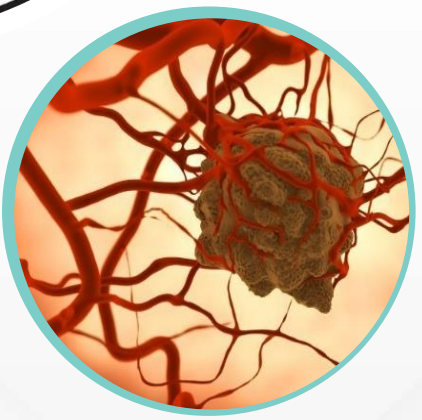
NEWSLETTER

INDIAN ASSOCIATION FOR CANCER RESEARCH

2025



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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

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Section 1- IACR 2025 Theme

IACR 2025: Overview

Chittaranjan National Cancer Institute and IACR West Bengal Chapter

organizes

44th Annual Meeting of the Indian Association for Cancer Research and International Conference on Convergence of Fundamental and Translational Approaches in Cancer Theranostics

Biswa Bangla Convention Centre, Kolkata
16 - 18 January, 2025

The **44th Annual Meeting of the Indian Association for Cancer Research (IACR) and International Conference on "Convergence of Fundamental and Translational Approaches in Cancer Theranostics" was held** at the Biswa Bangla Convention Centre, Kolkata from 16-18 Jan 2025. This year the conference was jointly organized by **Chittaranjan National Cancer Institute (CNCI)** and the **IACR West Bengal Chapter** which represented 10 institutions and universities across the state.

The conference opened with two **pre-conference workshops on 15th Jan 2025**:

- *Career Crafting and Science Communication*
- *Advanced Flow Cytometry in Immunophenotyping and Data Analysis*

These sessions were designed to empower postgraduate and PhD scholars with practical insights and advanced technical skills.

The **inaugural session** of the main conference featured Dr. Jayanta Chakrabarti (Director, CNCI), who emphasized the value of collaborative, time-sensitive research linking basic science with translational outcomes. Dr. Sorab N. Dalal, President of IACR, reinforced the association's ongoing commitment to fostering innovation in cancer research. The insightful words of Chief Guest, Shri Narayan Swaroop Nigam, IAS, Principal Secretary, Dept. of Health and Family Welfare, Govt. of West Bengal sparked motivation for the entire cancer research fraternity.

The **M.G. Deo Oration Lecture** by Prof. Sharmila Bapat, Director-in-Charge, NCCS, Pune enlightened the audience with "Conundrum called Cancer".

The entire conference featured 12 scientific sessions and two panel discussions, spotlighting the latest trends in cancer research and treatment. Over the three-day event, attendees engaged in **keynote lectures, plenary talks, panel discussions, oral and poster presentations** spanning a diverse range of topics:

- *Fundamental and Translational Approaches to Early Detection*
- *Strategies for Diagnostic and Prognostic Markers Development*
- *Cellular Plasticity, Tumor Microenvironment and Immunotherapy*
- *Cancer Recurrence and Multi-Omics Investigations*
- *Cancer Genomics and Precision Oncology*
- *Epigenetic Approaches in Cancer Research*
- *Artificial Intelligence as Novel Treatment Strategies*
- *Upcoming Drugs and Clinical Trials*
- *Interface of Industry with Cancer Research*

There were some special sessions in this meeting which drew much attention –

- Convergence of clinicians and researchers through special panel discussions, technical sessions and poster presentations addressed thought provoking arenas in clinical cancer research.
- Prominent pharmaceutical companies and organizations specializing in artificial intelligence and computation supported the conference, underscoring the importance of industry-academia collaboration in advancing cancer research.
- The Kamat-Jaju session gave a platform to the young Indian investigators to present their ground breaking research in their combat against cancer.

Overall, the conference had over 350 attendees from more than 60 renowned institutes all over India. The event served as a vibrant platform for knowledge exchange, particularly for young researchers, who had opportunities to present their work, network with leading experts, and explore interdisciplinary collaborations. There were more than 200 poster presentations that sparked dynamic discussions around emerging technologies with potential to transform clinical practice. The meeting concluded with an awards ceremony, celebrating exceptional contributions from early-career scientists and students. This successful gathering of minds showcased the evolving landscape of cancer research and reaffirmed IACR's pivotal role in uniting science and practice for improved cancer care.

Section 2- Events
M.G.Deo Oration

M. G. Deo Oration

44th Annual Meeting of The Indian Association for Cancer Research

A CONUNDRUM CALLED CANCER

Sharmila Bapat

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The word 'Conundrum" refers to a confusing and difficult problem or question, one that is even difficult for the experts. It also refers to an unsolved mystery, enigma, puzzle, riddle, problem, secret, mystification, challenge riddle or puzzle, besides sometimes including a play on words or pun. Cancer as we understand today, presents a diverse, almost innumerable assortment of puzzles that has proved to be a daunting task keeping researchers engaged over several decades.

While each hallmark of cancer generates its own set of related conundrum(s), it is realized that the cellular context in which molecules and processes are wired in the transformed state are different than those under normal conditions. As an early cancer researcher, I faced several questions relating to some of the cellular mechanisms especially, (i) those relating to stem cell-like regeneration-associated mechanisms of organ homeostasis, and (ii) epithelial to mesenchymal transition, a development and repair associated pathway that is reactivated in the context of cancer. Over the last 2 decades and more, I had the opportunity to work alongside several Master's - PhD students and trainees who with their hard work and young, inquisitive minds have fuelled the above specific research conundrums in my lab.

