precursor in the order NH2-C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5-COOH, where C is the capsid protein, M is the membrane-associated protein, E is the envelope protein, and NS1 through NS5 are nonstructural proteins(See Fig.1).

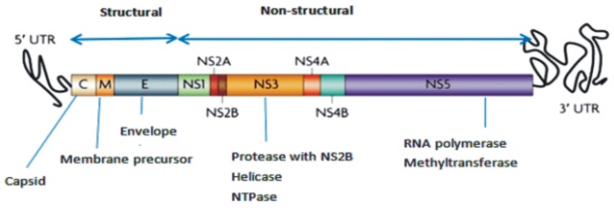


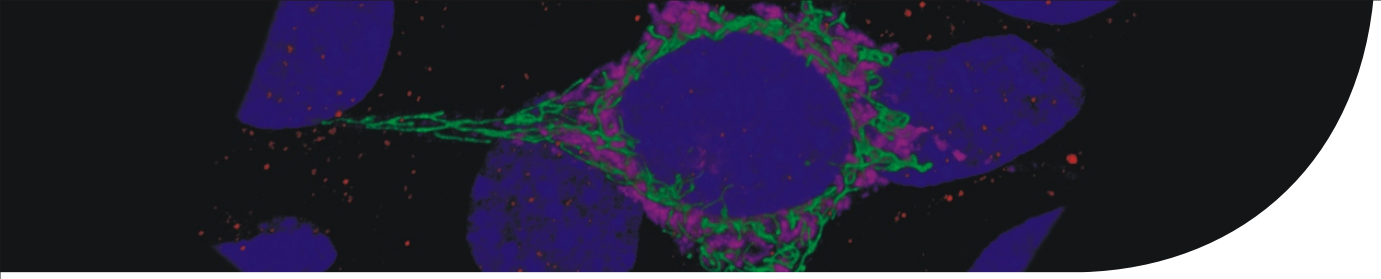
Fig.1: Schematic representation of the DENV genome. (https://www.cusabio.com/c-20884.html.)

NS5 is the Non-structural protein which is the largest protein. The N-terminal region of NS-5 consists of methyltransferase (MTase) domain and the two-thirds of C-terminal is an RNA-dependent RNA polymerase (RdRp) domain. The linker of these two domain of is of low conseved region.5 Viral replication is mainly carried out by the DENV NS5 RdRp. Viral replication begins with the synthesis of minus-strand RNA from the dengue virus positive-strand RNA genome, which is subsequently used as a template for synthesizing additional plus-strand RNA genomes. This essential function for the production of new viral particles is catalyzed by the NS5 RdRp. Thus Dengue virus NS5-RdRp is a well validated target for drug discovery.

A Cap structure (m7GpppAm) is present at the 5'-end of the 5'-RNA terminal cap I of the virus.6 MTase enzyme is responsible for the viral RNA capping via sequential methylation of the N7 atom of guanine and 2' O atom of ribose sugar, in which S-adenosyl methionine (SAM) is used as co-factor which donates mythyl group for the reation.7 Viral capping prevents mRNA degradation from RNAse and enhances interaction with the ribosome for translation.8 Viral multiplication are significatly decreased due to defect in capping, resulting in the attenuated viruses production, which are more sensitive towards the human innate immune system.9

Aims and Objectives

- Transformation, expression and purification of DENV target proteins NS5-MTase and NS5-RdRp.
- To screen plants based natural product against dengue virus target protein NS5-MTase and NS5-RdRp first through docking based virtual screening and then through biophysical screening using Biolayer Interferometry (BLI) and Mass Spectrometry followed by confirmation through enzymatic assays.



- To screen plants based natural products (extracts/compounds) against dengue virus using cell based plaque assay to find entry inhibitors for dengue.
- Plant based molecules high activity (with IC50 < 5μM) may be considered as hits and would be tested for cell based activity in dengue virus plaque assays.
- We aim to find a formualtion containing multiple plant based products (about 3-5 compounds or the extracts containing those compounds) which show high activities against different dengue protein targets for further developments of this neglected disease.

Work Achieved:

Expression and purification for NS5-MTase:

The target protein NS5-MTase with N-term 6-His tag has been expressed using pNIC vector in E. Coli bacteria (BL21). Fig 2A shows Double digestion of our pNIC plasmid construct which shows the faint band corresponding to ~900 bp confirming MTase gene insert. After transformation in E.Coli and induction with IPTG protein band corresponding to MTase protein is observed (~34 kDa) (Fig-2B). Native purification using Ni-TNA column as per Qiagen expression handbook showing the purified band (~34 kDa) of NS5-MTase. (Fig-2C.). The protein was further purified using Size Exclusion Sephacryl S-100 column (not shown).

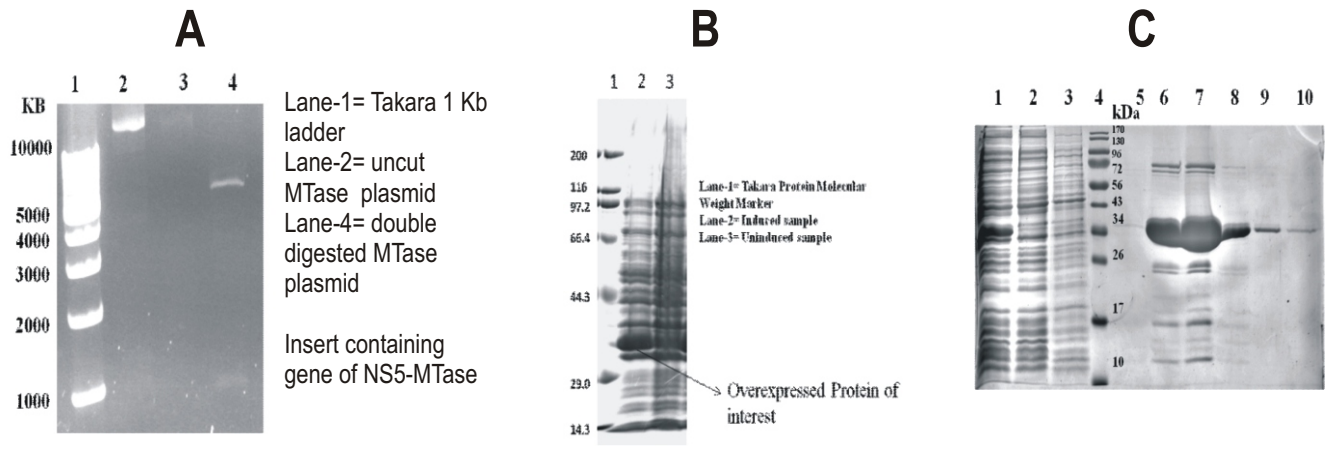


Fig2: Agarose gel showing digestion of NS5-MTase Plasmid (A); SDS-PAGE showing expression of NS5-MTase (B) and SDS-PAGE showing purification of NS5-MTase using Ni-NTA column(C).

Expression and purification of dengue NS5-RdRp:

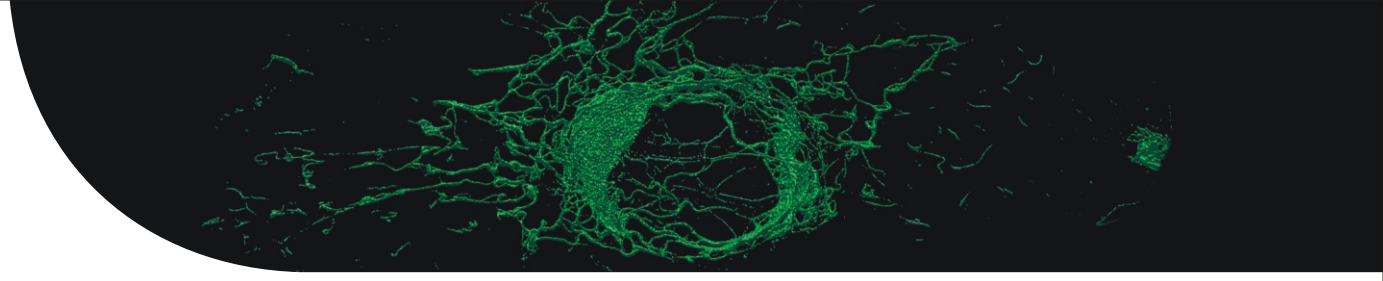
The construct for target protein NS5-RdRp with N-term 6-His tag has been prepared and the protein expressed using pET-15b vector in E. Coli bacteria (BL21). Further work on this target protein and assay development is in progress.

Virtual Screening against NS5-MTase and Isolation of Hit molecules from plants:

We took 1000 carefully selected plants based natural product molecules from the literature and performed molecular docking with dengue serotype-3 NS-5MTase (PDB ID 5EC8) by using PyRx 0.8 and Autodock Vina. We identified four plants named as Swietenia macrophylla, Andrographis peniculata, Swiretia chirata and Azaderchita indica, which contain our virtual hit molecules for NS5-MTase. So far we have already isolate five hit-molecules from these four plants by extraction (cold percolation method) and followed by isolation (normal phase column chromatography by using different size of silica gel like 60-120, 100-200, 230-400 mesh size). Isolated compounds are determined by using modern spectroscopic method like Mass spectroscopy, NMR spectroscopy and single x-ray crystallography.

Biolayer interferometry (BLI) based binding experiments using NS5-MTase:

For the measuring of biomolecular interaction (like protein –protein, protein-ligand interaction) the BLI technique was used. It is a optical technique which measure thickness of bound molecular layers by the interference of light. First protein molecules are attached on the probe, the unbound protein is



washed off. Then the probe measures the ligands binding to the already bound protein molecules. By using this technique we can determine binding specificity, rates of association and dissociation, with high precision and accuracy. Equilibrium dissociation constant (KD) calculate by using KD = Koff / Kon, whereas Kon is ligand association rate and Koff is ligand dissociation rate.10 Some of our natural product identified from virtual screening experiments show good interaction with DENV-3 NS5-MTase protein in our biophysical experiments as shown in Fig3 and Table1 along with known standard inhibitor S-Adenosyl homocysteine (SAH). This confirms their binding with the target protein NS5-MTase.

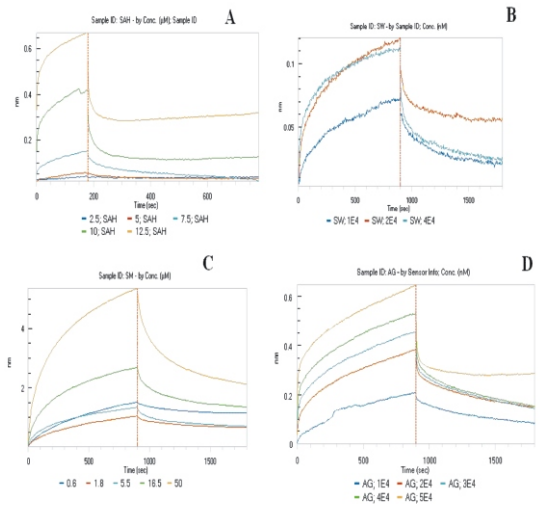


Fig3: BLI sensograms showing NS5-MTase-SAH interaction (A); MTase-SW (Compound 1) interaction (B); MTase-SM (Compound 4) interaction (C); and MTase-AG (Compound 5) interaction (D).

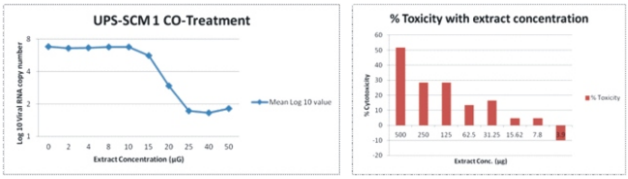
Table 1 Dissociation constant (KD) of different compounds obtained by BLI experiments.

Sl. no	Compound name	KD value (μM)
1.	SAH (a known standard inhibitor)	1.86 (0.07) (IC_{50} = 0.34)10
2.	SW (compound 1)	0.18 (0.001)
3.	SM (compound 4)	5.73 (0.08)
4.	AG (compound 5)	0.70 (0.003)

Our experiements show 2-3 potent inhibitors for NS5-MTase with good activities (KD values in μM and sub-μM range).

Cell based Dengue plaque assay for finding entry inhibitor for dengue virus

Several compounds and plant extracts were screened using cell based Plaque assay in collaboration with lab of Dr. K. Alagarasu of NIV-Pune, for discovery of new entry inhibitors for prophlactic uses in dengue. We have found an extract which is able to prevent dengue infection when cells are exposed to the virus in presence of extract (Fig4a). The extract (UPS-SCM1) is shown to be well tolerated with cytotoxicity value CC_{50} ~500 μg which is more than 30 time higher than the IC_{50} value of about 15 μg (Fig4b).



(a) **(b)**

Figure 4 : (a) The activity of extract (UPS-SCM1) at different dose to prevent dengue infection in cells. IC_{50} value is about 15 μg. (b) The cytotoxicity of the extract at different doses. The CC_{50} value (50% cytotoxicity) is about 500 μg which is more than 30 times the IC50 value.

Future Research Plans

Presently we are doing expression and purification of some other target protein like NS5-RdRp and NS3/NS2B-protease etc. Using these proteins we plan to do more biophysical screening (after virtual screening) such that we are able to cover biophysical screening of most of the dengue targets and a large number of natural products against each of them. Our aim is to find a large number of dengue inhbitors with specificity for different dengue target proteins. Eventually we would like to make a formulation for treatment of dengue fever containing about 3-5 different molecules/plant exptracts which inhibit different target-proteins of dengue to provide cure for this viral disease.

PUBLICATIONS

AWARDS / HONOURS / MEMBERSHIPS **Faculty**

Scientist's Name Surname Umesh Prasad Singh

Awards / Honours

Memberships

- Life Member of the Chemical Research Society of India (CRSI)
- Life Member Indian Crystallographic Association (ICA)





Dr. Shila Elizabeth Besra

shilabesra@iicb.res.in

A Comparative Investigation of the Ability of Various Aptamer-FunctionalizedDrug Nanocarriers to Induce Selective Apoptosis in Neoplastic Hepatocytes: In Vitro and In Vivo Outcome

Participants

SRF : Samrat Chakraborty, Nilanjana Deb
JRF : Kanika Kisku

Collaborator(s)

Name of collaborator outside CSIR-IICB

Dr. Santanu Basu, E. S. I. Hospital Sealdah, Kolkata.

Prof. Biswajit Mukherjee & Prof. Tarun Jha Jadavpur University, Kolkata.

Name of collaborator within CSIR-IICB

Dr. Snehasikta Swarnakar, Cancer Biology & Inflammatory Disorder Division.

Dr. P. Jaishankar Organic & Medicinal Chemistry Division.

Background

Hepatocellular carcinoma (HCC) is the 5th most commonly diagnosed malignancy and is the 2nd leading cause of cancer-related death globally. HCC is highly resistant to chemotherapy, which is the only treatment option available till date in intermediate and advanced stages of HCC Significant efforts have been made globally with the advent of potent therapeutics against HCC to produce a remarkable reduction in the mortality of patients suffering from HCC. In the last couple of years, the United States Food and Drug Administration (USFDA) has approved certain multikinase inhibitors such as Sorafenib, regorafenib, and immunotherapeutic(such as nivolumab) for the improvement in overall survival of patients suffering from HCC. Despite their usage in the therapeutic regimen of HCC, no notable improvement in the survival of the patients (e.g., only 3 months' prolongation of median survival of HCC patients with Sorafenib) has been reported. The prime factors responsible for poor response of HCC against chemotherapeutics are multidrug resistance, faster clearance rate, low drug concentration inHCC cells (only 5–10% of the accumulated dose in the normal organ), and non-specific distribution of the therapeutics causing severe side effects in healthy tissues resulting in severe mortality. Thus, the induction of apoptosis preferentially in neoplastic hepatocytes is one of the vital factors to remarkably improve the survival of HCC patients. Several ligands have been explored so far by the researchers to deliver therapeutics preferentially into neoplastic hepatocytes. Among them, aptamers are preferred over the other targeting ligands especially due to their stability, non-immunogenicity, lower production cost, high affinity towards the target, and lower possibility of structural variation during their synthesis. Aptamers are recognized as short chemically synthesized single-stranded (ss) DNA or RNA oligonucleotides, which fold into specific threedimensional structures. They have high target selectivity as the dissociation constant (kd) of aptamers lies between picoto nano-molar range.

