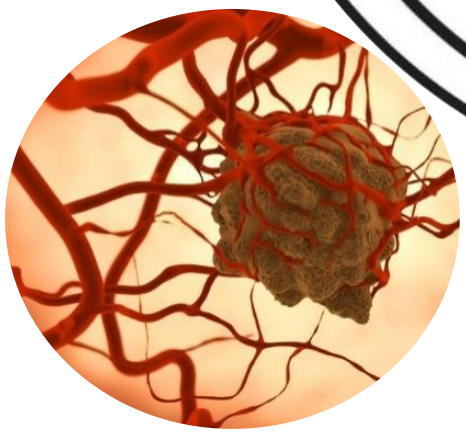
NEWSLETTER



INDIAN ASSOCIATION FOR CANCER RESEARCH

IACR-EXECUTIVE COMMITTEE

Message from the President's desk

Dear IACR members,

On behalf of my colleagues on the Executive Committee, I am happy to share the current newsletter with you. I would especially like to thank Dr. Shilpee Dutt and Dr. Sejal Patwardhan for putting the newsletter together.

The membership of IACR is continually increasing and reflects the growth of research in cancer in India. The recently concluded annual IACR conference at TMC-ACTREC was extremely well-received as we had over 300 registered participants and a wonderful slate of talks by invited speakers covering basic, translational and clinical research in cancer biology. I hope that attending the meeting was fruitful for our young colleagues who are working in the field of cancer biology and will hopefully go on to careers in cancer research, whether in industry or academia.

At this time it is imperative that we bring the basic and clinical sciences together to improve patient outcomes. It is my hope that IACR will play a role in bringing these diverse streams together and that future IACR meetings will lead to breakthroughs in understanding cancer biology and novel therapeutic strategies.

I look forward to seeing you at the next IACR conference in IISER Pune.

Best Regards,

S.N. Dalal

Sorab N. Dalal
President-IACR

Table of Contents

SECTION 1- IACR 2023 THEME

IACR 2023: Overview

The 42nd annual conference of the Indian Association of Cancer Research (IACR) is being held at ACTREC-TMC from the 12th to 16th of January, 2023. The focus of the meeting is "Bringing basic and translational research to the clinic: Challenges and Opportunities".

This conference will celebrate and discuss the advances made in cancer biology over the last twenty years while focusing on how to bridge the gaps between laboratory research and the clinic.

We have made huge strides in our understanding of the cellular and molecular processes underlying tumor progression. However, this has not been completely translated to better patient care. In an effort to bridge the gap between basic and translational research and medical practice, the focus of this meeting is to bring clinicians and scientists under the same roof to identify areas and propose ideas that might lead to better outcomes for patients.

In addition, this conference will expose budding scientists and clinicians to ideas that will inform their research and hopefully their clinical practice.

SECTION 2- EVENTS

ORATION AWARD:

Indian Breast Cancer Genome Atlas -The Developing Story

DR. SHANTANU CHOWDHARY

Institute for Genomics and Integrative Biology, New Delhi

Genomic profiles of cancers at population level scales are rapidly changing how patients are being treated globally. Resulting in improved management/treatment of cancer patients. Lack of such data for Indian patients remains a critical gap, and unmet clinical need. This multi-centre program is an initiative towards bridging this gap through genomic profiling of 1000 breast cancer patients, with 3-year follow-up to characterize potential genomic signature(s) associated with response to therapy. Data from the study comprise whole genome sequencing at relatively high depth, transcriptome and epigenome sequencing. Overall the program seeks to not only create Indiaspecific cancer genomic resources, but also aid in identifying actionable molecular signatures of clinical significance. Update from the recently initiated program will be presented.

Dr.Shantanu Chowdhary

Section 2- Events

IACR Poster and Oral Presentation Awards

Late. Shri Sitaram Joglekar Award- Best oral presentation

Anchala Pandey

Hypoxia Dependent Interplay of Ctcf And Boris Mediated Alternative Splicing Of Bnip3l And Regulation Of Autophagy In Breast Cancer

Anchala Pandey, Parik Kakani, Sanjeev Shukla
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Hypoxia is a physiological stress that manoeuvres several adaptive processes fostering breast cancer growth. Autophagy is one such heuristic tool for adapting the succession of hypoxic condition which is instrumental in breast cancer progression. Alternative splicing (AS) and epigenetics are two conserved regulatory processes that assist breast cancer cells to circumvent stressful conditions. However, orchestration of both in regulating hypoxia dependent autophagy is still under investigation. For the first time, our study reports the hypoxia-driven AS of BNIP3L aided by counter interactive participation of epigenetic factors together with a splicing factor. We demonstrate that hypoxia-driven participation of CTCF, an 11-zinc finger binding (ZFB) protein resuin AS of BNIP3L to give rise to a functional isoform undhypoxia. This functional isoform (BNIP3L201) therefore, interacts with BNIP3 and promotes hypoxia-induced autophagy in breast cancer.

Interestingly, we also observed that BORIS, the paralogue of CTCF, showed antithetical results under normoxia by yielding a shorter truncated isoform (BNIP3L 202) inhibiting autophagy. Mechanistically, demethylation at exon1 of BNIP3L gene under hypoxia recruits CTCF. This results in pausing of RNA Pol II and inclusion of exon1 leading to higher expression of functional BNIP3L 201 isoform. Contrarily, under normoxia, exon1 of BNIP3L gene remains methylated favouring the binding of BORIS, which in this case recruits a splicing factor SRSF6 promoting exclusion of exon1 and production of the truncated BNIP3L 202 isoform. Taken together, we report an interesting hypoxia-dependent interplay of CTCF and BORIS with the aid of SRSF6 in regulating the AS of BNIP3L and affecting hypoxia induced autophagy in breast cancer.

Megha Mehrotra

Targeting PIK3CA in ovarian cancer: Alpelisib enhances cisplatin mediated cytotoxicity

*Megha Mehrotra1,6,, Asmita Sakpal1, Ajit Dhadve1, Elveera Saldanha3, Rohit Mishra5, Pradnya Kowtal4,6, Pratik Chandrani3,6, Jaya Ghosh2,6, Sudeep Gupta2,6, and Pritha Ray1,6**

Standard therapy for High Grade Serous Ovarian Cancer (HGSOC), the most prevalent subtype of ovarian cancer, includes platinum-taxol based chemotherapy, which despite of an abysmal five-year survival rate (~40 %), has remained largely unchanged. Targeted therapy works only in a small subset of patients and acquirement of platinum-resistance and recurrence still remains a challenge. Therefore, there is a need to devise new therapeutic approaches based on the mutational landscape of HGSOC, which majorly harbour TP53 mutations and PI3K/AKT gene amplifications. We aim to study the molecular association of mutant p53 with the oncogenic PI3K/AKT signalling pathway, and assess the efficacy of PIK3CA inhibitor-Alpelisib in HGSOC. Creating a small library of oncogenic p53 mutants, in p53-null SKOV3 cells, we observed differential response to platinum, varied clonogenic potential and altered p53 phosphorylation in mutant expressing cells. p53 mutants- R282W and R175H, with upregulated PIK3CA expression post Cisplatin treatment, showed increased sensitivity to Cisplatin and Alpelisib combinatorial treatment. We further validated this drug combination in malignant ascites derived tumor cells from a small cohort of primary and relapsed HGSOC patients. Intriguingly, combination of Cisplatin and Alpelisib induced higher cell death in 33% of the samples which majorly (80%) possessed PIK3CA amplification. Through next-generation sequencing, we identified a novel TP53 mutation (R196Q), not previously reported in ovarian cancer, which also showed significant sensitivity to Cisplatin-Alpelisib treatment.

Similar response was observed in SKOV3 cells expressing R196Q. Herein, we show for the first time, the efficacy of

Cisplatin-Alpelisib combination in a subset of HGSOC patients.

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Somesh Kumar Jha

Engineered Chimeric Hydrogel Implants using Combination of Chemotherapeutic Drugs and TLR7/8 Agonist Mitigates Tumor Progression.

*Somesh K. Jha, Dolly Jain, Kajal Rana, Nishant Pandey, Devashish Mehta, Avinash Bajaj**

Laboratory of Nanotechnology and Chemical Biology, Regional Centre for Biotechnology, Faridabad-121001, Haryana,

Evasion of immune response and uncontrolled proliferation are two key hallmarks of cancer that helps in sustained proliferation of cancer cells in solid tumor with either quiescent immune cells or absence of anti-tumour immune cells. Chemotherapeutic drugs are known to cause immunogenic cell death by releasing the tumor-associated antigens and damage-associated molecular patterns. Immunoadjuvants are small molecules that can enhance the immunogenicity of tumor antigens by activating the antigen-presenting cells (dendritic cells and macrophages). We hypothesize that combination of immunoadjuvants like imiquimod (TLR7/9 agonist) with chemotherapeutic drugs can cause immunogenic cell death (ICD) and also activate the antigen-presenting cells. In my poster, I will present our combinatorial approach using localized hydrogel implants that can allow chemotherapy-induced immunogenic cell death, and activation of adaptive immune response by imiquimod-mediated polarization of macrophages and activation of T cells. I will also show that use of ICD inducing drugs and immunoadjuvants can effectively modulate the cold tumor microenvironment into hot, and show efficacy across different syngeneic mice tumor models.

Midhunaraj K

PiwiL1 Misregulation in cervical cancer: Are hpv Oncoproteins responsible?