I am truly humbled and honoured by the invitation to deliver this prestigious IACR oration, moreover since it is in the name of Dr. M.G.Deo who I admire and respect as an enthusiastic researcher, innovator, socially conscious lateral thinker and supporter of 'scientific reasoning'. I have interacted in workshops conducted by the Moving Academy of Science for students from tribal areas and medical colleges and have received immense support, appreciation and constructive criticism from participants and from Dr. Deo.

From left to right Prof. Rita Mulherkar, Prof. Sharmila Bapat and Dr. Sorab N. Dalal

Section 2- Events

IACR Jaju & Kamat Awards

Dr. Ramnath Hiralal Jaju award for mid-level scientist

Dr. Asmita Gupta

TOWARDS A COMPREHENSIVE CHARACTERIZATION OF GENE FUSIONS IN EARLY ONSET COLORECTAL CANCER (EOCRC) AND PAN CANCER TYPES

Asmita Gupta, Murali Dharan Bashyam*

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Background: Gene fusions are a class of widely studied somatic structural variations (SVs) in cancers that may play key roles as tumor drivers. They primarily arise as a result of aberrant genomic rearrangements, which are considered as major hallmarks of the cancer genome. Considerable efforts have been undertaken to identify gene fusions that can act as potential therapeutic candidates (e.g., BCR-ABL fusion in chronic myelogenous leukemia*)* or diagnostic markers (TMPRSS2-ERG in prostate cancer) in clinical settings.
Objectives: We aimed to comprehensively analyze the influence of chromatin architecture, genome stability and replication stress towards fusion formation in early-onset colorectal cancer and other cancer types. In addition, we endeavored to study the enrichment of gene categories, protein domains, and regulatory elements in the fusion partners.
Materials and Methods: Gene fusions were detected from transcriptomics data obtained from early-onset sporadic colorectal cancer (EOCRC), using Arriba and STAR-Fusion. For a pan cancer analysis of gene fusions, transcriptomics data from The Cancer Genome Atlas Pan Cancer was accessed and analyzed. A combination of *in silico* approaches including logistic regression and deep learning models were implemented to analyze association of fusions with several molecular and functional features, and with determinants of genome organization and stability.
Results and Conclusions: A comparative analysis between fusion breakpoints and contact data from chromatin conformation capture assays revealed a set of fusions formed between genes located at the anchor points of chromatin loops. A fraction of these pairs arose from functionally significant enhancer-promoter looping points and the partner genes showed an enrichment of cancer associated pathways. Further, logistic regression analysis suggested that potential breakpoint containing loci were positively correlated with Alu repeats. A detailed investigation on the association of these loci with replication stress and chromosome fragile sites is currently underway. The observations presented here would thus provide critical insights into the close interplay between gene fusion biogenesis, genome stability and organization.

Keywords: Gene Fusions, Colorectal cancer, Deep learning, Transcriptome profiling
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Section 2- Events

IACR Jaju & Kamat Awards

Dr. Virendra Balkrishna Kamat Jaju award for mid-level scientist

Dr. Nathiya Muthalagu

MYC DEPENDENT MOUSE MODEL OF PANCREATIC NEUROENDOCRINE TUMOURS: A PRECLINICAL MODEL FOR AGGRESSIVE PROLIFERATIVE SUBTYPE

Vineetha NN[1], Yogheshwer Raja G[1], Meiyappan Lakshmanan[1], Daniel Murphy[2] and ***Nathiya Muthalagu[1]***

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Background: Pancreatic cancer (PC) is a deadly disease accounting for 4.5% of all global cancer related deaths. Despite the advancement in cancer detection and treatment strategies, the 5-year survival rate of pancreatic cancer patients still stands at dismal 9%. Pancreatic ductal adenocarcinoma (PDAC) and Pancreatic neuroendocrine tumours (PanNET) are 2 distinct histological subtypes with different molecular and clinical features.
Objectives: To develop and characterize genetically engineered mouse models (GEMM) of pancreatic cancer.
Results and Conclusion: Our work revealed that oncogene MYC can drive PanNET tumours, whereas it drives PDAC when combined with mutant KRAS. Histological analysis of PanNET tumours revealed that these mice develop mixture of functional tumours and aggressive poorly differentiated tumours. Furthermore, RNA sequencing analysis of end stage PanNET tumours revealed that the pathways upregulated in human PanNET were represented in the mouse tumours, particularly of highly aggressive proliferative subtype. These GEMM models also unveil MYC induced epithelial-neuroendocrine plasticity, which provide opportunity to unravel molecular signatures of PanNET tumours, with the aim of identifying novel therapeutic targets for the same. In line with this, we validated key cell cycle regulators as a potential therapeutic target for PanNET.

Keywords: Pancreatic cancer, MYC, tumour heterogeneity
Ethical Declaration: All the works involving animals were duly approved by concerned ethics committee

Section 2- Events

IACR Poster Presentation Awards

Shri Rajanikant Shivprasad Baxi Award – Best Poster Presentation

Dr. Parthiban Balakrishnan

PREVALENCE AND GENETIC CHARACTERISATION OF CARBAPENEMASE PRODUCING ENTEROBACTERIALS (CP-CRE) ISOLATED FROM BLOOD CULTURE SAMPLES IN A TERTIARY CARE CANCER INSTITUTE OF EASTERN INDIA