Aims and Objective:

- Site-specific delivery of chemotherapeutics specifically to neoplastic hepatocytes without affecting normal hepatocytes should be a focus for potential therapeutic management of hepatocellular carcinoma (HCC).
- The aptamer TLS 9a with phosphorothioate backbone modifications (L5) has not been explored so far for preferential delivery of therapeutics in neoplastic hepatocytes to induce apoptosis.
- To provide a special emphasis on the toxicological aspect of drug nanocarriers to develop a potent neoplastic hepatocyte-specific therapeutic without producing any notable toxic insult in normal hepatocytes.
- To identify the target protein(s) on neoplastic hepatocytes responsible for ligand-receptor interaction of L5.

Work Achieved

Aptamers offer a significant promise to target various cancers includinghepatocellular carcinoma (HCC), for their high affinity and ability to reach the target site(s), non-immunogenicity, and low cost. The targeting ability to neoplastic hepatocytes by the aptamer, TLS 9a with phosphorothioate backbone modification (designated as L5), has not been explored yet. Hence, we investigated the comparative potential of L5 with some other

previously reported liver cancer cell-specific aptamers, conjugated on the surface of drug nanocarriers. Various in vitro studies such as cytotoxicity, in vitro cellular uptake, cell cycle analysis, and investigations related to apoptosis were performed. In vivo studies carried out here include macroscopic and microscopic hepatic alterations in chemically induced hepatocarcinogenesis in rats, upon experimental treatments. The outcome of the investigations revealed that L5-functionalized drug-nanocarrier (PTX-NPL5) had the highest apoptotic potential compared with the other aptamer-conjugated experimental formulations. Further, its maximum internalization by neoplastic hepatocytes and minimum internalization by normal hepatocytes indicate that it had the potential to preferentially target the neoplastic hepatocytes. Data of in vivo studies revealed that PTX-NPL5 reduced tumor incidences and tumor progress. Superior potency of PTX-NPL5 may be due to the maximum affinity of L5 towards neoplastic hepatocytes resulting in maximum permeation of drug-nanocarrier in them. An effective site-specific targeting of neoplastic hepatocytes can be achieved by L5 for preferential delivery of therapeutics.

Future Research Plans

- To establish theaptamer-functionalized drug nanocarrier improves hepatocellular carcinoma toward normal by targeting neoplastic hepatocytes.
- To establish the potential PLGA nanoparticle encapsulating the anticancer compound in-vitro as well as in-vivo.

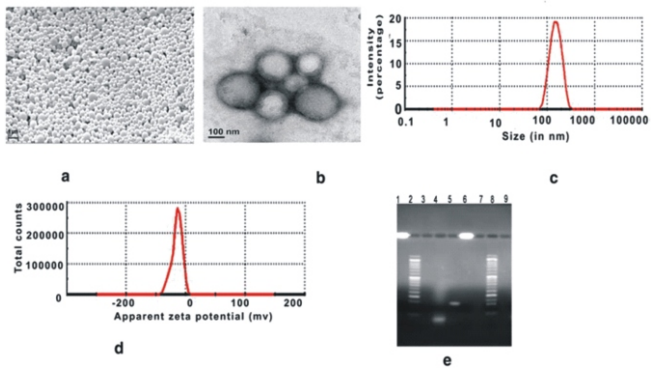


Fig. 1: Physicochemical characterizations of PTX-NPL5. a FESEM image (scale bar 1 μM) shows thickly distributed PTX-NPL5 with theirsurface morphology. b TEM image (scale bar 100 nm) of PTX-NPL5. c Data of particle size analysis by intensity, showing average particle size 156.9 nm of PTXNPL5. d Zeta potential value of PTX-NPL5. e Image of agarose gel electrophoresis, lane 1-PTX-NPL5, lane 2–DNA ladder, lane 4-aptamer L5, lane 5-aptamer L2, lane 6-PTX-NPL2, and lane 8-DNA ladder.

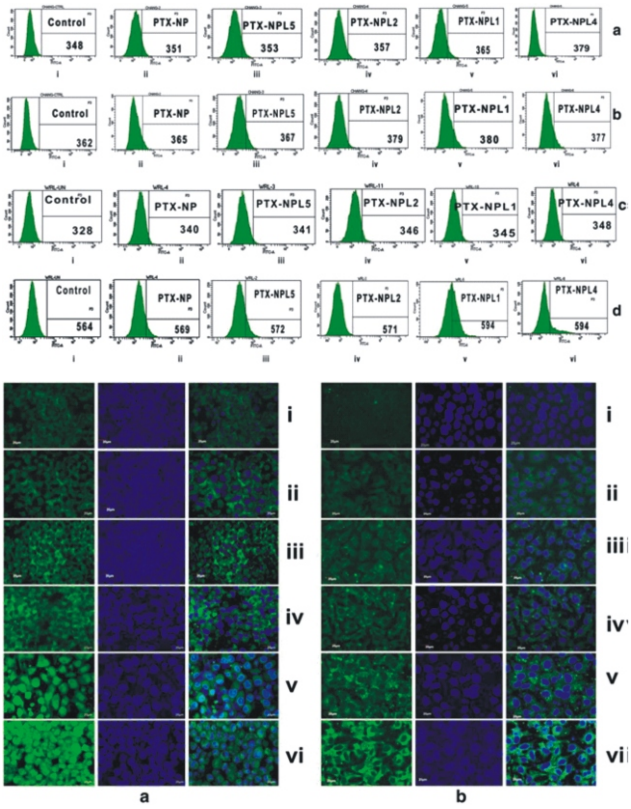


Fig. 2(A): Quantitative estimation of cellular internalization of FITC-conjugated different aptamer-functionalized nanoparticles in normal hepatocytes by flow cytometer. a and b represent uptake of the nanoparticles in Chang liver cells at 1 and 4 h, respectively, and c and d represent uptake the nanoparticles in WRL-68 cells at 1 and 4 h, respectively. In all the figures, number in each block represents FITC-mean median value of cells upon treatment with an experimental formulation Cells without treatments were considered as control. Insignificant difference between the FITC-mean values of control and treated cells signifies poor internalization of experimental nanoparticles in normal hepatocytes

Fig.2(B). Qualitative assessment of internalization of FITC-conjugated different aptamer-functionalized nanoparticles byconfocal microscopy a in HepG2 cells and b in Huh-7 cells, respectively. (i, ii, and iii) represent images showing uptake of

PTX-NP, PTX-NPL2, and PTX-NPL5, respectively, at 1 h, and (iv, v, and vi) represent uptake of those formulations, respectively, at 4 h (scale bar 20 μM).

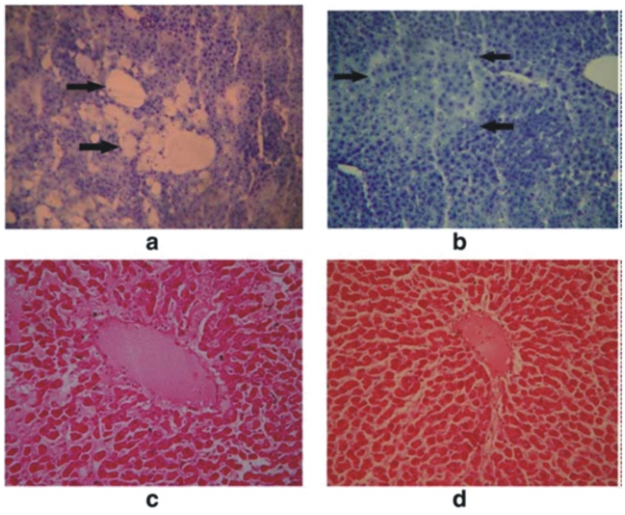


Fig. 3. Histopathological analysis of liver of carcinogen-control rats. a and b carcinogencontrol rats and c and d carcinogen-control rats treated with PTX-NPL5. a and b depict occurrence of spongiosis hepatis an and basophilia with tumor lesion b, at 100× magnification upon staining with Periodic acid-Schiff reaction and toluidine blue, respectively. c represents sequential improvement in hepatic architecture upon staining with hematoxylin and eosin (H&E) at 100× magnification. d Restoration of liver architecture towards normal upon H&E staining at 100× magnification.

PUBLICATIONS

1. Samrat Chakraborty, Zewdu Yilma Dlie, Biswajit Mukherjee, Shila Elizabeth Besra, Soma Sengupta, Ramkrishna Sen, Alankar Mukherjee, A Comparative Investigation of the Ability of Various Aptamer-Functionalized Drug Nanocarriers to Induce Selective Apoptosis in Neoplastic Hepatocytes: In Vitro and In Vivo Outcome, AAPS Pharm SciTech (2020) 21: 89, DOI: 10.1208/s12249-020-1629-z.
2. Gaurav Arya, Nilanjana Deb, Piyali Das, Vishal Sharma., Kanika Kisku, Shila Elizabeth Besra, (2019), Anti-neoplastic effect of Ocimum sanctum methanol extract on colorectal carcinoma, gastric carcinoma, hepatocellular carcinoma & normal cells.World Journal of Pharmaceutical Research, 2019;8(9):984-1001.
3. Shila Elizabeth Besra,Puja Bharti, Anamika Kumari, Twinkle Roy, Nilanjana Deb, J.R. Vedasiromoni, "Litchi chinensis leaves cause cell death via caspases on hepatocellular carcinoma cells". Int. J. Pharm. Sci. Rev. Res., 2019, 59(1); 106-111.
4. Anamika Kumari, Puja Bharti, Twinkle Roy, Nilanjana Deb, J.R. Vedasiromoni, Shila Elizabeth Besra, Apoptosis activity of Swietenia mahagoni leaf extract (SMLE) against glioma cell lines." Journal of PharmaceuticalBiology, 2019 ,9(3):2249-7579.

Invited Reviews

1. Reviewed paper for the Journal of International Journal Pharmacy and Pharmaceutical Science (IJPPS) on May 2019. The manuscript entitled: A prospective analysis on the pattern, laboratory variations and management of acute poisoning in a territory care hospital.
2. Reviewed paper for the journal AJHMS- 2019, ATINARThe manuscript entitled"Altered neural response induced by central-fatigue in the cortical area during high-intensity interval pedaling."
3. Reviewed paper for the JournalAJHMS -2020, ATINAR. The manuscript entitled "Practices and determinants of exclusive breast feeding among young mothers attending a secondary health care facility–A: cross sectional study"

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". Organized 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". Organized by Gupta College of Technological Sciences, Ashram More, Asansol- 713301.

Extramural Funding:

DBT- BIOTECH RISE PROJECT (Project no- P9080)

Engineering Services Unit (ESU)

The Engineering Services Unit (ESU) is comprised of Civil Engineering, Electrical Engineering and Air-conditioning & Refrigeration sections.

Members:

Dr. Parasuraman Jaisankar (Head)

Civil Engineering : Sandip Saha, Susanta Ray, Nirali Bage, Debasish Banik, Avijit Paul, Saheb Ram Tudu, Shyamal Kumar Ghosal and Pradip Kumar Mondal (Horticulture).

Electrical Engineering : Chairantan Debdas, Ujjal Roy, Sourin Ghosh, Abhijit Paul, Samir Majumder, Anup Karmakar, Tanmoy Biswas.

Air-conditioning: Prosenjit Gangopadhyay, Shubhendu Ghosh, Sanjib Biswas, Prabir Kumar Das and Manoranjan Adhikary.

Works Section: Sujit Majumder and Muktar Ahamed.

Preamble:

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, the Scientists' Apartment premise at P.A. Shah Road, Kolkata and the Land at Baruipur, South 24 parganas. 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. Superintending Engineer), Nine Technicians (Technician-1 to Sr.Technician-2) and two support staffs. This Engineering Unit always works as a team. Apart from this, the works Section, where two Technicians are there, plays important roles to complete all the official formalities of this Division. Beside Engineering and Technical works and services, ESU have various activities like, arranging different Institutional programs and managing Audio-visual systems 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 Gardening & Horticulture, Housekeeping, Management of Scientific Support Services, management of Guest House (CSIR-IICB Guest House) located at Salt Lake campus.

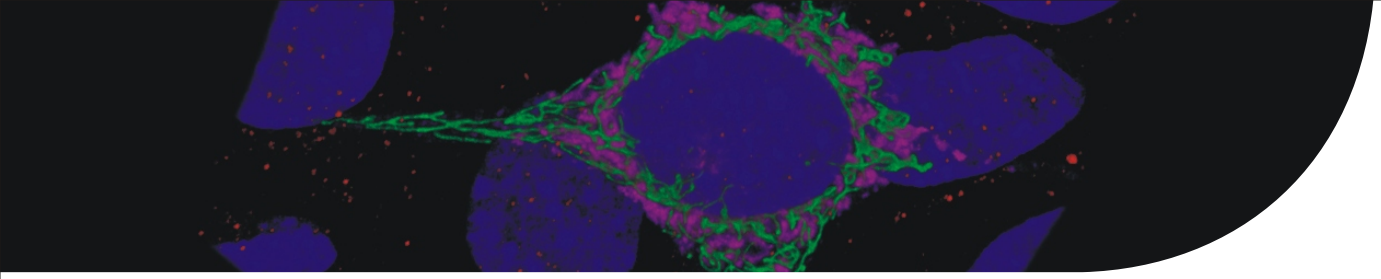
Civil Engineering Section

The Civil Engineering Division under Engineering Services Unit of CSIR-IICB takes major role to render services in board 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, cleaning and house-keeping work at both the campuses at Jadavpur as well as Salt Lake.

Civil Works:

The major repair & renovation works taken up in the Financial year 2019-2020 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.
- Civil works for repair and renovation of Toilets at CSIR-IICB Jadavpur, Kolkata.
- Rrepair and renovation of flooring in 3 Nos corridor (West Side) at CSIR-IICB, Jadavpur Campus



- Repair & renovation of Different laboratories and rooms at IICB, Jadavpur campus (Phase-A)
- Repair & renovation of Chemical Store at CSIR-IICB, Jadavpur, Kolkata
- Repair & renovation of Different laboratories and rooms at IICB, Jadavpur campus (Phase-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
- Replacement of wooden doors by aluminium dorrs in ground floor at CSIR-IICB, Jadavpur, Kolkata
- Making a service toilet at CSIR-IICB, Salt Lake campus.
- Repair & renovation boundary wall at CSIR-IICB, Jadavpur Campus
- Repair & painting boundary wall at CSIR-IICB, Salt lake Campus
- Setting up of aluminium cubicles at RL Block Room no. 112, 122, 211, 231, 315, subs-stations and other four cubicles at CSIR-IICB, Salt Lake campus.
- Civil works for repair and painting of Room nos. 312,313,315,234,G35,G32, & G43 at IICB Salt Lake campus.
- Repairing and polishing of conference chairs and tables in Director Conference Room and Seminar Rooms at IICB, Jadavpur campus
- Supply and erection of modular work station including repairing and painting at Room no. G44 at salt Lake campus.
- Repair & renovation of Different rooms at CSIR-IICB, Jadavpur campus (Phase-C)

In addition to the above, Civil Engineering Section looks after the Lab Supervision works, Cleaning, Sweeping & Housekeeping Services, Guest House Management Services, Gardening and Horticulture works and Scientific Support Services at this Institute.