Midhunaraj Kunnummal 1, 2, Pooja Sherly Raveendran1, 2, Budhaditya Basu3, 4, Riya Ann Paul3, 5, Krithiga K6, Sivakumar K C7, Mary Angelin1, Joby Issac1, Jackson James3, Ani V Das1,

Piwi proteins are a subclass of the argonaute proteins, which play a crucial role in germline development. Recent reports showed aberrant expression of Piwi proteins in various cancers. However, the molecular mechanism by which these proteins contribute to tumorigenesis and their regulation in cancer cells is still unclear. We found that among four Piwi variants, PiwiL1 showed higher expression and a positive correlation with HPV. To understand the role of PiwiL1 in tumorigenesis, it was knocked out in CaSki cells using CRISPR/CAS9, which resulted in a marked decrease in cell proliferation, migration, colony formation, and sphere formation in vitro. Further, in vivo studies revealed that tumor formation was also significantly compromised. On the other hand, ectopic expression of PiwiL1 in HaCaT cells, induced malignant transformation both in vitro and in vivo. We observed a positive correlation of PiwiL1-HPV, which suggested a potential interaction between PiwiL1 and HPV oncoproteins E6 and E7. We found that over-expression of E6/E7 could induce the expression of PiwiL1 in HaCaT cells. Further, an in silico analysis suggested a possible binding for E2F1 and p53, the two downstream targets of E6/E7. While E2F1 notably increased PiwiL1 promoter activity, p53 acted as a negative regulator. Interestingly, we noted that both E2F1 and p53 differentially bind and regulate PiwiL1 promoter in normal and malignant conditions. Together, our findings point out that the differential binding of these transcription factors and their regulation of the PiwiL1 promoter could be one of the reasons for its over-expressed status in cervical cancer.

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Dr.Shankhadeep Dutta

Integrative analysis of coding and non-coding transcriptome from HNSCC patient identifies plasma-based miRNA biomarkers for early, non-invasive detection of oral lesions

Rituparna Roy[1], Md Sadi Khan[1], Sukanya Naskar[2], Sagar Sen[2], Rajdeep Guha[2], Jayanta Chakrabarti[2], Bishnu Pada Chatterjee[1], Gourab Das[3], Chinmay Kumar Panda[1], Sankhadeep Dutta[1#]

Introduction

Prognostic outcome of Head and Neck Cancer (HNSCC) patients in India is poor due to late diagnosis in advanced stages. Conventional invasive histopathological assessment of incisional biopsy is discouraging to the patients to undergo the entire diagnosis procedure. Hence, finding a non-invasive, molecular biomarker for early detection of the disease and therapeutic implication is of utmost importance.

Objective

Here, we aim to identify the clinically relevant miRNA-panel and their downstream target genes/pathways showing significant expression-dysregulation in HNSCC patient samples for biomarker detection.

Methods

We performed coding and non-coding RNA-sequencing in 5-paired HNSCC samples (5 primary-tumors and their adjacent-normal) to identify significantly altered mRNAs. Simultaneously, small-RNA library was prepared from the same 5-paired HNSCC samples and corresponding plasma. The identified, differentially expressed miRNAs and their downstream target genes' expression were validated in independent sample-set by qRT-PCR. MiRNA/mRNA dysregulation and associated pathway alterations were further identified by Pathway enrichment analysis.

Results

The transcriptome analysis revealed 704 statistically significant differently expressed genes (DEGs). Pathway enrichment analysis uncovered association with DNA damage response, protein ubiquitination, HPV infection etc. 127 conserved targeting miRNAs were predicted against the top 25 downregulated genes, among which 25 common miRNAs (≥2DEGs) were sorted. Parallelly, from the small RNA library 871 known miRNAs belonging to 461 miRbase families were identified. From these differentially expressed miRNAs, top 25 upregulated and downregulated miRNAs were sorted ($p \leq 0.05$). Finally, 5 miRNAs (i.e., hsa-miR-15b-5p, hsa-miR-424-5p, hsa-miR-30a-5p-Upregulated and hsa-miR-96-5p-downregulated) were identified, that are common in both our predicted and experimental miRNA list. Among these, hsa-miR-15b-5p and hsa-miR-424-5p are from the same seed family having common targeting genes. The pathway enrichment revealed involvement of 5 miRNAs in homologous recombination, cell cycle and different immunological pathways. We have also identified hsa-miR-135b-5p, which is upregulated in all patient samples either in tumor/plasma/both, and also in our predicted miRNA list. Expression of hsa-miR-135b-5p was further validated in independent, primary HNSCC samples (N=10) and their plasma by qRT-PCR.

Conclusion

Thus, we identified a panel of 5 dysregulated miRNAs in HNSCC patients. A large-scale validation of this panel in patient plasma will prove its potential as non-invasive biomarker for HNSCC.

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Pooja Yadav

Hypoxia-induced loss of SRSF2-dependent DNA methylation promotes CTCF-mediated alternative splicing of VEGFA in breast cancer

Pooja Yadav[1], Anchala Pandey[1], Parik Kakani[1], Srinivas Abhishek Mutnuru[1], Atul Samaiya[2], Jharna Mishra[3,$], Sanjeev Shukla[1,]*

Vascular endothelial growth factor A (VEGFA) is an active accomplice in regulating angiogenesis. VEGFA undergoes alternative splicing (AS), giving rise to several isoforms distilling distinct roles in tumor angiogenesis. Although remarkable progress has been made in understanding the role of VEGFA, its AS and the underlying mechanism in the hypoxic tumor microenvironment require meticulous pursuance. VEGFA exon-8 consists of mutually exclusive pro-angiogenic exon-8a and anti-angiogenic exon-8b. We systemically demonstrated that the splicing factor SRSF2 causes the inclusion of exon-8b, leading to an anti-angiogenic 165b isoform under normoxic conditions. Interestingly, SRSF2 also interacts with DNMT3A and maintains methylation over exon-8a, inhibiting CTCF recruitment and RNA polymerase II (pol II) occupancy, resulting in exon-8a exclusion and reducing expression of pro-angiogenic VEGFA-165a. In contrast, under hypoxia, SRSF2 is downregulated by HIF1α induced miR-222-3p; therefore, it is unable to induce the inclusion of exon-8b, reducing the expression of VEGFA-165b.

Additionally, reduced SRSF2 under hypoxic conditionsallowed increased hydroxymethylation over exon-8a, resulting in increased CTCF recruitment and pol II occupancy, exon-8a inclusion, and increased VEGF-165a expression. Overall, we unveil a specialized dual mechanism of VEGFA-165 AS instrumented by the cross-talk between SRSF2 and CTCF, thus promoting angiogenesis under hypoxia.

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Shreosi Chatterjee

Reprogramming altered nuclear and nucleolar morphology by genetic mutations of extranuclear factors

Shreosi Chatterjee[1,2] and Dibyendu Bhattacharyya[1,2,3]

Nuclear and nucleolar hypertrophy are hallmark features of cancer cells. Reprogramming altered organelle size in disease cells has long been conceived as a hypothetical therapeutic approach as it may cause remission of the disease phenotype or selectively kill the disease cells. However, a method of reprogramming nucleolar morphology has yet to be established. In the present study, we addressed this issue in the budding yeast *Saccharomyces cerevisiae*. We first created a class of nuclear and nucleolar hypertrophy mutants. Next, we selected mutations that usually caused a nuclear or nucleolar size reduction. Finally, we tested whether such mutations can suppress the enlarged nuclear and nucleolar morphology caused by the first class of mutations. While the null mutants of the motor proteins, kar3 & cin8, and the temperature-sensitive mutant of Prp45 caused an increase in the nuclear and nucleolar size and shape, the deletion phenotype of the Rab proteins, ypt6 & ypt32 displayed a reduced nuclear and nucleolar size and shape phenotype.

When combined with the cin8 deletion or prp45 temperature-sensitive mutant, both ypt6 & ypt32 deletion mutants resulted in rescuing the previously enlarged nuclear and nucleolar phenotype. Such rescue confirms the possibility of reprogramming altered nuclear and nucleolar morphology upon specific cues in the cell. The role of the extranuclear secretory pathway protein, ypt6, and its effector protein, ypt32, in the nucleolar size regulation seems significant. The possible involvement of Maf1 that genetically interacts with ypt6 and shuttles between the nucleus and the cytosol is also being studied.

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Abhiram Girish Natu

Chromatin organisation: a key determinant for cisplatin resistance in cervical and liver cancer

Abhiram Natu[1,2], Bharat Khade[1], Rahul Thorat[3] and Sanjay Gupta[1,2].

Cisplatin is an alkylating class of chemotherapeutic drug used to treat patients with cervical cancer, squamous cell carcinomas, bladder cancer, and liver cancer. However, failure in long term treatment and proving better survival to patient caused due to tumor relapse. Drug resistance is the major reason for tumor recurrence. Hence, understanding the mechanism of acquirement of chemoresistance is essential for developing novel therapeutic approaches. In this study, we have developed *in vitro* cisplatin-resistant model of cancer cell lines. Gene ontology and GSEA of differentially expressed genes between parental and resistant cells suggest that PI3K-AKT signalling, central carbon metabolism, and epigenetic-associated phenomenon alter in cisplatin-resistant cells. Further, the data showed that a relationship between metabolism, epigenetic changes and PI3K-AKT signalling.

We observed that increased glucose transport, alteration in activity of histone modifying enzymes and acetyl-CoA levels in resistant cells was correlated with an increase in histone acetylation. Enrichment of histone acetylation on effectors of PI3K-AKT and glycolysis pathway provides evidence of epigenetic regulation of the key molecules in drug resistance Moreover, cisplatin treatment to resistant cells showed no significant changes in histone acetylation marks since drug treatment alters cell epigenome.