Parthiban Balakrishnan, Sankar Sengupta, Subhranshu Mandal*

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Background/Introduction: Increasing resistance to antimicrobial agents is an important threat in the management of hospitalised patients. Enterobacterales, commonly isolated pathogens in clinical settings, are developing resistance, especially via carbapenemase production. This study aims to assess the prevalence and carbapenemase-producing genes of enterobacterales isolated from blood cultures in a tertiary care cancer institute.
Objectives: To identify the prevalence of carbapenemase-producing enterobacterales and to genetically characterize the resistant organisms using a lateral flow assay kit.
Materials and Methods: A prospective, observational study was conducted at the Chittaranjan National Cancer Institute, Kolkata. Blood culture samples from patients with bloodstream infections were analysed for carbapenem resistance. Genetic characterization was performed using the RESIST-5 O.K.N.V.I. assay kit.
Results and Conclusions: Preliminary results indicate a rising prevalence of carbapenem-resistant Enterobacterales, with Klebsiella pneumoniae being the most commonly isolated organism in blood culture samples in our institute and New Delhi Metallo-beta-lactamase (NDM) being the most common carbapenemase producing genes from the isolates. Gene characterization of the organisms can give significant insights on precision antibiotic therapy for these MDR/XDR organisms, which have very limited treatment options and can cause a significant rise in mortality to cancer patients due to their low immune status.

Key Words: Carbapenemase, Enterobacterales, Bloodstream infections, antimicrobial resistance, Genetic characterization
Ethical Declaration: The study has been approved by the Institutional Ethics Committee, and informed consent was obtained from all participants.
Acknowledgements: We acknowledge the support of the Chittaranjan National Cancer Institute, Kolkata.
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Deepti Parida

A NOVEL PROBIOTIC COMBINATION SUPPRESSED DIETARY CHOLESTEROL AND CHOLIC ACID INDUCED FATTY LIVER AND PANCREATIC CANCER PROGRESSION IN VIVO

Deepti Parida[1,2], Swayambara Mishra[1,2], Manisha Sethi[1], Amlan Priyadarshee Mohapatra[1,2], Salona Kar[1,2], Shantibhusan Senapati[1*]

Background: Pancreatic ductal adenocarcinoma is one of the most aggressive and lethal malignancies. Various risk factors have been associated with the onset of PDAC and one among them which is clinically correlated to PDAC is Non-alcoholic fatty liver disease (NAFLD). Few studies have demonstrated the clinical association between NAFLD and PDAC, but no experimental association between lean NAFLD and PDAC has been reported yet.
Objectives: We aimed at establishing a link between non-obese fatty liver and pancreatic cancer, and how gut microbiota or probiotics could alleviate these disease progressions.
Methods: We used a KC mouse model of spontaneous pancreatic cancer and an HCC (high cholesterol and cholic acid) diet model.
Results: HCC induced phenotypes similar to lean NAFLD and manifested early incidence of PanIN lesions, higher infiltration of immune cells and upregulated expression of pro-inflammatory cytokines. We have also screened and used a novel probiotic formulation to check its efficacy against HCC-induced metabolic disorder and its driven pancreatic cancer. Interestingly a novel probiotic formulation significantly reduced HCC-induced fatty liver in vivo and decelerated the PC progression. Besides, it also increased the survival percentage of the KC mice. The probiotic intervention defended the intestinal disruption, leaky gut and also resulted in a significantly less inflammatory milieu at different tissue levels. Moreover, the probiotic therapy also reduced the bacterial translocation to liver and pancreas which was increased considerably due to HCC. Together, the study provides mechanistic experimental evidence that suggests potential use of probiotics against PDAC and warrants further clinical investigation.

Keywords: NAFLD, Probiotics, Pancreatic cancer, Leaky gut, Bacterial translocation
Ethical Statement: All the animal work has been conducted by taking prior ethical permission according to the institutional guidelines of Institute of Life Sciences, Bhubaneswar

Section 2- Events

IACR Oral Presentation Awards

Late. Shri Sitaram Joglekar Award – Best Oral Presentation

Arunima Acharya

SINGLE-CELL AND BULK TRANSCRIPTOMICS REVEAL NOVEL MALIGNANT CELL DYNAMICS IN ORAL TUMOR ECOSYSTEM OF PATIENTS WITH ORAL SUBMUCOUS FIBROSIS

Arunima Acharya[1], Sumitava Roy[1], Subhankar Bandyopadhyay[2], Sillarine Kurkalang[2,3], Sahana Ghosh[1], Shekhar Ghosh[1], Subrata Patra[1], Sudip Kundu[1], Sumanta Sarkar[1], Sandip Ghose[2], Partha P. Majumder[4], Arindam Maitra[1*]

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Introduction: Oral squamous cell carcinoma (OSCC) is one of the most common cancers in India associated with poor prognosis and high recurrence rates. Due to widespread areca nut consumption in the South Asian diaspora, oral submucous fibrosis (OSMF) is a highly prevalent oral premalignant disorder with a malignant transformation rate of 7-13%. There exists a significant opportunity in improving patient outcomes by understanding differences between OSMF-associated OSCC and OSCC without OSMF and treating them as distinct clinico-pathological entities.
Objectives: The study aims to elucidate differential gene expression landscape of malignant cell-states that underpin OSCC tumorigenesis in OSMF patients.
Materials and Methods: Single-cell RNA sequencing of fifteen OSMF-associated and twelve non-OSMF OSCC samples was performed. Gene expression programs, enriched pathways, differentiation trajectories and cellular interactions of the malignant cell-states were investigated. Bulk transcriptomic data was de-convoluted to assess the prognostic implications of these cell-states.
Results and Conclusions: The OSCC tumor ecosystem contains four distinct malignant cell-states (Mal_1-4). Mal_1 and Mal_3 are prevalent across both OSCC types, while Mal_2 and Mal_4 are enriched in OSMF-associated OSCC. Metabolically active Mal_1 expresses immunoglobulins and correlates with poor patient prognosis. Mal_2 engages in partial EMT through the *COL1A1-CD44* axis. This cell proportion increases with OSMF grade suggesting a potential role in malignant transformation. Mal_3 and Mal_4 exhibit oncofetal reprogramming with distinct bioenergetics and immune response. A panel of signature genes has been developed for each malignant cell-state with prognostic significance. This comprehensive investigation highlights subtype-specific roles in tumor progression and could potentially aid in stratification of OSMF patients for risk of OSCC development.