Electrical Engineering Section

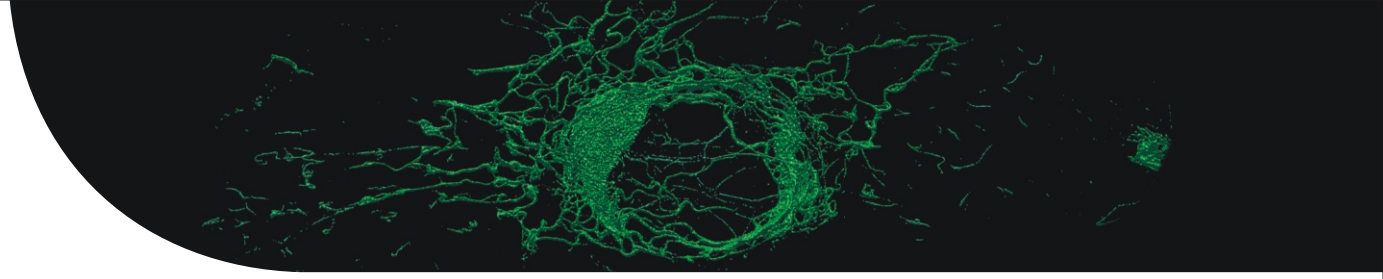
Electrical Engineering Section under ESU has various activities and involvements towards overall management of Electrical Power Distribution systems installed at the Campuses of CSIR-IICB at Jadavpur and Salt Lake. In addition to this, ESU Electrical Section having regular activities for Estimation, 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 Works undertaken by ESU Electrical Section of the Institute.

- Up gradation of existing Electrical Substation and setting up of 11 KV HT Substation at IICB Jadavpur Campus.
- Major Repair and Renovation of Animal House at CSIR-IICB, Salt Lake Campus, Kolkata to facilitate Animal Experimentation Facility at CSIR-IICB, Salt Lake Campus.
- Implementation of Grid Connected Roof Top Solar Photo Voltaic (PV) system at IICB Jadavpur Campus.
- Modification of Electrical Power Distribution Network for effective utilization of Solar Electric Power at CSIR-IICB, Jadavpur Campus etc.
- For the work of "Supply, Installation, Testing and Commissioning of Fire Fighting System at CSIR-IICB, Jadavpur Campus, Kolkata-700032." the preliminary Estimate amounting Rs.220 Lakh has already Approved by CSIR, New Delhi. ESU Electrical Section having various involvements for detail Estimation, Planning and Engineering documentation works.

Air-Conditioning Section

Air Conditioning section is one of the important



functioning groups under ESU. Primarily, this is a sub-section that works under Electrical Engineering Section 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 6Nos. 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.

Computer Division

CSIR-IICB Jadavpur Campus Members :

Dr. Sucheta Tripathy, Sr. Principal Scientist, Head
Dr. Subhagata Ghosh, Principal Technical Officer, Deputy Head
Mr. Pradeep Sypureddi, Technical Officer
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 (2) [till October 2019]

Introduction:

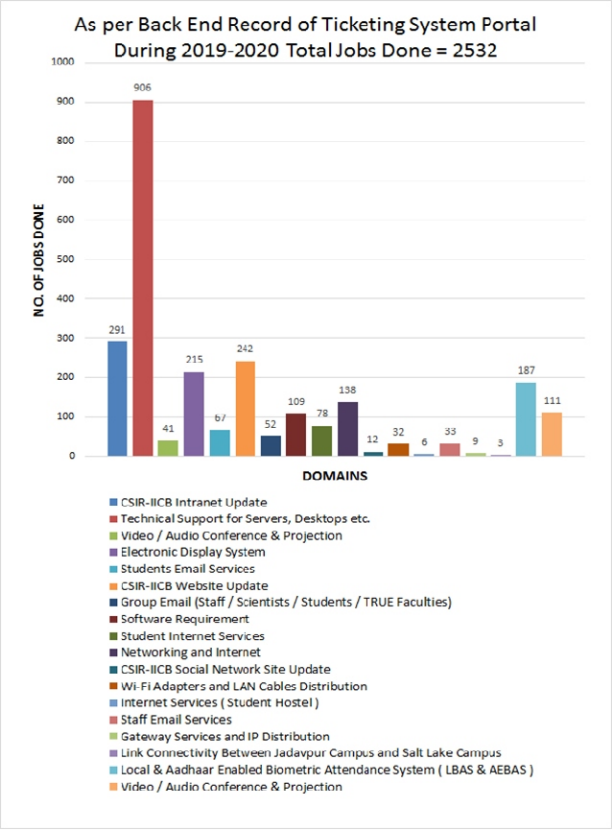
Computer Division provides the primary IT support to the scientists, students and staff members of CSIR-IICB. The IT group works towards maintaining the uninterrupted services to both the campuses of the Institute. It has been in the forefront of deploying information technologies towards modernizing the IT infrastructure.

The Division helps in providing support to Desktops, Laptops, Printers, Scanners, Softwares, Video Conferencing, Biometric System and Network infrastructure services as and when required 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.

MAJOR ACHIEVEMENTS IN 2018-2019: Few steps towards modernization

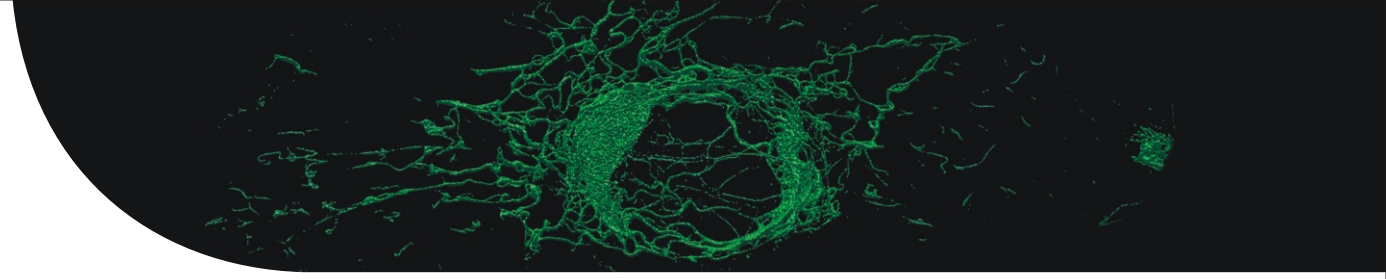
1. Upgradation of Point to Point Connectivity Link between Jadavpur Campus and Salt Lake Campus from10 Mbps to 30 Mbps – Faster Connectivity
2. New Hindi Version of CSIR-IICB Website integrated and hosted as per Government Website Compliance Rule –Representing the Institute to the non-English Speaking population
3. New website has encryption technology for data security with SSL certificate – Ensuring Digital Safety for English and Hindi version
4. Digital Display Facility extended to IICB TRUE campus, Salt Lake– Information Dissemination
5. Introducing New NIC Group Email for Student Communication –Faster Communication
6. Effective Information Portal for Skill Development Cell– Information Dissemination



Routine Technical Services:

1. IT and Network Infrastructure Management Services for both the IICB campuses:

- Jadavpur campus: Maintenance of Sophisticated Core level, Distribution level and Access level equipment like Network Routers, Switches, Access Points etc., Firmware up gradations, IP Schema and Distribution, Band Width Control, LAN and Wi-Fi services, Upgradation & Implementation of



DHCP Service for IP distribution, Proxy Services, Other administrative tasks like Log Monitoring, Network Monitoring, MAC Authentication etc.

- Salt Lake campus: Salt Lake Point to Point Connectivity Services, IP Distribution, Campus to Campus IT Services Integration like Access of internal Servers and IT recourses, Extension & Integration of Services like Intranet, Biometric, Video Conferencing systems etc. to Salt Lake Campus, All other Maintenance of equipment and Administration.

2. Gateway, Firewall Security and IICB VPN Services:

- Firewall Policy implementation for all Internal and External Traffic flow for both campuses
- DMZ Zone Implementation
- Handling of Security incidents
- Maintenance of sophisticated Core level equipment's like UTM Firewall appliances, Analyzers including Intrusion Protection System, Web filtering & Application Control, Malware Protection etc.

3. Email Services for Staff & Student and NIC VPN Services:

- IICB Staff Emails [https://email.gov.in]: Accounts Creation, Passwords Reset, IMAP activation, Deactivation of email accounts for retired staff, Validity extension and all other email services. NIC Group Emails: Approval of Group emails, Member Subscription etc.
- NIC VPN Services for Group & Email: VPN certificates extension, installation etc. Student Email Services: Creating Email accounts, Passwords reset etc.

4. Hosting Websites and Content Management Services:

- CSIR-IICB Website Content management including uploading ESU and Purchase Section Tenders, Faculty Updates, Staff Profile Updates, Research Highlights etc., SSL certificate installation for additional security to the website etc.
- CSIR-IICB SDP Portal of the institute including maintenance of Students Data bases for session wise and content updates CSIR-IICB Intranet website updates, Uploading Office Memorandums, Committees or Teams OM Uploads, Notices Uploads, Staff Profile Updates

5. Administration and Maintenance of Central Servers:

- Administration and Maintenance of IICB Computer Division Central Servers like DNS Server including Mail Records, Proxy Server, IICB Web Server including Intranet, Ticketing System Website Server etc. to keep maximum uptime Monitoring Server Room Infrastructure facilities like Room Temperatures, Dehumidifier, UPS Systems etc.

6. Biometric, Video Conferencing and Display System Services:

- Technical Support for Biometric Attendance Systems for CSIR-IICB staff and students
- Video Conferencing Services with CSIR HQ and other CSIR Labs Administration of Video conferencing systems of the institute through MS Team, Skype support
- Integration of Jadavpur VC system with Salt Lake CampusVC system.
- Digital Display System Services to upload instant notices from including maintenance.

7. IT Facilities Arrangements, Technical Support Services and Call Assignment & Monitoring Services:

- IT Facilities arrangements and Technical Support Services for (i) India International Science Festival –Nov. 2019, (ii) All India Congress of Genetics and Genomics, Dec. 2019 (iii) 3rd EMBO practical course on Cryo-Electron Microscopy (CEM3DIP), Jan,2020
- IICB Skill Development Program (SDP) – 2019 & 2020, Ph.D. Course Works etc.
- Monitoring and Call Assignment through Ticketing System for day to day job requests for all computer division services
- Maintenance of Virus free digital environment.

8. Documents Preparation and Other Special Services:

- Preparation and Documentation for ICT, Tenders, AMC & Procurement process, Budget preparation, IT Audit documentation
- ICT up gradations and other Technical & ICT services from time to time

Future Plans:

- Implementation of virtual platforms for communication and meetings
- Procurement of new Cyber Security Appliances and implementation of the same
- Upgradation or Extension of LAN and WI-FI System of Salt Lake Campus, CSIR-IICB
- Implementation of in house Network Monitoring System for Jadavpur campus and Salt Lake Campus

Human Resource Group (HRG)

Dr. Sanjay Dutta and group

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 HRD 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 provides assistance in the preparation of teaching and research materials and co-ordination of various programs 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.

Activities, Guidance and Initiatives:
Student Affairs & Academic Affairs

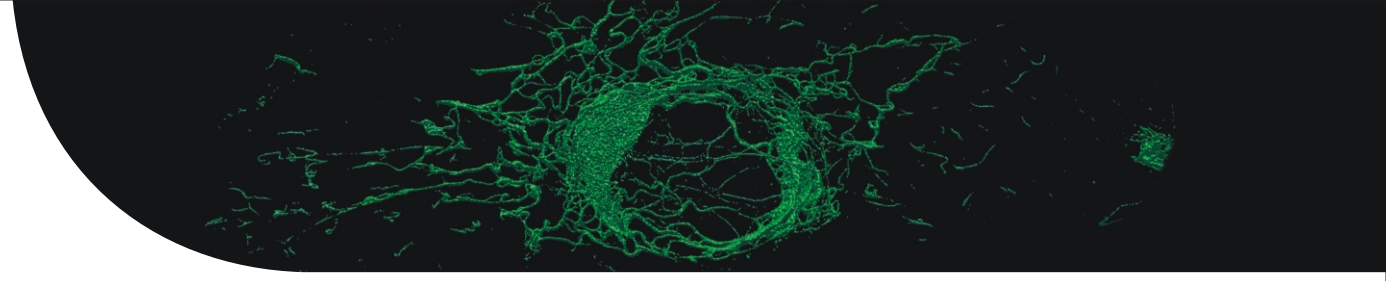
1) PhD course work and PhD program: Management of Course work schedule, course administration and curriculum planning, attendance and class schedule, coordination with the teachers, management of semester examinations, evaluation, seminar, and publication of result, issuance of certificates and statement 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.

Human Resources: PhD students (as on March 2019)

At a Glance: Number of existing Research Fellows: 257 (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 (2019-20): 99

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(AAC)**" acts as an Advisory Committee to the Academic Affairs Division/HRG in connection with CSIR-IICB PhD program and the AcSIR programme.

Members of AAC are as follows :

Members of AAC are as follows :

1. Dr. Suvendra Nath Bhattacharyya, Chairperson
2. Dr. Sib Sankar Roy, Member
3. Dr. P. Jaisankar, Member
4. K. Chattopadhyay, Member
5. Dr. Mrinal K. Ghosh, Member
6. Dr. Chinmay Chowdhury, Member
7. Dr. Jayati Sengupta, Vice-Chairperson
8. Dr. Subhas C. Biswas, Member
9. Saikat Chakraborti, Member
10. Dr. Debabrata Biswas, Member
11. Dr. Partha Chakrabarti, Member
12. Dr. Sanjay Dutta, Member - Convener

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.

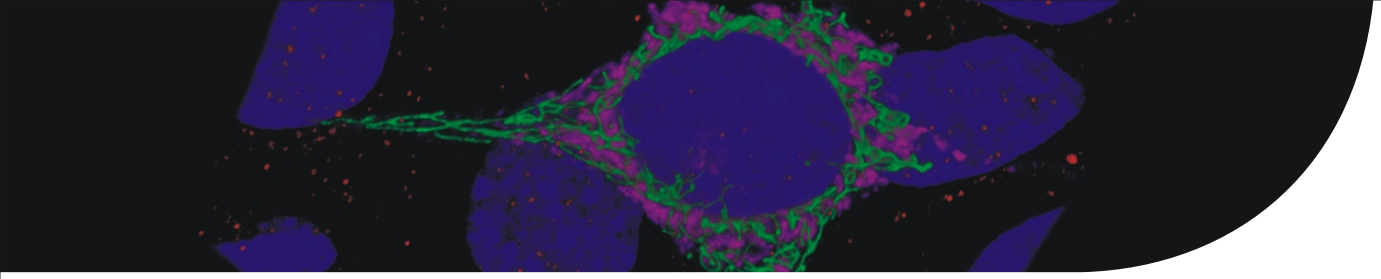
Total number of Course work students for 2019: 52 (Chemistry - 06 , Biology - 46)

Program organized by Academic Affairs- HRG-IICB:

- As a part of the CSIR-IICB PhD course work the students participated in the Hands on Training Programme on NMR and Cryo EM.
- For NMR: all 52 students participated in small groups of 5/6 students during 22nd to 29th April 2019.

  For Cryo-EM: all 52 students participated in small groups of 8 students during 01st to 09th August 2019.

- A one-day workshop was organized on 'Research Ethics' for PhD students on 10th December 2019 at CSIR-IICB. The program was co-ordinated by Dr. Saikat Chakrabarti with



HRG. The following Faculty members presented the various aspects of Ethics involved in the Scientific Reasearch field.

a) Scientific writing and data preparation: Dos and Don't : by Dr. Partha Chakrabarti,
b) Plagiarism: Why should we care.?: by Dr. Arindam Talukdar
c) Managing the common resources (instruments and ingredients): How not to cross the line: by Dr. Suvendra N Bhattacharyya.,
d) Handling human and animal subjects: Permissions and Responsibilities : by Dr. Dipyaman Ganguly
e) Digital and physical data management and archiving: Today's pain, tomorrow's gain: by Dr. Sandip Paul.