In continuation, targeting PI3K-AKT signalling and glycolysis leads to alteration in histone acetylation levels and re-sensitization of resistant cells to chemo-drug. This provides evidence for importance of the pathways in regulation of histone acetylation and cell survival of cisplatin resistant cells. Our study implies that we can explore metabolic adaptations and epigenetic changes to achieve better outcomes for targeting drug-resistant cells.

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Arundhathi Dev J R

Prognostic and therapeutic relevance of HuR in Triple Negative Breast Cancer (TNBC)

Arundhathi Dev J R1, Ajay Gogia2, Sandeep R Mathur3, SVS Deo4 and Chandra Prakash Prasad1

The RNA binding protein HuR/ELAVL1 regulates key signalling pathways in cancer through post-transcriptional regulation of its mRNA targets. Increased cytoplasmic HuR expression positively correlates with disease progression, aggressiveness, chemo and radiotherapy resistance in various cancers. The present study investigates the clinical significance of HuR in TNBCs, an aggressive subtype of Breast Cancer.

Meta analysis performed using Liu-2014 TNBC dataset revealed correlation between high HuR protein expression and reduced patient survival. For *in vitro* analysis, two TNBC cell lines were used i.e., MDA MB-231 and MDA MB-468. Western blotting and Immunofluorescence assay established that both TNBC cell lines express substantial total as well as cytoplasmic HuR. Inhibition of HuR using the specific inhibitor CMLD2 resulted in downregulation of the protein expression and a subsequent downregulation of CDK2, MMP9 and β catenin.

It also compromised TNBC cell proliferation, migration and clonogenicity. CMLD2 treatment led to an inhibition of EMT which was assessed by monitoring the levels of E Cadherin, N Cadherin, Vimentin and β catenin. Further, combined treatment with CMLD2 also sensitised TNBC cells to cisplatin.

Overall, the results demonstrate that elevated HuR levels are associated with TNBC progression and relapse. Moreover, the ability of CMLD2 to inhibit cytoplasmic HuR protein provides a rationale to consider it as potential anticancer agent for treating aggressive TNBCs.

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Bibhudev Barik

Role of Polypyrimidine Tract Binding Protein 2 (PTBP2) in Chronic Myeloid Leukemia

Bibhudev Barik[1,2] ,Shristi lama[1,2], Sutapa Biswas[3], Sonali Mohapatra[4], Ghanashyam Biswas[3], Soumen Chakraborty[1,2,]*

The RNA-binding proteins act as regulators of multiple critical biological processes relevant to cancer initiation, progression, and drug resistance. Several ongoing studies underscore the role of the RNA-binding protein polypyrimidine tract binding protein 2 (PTBP2) as an alternative splicing regulator in neuronal cells, muscle cells, and Sertoli cells. A recent report also suggests the role of PTBP2 in B-cell development. We reported the expression of PTBP2 protein, preceded by the inclusion of exon 10 in paired cases of Chronic Myeloid Leukemia (CML). Thus, a splicing regulator required for B-cell development but inappropriately expressed in myeloid leukemia begs further investigation. In the present study, we have shown the expression of PTBP2 in several CML and Acute Myeloid Leukemia cell lines. PTBP2 depletion from cell lines reduced the proliferation rate and the cell's repopulating ability. Furthermore, mitochondrial morphology changes were observed in the knocked-out condition, in addition to a decrease in ROS level and low oxygen consumption rate.

When both the cell types PTBP2 wild type (WT) and knock out (KO) were treated with imatinib (the first-line drug for CML), dasatinib, and nilotinib (2nd line drug for CML), the PTBP2 KO cells showed sensitivity to imatinib compared to the WT cells. *In vivo* study showed a reduction in tumor volume in the KO group compared to the WT group in both subcutaneous and intravenous models conducted on athymic nude mice. Data here suggests that RNA binding protein PTBP2 can be used as an efficient therapeutic target for CML/AML patients.

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Chigicherla Venkata Sai Prasanna

Effects of spatial heterogeneity in multicell cancer metastasis model

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Cell-cell, cell-extracellular matrix (ECM) adhesion and remodelling of matrix are important processes that can influence the way cancer cells invade and spread throughout the body. At the molecular level, adhesion and remodelling involve the interactions between tumour cells and their extracellular environment, allowing cancer cells to move, attach to surfaces, and invade surrounding tissue. An Insilco study of two-dimensional model consisting of tumor cells and its interaction with microenvironment is done combining biophysics based Cellular Potts model (CPM), Chemotaxis and Matrix metalloproteinases (MMP), Tissue inhibitor matrix metalloproteinases (TIMP) secretions from cells governed by Reaction-Diffusion equations in Compucell3D explaining different modes of cancer invasion viz.; Single cell / Dispersed migration, Collective cell migration and Multimodal mode of invasion.

To understand the effects of the contact energy (adhesion) inputs in the model on the outputs and two incorporate the aspect of tumor heterogeneity, simulations involving two cell types in various spatial configurations were performed. These heterogeneous simulations have one of the contact energies either halved or doubled for one set of cells while the other set of cells have that contact energy at normal value. Consecutive Horizontal, Consecutive Vertical, Alternate Horizontal, Alternate Vertical and Checkered are the different spatial configurations that have been tried out and Checkered configuration either had higher or lower invasion over other spatial arrangements. This gives an insight that spatial arrangement of sub populations in tumor influencing the extent of invasion. Finally, Cell-Cell and Cell-ECM contact energies were varied together in a simulation which showed subadditivity effect on the output area of largest cell cluster / invasion.

Anjitha Nair

Nuclear lamins modulate DNA damage response during cell migration

Anjitha Nair, Sanika Jahagirdar*, Shruti Deshpande*, Aditi Kumthekar*, Bushra Khan*, Pooja Patkulkar*, Faseela EE[#], Sabarinathan Radhakrishnan[#], Mohit Kumar Jolly[$], Kundan Sengupta**

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Lamins are intermediate filament proteins localized at the inner nuclear envelope that maintain nuclear morphology. Lamins regulate multiple cellular processes such as differentiation, DNA repair, DNA replication, transcription, and chromatin organization, among others. Lamins protect cells from genome instability and are involved in critical signalling pathways, including Wnt/β-catenin, TGF-β, and Notch. Lamin loss destabilizes the nuclear envelope, which is associated with increased cell plasticity. Mutations in lamins are implicated in diseases such as cardiomyopathy, muscular dystrophy, lipodystrophy and progeria. Of note, the expression and localization of Lamins are altered across cancers. Persistent DNA Damage can lead to chromosomal aberrations, such as deletions and translocations, as detected in aggressive cancers. Downregulating Lamins induces DNA damage and chromosomal instability in numerous cancer sub-types.

Low Lamin levels allow the nucleus to be flexible, associated with Epithelial to Mesenchymal Transition, which induces cell migration, metastasis and cancer progression. During metastasis, cells migrate through narrow interstitial spaces, rupturing the nuclear envelope and damaging DNA. Hence, it is crucial to study the role of nuclear Lamins in DNA damage response pathway in the context of metastatic tumors. Our studies reiterate that cisplatin, a chemotherapeutic drug, induces DNA double-strand breaks, triggers Non-Homologous End-Joining repair pathway, and elevates the expression of γH2AX. Furthermore, Cisplatin decreased cell migration in lung adenocarcinoma cells, whereas Lamin depletion independently enhanced cell migration. Further, inducing DNA damage in Lamin-depleted cells using cisplatin altered cell migration rates. In summary, nuclear lamins function as key modulators of the DNA damage response machinery during cell migration.

Ankush Paladhi

Exploring the induction of immunogenic cell death (ICD) and enhancement of dendritic cell function by targeting thymidine phosphorylase in colon cancer

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Immunogenic cell death (ICD) is a form of apoptosis that kills susceptible populations of cancer cells while teaching the immune system to attack the remaining resistant cells and may promote immune-mediated elimination of the cancer cells in the tumor microenvironment (TME). ICD induction via physical therapy and combination therapy has emerged as a novel cancer therapy. Thymidine phosphorylase (TYMP) plays a decisive role in inducing systemic T-cell exhaustion, which abrogates immunotherapy efficacy in MSS-type CRC. When a low or suboptimal dose of tipiracil hydrochloride (TPI) is used, it downregulates TYMP and turns tumor cells immunogenic via induction of ICD to present tumor antigens to DCs to recruit T cells and modulate tumor-infiltrating lymphocytes (TILs). As we demonstrate that TPI treatment induces immunological cell death in vitro to confirm the same in vivo, a vaccination experiment should be performed as the gold standard approach to assess the ability of dying cells to initiate adaptive immunity: cancer cells are exposed to a potential ICD inducer in vitro and then administered as a vaccine in the absence of any immunological adjuvant and on the removal of exogenous chemical entities (if any, such as the ICD inducer itself). ICD converts tumor cells into "tumor vaccines" by releasing DAMPs and promoting tumor cell recognition and processing by DCs in vivo.

The same was also confirmed by increased expression of the DC-specific activation markers CD80, CD86 and CD69 in the case of vaccination with TPI-treated tumor cells. Induction of ICD turns CT26 colon tumors immunologically hot.