Keywords: oral squamous cell carcinoma, oral submucous fibrosis, single-cell RNA sequencing, oncofetal reprogramming, partial EMT
Ethical Declaration: The study was approved by the Institutional Ethics Committees of Dr. R Ahmed Dental College and Hospital and the BRIC-National Institute of Biomedical Genomics, India.
Acknowledgements: I would like to express my gratitude to the International Cancer Genome Consortium (ICGC) and Systems Medicine Cluster (SyMeC) supported by the Ministry of Science and Technology, Department of Biotechnology (DBT) for their generous funding of this work. My sincere thanks also go the National Genomics Core of NIBMG for providing support in sequencing data generation and to the intramural support provided by NIBMG for this study.
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Srinivas Abhishek Mutnuru

PRMT5-MEDIATED HISTONE METHYLATION REGULATES ALTERNATIVE SPLICING OF TCF3 VIA MECP2-PTBP1 TO PROMOTE EMT IN BREAST CANCER HYPOXIA

Srinivas Abhishek Mutnuru[1], Pooja Yadav[1,2], Parik Kakani[1], Shruti Ganesh Dhamdhere[1], Poorva Kumari[1], Shruti Agarwal[3], Atul Samaiya[3], Sanjeev Shukla[1*]

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Background: Tumor hypoxia induced alterations in the epigenetic landscape and alternative splicing influence cellular adaptations. PRMT5 is a type II protein arginine methyltransferase that regulates several tumorigenic events in many cancer types. However, the regulation of PRMT5 and its direct implication on aberrant alternative splicing under hypoxia remains unexplored.

Objectives:

i) Delineating the mechanism of regulation of PRMT5 expression under hypoxia.
ii) Understanding the effect of PRMT5 on tumor progression and alternative splicing under hypoxia.
iii) Investigation of alternative splicing regulation via PRMT5 mediated histone methylation under hypoxia.

Materials and Methods: ChIP-qPCR, PAR-CLIP-qPCR, MeDIP-qPCR, dCAS9 epigenome editing, IHC-F, Immunoblotting, qRT-PCR, Luciferase.

Results and Conclusions:

PRMT5 is upregulated under hypoxia via CTCF, and its upregulation promotes EMT and invasion in hypoxic breast cancer cells. Globally, PRMT5 affects cassette exon events under hypoxia including the genes involved in EMT. PRMT5 mediated symmetric arginine dimethylation of histones (H4R3me2s/H3R8me2s) is necessary for regulation of *TCF3* alternative splicing involving exon 18A and exon 18B under hypoxia leading to the production of the pro-invasive *TCF3*-18B isoform. Under hypoxia, PRMT5 mediated H4R3me2s is responsible for DNMT3A recruitment and DNA methylation at the intronic conserved region (ICR) present between exon 18A and exon 18B of *TCF3*. DNA methylation is recognized and bound by MeCP2 resulting in RNA pol II pause and recruitment of PTBP1 at the ICR of the *TCF3* mRNA. PTBP1 results in exclusion of exon 18A under hypoxia leading to the production of *TCF3*-18B isoform thereby promoting EMT and invasion in hypoxic breast cancer cells.

Keywords: PRMT5, hypoxia, alternative splicing, EMT, breast cancer

Acknowledgements: This work was funded by a grant from (SERB) (CRG/2021/004949) and Department of Biotechnology (BT/PR44309/MED/30/2364/2021).

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CHITTARANJAN NATIONAL CANCER INSTITUTE AND IACR WEST BENGAL CHAPTER









Section 2- Events

IACR Conference Poster presentation Award

Aayushi Agrawal

KAT5 ACETYLATES CHROMATIN PROTEIN, PC4: IMPLICATION IN DNA REPAIR AND CANCER

Aayushi Agrawal[2,3], Sweta Sikder[1], Siddharth Singh[1], Sourav Mondal[5] Rakesh Kumar Sharma[2,3], Nikhil Pallaprolu[4], Kalyan Mitra [2,3], Rupa Mukhopadhyay[5], Ramalingam Peraman[4], Ravichandran Velayutham[4], Jayanta Sarkar[2,3] and Tapas K. Kundu[1*]