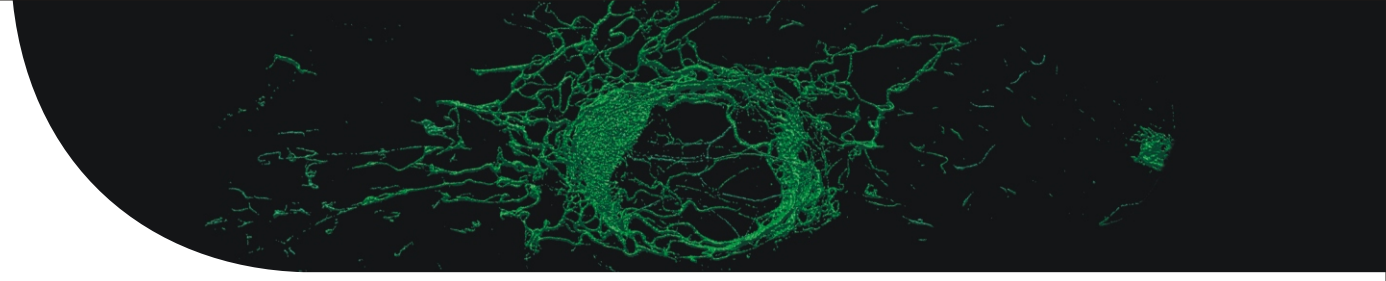
Skill Development Programme

Nodal Officers : Dr. P. Jaisankar, Dr. R. Natarajan

This program is an initiative launched with a view to accelerate the aptitude towards research in students and to provide extensive practical exposure in latest technologies. Institute had offered 13 certificate courses under CSIR-IICB Skill Development Programme during 2019-2020. These courses had provided an opportunity to our youth for hands-on-training, scientific knowledge, analytical perspective & technical skill for understanding the latest technologies used in a research field. The trainees had received 2-weeks exposure in different skilling programs in various advanced areas of IICB expertise through lectures and practical sessions.

During 2019-2020, CSIR-IICB had conducted its various skilling courses under the CSIR-Integrated Skill Initiative. Three sessions

Course	Session-I	Session-II	Session-III	Grand Total
Photochemical Analysis of Medicinal Plants using Advanced Analytical Techniques	03	-	-	03
Liquid Chromatography – Mass Spectrometry (LC-MS)	02	08	05	15
Nuclear Magnetic Resonance spectroscopy (NMR)	01	-	02	03
Separation Techniques for Organic Molecules	01	03	01	05
X-ray Crystallography	01	02	02	05
High Performance Liquid Chromatography (HPLC)	01	04	05	10
Gas Chromatography-Mass Spectrometry (GC-MS)	-	-	02	02
High end equipments for clinical applications- Optical Microscopy	-	04	06	10
High end equipments for clinical applications -Flow Cytometry	-	20	11	31
Clinical Biochemistry, Microbiology and Pathology Techniques for Biomedical Applications	03	14	09	26
Advanced BioInformatics	-	18	08	26
Plant Tissue Culture	-	04	-	04
Protein X-ray crystallography	-	-	08	08
Total	12	77	59	148



of Skill Development Program were conducted during this period in which-

- 07 skill courses were run parallel in the Ist session(held during June 2019)
- 09 skill courses were run parallel in the IInd session(held during Sept 2019)
- 10 skill courses were run parallel in the IIIrd session (held during Jan 2020)

The Courses conducted and Number of Candidates trained during the 2019-20 20 are tabulated below-

Training Programme:

Several CSIR-IICB staff members participated in various training programs as follows:

A. 'Zonal Workshop on One CSIR ERP Protal- HR module' organized by CSIR-HRDC during 29th to 30th Aug 2019 at CSIR-CGCRI. Members participated are:
   1. Shri. A.K. Pandey, SPO
   2. Shri Ratan Bage SO (S&P)
   3. Shri Kanu Mondal SO (G)
   4. Mrs. Monalisa Bhattacharyya ASO (G)
   5. Mrs. Sanhita Ganguly ASO (G)
   6. Shri Prem Singh ASO (G)
   7. Shri D. K. Kisku ASO (G)
   8. Shri Jayanta Pal ASO (G)
   9. Shri Bisweswar Das ASO (S&P)
   10. Mrs. Bula Pal ASO (S&P)
   11. Shri Sukhendu Biswas SSA (G)
   12. Shri Raju Kumar SSA (G)
   13. Shri Vishal Aggarwal SSA (F&A)
   14. Shri Gautam Saha Sr. Stenographer
   15. Shri Samir Thami Technician (2)
   16. Shri Sankar Bhakta Sr. Stenographer
   17. Shri Sisir Banik, Lab Asst.

B. 'RAB Assesment Module Training' organized by CSIR-HRDC on 08th August 2019. Members participated are:
   1. Smt Shampoo Sengupta, SO (G)
   2. Shri Saugata Das, ASO (G)

C. 'Training on Rajbhasha' organized by CSIR-HRDC during 01st & 02nd Aug'2019. Smt Ambalika Nag Hindi Officer participated in this program.

D. 'CSIR Manual on Procurement of Goods 2019' organized by CSIR-HRDC during 16th to 17th Sept 2019 at CSIR CGCRI. Members participated are:
   1. Dr. K. N. Chattopadhyay, Senior Principal Scientist
   2. Dr. Ranjan Jana, Senior Scientist
   3. Dr. Subhajit Biswas, Senior Scientist

E. 'CSIR Manual on Procurement of Goods 2019' organized by CSIR-HRDC during 16th to 20th Sept 2019 at CSIR CGCRI. Members participated are:
   1. Dr. P. Jaisankar, Chief Scientist
   2. Shri S. Halder, A.O.
   3. Shri Kanu Mondal SO (G)
   4. Shri. A.K. Pandey, SPO
   5. Shri Ratan Bage, SO (S&P)
   6. Shri Manoj Kumar F&AO
   7. Shri S. K. Mukhopadhyay ASO (F&A)
   8. Shri A.B.S. Roy ASO (S&P)
   9. Shri Rajib Ray, ASO (S&P)
   10. Shri Bisweswar Das ASO (S&P)
   11. Mrs. Bula Pal ASO (S&P)
   12. Shri Pradipta Sarkar SSA (S&P)
   13. Shri Arnab Sen SSA (S&P)
   14. Shri Shyama Ch Bose SSA (S&P)
   15. Shri S.K. Banik Lab Asst.

F. 'Managerial Effectiveness for TO' organized by CSIR-HRDC during 29th to 31st May 2019. Members participated are:
   1. Shri Soumik Laha Tech Asst.
   2. Shri Akash Gupta, Technician (1)

G. 'Effective implementation of RTI-Act & Record Management organized by CSIR-HRDC during 29th to 30th April 2019. Members participated are:
   1. Smt Shampoo Sengupta, SO (G)
   2. Mrs. Sanhita Ganguly ASO (G)

H. Training programme on "Work-Life Balance for Women Scientists and Officers" during 24th to 26th Sept,2019 organised by CSIR-HRDC. Members participated are -

1. Smt. Arti Grover, STO(1)
2. Smt. Sanhita Ganguly, ASO(G)

Members :
Dr. Siddhartha Majumdar, Head HRG [till Jan. 2020]
Dr. Sanjay Dutta, Head HRG [From Feb. 2020]
Ms. Arti Grover, Sr Technical Officer (1)
Ms. Debasree Das, Technical Officer
Mr. Md. Ayub Shah, Sr. Technician (2)



Workshop on Research Ethics for CSIR-IICB PhD course work students: 2019 batch



Hands On Training - NMR



CSIR-IICB PhD course work students - Examination



Glimpses of CSIR-IICB Skill Development Programme



Course-Coordinators of CSIR-IICB Skill Development Programme



Inaugural Day of SDP-Sept session









Practical sessions during Skill Development Programme



Inaugural ceremony of SDP-Jan session



Practical sessions during Skill Development Programme





Practical sessions during Skill Development Programme



Candidates enrolled in SDP Jan session





Inaugural Day of SDP-Jan session





Enrollment of candidates



Valedictory session of SDP-Jan session



Awarding certificates to SDP candidates

Library & Documentation Division
Knowledge Resource Centre (KRC)

Members:

Dr. Krishnananda Chattopadhyay (Head), Dr. SankarMaitra (since 18.08.2017), Mr SK Naskar (until Oct 31 2020), Mr Tapan Das (since Aug 12, 2020), Mr S Nath &Mr Asoke Ram

Knowledge Resource Centre (Library& Documentation Division) is actively engaged in giving access to the information sources online and off-line. The KRC has been continuing its efforts in expanding services to the users' community through its information base. The Division is playing a pro-active role in establishing itself as one of the important infrastructure divisions by providing literature supports to the scientific community.

Collections	Up to 31.03.2018
Books (including Hindi)	14,430
Journals (online only)	109
Bound volumes	33,860
Science-Direct (Back files) (Http://www.iicb.res.in/bkfiles_library.html)	202 journals full text up to 1994
Newspapers (English, Bengali & Hindi)	3

National Knowledge Resource Consortium (NKRC) :

NKRC is a strong network of all CSIR & DST Institutions for pooling and sharing of Knowledge Resources for catering best possible services to their users. The CSIR-NISCAIRis the nodal agency for implementing and monitoring the activities of the NKRC and venturing the project successfully. Presently, about 5000 scholarly journals are accessible in full-text through NKRC across the CSIR & DST Institutions

Services:

The KRC serves as an important interface between users and the literature by ensuring uninterrupted access to the subscribed content besides regular services like **circulation, reference** and **referral, photocopying** and **printouts** services including the following others.

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 search interface for the 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 repositoryishttp://www.eprints.iicb.res.in. So far 2006 documents in full-text have been uploaded to the repository.

Resource sharing among CSIR & DST Libraries based on the demand placed by the users. **Similarity Index Report** generation for all the theses and research papers from IICB before submitting and communicating accordingly.For reviewing the manuscripts,iThenticate – plagiarism detection database service is available in KRC.

The KRC provides personal information services using Science Citation Index Expanded. IICB-KRC has been subscribing the '**Web of Science**'for such services.

CSIR Virtual Union Catalogueis available with the URL http://14.139.223.115/ for resource sharing among CSIR KRCs.

Several'User Awarenesscum Training Programmes" organized by the KRC to maximize its utilization among the researchers.

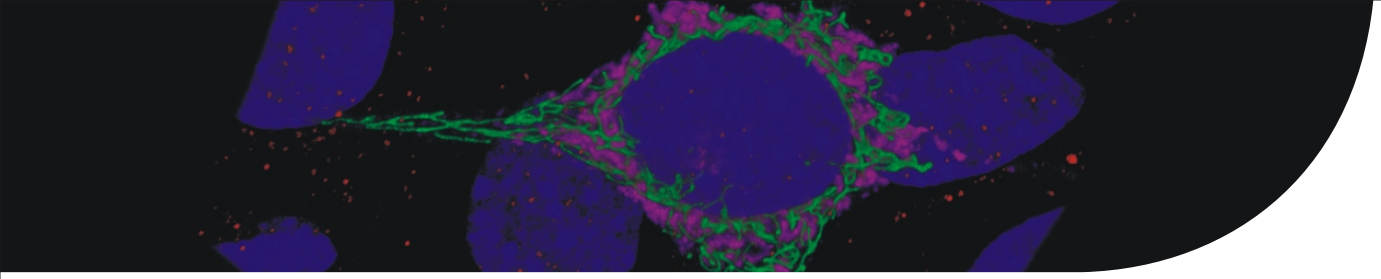
A collection on **Hindi books** has been developed by KRC as advised by Official Language Implementation Committee **(OLIC)**.

Planning, Monitoring and Evaluation (PME) Section

Members: Dr. Rupak K. Bhadra (Head), Mrs. Purnima Chatterjee, Mr. Tapan Das, Mr. Soumalya Sinha and Mr. Samir Thami

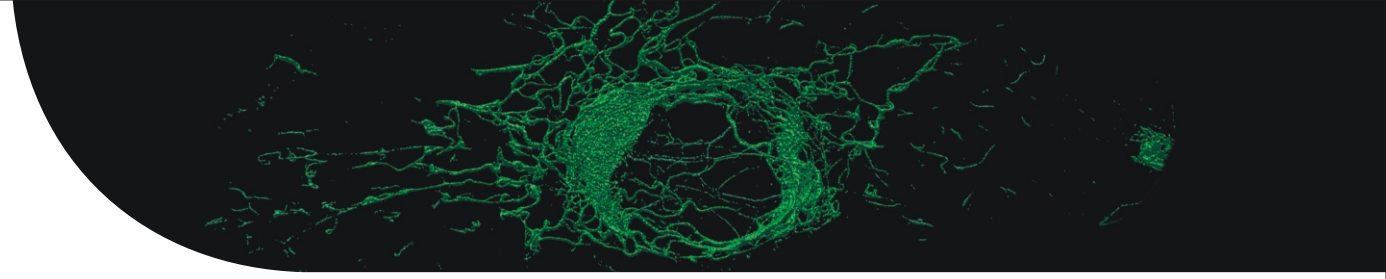
The Planning, Monitoring and Evaluation (PME) Division manages the Institute's plan and non-plan projects, grant-in aid projects (GAP), sponsored and collaborative R&D projects, consultancy and technical service projects. This division maintains liaison with Scientists and Technical officers who are 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-IIICB, 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.





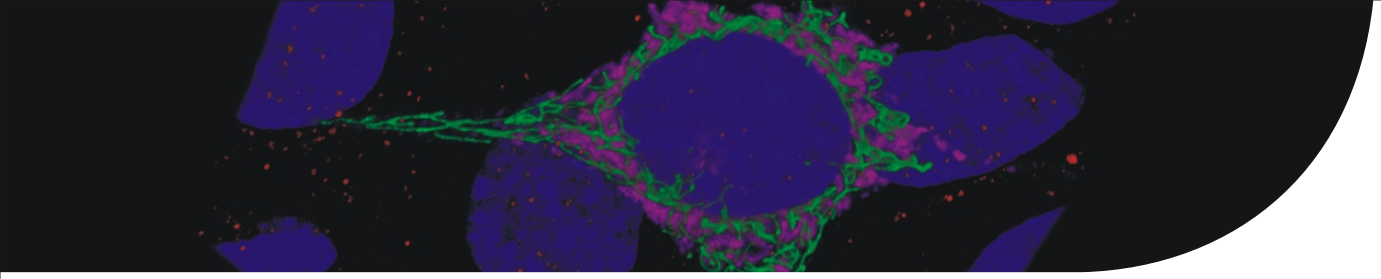
Completed Extramural Projects (2019-2020)