Key Words: Colon Cancer, Thymidine Phosphorylase, Tipiracil hydrochloride, Immunogenic Cell Death

Reference:

1. *Paladhi et al. Front. Immunol. 13 (2022) 988071.*

Neelima Yadav

Progesterone modulates the *DSCAM-AS1/miR-130a/ESR1* axis to suppress cell invasion and migration in breast cancer

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Background: A preoperative-progesterone intervention increases disease-free survival in patients with breast cancer, with an unknown underlying mechanism. We elucidated the role of non-coding RNAs in response to progesterone in human breast cancer.

Methods: Whole transcriptome sequencing dataset of 30 breast primary tumors (10 tumors exposed to hydroxyprogesterone and 20 tumors as control) were re-analyzed to identify differentially expressed non-coding RNAs followed by real-time PCR analyses to validate the expression of candidates. Functional analyses were performed by genetic knockdown, biochemical, and cell-based assays.

Results: We identified a significant downregulation in the expression of a long non-coding RNA *Down syndrome cell adhesion molecule antisense DSCAM-AS1*, in response to progesterone treatment in breast cancer. The progesterone-induced expression of *DSCAM-AS1* could be effectively blocked by the knockdown of progesterone receptor (PR) or treatment of cells with mifepristone (PR-antagonist). We show that knockdown of *DSCAM-AS1* mimics the effect of progesterone in impeding cell migration and invasion in PR-positive breast cancer cells, while its overexpression shows an opposite effect. Furthermore, *DSCAM-AS1* sponges the activity of *miR-130a* that regulates the expression of *ESR1* by binding to its 3'-UTR. Consistent with our findings, TCGA analysis suggests that high levels of *miR-130a* correlate with a tendency towards better overall survival (that couldn't attain statistical significance) in patients with breast cancer.

Conclusion: This study presents a mechanism involving the *DSCAM-AS1/miR-130a/ESR1* genomic axis through which progesterone impedes breast cancer cell invasion and migration. The findings highlight the utility of progesterone treatment in impeding metastasis and improving survival outcomes in patients with breast cancer.

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Monika A Jaiswal

Determining the role of 14-3-3ε in regulating centriole duplication

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The centrosome is a non-membraneous organelle that serve as Microtubule Organising Centers that is important for cell division and polarity determination in animal cells. Increased centrosome number is often associated with high-grade tumors and increased aneuploidy. Studies from our laboratory have shown that loss of either 14-3-3ε or 14-3-3γ leads to centrosome amplification. In addition, 14-3-3 proteins bind to several centrosomal proteins implying that they may regulate centrosome duplication via multiple pathways. The 14-3-3 proteins form a complex with proteins containing one of the three consensus motifs in a phosphorylation-dependent or independent manner. An analysis of amino acid sequence alignment of the peptide binding groove across 14-3-3 isoforms showed that in addition to the positively charged residues (Arginine and Lysine) critical for ligand binding there were two negatively charged residues (Aspartate and Glutamate) which were highly conserved across the species and isoforms.

Since 14-3-3 proteins bind to the phosphorylated ligands, we attempted to determine the role of the conserved negatively charged amino acid residues (D127 and E134) of 14-3-3 ε in ligand binding and the effect mutants (D127A and E134A) have on the centrosome cycle. To our surprise, the Alanine mutant of both the mutants has an opposite effect on centrosome number serving as an amazing on/off switch by mediating either engagement or disengagement of centrioles where overexpression of D127A mutant show presence of single centrosome and E134A shows >2 centrosomes in mitotic cells. Based on the data we speculate that 14-3-3ε protein might be regulating the centriole disengagement via its interaction with Plk1.

Jiyauddin

Metabolic Reprogramming of Cancer Cells: Effect of Mutational Status of P53, A Tumor Suppressor Protein

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TP53 is a critical regulator of major metabolic pathways. Metabolic reprogramming one of the "hallmarks of cancer" and drives tumorigenesis. Frequent p53mutations not only eradicate tumor suppressor capacities but also confer various activities that impact in alteration of metabolic pathways now regarded as central for tumor development and progression. We selected three hotspot mutants (R175H, R273H and R249S) and wtp53 to evaluate the effects in human non-small cell lung carcinoma cell line (NCI-H1299). Differential expression of p53 mutants observed in normal and glucose/glutamine starvation. However, WTp53 expression was not found to be affected. Under both the glucose and glutamine starvation, inhibition of the cell growth and migratory potential of mutant cells was observed which was more prominent in glutamine-starvation. Basal respiration and ATP production in $p53^{-/-}$ R273H and R249S significantly increased under glucose starvation. However, Non-mitochondrial oxygen consumption, maximal respiration was found to be decreased in all the cell lines. Importantly, the cells harboring mutation R175H increases the glycolysis and TCA cycle.

The metabolic intermediates of urea cycle were found to be increased by nearly four folds in R273H cells. Indicating increased utilization of urea cycle instead of TCA cycle; which have been known to be fueled by glutamine for anaplerosis. This study demonstrate that mutp53 influence several metabolic processes and have influence on the cancer cell aggression under starvation of main carbon sources (Glucose and Glutamine). In starved conditions, cells with p53 mutations enhances mitochondrial activity and uses alternative pathways in Non-small cell lung cancer cells. This might provide a foundation for the development of more effective targeted therapeutics/pharmacological approaches toward variants of mutant p53.

Pradyumna

Functional resilience of mutually repressing motifs embedded in larger networks

Epithelial and Mesenchymal master regulators in carcinomas act via mutually repressive feedback regulations. However these interactions do not work in isolation but are a part of a larger cell systems level gene regulatory network (GRN) connecting various biological axes of cancer hallmarks. Elucidating the design principles of these sub-networks has important implications in understanding Epithelial to Mesenchymal Transition (EMT) and developing strategies to identify targets to efficiently tackle EMT. Mutually repressing feedback loops between 'master regulators' of EMT can exhibit multistable dynamics, thus enabling multiple "single-positive" phenotypes: (high Epithelial, low Mesenchymal) and (low Epithelial, high Mesenchymal) for a EMT GRNs. However, the dynamics of these two network motifs has been interrogated in isolation *in silico*, but *in vitro* and *in vivo*, they often operate while embedded in larger regulatory networks.

Here, we embed these network motifs in complex larger networks of varying sizes and connectivity and identify conditions under which these motifs maintain their canonical dynamical behavior, thus identifying hallmarks of their functional resilience. We show that an increased number of incoming edges onto the epithelial or the mesenchymal programme leads to a decay in their canonical stand-alone cell states, as measured by multiple metrics based on pairwise correlation among nodes, bimodality of individual nodes, and the fraction of "single-positive" states. We also show that this decay can be exacerbated by adding self-inhibition, but not self-activation, loops on the 'master regulators'. These observations offer insights into the design principles of biological networks containing these motifs, and can help devise optimal strategies for integration of these motifs into larger synthetic networks.

Shanooja Shanavas

Vitamin C low dose instigates reversal of Epithelial to Mesenchymal Transition (EMT) in HT-29 derived colon cancer stem cells

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Cancerous mass is fortified with distinct morphological and phenotypic profiles. The extremely heterogeneous metabolic features, proliferative potential, due to the genetic and epigenetic variations in intra-tumoral subpopulations, provide the cancer cells with an underlying drug escape strategy. One of the well-acclaimed phenomena for drug-escapism is the cancer stem cells (CSCs) or tumour-initiating cells (TICs). Epithelial to mesenchymal transition (EMT) has been proven as a critical regulator of CSC physiology in many cancer types, including colorectal cancer (CRC). Often, the EMT reversal is associated with cancer mitigation. The sensitivity of colorectal and breast cancer stem cells towards Vitamin C has been identified hitherto, unveiling a dose-dependent opposing effect, explicitly as cell proliferation and cell death mediated by low versus high doses, respectively.

The present study specifies the mechanism of cell proliferation mediated by Vitamin C low doses (2 µm to 10 µm) on HT-29 cell line-derived colorectal CSCs. The colorectal CSC marker CD44 tends to decrease with low-dose Vitamin C treatment, thereby indicating a loss of stemness. Simultaneously, the EMT reversal and attainment of MET (Mesenchymal to Epithelial Transition) as indicated by the increase in E-cadherin expression were also observed in colorectal CSCs upon treatment with the low dose ranges of Vitamin C. Accordingly, loss of stemness and MET were elucidated as the underlying mechanisms to mitigate colorectal CSCs and their conversion to the wild type (WT) phenotype. Hence, low-dose Vitamin C can be further explored as a complementary strategy, accompanying conventional therapeutic approach for targeting advanced colorectal cancer.

Srimanta Patra

Gallic acid mediated SIRT1 activation directs asymmetric mitochondrial fission followed by mitophagic flux inhibition to induce apoptotic cell death

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Distinct mitochondrial fission parameters predict cancer cell survival and death owing to their fission site. Symmetric fission leads to cell survival with subsequent mitochondrial biogenesis; while, asymmetric fission leads to mitophagic clearance of dysfunctional mitochondria. The present study unveils imperative molecular regulation of SIRT1 (NAD-dependent protein deacetylase sirtuin-1), a class III HDAC as a critical controller of asymmetric mitochondrial fission. Gallic acid (GA), a small molecule activator of SIRT1, primarily induces DNM1L-mediated mitochondrial fission and perinuclear clustering with a subsequent decrease in the expression of RHOT1. Further, GA induced SIRT1 activation directs FIS1 recruitment to the asymmetric fission sites to the mitochondrial daughter filaments having low mitochondrial membrane permeability, higher mitochondrial superoxide, low mtDNA content, and high calcium efflux. In addition, our data showed that parkin was recruited to the asymmetrically fissioned mitochondrial sub-population to be engulfed by mitophagy.