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Background: Human Positive Coactivator 4 (PC4) is a highly abundant non-histone chromatin protein involved in key cellular processes such as transcription regulation, genome stability, and DNA repair. We have shown before that PC4 is significantly downregulated in breast cancer patient's samples and cell lines. This downregulation promotes autophagy and confers resistance to radiation. PC4 knockdown causes chromatin decondensation, and increased DNA damage susceptibility, likely by altering the epigenetic landscape and disrupting DNA repair mechanisms.
Objective: PC4 is a multifunctional chromatin protein that plays a role in a variety of cellular processes. Its functions are primarily regulated through post-translational modifications. While a few studies have suggested a role for PC4 in DNA damage repair, its specific involvement and the impact of its modifications remain unclear. In this study, we aim to explore the role of PC4 and its modifications in DNA repair and to investigate how these processes are regulated.
Material and Methods: In this study, we generated stable cell lines expressing both wild-type and acetylation-mutant PC4. Using mass spectrometry, we identified the acetylated PC4 interactome following DNA damage. To investigate chromatin dynamics in response to DNA damage, we employed transmission electron microscopy (TEM) and atomic force microscopy (AFM).
Results and Conclusion: Here, we report that other than p300, PC4 also gets acetylated by DNA repair facilitating lysine acetyltransferase KAT5 (Tip60), at a specific lysine residue (PC4K80), when the cells are subjected to DNA damage. The vulnerability of DNA in PC4 devoid cells was substantially reduced by reintroducing wild-type PC4 to the cells but not the mutant PC4 (PC4K80R), defective in KAT5-mediated acetylation. Significantly, in ZR-75-1, a patient derived breast cancer cell line showed significant reduction in autophagy and rescue in DNA damage repair upon wild-type PC4 reintroduction. These findings suggest that PC4 is crucial for maintaining chromatin integrity and cellular responses to DNA damage, with its loss potentially contributing to tumorigenesis.

Key Words: Lysine acetyltransferases (KATs), non-histone chromatin protein, DNA damage, Atomic Force Microscopy (AFM), Positive coactivator 4 (PC4).
Acknowledgements: This work was supported by Programme Support on 'Chromatin and Disease' Grant No. BT/01/CEIB/10/III/01). S.S. is supported by CSIR, India. T.K.K. is a Sir J.C. Bose National Fellow. We acknowledge Prof. Ganesh Nagaraju for his scientific inputs and suggestion. Special thanks to the late Ms. Varsha Singh for her considerable help and support.
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Section 2- Events

IACR Conference Poster presentation Award

Afiya Dalwai

PATIENT-DERIVED ORGANOIDS AND XENOGRAFTS UNCOVER THERAPEUTIC VULNERABILITIES IN COLORECTAL SIGNET RING CELL CARCINOMAS

Nazia Chaudhary[1$*], Alessandro La Ferlita[2,3#], Bhagya Shree Choudhary[1,13#], Eeshrita Jog[1#], Mufaddal Kazi[4,10,13], Showket Yahya[1], **Afiya Dalwai[1]**, Vikas Ostwal[5,10], Satishkumar Singh[2,3], Siddhi Redkar[6], Nileema Khapare[1], Vaishali Kailaje[7], Akshaya B[1], Poonam Gera[8], Munita Bal[9], Nandini Verma[11,13], Rahul Thorat[12], Avanish Saklani [4,10,13], Lalit Sehgal[2,3$]and Sorab N. Dalal[1,13$]

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Background: Identifying therapeutic targets for Signet Ring Cell Carcinoma (SRCC) of the colon and rectum is a clinical challenge due to the lack of Patient-Derived Organoids (PDO) or Xenografts (PDX). We present a robust method to establish PDO and PDX models to answer address this unmet need. We demonstrate that these models identify novel therapeutic strategies targeting therapy resistance and peritoneal metastasis.

Methods: We derived nine PDO and PDX models from colorectal SRCC patients. Detailed histopathological characterization confirmed the fidelity of these models to the original tumors. Drug sensitivity assays were conducted *in-vitro* and *in-vivo* to assess therapeutic efficacy and impact on peritoneal metastasis. An RNA-seq analysis was performed to identify critical pathways contributing to therapy resistance and metastatic progression.

Results: We successfully developed and characterized PDO and PDX models from nine SRCC patients. The SRCC PDO and PDX models exhibited histopathological features consistent with the original tumors, including high mucin content and eccentric nuclei. They demonstrated increased sensitivity to FOLFIRI combined with Paclitaxel or vincristine, reducing peritoneal metastasis. RNA-seq analysis revealed the upregulation of autophagy genes in SRCC. Treatment with Chloroquine alone resulted in decreased tumor growth and peritoneal metastasis.

Conclusions: Our study establishes PDO and PDX models as robust platforms for studying SRCC and identifying potential therapeutic strategies. Combining FOLFIRI with paclitaxel/ vincristine or Chloroquine alone inhibits tumor growth and prevents peritoneal metastasis, showing promise for clinical translation. These findings suggest that combining FOLFIRI with IP paclitaxel warrants further investigation in Phase-I clinical trials for SRCC patients.

Keywords: SRCC, Rare cancer, peritoneal metastasis, PDX, PDO, Autophagy, combination therapy.

Ethical Declaration: All protocols utilized in this report were approved by the Institutional Animal Ethics Committee (IAEC) of the ACTREC. The study's project number is 38/2021. For human tumor samples, study number 900912 was approved by The Institute Ethics Committee III (IEC III), ACTREC, Tata Memorial Centre (TMC), on 01/06/2022. Counselling followed by informed consent was obtained from each patient before the surgery.