Sl. No	Name of the project	Project Code	Name of PI	Project Cost (Rs. In lakh)	Funding Agency	Start Date	Completion date
1	Targeting Deadenylation-Mediated Kinetoplastidae Prasite-Specific Polycistronic Gene Regulation for Therapeutic Intervention	GAP-337	Dr. Pijush K Das	48.95	DBT, Govt. of India	13.05.16	12.05.19
2	Assessing the genome sequences of Termitomyces clypeatus for novel metabolite discovery through whole genome sequencing methond and characterization of the metabolites for application in biotechnology	GAP-342	Dr. Sucheta Tripathy	55.56	DBT, Govt. of India	01.04.16	31.03.19
3	MiRNAs in trophoblast stem cell differentiation Development of anti-alzheimer peptide from taxol binding	GAP-343	Dr. Rupasri Ain	46.48	SERB, Govt. of India	03.06.16	02.06.19
4	Development of anti-alzheimer peptide from taxol binding pocket of of B-tubulin	GAP-344	Dr. Surajit Ghosh	57.24	SERB, Govt. of India	11.07.16	10.07.19
5	Role or type I interferons in cerebral malaria	GAP-345	Dr. Dipyaman Ganguly	55.26	DBT, Govt. of India	01.07.16	30.06.19
6	Role of sialylated glycan on Pseudomonas aeruginosa in interactuion with innate immune cells: A glyco-proteomics approach	GAP-346	Prof. Chitra Mandal	67.03	DBT, Govt. of India	27.07.16	26.07.19
7	Indo-Belgian research proposal: Support of Networking Activities	GAP-347	Dr. Suvendra Nath Bhattacharya	21.57	Belgian Federal Science Policy Office (BELSPO) & DST	29.06.16	28.06.19
8	A Prosperative study on the role of incertin hormones in patients undergoing bariatric surgery	GAP-348	Dr. Partha Chakrabarti	23.98	DBT, Govt. of India	24.08.16	23.08.19
9	Investigation of the folding and aggregation landscape of superoxide dismutase in vitro and in live cells: its implications in Amyotrophic lateral sclerosis (ALS)	GAP-349	Dr. Krishnananda Chattopadhyay	45.94	DST, Govt. of India	27.09.16	26.09.19
10	Molecular epidemiology and characterization of occult hepatits B virus(HBV) infectious, particularly the role of S protein mutations leading to undetectable HBV surface antigen(HBsAg) in patient blood plasma	GAP-350	Dr. Subhajit Biswas	31.33	SERB, Govt. of India	30.09.16	29.09.19
11	Tumor supressor SMAR1 regulater transcription of β-catenin and protect from metastatic colon cancer	GAP-351	Prof. Samit Chattopadhyay	80.14	SERB, Govt. of India	29.09.16	28.09.19
12	Desighning bioactive peptides from whey liquid waste of the dairy industry: Functionally and health benefit in Obesity, Obesity associated disorders with exploration of molecular mechanism	GAP-352	Dr. Krishna Das Saha	21.18	DBT, Govt. of India	04.11.16	03.11.19
13	Stereoselective Total Synthesis of Marine Macrocyclic Lactone Biselyngbyaside and its Variants and Their Biological Activities	GAP-353	Dr. Partha Chakrabarti	9.72	SERB, Govt. of India	01.11.16	31.10.19
14	Development of nano-partical based directed delivery systems for peptide therapeutics	GAP-354	Dr.Mrinal Kanti Ghosh	68.57	DST, Govt. of India	04.12.15	31.10.19
15	Utilization of pomegranate for development of functional Medicinal ingredients	GAP-356	Dr. Krishna Das Saha	22.00	AYUSH (SERB,Govt of India)	31.12.16	30.12.19
16	Elucidation of functional role of FKBP5 in eukaryotic transcriptional regulation	GAP-358	Dr. Debabrata Biswas	50.75	SERB, Govt. of India	22.03.17	21.03.2020
17	α- Ketothioesters : An Indispensable Building Blocks for Accessing Diverse Heterocycles via Sulfanyl Anions or Thiyl Radical Migration	GAP-359	Dr. Indrajit Das	62.82	SERB, Govt. of India	23.03.17	22.03.2020
18	Mechanism of Ets-1 transcription factor- mediated metabolic reprogramming and tumorigenesis in ovarian cancer	GAP-360	Dr. Sib Sankar Roy	39.05	SERB, Govt. of India	29.03.17	28.03.2020
19	Characterization of exosomes released by macrophages infected with leishmania donovani	GAP-361	Dr. Suvendra Nath Bhattacharya	15.00	DBT, Govt. of India	30.03.17	31.03.2020
20	Elucidation of Roles of Inflammatory Mediators in PancreaticCell and hepatocyte dysfunction Type 2 Diabetes	GAP-363	Dr. Partha Chakrabarti	13.69	ICMR, Govt. of India	29.03.17	28.03.2020



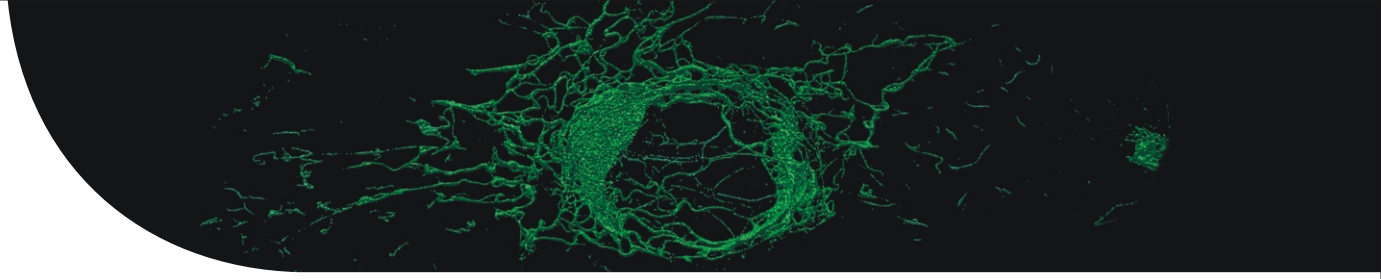
Santioned and Implemented Extramural Projects (2019-2020)

Sl. No.	Name of the project	Project Code	Name of PI	Project Cost (Rs. In Lakh)	Funding Agency	Start date	Completion Date
1	Scanning through the molecular interactome of dengue virus NS1 protein and host cell factors (miRNA, mRNA and proteins) to identify potential targets for anti-dengue antivirals	GAP-405	Dr. Upasana Ray	18.000	SERB, Govt. Of India	04.06.2019	03.06.2022
2	Project with "Natreon Inc."	SSP-407	Dr. P. Jaisankar	6.537	Natreon Inc.	10.07.2019	09.07.2020
3	Fabrication of 3D hybrid hydrogel: A novel safe-by-design concept with effective photothermal ablation of bacterial infection	GAP-408	Dr. Sujoy Das	43.733	SERB, Govt. Of India	13.08.2019	12.08.2022
4	Treating malaria by targeting the regulatory mechanism PfATPase2 and PfATPase8 required to maintain lipid asymmetry in parasite plasma membrane	GAP-409	Dr. Sudipta Das	50.729	SERB, Govt. Of India	06.07.2019	05.07.2022
5	Managing mitochondria from dopamine: Halting Parkinson's disease progression	GAP-410	Dr. Joy Chakraborty	43.7730	ICMR, Govt. Of India	11.09.2019	10.09.2021
6	Molecular regulation of spiral-artery remodelling	GAP-411	Dr. Rupasri Ain	68.9800	DBT, Govt. Of India	27.09.2019	26.09.2022
7	Cellular Prion : A novel regulator of decidual cell function at the maternal-fetal interface	GAP-412	Dr. Rupasri Ain	61.7700	ICMR, Govt. Of India	27.09.2019	26.09.2022
8	Mitochondrial clearance in aging brain: therapeutic approach against differential neurodegeneration in Parkinson's disease	GAP-413	Dr. Joy Chakraborty	39.5644	SERB, Govt. Of India	01.11.2019	31.10.2022
9	Mechanism of miRNA-dependent and independent targeting of mRNAs to P-bodies	GAP-414	Dr. Suvendra Bhattacharya	60.4500	CEFIPRA	19.11.2019	18.11.2022
10	Suicidal Genetherapy Using Engineered Secretary Carboxylesterse-2/ Camptotehecin-11 Targeting Chemoresistant Ovarian Serous Adenocarcinoma	GAP-415	Dr. Siddik Sarkar	30.2940	SERB, Govt. Of India	28.11.2019	27.11.2021
11	Synthesis and characterization of different chrysin derivatives followed by screening of anti-obesogenic activity in vitro: assesment of in vivo activity with the lead compounds	GAP-416	Dr. Krishna Das Saha	29.4330	DBT, Govt. Of India	27.09.2019	26.09.2022
12	Role of endoplasmic reticulum (ER) stress induced UPR signalling in regulating the metabolic fitness and functionality of CD8+ T cells in cancer	GAP-417	Dr. Shilpak Chatterjee	359.1170	DBT, India Alliance/Welcome trust	01.01.2020	31.12.2024
13	Understanding the early events of alpha-synucelin aggreagtion and its implications in Parkinson's disease related neurodegenration	GAP-418	Dr. Krishnananda Chattopadhyay	41.9330	DBT, Govt. Of India	11.11.2019	10.11.2022
14	Electrochemical nanosensor of BACE-1 for early detection for Alzheimer's disease	GAP-419	Dr.Prem Prakash Tripathi	6.18 (First year)	ICMR, Govt. Of India	13.01.2020	12.01.2023
15	Design and development of selective inhibitors of protein arginine methyltransferase 1 involved in epigenetic modifications	GAP-420	Talukdar Dr. Arindam	41.724	SERB, Govt. Of India	05.02.2020	04.02.2023
16	Impact of tryptophan derived bacterial metabolics on metaflammation	GAP-421	Dr. Partha Chakrabarti	56.844	SERB, Govt. Of India	06.02.2020	05.02.2023



Santioned and Implemented Extramural Projects (2019-2020)

Sl. No.	Name of the project	Project Code	Name of PI	Project Cost (Rs. In Lakh)	Funding Agency	Start date	Completion Date
17	Transcriptomic Analysis of µTumor Spheroid Derived from Single Cancer Stem Cell to Identify Novel Therapeutic Targets in Breast Cancer	GAP-422	Dr. Amit Kumar Srivastava	46.494	SERB, Govt. Of India	29.01.2020	28.01.2023
18	Evaluation of WISP3 in the context of progressive pseudo rheumatoid dysplasia (PPRD) using zebrafish as model organism	GAP-423	Dr. Malini Sen	42.228	SERB, Govt. Of India	07.02.2020	06.02.2023
19	Mechanistic exploration of the role of S1PR1 in regulating the functional fate of tumor infiltrating CD8 T cells	GAP-424	Dr. Shilpak Chatterjee	46.540	SERB, Govt. Of India	17.02.2020	16.02.2023
20	High-resolution structural description of HflX's interaction with 70s ribosome and ribosomal subunits to decipher its functional role in bacteria under stress	GAP-425	Dr. Jayati Sengupta	39.564	SERB. Govt. Of India	27.02.2020	26.02.2023
21	Affinity ultrafiltration liquid chromatography (UF-LC) assisted identification and characterization of a-glucosidase and a-amylase inhibitory constituents from Pterocarpus santalinus heartwood	GAP-426	Dr. Deepak Kumar	38.830	National Biodiversity Authority, Govt of India	24.03.2020	23.03.2022
22	Bio-assay guided isolation of anti-cancer compounds from Pterocarpus santalinus and assessment of cytotoxicity, pharmacokinetics and detailed molecular mechanism	GAP-427	Dr. Amit Kumar Srivastava	44.830	National Biodiversity Authority, Govt of India	24.03.2020	23.03.2022
23	BDevelopments in Indian genetics disease database: Updation, Analysis and Inclusion of Complex Diseases	GAP-428	Dr. Sandip Paul	14.856	DBT, Govt. Of India	25.02.2020	24.02.2023



Ongoing In-house projects (2019-20)

Sl. No	Title	Project Code	Nodal Scientist	Project cost (Rs. In Lakh)	Start date	Completion Date
1	Non-alcholoic Steatohepatitis (NASH)	MLP125	Dr. Partha Chakrabarti	80.00	Sep' 2018	March' 2020
2	Chronic Respiratory Disease Innovation and Solution Program (CRISP)	MLP126	Dr. U Mabalirajan	75.00	14.08.18	31.03.2020
3	Genomics and Epigenomics in Health and Disease (GEHeaD)	MLP127	Dr. Arun Badyopadhyay	15.00	14.08.18	31.03.2020
4	EXOsomal MIRna INhibitor: Identification of the new classes of inhibitors of miRNA trafficking via exosomes (EXOMIRIN)	MLP128	Dr. S N Bhattacharya	50.00	24.09.18	31.03.2020
5	CSIR Sickle Cell Anaemia Mission	HCP-0008	Dr. Amitava Sengupta	434.96	22.09.17	21.09.2020
6	CSIR Phytopharmaceutical Mission	HCP-0010	Prof. Samit Chattopadhyay	629.24	08.02.17	07.12.2020
7	INPROTICS-Pharma and Agro	HCP-0011	Dr. Indu Bhusan Deb	300.00	12.02.18	11.02.21
8	Nano Biosensors and Microfluids for Healthcare	HCP-0012	Dr. Subhajit Biswas	292.07	13.03.18	12.03.2020
9	Crop Protection Chemicals	HCP-0021	Dr. Indrajit Das	190.00	09.01.19	31.03.2020
10	CSIR Integrated Skill Initiative Program	NWP-0100	Dr. P Jaisankar/ Dr. Arun Bandyopadhyay	98.20	01.04.2018	31.03.2020
11	JIGYASA Project	NWP-101	Dr. Neeta Khalkho	30.20	25.02.18	31.03.2020

Science Popularization Section

Members :

Dr Neeta V.M. Khalkho (Head), Mr Saibal Giri, Mr Paresh Sarkar, Ms Sutapa Ganguly & Mr P.C. Dehuri



Science Popularization Section (Left to Right): Mr P.C. Dehuri, Ms Sutapa Ganguly, Dr Neeta V.M. Khalkho (Head), Mr Paresh Sarkar & Mr Saibal Giri

The SPS undertakes and deals with a wide range of informational activities and the publication of reports related to these outreach activity such as JIGYASA, participation in technology fairs (both at the local and national levels). Such information is endeavored to be disseminated both in electronic and printed forms for extensive publicity of CSIR-IICB technologies, products and innovations. The major contribution of SPS lies in assisting scientists to organize outreach regarding above-mentioned technologies, products and innovations. The section was involved in the following programmes during the reporting year:

Preparation of documents released during events such as JIGYASA, and updating the English and Hindi technology pamphlets to be made available at periodic intervals. SPS also undertook dissemination of information to the scientific milieu on relevant subjects. SPS also maintains record for testing and calibration and updates SPS events and ancillary information on the CSIR-IICB website. The SPS is also entrusted with the



CSIR-IICB Technology Exhibition Team

responsibility of science news dissemination and display achievements of the institution through exhibitions.

The section was further involved in various outreach activity throughout the year under 'JIGYASA'. We have organized a total of 18 popular science talks, where our scientist was actively involved in visiting various Kendriya Vidyalayas and Government Schools, in and around Kolkata.



Scientist-Student Interaction at Kendriya Vidyalaya Santragachi



Scientific talk at Kendriya Vidyalaya, Garden Reach

We have organized a JIGYASA Autumn Camp in August on both Campuses of CSIR-IICB. Students and teachers of Kendriya Vidyalaya, Joka and Kendriya Vidyalaya, Icchapur No 2 were the participants for a Three days long event. Students were provided with a kit containing JIGYASA bag, stationery items, and protocol booklet. They visited laboratories of different scientific departments related to chemistry, biology, bioinformatics, genetics, cancer, etc. Students gained a first-hand experience of the experimental laboratory.

They saw a demonstration of sophisticated scientific instruments, attended biology and chemistry-theme lectures, among other popular lectures. Moreover, they had a very fruitful interactive session with scientists, technologists and Ph.D. scholars of this Institute. There was a practical demonstration event of soap-making and a science magic show during the camp wherein students participated with great interest and enthusiasm. On the last day of the programme, participants were provided with certificates of completion.



JIGYASA Camp: Student felicitation



Laboratory visit by students

Apart from these activities, we organized 7 One-day Scientific Exposure Trips where various school and university students participated. Yearlong activities under JIGYASA assured participation of more than 3450 students and 38 teachers.



K.V. students Interaction with Technologist



Moula Netaji Vidyalaya students at CSIR-IICB

The 'Technology Exhibition Unit' has participated in exhibitions and outreach programmes at national and state-level such as the 23rd National Exhibition, Sodepur, 7th Indian National Exhibition-cum-Fair, Garia, Sundarban Kristi Mela O Loko Sanskriti Utsab, Kultali, 24 Parganas, 107th Indian National Science Exhibition, Bengaluru.



23rd National Exhibition, Sodepur



7th Indian National Exhibition-Cum-Fair, Garia

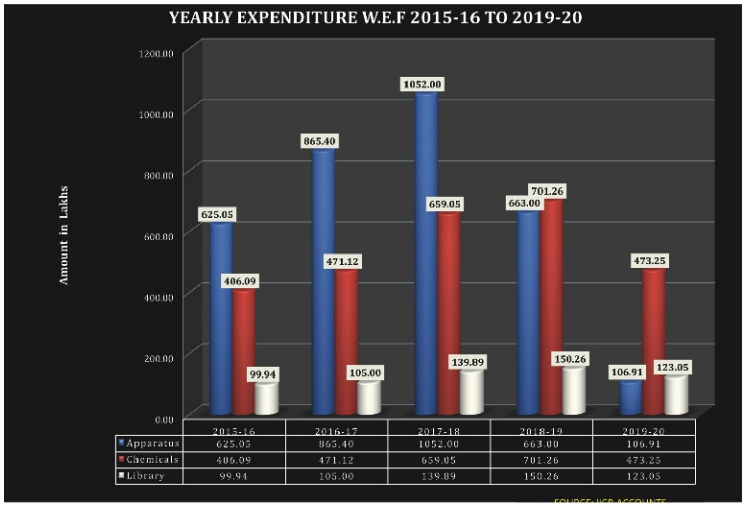
In the 5th India International Science Fair ('IISF') at MEGA Science Technology & Industry Expo, Science City (Kolkata) the section was responsible for managing 3 pavilions namely, Technology, Skill Development and JIGYASA. SPS also organized a science quiz for 2000 students out of which 500 winners were felicitated with certificates. The DG-CSIR along with the Secretary DST also graced us with their presence at the JIGYASA Pavilion at IISF 2019.