Mechanistically, the nuclear translocation of SIRT1 after gallic acid treatment redirects deacetylated LC3 from the nucleus to the cytoplasm to induce autophagy. Further, the induction of mitophagy followed by asymmetric mitochondrial fission is SIRT1 dependent as inhibition of SIRT1 blocks mitochondrial fission and mitophagy. Furthermore, GA impairs autophagic flux through decreased expression of RAB7A and its recruitment to lysosome and autophagosome. The subsequent accumulation of mitophagosome enhances generation of mitochondrial superoxide leading to apoptotic cell death in oral cancer cells.

Keywords: Asymmetric mitochondrial fission, Gallic acid, Mitophagy, Oral cancer, SIRT1

Tripti Verma

Replication dependent histone polyadenylation: A crucial factor in cancer development?

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The development and progression of cancer associates with multiple stress factors like hypoxia, angiogenesis etc. Moreover, exposure to stress downregulates stem loop binding protein (SLBP) resulting in loss of stem loop at the 3' UTR and polyadenylation of replication dependent histone (RDH) transcripts. The present study in human breast tumor tissues showed SLBP loss with accumulation of polyadenylated RDH mRNA as compared to normal. Interestingly, breast cancer versus normal cell lines showed no significant change in SLBP levels. Therefore, to understand whether SLBP loss and RDH polyadenylation is a phenomenon of stress in tumor tissues, MCF7 cells were exposed to stressors like heavy metals, hypoxia and chemo-drugs. Similar results were obtained as observed in human breast tumor tissue samples. Moreover, cell lines data showed that the stability of RDH polyadenylation is regulated by the intricate balance between RNA binding stabilising proteins, HuR and destabilising protein, BRF1 at common ARE locus at 3'UTR.

In vitro shRNA-mediated knockdown (KD) of SLBP showed arrest of cells in G0-G1 phase of the cell cycle. However, supplementing KD cells with CAFs (cancer associated fibroblasts) resulted in enhanced proliferation of the KD cells. Moreover, the KD cells when injected in NOD-SCID mice also showed enhanced proliferation with tumor development.

The study suggests the importance of tumor micro environment in cellular proliferation in SLBP-KD cells. Overall, our study for the first time showed the importance of cancer associated stress leading to RDH polyadenylation and their presence throughout the cell cycle. In consequence, there is an increase in histone pool leading to disturbance in DNA: histone stoichiometry favouring aneuploidy, a crucial factor in inducing cancer initiation and progression.

Ritu Agrawal

Non canonical regulation of DREAM complex through p53

Ritu Agrawal, Nitin Kumar, Sagar Sengupta
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DREAM complex is one of the master regulators involved in repression of genes. It is thought that the activation of wildtype p53 leads to induction of p21, expression. p21 induction causes hypo-phosphorylation of p107 and p130, leading to the formation of E2F4 containing DREAM complex, which cause repression of target genes.

To evaluate the role of wildtype p53, different DREAM complex targets were explored. It was found in absence of p53, transcript and protein levels of BLM (a predicted target) and RAD51, RAD54 and BRCA1 (known targets) are all enhanced. BLM transcript levels were however restored to basal levels upon shutdown of DREAM complex subunits and HDACs in p53 wildtype cells. ChIP carried out on BLM promoter indicated E2F4 enrichment at putative DREAM complex binding sites in presence of p53 whereas DP1 and FOXM1 enrichment was seen in absence of p53. To explore the direct role of p53 in DREAM complex regulation, E2F4, p53 sequential Re-chip was performed. We observed enrichment of E2F4 and p53 were enhanced on BLM promoter in cells expressing wildtype p53.

To understand the mechanism of suppression of DREAM complex targets by p53, luciferase assays were carried out using the respective promoters upstream to TSS. In each case the basal luciferase activities were decreased in the presence of wildtype p53. Interestingly while a p53 transactivation dead mutant p53 (22,23) repressed the DREAM complex target promoters, p53 hotspot mutants in colon cancer were incapable of repression, thereby indicating the presence of alternate processes by which p53 controls DREAM complex recruitment to the target promoters.

Western analysis of paired Indian colon-cancer tissue samples revealed decreased BLM protein in colon-cancer tissue as compared to normal-adjacent tissue. Moreover BLM and p53 protein levels were inversely correlated, thereby indicating a clinical significance of BLM-p53 axis in colon-cancer. These results will allow us to postulate that a non-canonical pathway exists by which DREAM complex is regulated by p53 in eukaryotic cells.

Sara Anisa George

Identification of novel oncogenic targets of mutant p53 in esophageal squamous cell carcinoma

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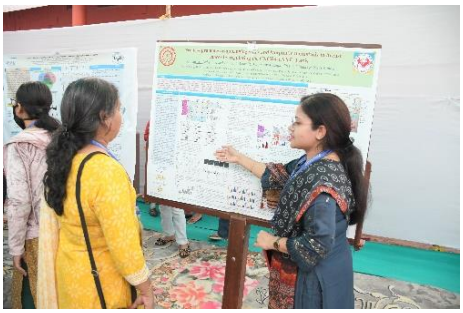
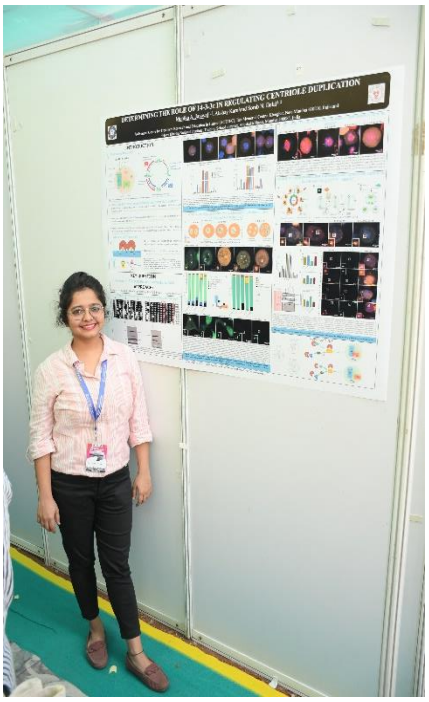
Missense mutations in the *TP53* DNA binding domain occur frequently in Esophageal Squamous Cell Carcinoma (ESCC). Patients with tumours harbouring *TP53* mutations also exhibit significantly poorer chances of survival. Certain p53 mutants exhibit a gain-of-oncogenic function possibly through their ability to activate the transcription of oncogenes. However, most studies focus on understanding the transcriptional networks regulated by recurrent 'hotspot' p53 mutants while rarer mutants are inadequately characterized. The current research thus aimed to identify and characterize differentially-expressed genes associated with rare 'non-hotspot' p53 mutants identified in Indian ESCC samples. Tumorigenic assays, performed following ectopic-expression of wild-type and mutant p53 proteins, confirmed the oncogenic ability of 'non-hotspot' p53 mutant proteins. Gene-expression-microarray analysis, performed on esophageal tumours stratified by p53 status, revealed novel transcriptional targets of 'non-hotspot' p53 mutations. These results were validated by RT-qPCR. *ARF6*, *C1QBP* and *TRIM23* were selected for further analysis due to their previously reported association with cancer. Target-gene activation was evaluated by ectopic expression of p53 mutants followed by RT-qPCR in several cell lines. Chromatin affinity-purification and promoter-luciferase assays assessed the recruitment of p53 mutants to their target promoters and their ability to activate gene-expression. Certain ectopically-expressed p53 mutants induced the increased expression of the targets through localization to and activation of the target gene promoters. Phenotypic assays assessed the effect of target-gene knockdown on the oncogenicity of cancer cells. Sh-RNA based knockdown of the targets resulted in a significant suppression of the tumorigenicity of cancer cells grown *ex-vivo* or as xenografts in nude mice, which were rescued by target-gene over-expression. Thus, three novel oncogenic targets of 'rare' p53 mutant proteins in ESCC were identified, thus revealing the heterogeneity in the functioning of different mutants.