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Section 2- Events

IACR Conference Poster presentation Award

Banani Majumdar

THE IOTA OF INFLAMMATION AND MACROPHAGES IN BREAST CANCER SUBTYPES: MECHANISTIC INSIGHT THROUGH *IN VITRO* CO-CULTURE BASED FUNCTIONAL AND PROTEOMICS STUDY

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Background: Inflammation played a critical and dynamic role in cancer progression. Macrophages, as key effectors in the tumor microenvironment, modulated the inflammatory milieu and influenced tumor behaviour. Tumor-associated macrophage (TAM) demonstrated variable responses and recurrence, underscoring the complexity of their role in cancer progression.
Objectives: This study investigated the mechanistic role of the inflammatory microenvironment and the contribution of macrophages in different subtypes of breast cancer.
Methods: Human monocyte-derived THP-1 cells were polarized into different macrophage subtypes and co-cultured with luminal A breast cancer cells (T47D) and basal-like triple-negative breast cancer cells (MDA-MB-231) in the presence or absence of lipopolysaccharide (LPS). Cellular proliferation, migration, invasion, and apoptosis assays were performed. Immunophenotyping and cytokine array analyses were conducted to assess expression patterns. Proteomic profiling was carried out using a nano-LC-MS system, and R-based packages were employed for proteome data analysis.
Results and Conclusions: T47D cells induced an M1-like macrophage phenotype characterized by CD80 expression and increased pro-inflammatory cytokine production. In contrast, MDA-MB-231 cells induced an M2-like phenotype, exhibiting both CD206 and CD80 expression and elevated anti-inflammatory cytokine levels. T47D cells exposed to macrophage-derived conditioned media (CM) or LPS exhibited reduced proliferation, migration, and increased apoptosis. Conversely, macrophage-derived CM and LPS enhanced proliferation, migration, and reduced apoptosis in MDA-MB-231 cells. GSEA analysis of the proteomic data revealed positive enrichment of interferon alpha and gamma responses, and negative enrichment of MYC, mTORC1, EMT, hypoxia response, and DNA repair pathways in T47D cells. In MDA-MB-231 cells, estrogen response, MYC, TNF-α, and NF-κB pathways were positively enriched. These findings provide novel mechanistic insights into the inflammatory responses in the tumor microenvironment, showing inhibitory effects in luminal breast cancer and an stochastic pathway for aggressive phenotype in TNBC.

Key Words: Breast Cancer, Inflammation, LPS, Macrophage, Proteomics
Acknowledgements: The University of Burdwan, NIBMG, Kalyani, DBT – Govt of India,
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Section 2- Events

IACR Conference Poster presentation Award

Medha Karnik SR

VARIATIONS IN THE MICROBIOME AND CYTOKINOME IN THE CERVICO-VAGINAL LAVAGE (CVL) OF HPV INFECTED CERVICAL CANCER PATIENTS, AND HPV POSITIVE AND HPV NEGATIVE CONTROLS

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Background: Persistent infection with one or more high-risk genotypes of human papillomavirus (HPV) is the primary cause of cervical cancer (CC). Thorough understanding of the interactions between the microbiome and cytokinome of cervicovaginal lavage (CVL) is likely to help in the development of better strategies for the treatment of cervical cancers. Therefore, we compared the

microbiome and cytokinome of HPV positive CC, HPV negative, and HPV positive non-CC individuals.

Materials and Methods: The study was approved by the Institutional Ethics Committees of the participating institutions. CVL was collected from 90 non-pregnant women attending the tertiary care hospitals in Mysore. Papanicolaou (Pap) test was performed for cytological examination. DNA was extracted and HPV positive samples genotyped using TRUPCR® HR-HPV Genotyping Kit. The diversity of microbial population was identified using 16srRNA metagenomics (V3-V4 region). *Trichomonas vaginalis* and *Candida Sp.* were detected by PCR. The pro- and anti-inflammatory cytokines were measured by ELISA.

Results and Conclusion: Among 90 participants, 50 participants (55.5%) had no abnormalities by Pap test, while the remaining 40 participants (44.5%) had abnormal Pap results or biopsy reports. Analysis of HPV screening data showed that 20 participants (40%) among 50 healthy individuals were positive for HPV. All the 40 Pap positive cases were concurrently positive for HPV DNA by PCR. A significant increase in *Lactobacillus iners* was observed in HPV-positive healthy women (n=20). Relative species abundance data showed the predominence of Actinobacteria, Prevotella and Porphyromonas in HPV positive cervical cancer cases. TGF-β was significantly higher in the CVL of cervical cancer patients when compared to the control.

Key Words: Cervical Cancer, HPV, V3-V4 Microbial profiling, *Trichomonas vaginalis*, *Candida Sp.*, Inflammation.

Ethical Declaration: This study was approved by Institutional Ethics Committee of JSS Medical College & Hospital (JSSMC/IEC/270821/12NCT/2021-22) and Mysore Medical College & Research Institute (MMC/EC/50/21), and Public Health Research Institute of India (PHRII; # 2022-01-29-65).

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Section 2- Events

IACR Conference Poster presentation Award

Nabanita Das

UNREVEALING THE ROLE OF NPM1 (NUCLEOPHOSMIN) AND NPM2 (NUCLEOPLASMIN) IN ORAL CANCER

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Background: Despite great advancements in cancer diagnostics and therapy, the rate of cancer incidences and deaths is rising at an alarming rate. Most of the cancer cases get diagnosed at a very late stage which results in low survival expectancy. Biomarkers and prognostic markers are urgently needed to combat this burning problem. Our study aims to establish a prognostic marker (NPM1 and AcNPM1) to predict oral cancer progression at an early stage and investigate the significance of novel pathways in the manifestation of oral cancer.

Objective: Based on our research, we have shown that NPM1 was found to be highly over-expressed and hyper-acetylated in oral cancer, increasing with the grade and stage of the tumor. Importantly, NPM1-mediated transcriptional activation in oral cancer seems to be critical for oncogenesis. Thus, we wish to establish NPM1 and AcNPM1 as a crucial biomarker in oncogenesis. Interestingly, NPM2 has been studied extensively in *Xenopus* but not in vertebrates. Being an important member of the Nucleoplasmin family, we also wish to explore the role of NPM2 (nucleoplasmin) in oral cancer manifestation.