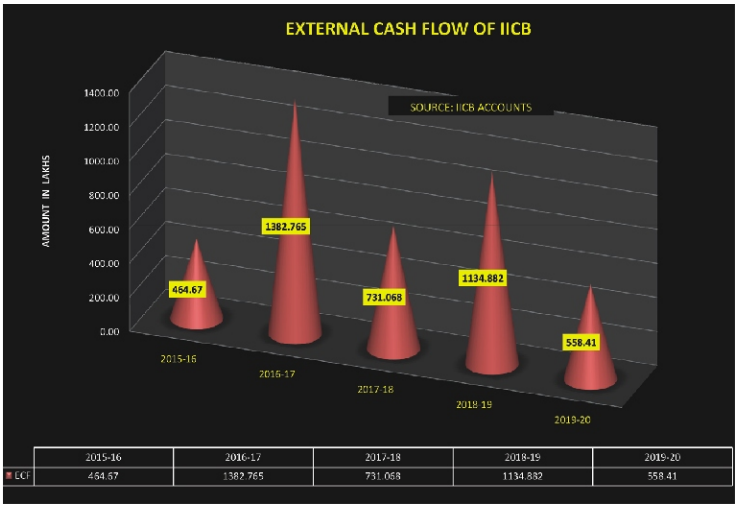


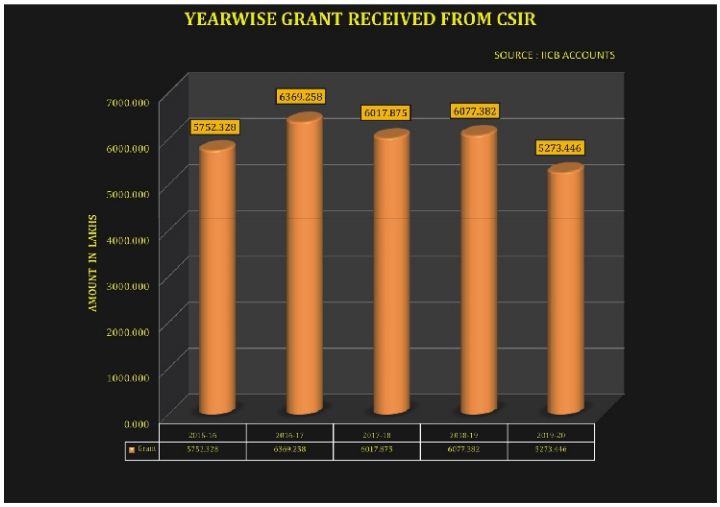
DG-CSIR at the JIGYASA pavilion at IISF 2019

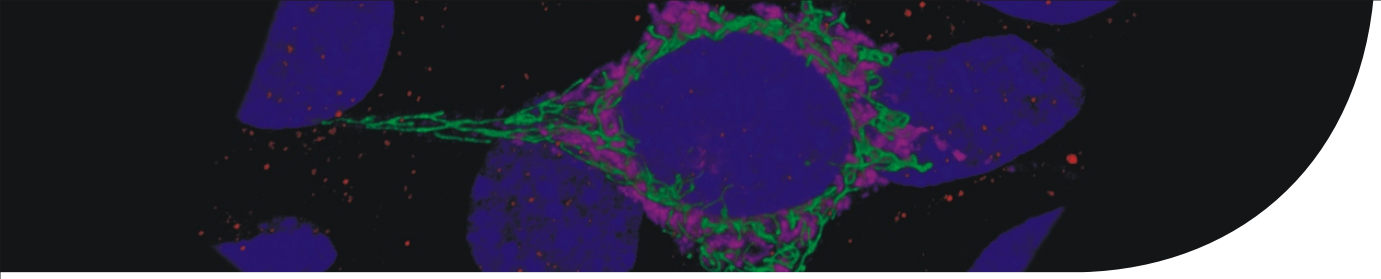


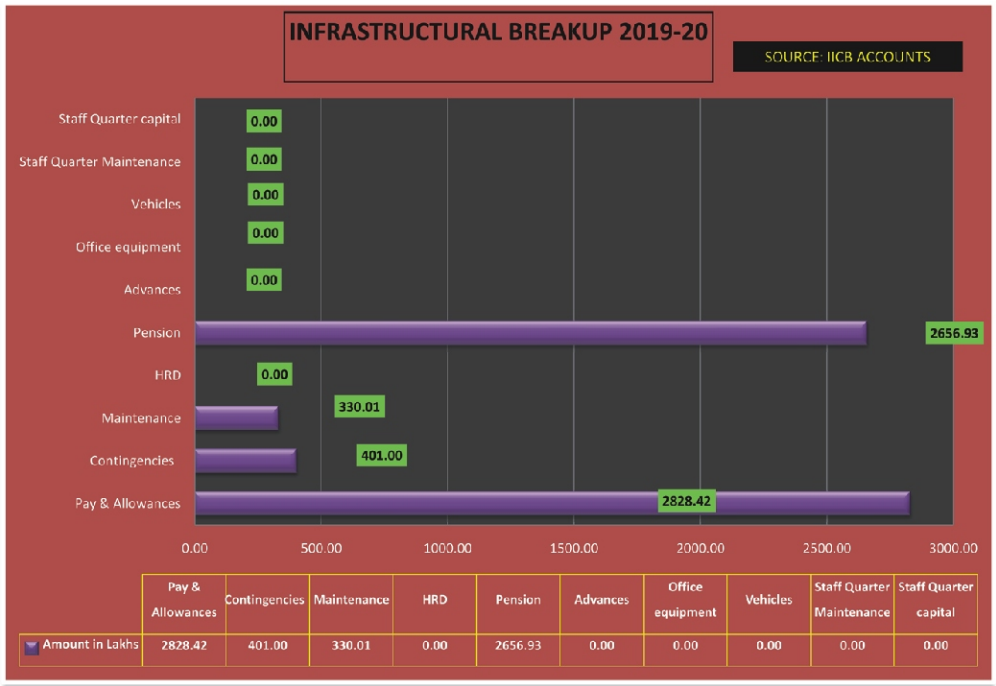
Secretary DST at the JIGYASA pavilion at IISF 2019


YEARLY EXPENDITURE W.E.F 2015-16 TO 2019-20
Amount in Lakhs
1200.00
1000.00
800.00
600.00
400.00
200.00
0.00
625.05
406.09
99.94
865.40
471.12
105.00
1052.00
659.05
139.89
663.00
701.26
150.26
106.91
473.25
123.05
2015-16 2016-17 2017-18 2018-19 2019-20
Apparatus 625.05 865.40 1052.00 663.00 106.91
Chemicals 406.09 471.12 659.05 701.26 473.25
Library 99.94 105.00 139.89 150.26 123.05

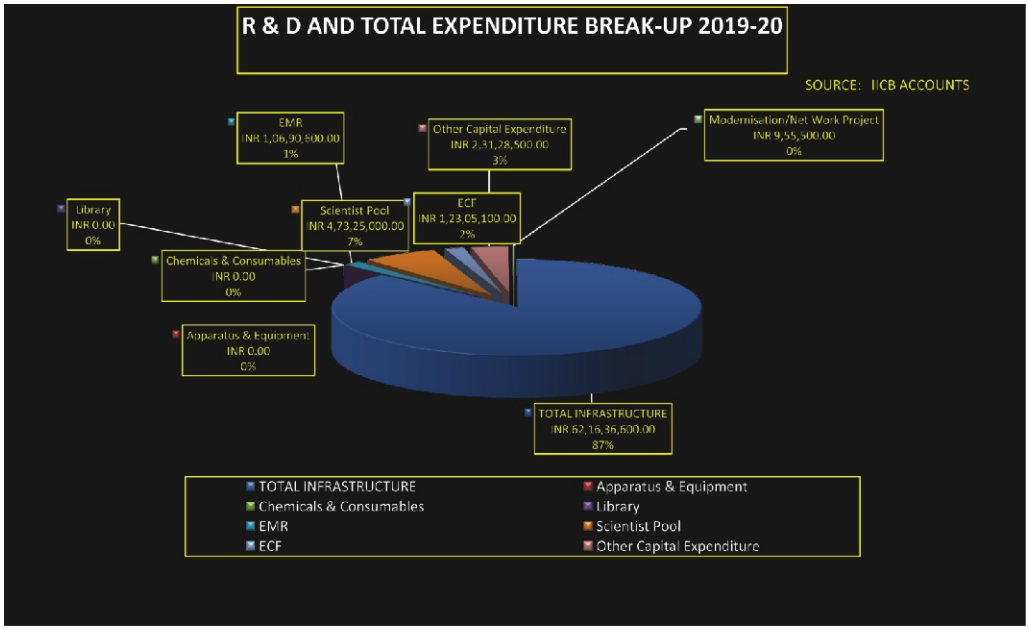

EXTERNAL CASH FLOW OF IICB
SOURCE: IICB ACCOUNTS
AMOUNT IN LAKHS
1400.00
1200.00
1000.00
800.00
600.00
400.00
200.00
0.00
464.67
1382.765
731.068
1134.882
558.41
2015-16
2016-17
2017-18
2018-19
2019-20
2015-16 2016-17 2017-18 2018-19 2019-20
ECF 464.67 1382.765 731.068 1134.882 558.41


YEARWISE GRANT RECEIVED FROM CSIR
SOURCE : IICB ACCOUNTS
AMOUNT IN LAKHS
7000.000
6000.000
5000.000
4000.000
3000.000
2000.000
1000.000
0.000
5752.328
6369.258
6017.875
6077.382
5273.446
2015-16 2016-17 2017-18 2018-19 2019-20
Grant 5752.328 6369.258 6017.875 6077.382 5273.446





	Pay & Allowances	Contingencies	Maintenance	HRD	Pension	Advances	Office equipment	Vehicles	Staff Quarter Maintenance	Staff Quarter capital
Amount in Lakhs	2828.42	401.00	330.01	0.00	2656.93	0.00	0.00	0.00	0.00	0.00



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 for facilitating the smooth functioning of the activities of the Institute by availing digital technology wherever available, providing 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 mechanism in placed and thus a number of checks and balances have been placed in the system to this effect.







Hindi Activities 2019-20

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 2019 saw many activities of the Official Language with organising Hindi workshop every quarter (three months). Regular Hindi classes were arranged in the Institute (both campuses) where in 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.

A quarterly Hindi workshop in science was held on 12th June 2019 (April to June, 2019). The topic "Development of Indian particle-accelerators and participation in nuclear energy delivered in Hindi language was very interesting. This scientific seminar was in itself a very innovative & interactive session. The workshop was conducted by Dr. Hemendra Kumar Pandey, Scientific Officer (G), Variable Energy Cyclotron Centre, Kolkata.

Hindi week was celebrated from 6 to 13 September 2019. 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 from all over Kolkata & Pune.

On 6th September, 2019 from 2:30 p.m. to 4:30 p.m. wherein Hindi Inaugural ceremony, Hindi recitation competition and extempore competitions were held in the Institute. On this day, the employees and researchers of the Institute participated very enthusiastically in the recitation competition in which Head of Hindi Department, Shri Shikshashyatan College Mrs. Alpana Rajvardhan and, Associate Professor Hindi Department, Yogesh Chandra Chaudhary College Kolkata, Dr. Mamta Trivedi ji were the judges. On the 9th September 2019 Hindi essay, noting & drafting competitions were held where many employees and research scholars participated.

On 11 September 2019, a Debate competition in Hindi was held in which large number of employees and researchers participated. The Chief Manager, (Official Language) UBI, Kolkata, Mrs. Rita Bhattacharya and Associate Professor, Department of Hindi, Khudiram Bose Central College, Dr. Shubhra Upadhyaya adorned the seats of judges.

On 11th September 2019, a one-day Hindi workshop was organized for the administrative staffs of the Institute. VECC, Technical Officer Mr. Vineet Kumar Rakesh conducted the workshop, which was very useful for the staff members where they were taught to use 'Unicode' to do official work in the official language in an easy manner. Overall the presentation was very interesting.

On 12th September 2019 (11:00 a.m. to 12:00 p.m.) a Hindi quiz competition was organized in the J. C. Ray Auditorium of the Institute. The competition was conducted by Dr. Umesh Prasad Singh, Principal Scientist and Mr. Manoj Kumar, Finance and Accounts Officer (Finance and Accounts). Staff members, scientist and researchers participated enthusiastically in this competition.

Dr. Sucheta Tripathi, Principal Scientist of the Institute, gave a popular lecture in Hindi on the topic 'Comui-tional genomics 'as a versatile tool for biotechnology applications'.

The Hindi cultural programme was held on 12 September 2019 from 3:00 pm to 5:00 pm in the J. C. Roy Auditorium. The entire programme was organized & performed It was a very colourful programme in Hindi by the researchers of the Institute.

Dr. Gyan Chandra Mishra, National Centre for Cell Science, Pune, a distinguished Professor, Padmashree Awardee, was the chief guest at the Hindi Week prize distribution program. Dr. Gyan Chandra Mishra appreciated the work being done in the Institute on Hindi in the program and expressed his views and gave his opinion on the official language and interest of people in it. Dr. Gyan Chandra Mishra inspired everyone to adopt Hindi and shared his life experiences with everyone in this context.

Hindi magazine 'Sanjeevani', was released by Dr. Gyan Chandra Mishra. Scientific articles and articles on general topics of our Institute are published in this magazine. This magazine is an attempt to popularize science among the layman in popular language Hindi and is very popular among all the members of Institute & outsiders.

Hindi day – 13th September 2019 was the last and final day of the week and the closing ceremony was organized on 13th September 2019. The prize distribution program was organized on the same day.

The prize distribution programme was organized on 13 September 2019. The successful participants in the competition were rewarded by the guests and many employees in the auditorium were awarded in a writing correct words in Hindi competition. The program was concluded with a vote of thanks by the Administrative Officer of the Institute.

Science IISF programme was organized on 5.11.2019 to 8.11.2019 all over India in all the scientific organizations. In this context quiz in Hindi for school children was conducted on behalf of IICB.

A one day quarterly Hindi workshop was organised on 12th December 2019 in the first floor seminar room of Institute. Technical officers / employees participated in this workshop. The Administrative Officer inaugurated the programme this day.

The workshop was conducted by Mr. Anup Kumar, Assistant Director (Hindi Teaching Scheme Home Ministry, Kolkata) on working in Hindi and use of official language using Unicode on computer.

Sri. Anup Kumar Ji, trained everyone with voice typing method on the computer mobile.

A quarterly Hindi workshop was held on 16th March 2020, Technical staff members were the participants. The workshop started by a speech delivered by the Hindi officer of the Institute.

The speaker of the workshop, Mr. Anup Kumar, Assistant Director (Hindi Teaching Scheme Home Ministry, Kolkata) took on working classes Hindi and using the official language on the computer using Unicode.

Annual report of the Institute was published in Rajbhasha in compliance with the official language policy of the government.