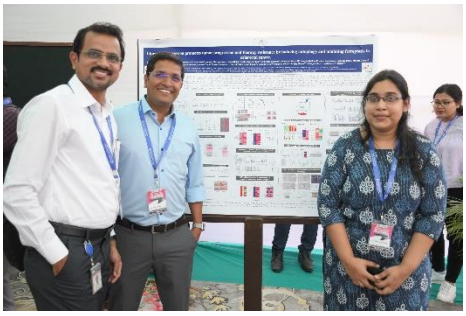





INTERPINNING THE ROLE OF H-RAS IN REGULATING CENTRIOLE DUPLICATION

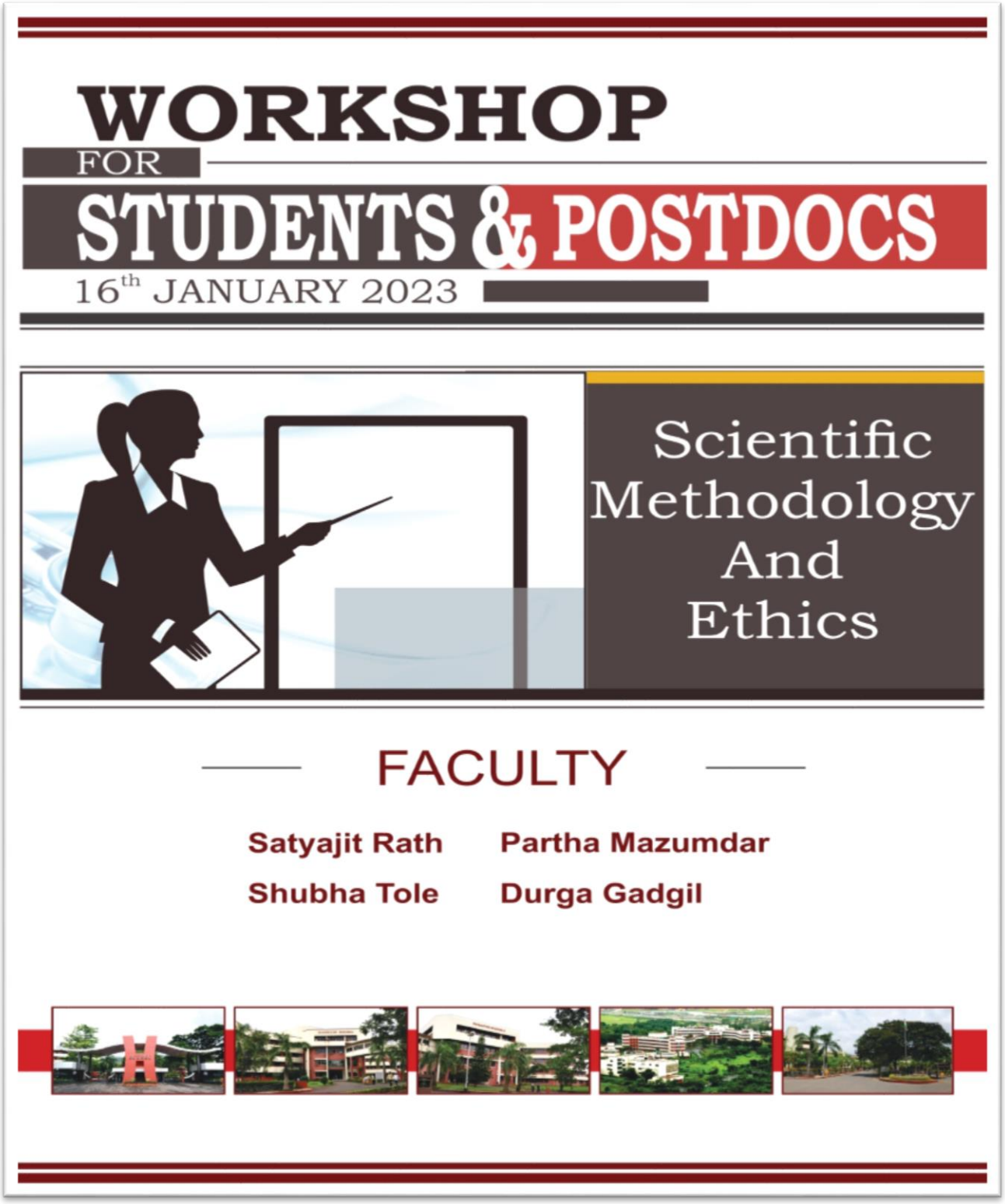

EMD flow based spatial visualization of

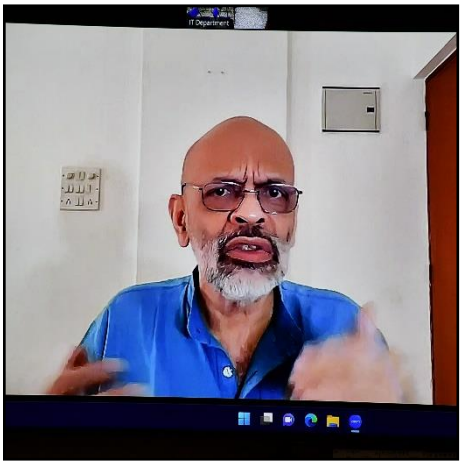




Section 2- Events

Workshop





SECTION 2- EVENTS

Winners of Annual Essay Competition

Essay Topic: Lack of reproducibility in cancer research: Potential causes and solutions

Sourav Chakraborty

Science and research has made great strides in the 21st century. From once being conducted in isolated groups by people then deemed heretics to now, wherein the scientific community has collectively worked together to make multiple breakthroughs in the wake of coronavirus pandemic, research has proved its prowess time and again. Even though the COVID-19 pandemic has ebbed away, the cancer crisis still looms large.

According to the data published by National Science Foundation, more than 350,000 articles have been published till 2020 in the field of biology and biomedical sciences alone. With this deluge of scientific knowledge getting published it is critical to conduct science and inculcate practices which are not only robust but also reliable. However one must ask oneself that as technology is evolving, are we generating data which is reliable or are we just creating sandcastles which wash away with a single riptide (1).

Ideally in experimental sciences like cancer research, any researcher should be able to generate the same result through re-creating experiments therefore reaching to the same conclusion. This not only validates the original work but also allows them to build up additional hypotheses so as to further develop the work in a particular direction. This essentially is the fodder to evolution in science. However, most often than not published scientific findings cannot be reproduced and remains unattainable. John Ioannidis, for his article in PLOS Medicine stated that reproducibility doesn't necessarily have to be about generating the same results but instead should ensure that the trend is essentially maintained owing to a detailed protocol (2). This remains paramount for all fields of research. In an attempt to address this "lack of reproducibility" The American Society of Cell Biology (ASCB) has developed a segregated definition of the term "reproducibility" to better incorporate the nuances associated with the same. *Direct replication* involves an attempt to reproduce previously observed results through the use of the same experimental designs and conditions as that of the published work; *analytic replication* is aimed at reproducing findings through reanalysing original data; *systemic replication* is carried out to observe similar findings in a different experimental conditions; and *conceptual replication* tries to validate a phenomenon using different experimental methods.In 2021, the Reproducibility Project: Cancer Biology (RPCB) – a collaboration between Centre for Open Science and Science Exchange, tried replicating 193 experiments from 53 high-profile papers that were published from 2010 – 2012 in the field of cancer biology. Their report suggested a failure to replicate 68% of the experiments. Most importantly, none of the 193 experiments were described sufficiently to allow replication (3). However, this lack of reproducibility exists in all fields of science. The onus of this emerging problem cannot be traced back to a single cause and is largely multi-

factorial. Firstly there is a severe lack of transparency that exists while publishing any work. The protocols and key research materials which goes behind achieving any particular data is not described in details and is mostly not paid much attention. Secondly it is essential that we start research with utmost caution. Multiples studies have highlighted that the lack of reproducibility also stems from simply using misidentified or cross-contaminated cell lines which question the credibility of the previously published work leading to erroneous conclusions (4,5). Proper designing and documentation of experimental protocols and parameters are equally important. The encouragement of poor research practises also cause a major hindrance in corroborating previously published work. There is also a current Influx of high-throughput data sets which remains unappreciated due to a lack of knowledge by researchers to analyse these big data using proper statistical formats (6). This also is a roadblock towards reproducing published data. Apart from these factors, researchers are additionally shrouded by their own cognitive bias leading to poor decision making when it comes to data interpretation. The failure to identify one's own biases is one cog in the giant wheel of the reproducibility crisis, the details of which have been extensively discussed by Regina Nuzzo in her article published in Nature (7). But most importantly, it is the hustle culture which is predominantly instrumental in peddling a majority of subpar work as high-calibre research thereby significantly affecting it's quality in recent times. Moreover, the academia's inherent bias towards encouraging novel positive results has further created a toxic environment for researchers wherein negative results seldom get any platform for publication and is mostly discouraged. This constant cheering for positive data leads to data fabrication and falsification which puts the credibility of scientific research in question (8). Thus it is really important that one must contemplate on how to get past these impediments that tarnish the nobility behind the purpose of conducting research. Several efforts at various capacities have been incorporated towards improving policies that potentiate better practices. While publishing data supporting one hypothesis it is also important to publish the raw data behind any result in a repository such that peers and individual researchers can identify discrepancies if any while trying to replicate an experiment. This further gives them the scope to also identify and troubleshoot any altered experimental conditions and/or a potential technical error. Furthermore, robust approaches towards confirming the genotypic and phenotypic traits of the biomaterials should be conducted to account for a more reliable data. This majorly is important for cancer research wherein the model systems are so vast that a single protocol used for one model might not yield the same result when the same is followed in a different cancer model. Owing to these many variables it is absolutely essential that one is sure of the biomaterials that they begin with. A thorough documentation of the exact experimental conditions and parameters should also be maintained to achieve a particular result. This will aid subsequent researchers in recapitulating a published result and further strengthen the foundation of their own hypothesis. It will also allow them to adopt a better strategy towards fine tuning the protocol in case of a different model system. Additionally it is also important that negative data be given equal precedence and forums must be created which allow scientists and students to share their ordeals with regards to designing and executing experiments. This open dialogue will instil a sense of accountability and inculcate transparency. Moving forward as more and more research will be conducted worldwide, there will always be a constant need to publish ones findings in fear of getting scooped. It is imperative that we carry scientific research with a sense of clarity and accuracy that is important for developing a credible body of work. The mere presence of policies will not guarantee reproducibility and transparency unless we take necessary steps as individuals to maintain the sanctity of research. Confidence in research

especially in cancer biology is paramount since majority of the work undertaken has a translational value to it. Hence, the stakes are high as it directly effects the society at large, influences health policies and public discourse. Under such circumstances it is important that one must stay true to their conscience and must contemplate: how should research be improved so as to generate reliable knowledge ? how does one veer away from internal biases to prevent misrepresentation ? If we are able to ask these questions then half the battle is won.