Materials and Methods: The hybridoma cell lines have already been established for the generation of monoclonal antibodies. IHC was performed with NPM1 and AcNPM1 antibodies, and patient samples were found to be tumor vs adjacent normal. We have also evaluated the H-Score for all the IHCs performed. Using in-vitro assays and ChIP-Seq, respectively, we have also shown that NPM1 gets Acetylated by p300 and colocalizes with RNA-Pol II at promotor sites. We have also established primary cell lines from OCSS patient tumor samples and checked the expression of NPM2 using western blotting.

Results and Conclusions: We have shown that both AcNPM1 and NPM1 get overexpressed in OSCC patients. Our IHC data and H-scoring indeed have shown that, indeed, the NPM1 is hyperacetylated and overexpressed in oral cancer patients' samples. Additionally, we are characterizing the newly established OCSS cell lines. Interestingly, we have also observed the over expression of NPM2 in oral tumor samples compared to adjacent normal.

Key Words: Prognostic markers, Nucleophosmin (NPM1) and Acetylated Nucleophosmin (AcNPM1), cancer stage, and grade prediction, cancer progression, and statistical analysis, Nucleoplasmin (NPM2)

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Section 2- Events

IACR Conference Poster presentation Award

Nandini Sahani

UNCOVERING THE ROLE OF FOXM1-hTERT AXIS IN CANCER PROGRESSION AND THERAPEUTIC INTERVENTION

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Introduction: Cancer treatment remains challenging due to gaps in understanding the fundamental mechanisms of oncogenesis. This study investigates the role of Forkhead Box M1 (FoxM1), an oncogenic driver, and its interaction with Human Telomerase Reverse Transcriptase (hTERT), which is critical for cellular immortalization. FoxM1 regulates cell proliferation and survival, while hTERT enables uncontrolled replication. Our analyses suggest that FoxM1 may directly regulate hTERT expression, potentially driving cancer progression and presenting a target for therapy.

Objectives and Methodology: Our study involves analysis of FoxM1 and hTERT expression across cancer types using bioinformatics, assessment of the clinical impact on survival outcomes via Kaplan-Meier analysis, confirmation of FoxM1 and hTERT expression in cancer cell lines using western blotting and evaluation of FoxM1's regulatory effect on hTERT through knockdown and TRAP assays. Additionally, identification of FoxM1 binding sites on hTERT promoter via sequence analysis and validation through Chromatin IP.

Results and Conclusions: Our analysis of the TCGA database revealed a correlation between FoxM1 and hTERT expression across several cancer types. Sequence analysis identified potential FoxM1 binding sites within the hTERT promoter, suggesting direct regulation. Experimental data confirmed a positive relationship between FoxM1 and hTERT protein levels in cancer cells. FoxM1 knockdown significantly reduced hTERT expression and abolished telomerase activity. This result was further reinforced by FoxM1 inhibitor treatment observations. Overall, these findings provide evidence that FoxM1 regulates hTERT expression and drives cellular immortalization and cancer progression via telomerase signalling. Hence, our investigation highlights the FoxM1-hTERT axis as a promising therapeutic target for cancer treatment.

Keywords: Oncogenesis, Cancer progression, FoxM1, hTERT and Anti-cancer treatment.

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Section 2- Events

IACR Conference Poster presentation

Niladri Haldar

APTAMER TETHERED HETERO-POLYMER CONJUGATED MESOPOROUS SILICA NANOPARTICLES (MSNPS) MEDIATED DELIVERY OF DUAL SIRNA TO INDUCE APOPTOSIS IN BREAST CANCER CELLS

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Background: Breast cancer is the most common and second-leading cause of cancer-related fatalities globally. Small interfering RNA (siRNA)-based therapy is effective for addressing resistant forms by inducing apoptosis. Having limited selectivity and the inability to penetrate cancer cells, it requires a carrier to transport it to cancer cells. A nanocarrier is a type of vehicle capable of delivering siRNA to selectively target cancer cells. In this study, we developed a multifunctional aptamer-tethered hetero-polymer conjugated MSNPs for the delivery of dual siRNAs to treat breast cancer.
Objectives: 1) Synthesis and characterization of hetero-polymer conjugated MSNPs, 2) Conjugation of PEG on amine terminal hetero-polymer through amide bond and conjugation of MUC-1 aptamer on PEG, 3) Evaluation of *in vitro* and *in vivo* breast cancer regression ability of dual siRNA loaded nanocarrier.
Methodology: MSNPs were synthesized using a sol-gel technique and conjugated with hetero-polymeric molecules [1]. Characterization was done using DLS, SEM, and FTIR. These nanocarriers were used to deliver dual siRNAs in MCF7 breast cancer cells. The gene silencing ability of the nanocarrier was assessed through real-time PCR and a caspase activation assay to evaluate cancer inhibition [2]. MCF-7 breast cancer xenograft in SCID mice and evaluate tumor regression ability.
Results and Conclusion: The studies confirmed the conjugation of hetero-polymer-conjugated MSNPs and showed that the targeted nanocarrier significantly inhibited target genes. The cell death assay using the MTT reagent showed that targeting dual anti-apoptotic genes can increase the rate of cell death in cancer cells. The caspase activation assay confirmed that dead cells had undergone apoptosis. These results suggest the synthesized nanocarrier has great potential as a therapeutic agent delivery vehicle in MCF-7 cells. Breast tumor was developed in mice and the study found that the dual siRNA-loaded nanocarrier greatly reduced the tumor than other groups.