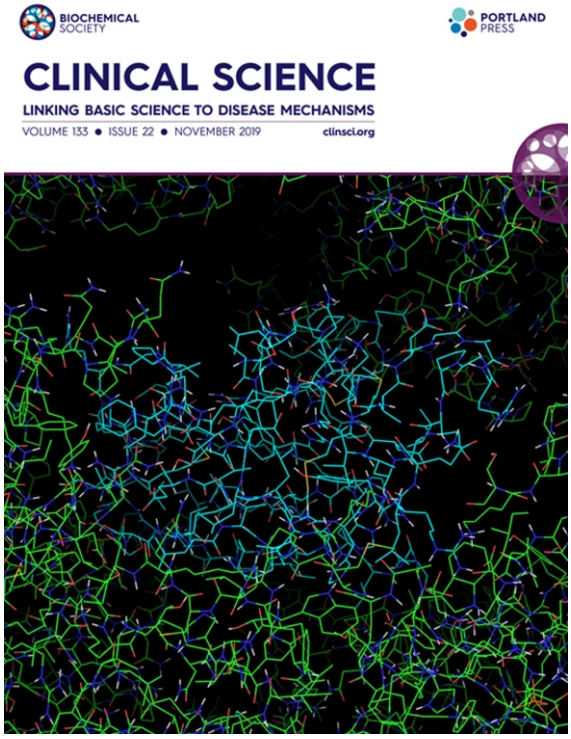








Cover Page Articles - 2019





Awards and Recognitions - 2019



Dr. Upasana Ray
Senior Scientist

SERB Women Excellence Award. Science and Engineering Research Board (SERB) – 2019



Dr. Shilpak Chatterjee
Senior Scientist

DBT/ Wellcome Trust Intermediate Fellowship 2020-2024 Award in January 2020 by the Department of Biotechnology India Alliance, Govt. of India



Dr. Suvendra Nath Bhattacharyya
Principal Scientist

Khosla National Award in Sciences/HSS/Management, IIT Roorkee – 2019-2020



Dr. Nakul Chandra Maiti
Senior Scientist

Author with the highest number of publications in the journal, Journal of Proteins and Proteomics in the last 10 years, by Springer Nature

Highest number of Cover Pages and Designed in the journal, Journal of Proteins and Proteomics by an Author between 2010 and 2018, by Springer Nature

Both the awards were conferred on Dec 04, 2019 during the International Conference on Proteomics for System Integrated Bio-Omics, One Health and Food Safety" from 2nd to 4th Dec 2019. ICAR-National Dairy Research Institute, Karnal-132001, Haryana, INDIA.

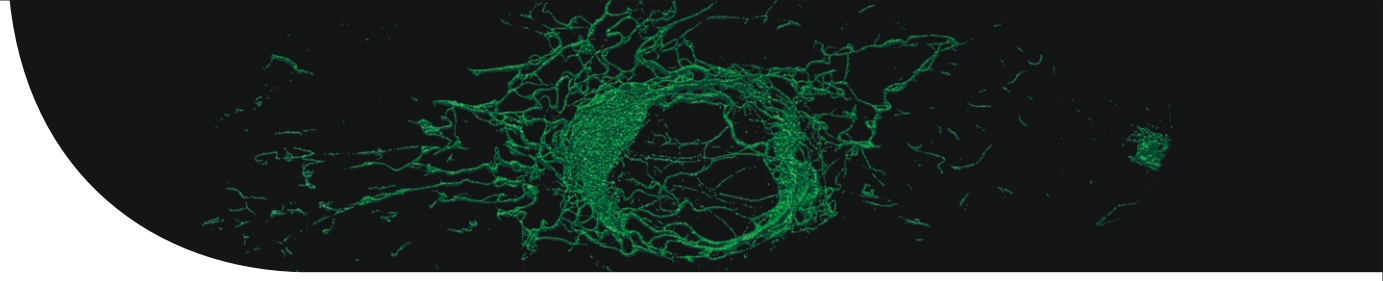


Dr. U. Mabalirajan
Senior Scientist

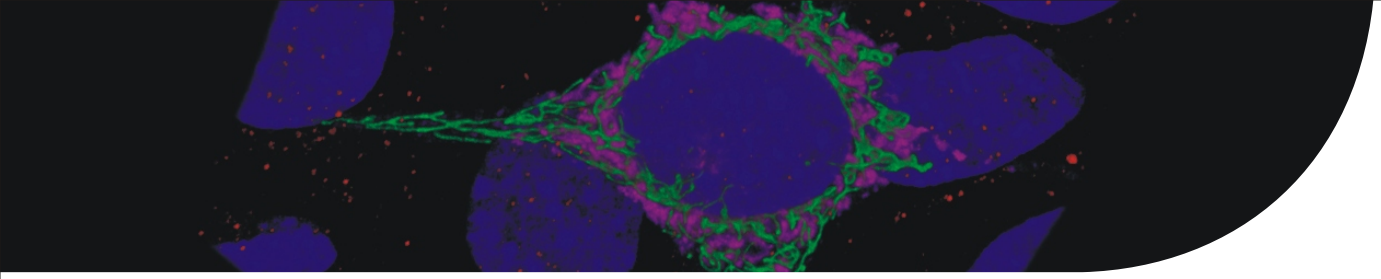
"Dr. P. Kutumbiah Lectureship Award" at Dr. ALM. P.G. Institute of Basic Medical Sciences, University of Madras, Chennai - 2020.

Doctorates from CSIR-IICB

Recipient's Name	Title of Thesis	University	Dt. of Award	Supervisor's name	Division
Dr. Swarnali Roy	Design and synthesis of potent small molecule antagonists of TLR9	JU	04-12-2019	Dr.ArindamTalukdar	Organic & Medicinal Chemistry
Dr. Ayan Mukherjee	Design and synthesis of potential anticancer therapeutic agents and human toll-like receptor 9 antagonist for the treatment of autoimmune disorder	AcSIR	03-06-2019	Dr. ArindamTalukdar	Organic & Medicinal Chemistry
Dr. Satadru Chatterjee	Synthetic And Biological Studies Towards Natural Product Derived New Anticancer Molecules	JU	24-12-2019	Dr. Biswadip Banerjee	Organic & Medicinal Chemistry
Dr. SuvankarBera	Studies Towards Exploring New Sunthetic Routes using Transition Metal Catalyzed C-H Bond Functionalization Strategy	JU	24-12-2019	Dr. Biswadip Banerji	Organic & Medicinal Chemistry
Dr. K. Chandrasekhar	Studies towards design, synthesis and biological efficacies of novel heterocycles	AcSIR	10-12-2019	Dr. Biswadip Banerji	Organic & Medicinal Chemistry
Dr. Dipika Yadav	The Role Of Human TFIID Complex In Regulating Transcription Beyond Initiation	CU	May-19	Dr. Debabrata Biswas	Molecular Genetics
Dr. Oindrilla Rahman	Cross-talk between plasmacytoid dendritic cells and B regulatory cells in Systemic Lupus Erythematosus	JU	16-01-2020	Dr. Dipyaman Ganguly	Cancer Biology & Inflammatory Disorder
Dr. Aniket Mishra	Transition Metal-Catalyzed C-C and C-Heteroatom Bond Formations via C-H Activation for the Rapid Construction and Late stage Functionalization of Nitrogen Containing Heterocycles	JU	18-11-2019	Dr. InduBhushan Deb	Organic & Medicinal Chemistry
Dr. Sumanta Ghosh	Biophysical Characterization Of Different Conformations In Aggregation Landscape Of Alpha Synuclein	CU	31-07-2019	Dr. Krishnananda Chattopadhyay	Structural Biology and Bioinformatics Division
Dr. Souravchowdhury	Dynamics and conformational study of beta sheet model proteins in vitro and in cultured cells	CU	25-04-2019	Dr.Krishnananda Chattopadhyay	Structural Biology and Bioinformatics Division
Dr. Arijit Chakraborty	Role of Wnt5a In LeishmaniadonovaniInfection in Macrophages	CU	26-06-2019	Dr. Malini Sen	Cancer Biology & Inflammatory Disorder
Dr. NeerajanaDatta	Mechanistic Study Of PML Regulation, Towards Curbing Oncogenesis	CU	24.09.2019	Dr.MrinalK.Ghosh	Cancer Biology & Inflammatory Disorder



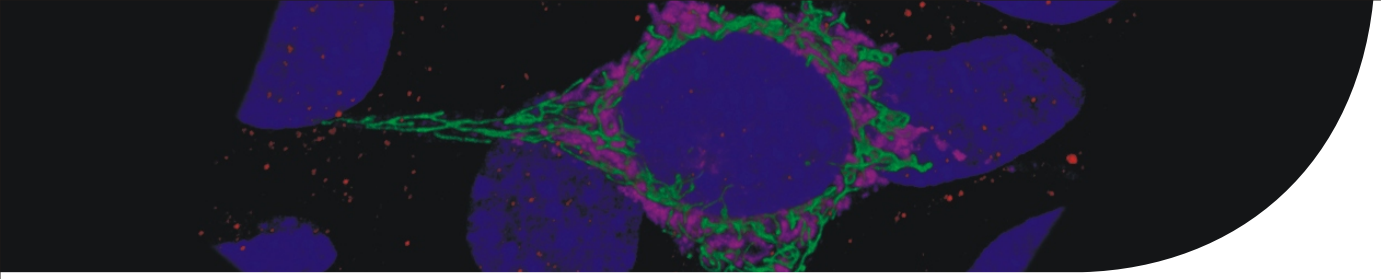
Recipient's Name	Title of Thesis	University	Dt. of Award	Supervisor's name	Division
Dr. VeenitaKhare	Involvement Of p68 In Oncogenic Signaling Pathways	CU	18.09.2019	Dr. MrinalK.Ghosh	Cancer Biology & Inflammatory Disorder
Dr. AbdusSabur	Prospects Of Cationic Liposomal Vaccine Formulations Against Visceral Leishmaniasis	AcSIR	Aug-19	Prof. Nahid Ali	Infectious Diseases and Immunology
Dr. Anupam Roy	Structural aspects of Amyloid aggregates	CU	29-05-2019	Dr. Nakul Chandra Maiti	Structural Biology and Bioinformatics Division
Dr. Sougata Niyogi	Role of Hepatic Microenvironment in Fatty Liver Disease	CU	06-02-2020	Dr. Partha Chakrabarti	Cell Biology & Physiology
Dr. Shovan Kumar Sen	Metal-organic cages and coordination polymers from Bile acids	AcSIR	26-11-2019	Dr. R. Natarajan	Organic & Medicinal Chemistry
Dr. Samir Kumar Bhunia	Development of sustainable C-H functionalization and carboxylation reactions	AcSIR	18-12-2019	Dr. Ranjan Jana	Organic & Medicinal Chemistry
Dr. Arghya Polley	Development of novel and environmentally benign methodologies for the synthesis of medicinal scaffolds	AcSIR	10-12-2019	Dr. Ranjan Jana	Organic & Medicinal Chemistry
Dr. Shreeta Chakraborty	NOSTRIN Is A Pleiotropic Regulator Of Utero-Placental Development: Implications In Intra-Uterine Growth Restriction	CU	22-08-2019	Dr. Rupasri Ain	Cell Biology & Physiology
Dr. SarbaniSaha	MicroRNA Mediated Regulation of Placental Development and Disease	CU	12-06-2019	Dr. Rupasri Ain	Cell Biology & Physiology
Dr. KalyaniMondal	Exploration of Molecular cues to cardio-metabolic risks in polycystic ovarian syndrome (PCOS)	JU	2019	Dr. S.N. Kabir& Dr. Sib Sankar Roy	Cell Biology & Physiology
Dr. UtpalBakshi	In-Silico analysis of enterococcal genomes from the human microbiota	AcSIR	19-08-2019	Dr. Snehasikta Swarnakar	Cancer Biology & Inflammatory Disorder
Dr.Shreya Roy Chowdhury	The Mechanisms of Invasiveness in Ovarian Cancer and identification of specific lectins as possible factors for Amelioration	CU	15-05-2019	Dr. Sib Sankar Roy	Cell Biology & Physiology
Dr. Aditi Mukherjee	Virulence of Leishmania major Requires NAD(P)H cytochrome b5 Oxidoreductase Enzyme	CU	Dec-19	Dr. Subrata Adak	Structural Biology and Bioinformatics Division
Dr. AyanAdhikari	Biochemical Characterisation of A Novel PAS Domain Containing	CU	Dec-19	Dr. Subrata Adak	Structural Biology and Bioinformatics Division



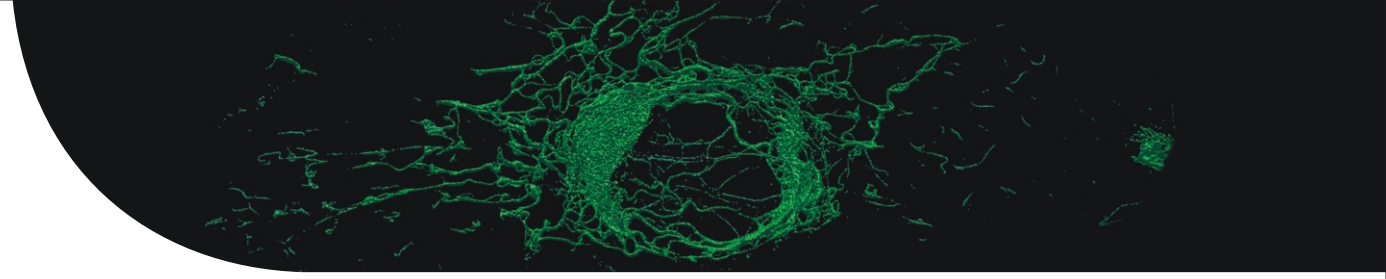
Recipient's Name	Title of Thesis	University	Dt. of Award	Supervisor's name	Division
Dr. Subhadeep Das	Phosphoglycerate Kinase from Leishmania major	AcSIR	20-06-2019	Dr. Sucheta Tripathy	Structural Biology and Bioinformatics Division
Dr. Arijit Panda	Development of integrative computational and statistical methods for the analysis of omics and clinical data	AcSIR	30-04-2019	Dr. Sucheta Tripathy	Structural Biology and Bioinformatics Division
Dr. Abhishek Das	A new paradigm in analyzing large and small genomes by sophisticated computational methods and workflows	AcSIR	12-10-2019	Dr. Sucheta Tripathy	Structural Biology and Bioinformatics Division
Dr. Gopa Mahesh	Setting up benchmark in analyzing genome, transcriptome and interaction data in simple and complex organisms	CU	04-04-2019	Dr. Sujoy Mukherjee	Organic & Medicinal Chemistry
Dr. Asim Azhar Siddiqui	Studies on The Serotonin (5 Hydroxytryptamine Or 5-HT) Subtype 2A Receptors	CU	03-12-2019	Dr. Uday Bandyopadhay	Infectious Diseases and Immunology
Dr. SubhroJyotiSaha	Characterization of Interacting proteins in retromer complex of human malaria parasite,Plasmodium falciparum	JU	17-09-2019	Dr.UdayBandyopadhay	Infectious Diseases and Immunology
Dr. Rudranil De	Design, Synthesis and Evaluation of Anti malarial Activity of a Novel class of Hydrazonophenols	CU	08-11-2019	Dr.UdayBandyopadhay	Infectious Diseases and Immunology
	Studies On The Mechanisms And Signalling Pathways Of Stress-Induced Mitochondrial Pathology And Associated Damage In Gastric Mucosal Cells				