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SECTION 2- EVENTS

Ankita Pal

The ground-breaking discoveries in the cancer biology field results from comprehensive and credible studies that have fuelled scientific advancements. Scientific progress to a large extent is dependent on a solid foundation of data credibility and reproducibility. Good research is often attributed to the ability to be replicated by peer groups. Although, the new emerging technologies in cancer biology are proven milestones. However, reproducibility in terms of scientific experiments have be a major impediment in claiming a true biological observation. The term reproducibility is defined as replicating experiments and arriving at the same results by drawing the same conclusions and utilizing pre-defined experimental setups to validate a finding. Failure to reproduce the scientific results is a major pitfall in the field of experimental research. Also, "Lack of reproducibility" is the daunting truth in a researcher's life. Although it can have multiple facets for different research groups. Therefore, to arrive at a common notion, the American society for cell biology (ASCB) has categorized the term reproducibility as direct replication, analytical replication, systemic replication, and conceptual replication. [1] Reproducing biological data is central to strong research conduct often complemented by high research integrity and ethics. It not only creates a strong scientific background but also provides demonstrated proof to the community and ensures a factor of trust in one's research. The principle of reproducibility in cancer research signifies mature and experienced scientific conduct and displays transparency in disseminating knowledge. On the contrary, failure to provide reliable results can collapse the basal hypothesis driving a research project. It can deteriorate health due to poor replicability output, delay progress, and create mistrust among peers with unfortunate monetary and intellectual losses. To dive into the root causes of the reproducibility crisis it is mandatory to know and understand the stumbling blocks and employ strict policies and guidelines to safeguard scientific credibility.

Various studies have been conducted to overcome the reproducibility crisis with numerous astounding revelations. A 2016 Nature survey displayed that 70% of scientists were unable to replicate data from other scientific communities and 50% of the scientific heads failed to replicate even their own data. Another famous project named the reproducibility project in cancer biology with the main aim of replicating pre-clinical research by repeating 193 experiments with 53 high-impact manuscripts in which experimental and data analysis protocols were to be peer-reviewed for acceptance prior to experimental work. This study faced a number of challenges while reproducing published scientific observations. First and foremost being that the papers were deficient in detailed logical statistical inferences. Despite contacting the actual authors, 68% of the data couldn't still be analyzed with statistical rigor. Second, none of these communications included a detailed methodology to create a perfect replica. Third, 67% of all the mentioned protocols needed amendments and only 41% of these could be incorporated. [2]

Roadblocks of reproducibility

Scientific cancer research is a complex and elaborate process involving various parameters like study design, duration, code of conduct, funding and IRB agencies, documentation, and several others. Since it is a multi-factorial avenue, it can't be footprinted to a single cause and is often imprinted by critical determinants which are discussed below.

Experimental designing is the initial step in carrying out cancer research. Poor experimental design with bad research practices would progress toward a dead end. Not only this, research groups at times are also blinded by a

prenotion ideology which can also be referred to as a cognitive bias. A bad experimental design with bias can both be detrimental to a study as it can falsify the basal hypothesis. Thus, tossing the project in a different trajectory. Another cause that proves to be one of the major hurdles of reproducibility in cancer research is the lack of access to methodological details, raw data, and research materials. Scientific journals often provide a word limit to describe the material methods which very often paves the way to brief protocols that are difficult to understand while replicating a technique. Accessibility to raw data is also one of the major hurdles in validating a prior scientific finding which becomes worse at every level of replication as the transparency of data sharing is lost. Adding ahead, some of the never-ending concerns in the field of cancer research are varied results when compared to the positive controls in the literature. This can be very well attributed to the cross-contamination of cell lines with other cell lines. One prime example is the HeLa cell line which is known to outgrow in culture conditions to contaminate other cells. Not only these cells are cross-contaminated but they also display heterogeneous genotypes and phenotypes due to prolonged passages and can also be misidentified in several instances. In such cases, the results obtained are not true which leads to false inferences. Thus, deciphering results and drawing conclusions from such cellular assays would lead to invalid results. Another dreadful reason for non-reproducibility in academia is the unrealistic time used for research and the unwanted pressure to "publish or perish" to compete for research grants and the lack of proper supervision further escalates the reproducibility crisis. Similarly, the hunger to publish great discoveries and be rewarded overpowers the arena of negative results which are undervalued and discarded from a study. In other words, replicating a scientific study is challenging due to existing uncontrolled parameters. [1]

Management of reproducibility crisis

Significant efforts have been taken by different research institutes, regulatory bodies, and editorial boards to overcome the barriers to reproducibility in cancer research. These bodies have undertaken several measures to identify the causes of the lack of reproducibility and planned out effective logical measures aimed at eliminating these root causes. Effective strategies with recommended good practices and strict policies have been outlined below, which will have a large impact on the existing reproducibility crisis in the field of cancer research.

Researchers should be open about sharing their scientific findings and hypothesis with their peers and the general public. All the raw data, materials, software, other tools, etc. used for drawing important conclusions should be provided to the publishing houses. This in turn should be additionally supported by depositing all the raw files on respective public domains for easy access. This allows constant dissemination of already validated results which would enhance the knowledge and quality of scientific interventions and would open doors to fruitful collaborations. Another important aspect of data sharing lies in providing detailed and thorough methodologies for successfully reproducing a scientific result. American association for cancer research (AACR) has come up with an innovative platform for publishing step-by-step protocols with unique DOI in the method section at protocol.io[3]. Apart, from robust data sharing, concerted efforts should be taken to strictly use authenticated cell lines. Publishing groups have now highly encouraged to provide the Short tandem repeat (STR) profile for all the cell lines used for publication purposes. Early passage cell lines with STR authentication are a reliable source of reproducible research. Using validated cells wouldn't compromise the genotype and phenotype of cells in *in-vitro* assays and would allow us to get rid of the heterogeneous biological observations. Thus, detailed methodology and authenticated biomaterials will greatly impact

scientific reproducibility in cancer research. In fact, a proper study design with great importance to correct and defined statistical rigor could further empower the scientific communities with reproducible work [4]. Group leaders should provide adequate supervision to guide a scientific project and also mentor their students in the careful and effective designing of experiments. They can ensure reproducibility by performing regular, clear, and concise documentation of results either manually or digitally. A system of checks and balances should always be in place and when in doubt the experiments must be repeated in a laboratory by different individuals in case of novel discoveries. Furthermore, research institutes should conduct training programs for early researchers in effective experimental design and conduct and proper data management and publishing skills. Various innovative strategies have now been adopted by AACR, ATCC, ASCB, NIH, etc. to improve reproducibility, and rigor and maintain transparency in the field of cancer research [5].

To conclude, the lack of reproducibility in cancer research raises a big question about the credibility of the scientific data. Various factors have largely contributed to this reproducible crisis which has been overshadowed in the past. However, in recent years these concerns have been discussed openly in scientific meetings and conferences and efforts are being taken to eliminate these existing hurdles in the field. Key stakeholders should be actively involved in spreading awareness about the problem and coming up with newer ideas to improvise on the reproducibility problem.

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SECTION 2- EVENTS

Akshit Vats

"After all, the ultimate goal of all research is not objectivity but truth."

Helen Deutsch

Scientific research is the best method that humans have for building knowledge. Researchers are trying to understand how the world works, and they do this by asking questions, coming up with hypotheses, and by testing them. Also, as an intelligent race, we keep on designing new methods, procedures, and techniques. This unique way of acquiring knowledge, and sharing scientific developments allows others also to create advancements. Also, it makes the scientific process more efficient and increases understanding of mankind and the universe.

As a student having been involved with research, I rely on published studies to educate myself and improve my current understanding of scientific discoveries. Scientific journals are the primary resource for scientists to share data and information to educate the world about recent scientific breakthroughs. This mode of information has remained the same since the invention of journals. These journals are the vast ocean of knowledge but carry some debris as well. By exploring them in depth we can study all discoveries made so far with evidence and proof of how they were unveiled. By deep analysis, some of them can be recreated or reproduced but not all cases. Often, reproducibility, transparency, and scientific evidence about these inventions are less reliable than we would hope they would be.[1]

Reproducibility depends on the data, methods, and codes and replicating them as reported earlier or creating an entirely new dataset to check whether similar conclusions were drawn. Transparency is regarded as a positive feature, yet its definition is too difficult to sum up in just one sentence. To be transparent, it is necessary to balance giving individuals the deserved information to evaluate the credibility of scientific claims and study design.[2-4] It also allows us to ask constructive questions and hold conversations openly, creating mutual understanding and sharing of materials and data, which increases research productivity. Recently Errington et al., while trying to study the reproducibility of various studies on cancer, could repeat only 27% of the experiments out of 195 experiments done in these studies. They cited insufficient methodological details, lack of appropriate statistics, and the need for protocol modification as significant barriers against data reproduction. Hence, a problem with the reproducibility of today's scientific findings do exists and is greatly unnoticed. Though there is no definitive verdict on a finding's replicability or credibility based on the failure to replicate, it may be that the original research was false positive or comprised a small sample size with low power, which signifies the low probability of finding actual effects. The reason, in my opinion, is that the scientific practices by the researchers across disciplines are not uniform in many aspects, reducing the replicability of their findings.