Staff List of CSIR-IICB as on March 31, 2019

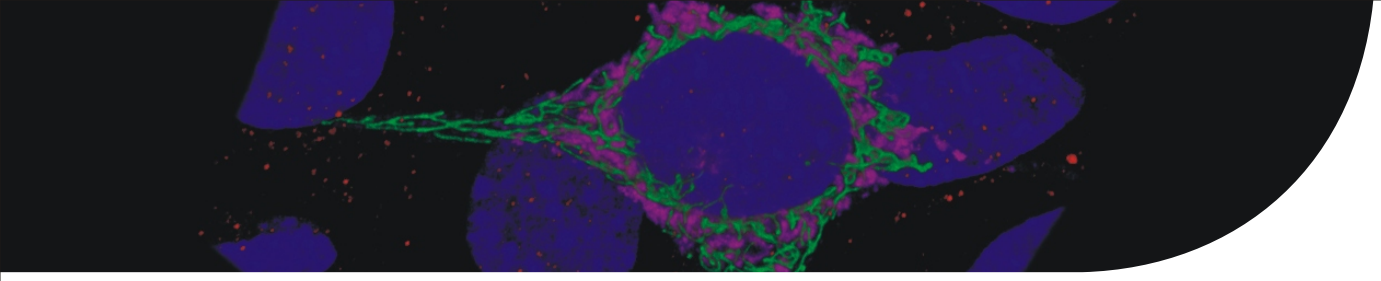
	Sl. No.	Details of the Staff Member		
		EMP.ID	Employee's Name	Designation
1	1	**445**	**Arun Bandyopadhyay Dr.**	**Director**
2	1	112	P. Jaisankar Dr.	Chief Scientist
3	1	443	Sib Sankar Roy Dr.	Senior Principal Scientist
4	2	441	Aditya Konar Dr.	Senior Principal Scientist
5	3	523	K.N. Chattopadhyay Dr	Senior Principal Scientist
6	4	524	Mrinal Kanti Ghosh Dr	Senior Principal Scientist
7	5	473	S. Swarnakar Dr.(Miss)	Senior Principal Scientist
8	6	520	Chinmay Chowdhury Dr.	Senior Principal Scientist
9	7	472	Subrata Adak Dr.	Senior Principal Scientist
10	8	530	S. N. Bhattacharya Dr.	Senior Principal Scientist
11	9	503	Saumen Datta Dr.	Senior Principal Scientist
12	10	563	Rupasri Ain Dr.	Senior Principal Scientist
13	11	527	Malini Sen Dr.	Senior Principal Scientist
14	12	540	Biswadip Banerji Dr.	Senior Principal Scientist
15	13	122	N. V. M. Khalkho Mrs. Dr.	Senior Principal Scientist
16	14	532	Jayati Sengupta Dr.	Senior Principal Scientist
17	15	570	Sucheta Tripathy Dr.	Senior Principal Scientist
18	16	547	Subhas Ch. Biswas Dr.	Senior Principal Scientist
19	2	580	Saikat Chakrabarti Dr	Principal Scientist
20	3	582	Debabrata Biswas Dr	Principal Scientist
21	4	584	Umesh Prasad Singh Dr.	Principal Scientist
22	5	551	Nakul Ch. Maiti Dr.	Principal Scientist
23	6	561	Partha Chakrabarti Dr.	Principal Scientist
24	7	571	Ranjan Jana Dr.	Principal Scientist
25	8	566	Sanjoy Datta Dr.	Principal Scientist
26	9	568	Siddhartha Ray Dr.	Principal Scientist
27	10	572	Arindam Talukdar Dr.	Principal Scientist
28	11	574	Ramalingam Natarajan Dr.	Principal Scientist
29	12	576	Indu Bhusan Deb Dr.	Principal Scientist
30	13	577	Dipyaman Ganguly Dr	Principal Scientist
31	14	578	Amitava Sengupta Dr	Principal Scientist
32	15	583	Subhajit Biswas Dr.	Principal Scientist
33	1	618	Sujoy Kr. Das Dr.	Senior Scientist
34	2	560	Indrajit Das Dr.	Senior Scientist
35	3	607	Upasana Ray Dr.	Senior Scientist
36	4	612	U. Mabalirajan Dr.	Senior Scientist
37	5	613	Shilpak Chatterjee Dr.	Senior Scientist
38	1	528	Saraswati Garai Dr.	Scientist
39	2	605	G. Senthil Kumar Dr.	Scientist



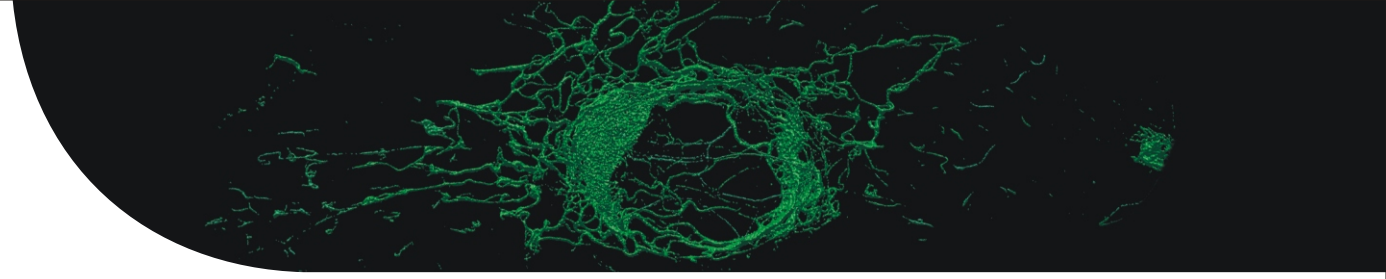
	Sl. No.	Details of the Staff Member		
		EMP.ID	Employee's Name	Designation
40	3	608	Prem Prakash Tripathi Dr.	Scientist
41	4	611	Siddik Sarkar Dr.	Scientist
42	5	614	Amit Kr. Srivastava Dr.	Scientist
43	6	615	Deepak Kumar Dr.	Scientist
44	7	616	Joy Chakraborty Dr.	Scientist
45	1	143	Krishna Das Saha Mrs. Dr.	Principal Technical Officer
46	2	145	S.E. Besra Dr. (Mrs.)	Principal Technical Officer
47	3	535	Chirantan Debdas Sri	Sr. Superintending Engineer (Electrical)
48	4	494	Sandip Saha Sri	Sr. Superintending Engineer (Civil)
49	5	448	Binayak Pal Sri	Principal Technical Officer
50	6	449	Aparna Laskar Mrs. Dr.	Principal Technical Officer
51	7	175	Ardhendu Kr. Mandal Dr.	Principal Technical Officer
52	8	177	Tapas Sarkar Dr.	Principal Technical Officer
53	9	179	Subhagata Ghosh Miss Dr.	Principal Technical Officer
54	1	174	Sankar Kumar Maitra Dr.	Sr. Technical Officer (3)
55	2	180	Arupesh Majumder Sri	Sr. Technical Officer (3)
56	3	184	Ramdhan Majhi Dr.	Sr. Technical Officer (3)
57	4	186	P. Gangopadhyay Sri	Superintending Engineer (Air Cond.)
58	5	188	Dipika Ray Mrs.	Sr. Technical Officer (3)
59	6	176	Banasri Das Mrs.	Sr. Technical Officer (3)
60	7	178	Diptendu Bhattacharya Sri	Sr. Technical Officer (3)
61	8	496	E. PadmanabanDr.	Sr. Technical Officer (3)
62	9	514	Susanta Ray Sri	Superintending Engineer (Civil)
63	1	411	Sandip Chowdhury Sri	Sr. Technical Officer (1)
64	2	466	Nirali Bage Mrs.	Asst. Executive Engineer (Civil)
65	3	463	Arti Grover Mrs.	Sr. Technical Officer (1)
66	4	465	Swapan Kr. Mondal Sri	Sr. Technical Officer (1)
67	5	513	Debashis Banik Sri	Asst. Executive Engineer (Civil)
68	6	516	Sandip Chakraborty Sri	Sr. Technical Officer (1)
69	1	495	Jishu Mandal Sri	Technical Officer
70	2	604	Sounak Bhattacharya Sri	Technical Officer
71	3	539	Muruganandan T. Sri	Technical Officer
72	4	552	M. Vigneshwaran Sri	Technical Officer
73	5	556	Santu Paul Sri	Technical Officer



	Sl. No.	Details of the Staff Member		
		EMP.ID	Employee's Name	Designation
74	6	557	Sandip Kundu Sri	Technical Officer
75	7	559	Debasree Das Ms	Technical Officer
76	8	550	Karri Suresh Kumar Sri	Technical Officer
77	9	569	Pradeep Sypureddi	Technical Officer
78	10	610	Arpita Maji Ms.	Technical Officer
79	1	579	Soumik Laha Sri	Technical Assistant
80	2	589	Sourin Ghosh Sri	Junior Engineer (Electrical)
81	3	529	Ujjal Roy Sri	Junior Engineer (Electrical)
82	4	600	Shubhendu Ghosh Sri	Junior Engineer (Air Cond.)
83	1	246	Tapas Chowdhury Sri	Sr. Technician (3)
84	1	251	S. R. Tudu Sri	Sr. Technician (2)
85	2	344	Ayub Shah Md.	Sr. Technician (2)
86	3	242	Sheo Shankar Verma Sri	Sr. Technician (2)
87	4	383	Pradip Mondal Sri	Sr. Technician (2)
88	5	247	Tarak Prasad Nandi Sri	Sr. Technician (2)
89	6	248	Sutapa Ganguly Mrs.	Sr. Technician (2)
90	7	249	Sanjib Biswas Sri	Sr. Technician (2)
91	8	250	R. P. Gorh Sri	Sr. Technician (2)
92	9	252	Nishikanta Naskar Sri	Sr. Technician (2)
93	10	345	Ranjit Das Sri	Sr. Technician (2)
94	11	450	Abhijit Paul Sri	Sr. Technician (2)
95	12	410	Anirban Manna Sri	Sr. Technician (2)
96	1	426	Samir Majumder Sri	Sr. Technician (1)
97	2	360	M. Ahmed Md.	Sr. Technician (1)
98	3	409	Paresh Sarkar Sri	Sr. Technician (1)
99	4	416	Sujit Kr. Majumdar Sri	Sr. Technician (1)
100	5	419	Mahua Bhattacharjee Mrs.	Sr. Technician (1)
101	6	418	Prabir Kr. Das Sri	Sr. Technician (1)
102	7	460	Tapan Das Sri	Sr. Technician (1)
103	8	417	Atanu Maitra Sri	Sr. Technician (1)
104	1	534	Anup Karmakar Sri	Technician (2)
105	2	546	Soumalya Sinha Sri	Technician (2)
106	3	553	Nita Chakraborty Ms	Technician (2)
107	4	555	Samir Thami Sri	Technician (2)
108	1	585	Avijit Paul Sri	Technician (1)
109	2	586	Tanmay Biswas Sri	Technician (1)
110	3	590	Shiv Kumar Gupta Sri	Technician (1)
111	4	591	Hari Sankar Beni Shri	Technician (1)
112	1	440	Bhaskar Basu Sri	Lab. Assistant



	Sl. No.	Details of the Staff Member		
		EMP.ID	Employee's Name	Designation
113	2	479	Madan Halder Sri	Lab. Assistant
114	3	282	Nimai Charan Prodhan Sri	Lab. Assistant
115	4	351	Sambhu Raul Sri	Lab. Assistant
116	5	353	Suresh Balmiki Sri	Lab. Assistant
117	6	361	S. K. Banik Sri	Lab. Assistant
118	7	352	Nanda Lal Routh Sri	Lab. Assistant
119	1	501	Ashoke Sardar Sri	Lab. Attendant (2)
120	2	502	Ram Kumar Sarkar Sri	Lab. Attendant (2)
121	3	519	Shyamal Nath Sri	Lab. Attendant (2)
				Lab.Attendant (1)
			ADMINISTRATION	
122	1	606	Suprokash Halder Sri	Administrative Officer
123	2	602	A.K. Pandey Sri	Stores & Purchase Officer
124	3	617	Asim Kr. Jha Sri	Finance & Accounts Officer
125	4	588	Monoj Kumar Sri	Finance & Accounts Officer
126	5	525	Shampoo Sengupta Mrs.	Section Officer (G)
127	6	392	Kanu Mondal Sri.	Section Officer (G)
128	7	428	M. Bhattacharya Mrs.	Section Officer (G)
129	8	397	Ratan Bage Sri	SO(SP)
130	9	343	Sanjoy Kr.Mukhopadhyay Sri	SO (F&A)
131	10	324	Pratima Banerjee Mrs.	Private Secretary
132	1	335	Prem Singh Sri	Assistant Section Officer (Gen)
133	2	340	D. K. Kisku Sri	Assistant Section Officer (Gen)
134	3	396	Alok Ray Sri	Assistant Section Officer (Gen)
135	4	510	Jayanta Pal Sri	Assistant Section Officer (Gen)
136	5	511	Saugata Das Sri	Assistant Section Officer (Gen)
137	6	508	Tarun Kr. Sinha Roy Sri	Assistant Section Officer (Gen)
138	1	507	Raju Pal Sri	Sr. Secretariat Assistant (Gen)
139	2	509	Ranjit Debnath Sri	Sr. Secretariat Assistant (Gen)
140	3	512	Sukhendu Biswas Sri	Sr. Secretariat Assistant (Gen)
141	1	565	Anirudha Das Sri	Sr. Secretariat Assistant (Gen)
142	2	593	Tanumoy Sen Shri	Sr. Secretariat Assistant (Gen)
143	3	594	Raju Kumar Shri	Sr. Secretariat Assistant (Gen)
144	4	595	Debtanu Pal Shri	Sr. Secretariat Assistant (Gen)
145	5	596	Sumit Kumar Singh Shri	Sr. Secretariat Assistant (Gen)
146	6	597	Ram Kanai Mondal Shri	Sr. Secretariat Assistant (Gen)
147	1	336	Asit Kr. Roy Sri	Assistant Section Officer (F&A)
148	2	338	M. K. Dutta Sri	Assistant Section Officer (F&A)
149	1	506	Vishal Agarwal Sri	Sr. Secretariat Assistant (F&A)



	Sl. No.	Details of the Staff Member		
		EMP.ID	Employee's Name	Designation
150	1	598	Chaitali Sarkar Miss	Sr. Secretariat Assistant (F&A)
151	1	536	Rajib Ray Sri	Assistant Section Officer (S&P)
152	2	342	Bisweswar Das Sri	Assistant Section Officer (S&P)
153	3	363	Bula Pal Mrs.	Assistant Section Officer (S&P)
154	1	505	Pradipta Sarkar Sri	Sr. Secretariat Assistant (S&P)
155	2	504	Arnab Sen Sri	Sr. Secretariat Assistant (S&P)
156	1	599	Shyama Chanran Bose	Sr. Secretariat Assistant (S&P)
157	1	325	Shankar Bhakta Sri	SR. STENOGRAPHER
158	2	393	Rabindranath Das Sri	SR. STENOGRAPHER
159	3	490	Sankar Santra	SR. STENOGRAPHER
160	4	453	Gautam Saha Sri	SR. STENOGRAPHER
161	5	491	Moumita Majumdar Mrs.	SR. STENOGRAPHER
162	1	405	Saibal Giri Sri	JR. STENOGRAPHER
			ISOLATED POST	
163	1	321	Ambalika Nag Mrs.	Hindi officer
164	2	567	Sabyasachi Karmokar Sri	Security Officer
			Gr-C (NT) / MTS	
165	1	348	Ashok Ram Sri	GR-C (NT) / MTS
166	2	365	Kailash Ch. Nayak Sri	GR-C (NT) / MTS
167	3	412	Gopal Ch. Mandal Sri	GR-C (NT) / MTS
168	4	413	Asit Mitra Sri	GR-C (NT) / MTS
169	5	431	Janmanjoy Midya Sri	GR-C (NT) / MTS
170	6	430	Pasupati Midya Sri	GR-C (NT) / MTS
171	7	423	Shyamal Kr. Ghosal Sri	GR-C (NT) / MTS
172	8	414	P. C. Dehury Sri	GR-C (NT) / MTS
173	9	425	Manoranjan Adhikary Sri	GR-C (NT) / MTS
174	10	424	Tapan Sarkar Sri	GR-C (NT) / MTS
175	11	451	Dinesh Mahali Sri	GR-C (NT) / MTS
176	12	619	Rintu Bhattacharjee Sri	Work Assistant
			Canteen	
177	1	371	Ashok Sadhukhan Sri	BEARER
178	2	370	Badal Haldar Sri	BEARER
179	3	374	Jagabandhu Biswas Sri	WASH BOY
180	4	376	Mantu Das Sri	SWEEPER

Annual Report Committee

Dr. Snehasikta Swarnakar (Chairperson)
Dr. Sucheta Tripathy (Convener)
Dr. Arun Bandyopadhyay (Member)
Dr. Suvendra Nath Bhattacharyya (Member)
Dr. Subhagata Ghosh (Member)
Dr. Indrajit Das (Member)
Mr. Binayak Pal (Member)
Mr. Anirban Manna (Member)
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