A scientific workflow generally includes searching and developing ideas; designing studies; collecting material; acquiring, interpreting and analyzing the data with the help of statistical and bioinformatic tools; writing reports, and finally sharing in the form of published literature. The first barrier to reproducibility is the workflow and decisions

made while documentation. Journals often limit how much information we can put in our script resulting in important information is often left out in the accepted final report. Also, there is a publication bias toward positive findings, and negative studies are sometimes ignored. Due to these limitations, we generally do not get enough information about evolution of the study question, methods, and analysis during research time.

Science can flourish if there is collaboration among scientists. Nevertheless, result reproducibility can be tricky if studies contain unsound scientific procedures and misinterpreted results. Other factors affecting reproducibility are poor study design, sloppy experimental work, flawed result verification, validation, data analysis, and derisory use of statistical methods, besides several administrative and financial issues.We live in a scientific climate flooded by more scrutiny, methodological reasons, and advanced statistics with constant pressure to publish. All these reasons ultimately jeopardize our scientific credibility. With the proper resources, we may realize our talent; the question of what else might be possible without these barriers is tantalizing in conjunction with emerging technologies. It is our right, as citizens, the primary funding source of such research, to support organizations that seek to dispel science in transparent, open, and understandable ways. There is no time to waste on that research locked away behind the price, non-transparent barriers, and discoveries. We must harness scientific transparency's power and create a more transparent, open, and understandable world. However, the research's politics and business aspects have presented roadblocks in high prices and a need for more openness.

To get away from scientific problems, we should discuss more the real things we can do to improve the rigor of scientific reproducibility. As individual researchers, we can preregister our plans that could bias the research later, like study design, randomization, primary and secondary outcomes, or any important decision. When preregistered, the erroneous protocols and analytical methods, if any, can be improvised based on peer-review comments prior to their publications. This can help to counter selective reporting, preventing people from switching outcomes. It has been seen that the pre-registered studies also reduce the publication biases toward positive findings. If all studies undergo a preregistration process, and if it becomes mandatory for publication in a journal, certainly it would increase the reproducibility of scientific research.[7] Moreover, it would facilitate distinction between confirmatory and exploratory tests. If a researcher finds something exciting, the preregistered analysis helps corroborate the story of something being significant because it is not a data-driven analysis. In fact preregistration in clinical studies has increased the number of null results reported in the literature. Hence this a solution that other disciplines could consider to decrease the level of biasness in their literature.[9]
Outcome reporting bias is still pervasive, as reflected by 62% of trials having at least one primary outcome changed, introduced, or omitted, and more than 50% of pre-specified effects just not reported at all. [9,10] Yet the solution remains the same as it is necessary that all trials should be registered and all results are reported. Maximizing transparency and reproducibility in science involves the collective effort of researchers, stakeholders, universities, journals, and companies, as well as general public novel guidelines that need to be created which explain how experiments were performed and the establishment of standards for data collection and the methods to use for analysis.
Finally, transparency is a fundamental part of science. To replicate and openly engage with other people’s research, to build on it or improve it, we need to know what was done; we need access to the material to use it for ourselves. We should be moving towards a scientific world where we share by default. And to establish a sense of scientific openness, we must first provide access to the research we hope to make

transparent through open-access publishing. There is always something we cannot share, such as sensitive or proprietary information. But, if we are open by default or deal with it responsibly, we will improve science efficiency.

The researchers of my age group struggle to keep up in a world where the hunt for money dominates scientific discovery instead of a desire to broaden our understanding of the world around us. Therefore, besides moral and ethical responsibility of researchers in assessing the reproducibility of their work, there is need of creating a method of more rigorous peer review, easy and open access of protocols to all interested scientists. Rewarding and acknowledging those practicing excellency and accuracy in their work may also promote a more unfailing work culture among the scientists.

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SECTION 3- PROGRAMS

IACR Mumbai Chapter: World Cancer Research Day Program

WCRD
WORLD CANCER RESEARCH DAY

ACTREC

IACR
INDIAN ASSOCIATION FOR CANCER RESEARCH

WORLD CANCER RESEARCH DAY

24th SEPTEMBER 2022

Organized by :
Mumbai Chapter of IACR

To celebrate the World Cancer Research Day (WCRD) on 24th of September, 2022, Mumbai Chapter of Indian Association for Cancer Research (IACR) and ACTREC, Tata Memorial Centre is jointly hosting a Webinar (hybrid mode)

This webinar will have topics covered by the following Indian Cancer Research Scientists

"Immunotherapy of cancer and beyond"

9.30-10.15 am
Prof. Gaurisankar Sa.
Professor of Molecular Medicine,
Bose Institute, Kolkata, India

"Histone Post-Translational Modifications in Cancer and their potential clinical applications"

10.15-11.00 am
Dr. Sanjay Gupta,
ACTREC, Navi Mumbai

"Nongenetic-heterogeneity': Driver of oral cancer"

11.00-11.45 am
Dr. Sandeep Singh, NIBMG,
Kolkata

"Stem cell and cancer stem cells: promises and challenges"

11.45-12.30 pm
Dr. Sanjeev Waghmare,
ACTREC, Navi Mumbai.

Venue: Main Auditorium, Khanolkar Shodhika , ACTREC, Navi Mumbai

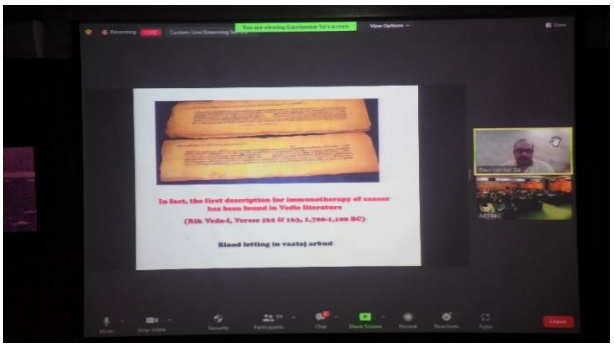
Time : 9.30 am to 1:00 pm

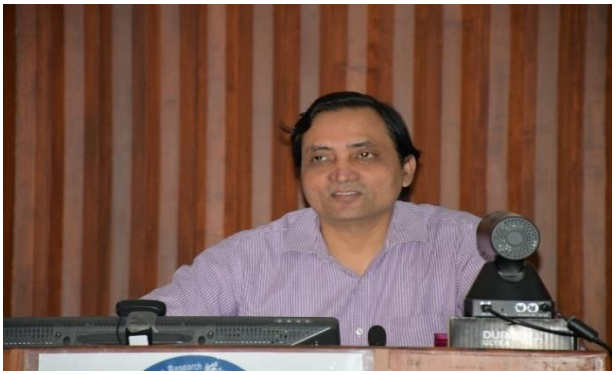
The first 100 participants can join on Zoom at the link -
https://us06web.zoom.us/j/82392514025?pwd=b25yci80T1NKZVBsNThOUkdHWXZDdz09
Meeting ID: 823 9251 4025 Passcode: 039884

The rest can follow the talks on the ACTREC YouTube channel. Channel Name:- ACTREC TMC

Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Sector -22, Kharghar, Navi Mumbai – 410210

IACR Mumbai Chapter: World Cancer Research Day Program





SECTION 4- CANCER AWARENESS CAMPAIGN

Breast Cancer Awareness among Student Community

Trishna Pani, Surabhi, and Ujjaini Dasgupta*
Amity University Haryana.
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Mortality and incidence rate of breast cancer is rapidly increasing in India. A higher number of breast cancer cases occur in metropolitan cities including Mumbai and Delhi along with states like Mizoram, Kerala, Karnataka and Haryana. As 10% of the cases are hereditary, remaining 90% arise due to lifestyle disorders. Although some cases cannot be controlled, a majority of the cases can be prevented by reducing behavioral and dietary risks. A major reason for concern in India is that, younger women are affected (average age 40-42 years) more as compared to an average age of 55-60 years in the west. Hence, awareness for breast cancer is absolutely essential right from an early age to make a significant impact.

To get the ball rolling in this direction we, at Amity University Haryana, started an awareness program targeted to the student community of Haryana so that they are conscious of the need to be prompt and most importantly, acquire the knowledge that early detection and intervention can make a huge difference in terms of prevention and disease-free survival. The aim is to sow the seed of knowledge and awareness in young minds that will create a large impact by spreading the word among family and friends. In collaboration with Dr Hari Sagiraju and Dr Jitendra K. Meena, Preventive Oncology group, All India Institute of Medical Sciences, Jhajjar, Haryana, we organized a breast cancer awareness drive at Amity University, Haryana on November 23, 2022.

More than 200 students, both female and male representing five departments covering life sciences, physical sciences, and data sciences were recruited for the program. Participants completed a pre-intervention questionnaire to estimate their knowledge, attitude, and practice (KAP) related facts. Following this, there was an intervention session via power point presentations and audio-video clips that told them about causes and symptoms of breast cancer, high risk groups, screening methods for early diagnosis, and self-breast exam (BSE) procedures and treatment options. Finally, impact of the intervention was assessed by a postintervention questionnaire that the students filled a month after the intervention program. Our analysis of the data showed that the understanding of symptoms and awareness about BSE as a detection method for breast cancer showed a marked improvement among students after they attended the intervention program. Attitude of participants towards importance of BSE and perception about breast cancer as a preventable disease also showed a positive increase. Overall, this was a very promising start to generate awareness among students, each of whom represent their family and together make up a community.

Its time now to take it forward to other Universities in Haryana! The initiative to spread the word of awareness must be taken up by everyone and most importantly by the young generation who represent the future of our country.

Breast cancer intervention program at Amity University Haryana on November 23rd 2022.