Keywords: Mesoporous silica nanoparticles, Dual siRNA, Anti-apoptotic genes, Breast cancer, MUC-1 aptamer.
Ethical Declaration: All experiments were conducted under the approved animal protocol (IAEC approval No. ARI/IAEC/2023/13) by the Institutional Animal Ethics Committee (IAEC) of Agharkar Research Institute, Pune, India.

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References:

[1] P. Kumar, R. Salve, K. M. Paknikar, and V. Gajbhiye, "Nucleolin aptamer conjugated MSNPs-PLR-PEG multifunctional nanoconstructs for targeted co-delivery of anticancer drug and siRNA to counter drug resistance in TNBC," *Int. J. Biol. Macromol.*, vol. 229, no. February, pp. 600–614, 2023, doi: 10.1016/j.ijbiomac.2022.12.266.

[2] P. Tambe *et al.*, "Targeted silencing of the MCL-1 gene using multi-layered dendrimer-based nanoconstructs achieves efficient tumor regression in xenografted mice models," *Int. J. Pharm.*, vol. 634, no. March, pp. 1–5, 2023, doi: 10.1016/j.ijpharm.2023.122659.

Section 2- Events

IACR Conference Poster presentation

Nilanjana Chatterjee

EXPRESSION DYSREGULATION OF miR-31-5p CURTAILS THE THERAPEUTIC EFFICACY OF EGFR - PATHWAY- TARGETING DRUG ERLOTINIB IN OSCC PATIENTS

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Background: Micro-RNA mediated downregulation of CBL stabilizes EGFR expression in oral cancer that might in turn curtail Erlotinib (oral metronomic chemotherapeutic drug/OMCT) efficacy in inhibiting the autophosphorylation of EGFR rendering to constitutive activation of downstream oncogenic pathways.

Objective: Primarily to analyze the expression dysregulation of EGFR, CBL, MIR31HG and hsa-miR-31-5p of EGFR signaling pathway in OSCC patients. Additionally, to make a comparative expression signature of hsa-miR31-5p between two independent cohorts of OSCC patients with or without receiving Erlotinib treatment for prognostic prediction.

Materials and Methods: Expression pattern of EGFR, CBL, MIR31HG, hsa-miR-31-5p were analysed from RNA sequencing data of OSCC patients (N=5) and their expression was validated in independent cohort with neoplastic oral lesions (N= 35) and adjacent normal, collected from ENT-OPD by quantitative Real Time PCR (qRT-PCR). Expression pattern of hsa-miR-31-5p was also analysed from FFPE tissues of OSCC patients (N=15) receiving erlotinib treatment and normal tissue (N=10) by qRT-PCR. Protein expression analysis of CBL and EGFR were done in tissue/oral cells by Immunohistochemistry and Immunocytochemistry and in cell line FADU by Western Blotting.

Results and Conclusions: EGFR (19/35; 54%), MIR31HG (15/33; 45%), hsa-miR-31-5p (18/34, 53%) showed upregulation in most of the OSCC samples, whereas, CBL showed downregulation in the same samples (17/26, 65%). Protein expression pattern of EGFR and CBL showed concordance with their respective mRNA expression in the same samples. Correlation is being made for miR-31-5p and CBL expression with prognosis of the patients received Erlotinib.

Keywords: OSCC, OMCT, EGFR, miR-31-5p, CBL

Ethics Statement: This study was approved by the Ethical Committee of Chittaranjan National Cancer Institute [Ref no: CNCI-IEC-SD-2019-8 dated 22.5.2019] and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Section 2- Events

IACR Conference Poster presentation

Padmaja KP

THE TRANSCRIPTIONAL REGULATORY ROLE OF TIF1γ IN SELF-RENEWAL LEADING TO RECURRENCE IN ORAL CANCER

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Background: In India, oral cancer is ranked second in mortality. The high mortality is due to high recurrence, which is induced by the self-renewing population. Our previous results confirmed the role of TIF1γ/TRRAP/H2A.Z complex in regulating self-renewal by the induction of *HES1*. Thus, the molecular mechanism behind the regulation of HES1 needs to be identified. Apart from *HES1* the other self-renewal molecules regulated by TIF1 needs to be identified.

Objectives:

1. To elucidate the role of TIF1γ& H2A.Z/TRRAP complex in recurrence.
2. To understand the molecular mechanism by which TIF1γ regulate *HES1*
3. To identify transcriptional targets of TIF1γ.

Materials and Methods: We performed immunohistochemistry on tissue array (TSA) to study recurrence. Extreme Limiting Dilution Assay (ELDA) was done to study self-renewal. Dual reporter assay was conducted to study the mode of *HES1* expression. The promoter occupancy was studied by ChIP-qPCR. RNA Seq analysis revealed the target genes of TIF1γ.

Results and Conclusions: The immunohistochemistry on TSA confirmed the role of TIF1γ/TRRAP/H2A.Z complex in recurrence, while ELDA confirmed its role in self-renewal. The ChIP assay confirmed the co-occupancy of TIF1γ/TRRAP/H2A.Z on *HES1* promoter and suggested that TIF1γ is reading H2A.Z acetylation induced by TRRAP to monoubiquitinate H2B, marking transcriptional activation. Further the RNA Seq identified the self-renewal genes regulated by TIF1γ.

So, in CSCs, TRRAP is recruited to the promoter to acetylate H2A.Z, which is read by TIF1γ that monoubiquitinates H2B switching on transcription of self-renewal genes leading to recurrence.

Keywords: Oral cancer, Cancer stem cells, Recurrence, TRRAP, H2A.Z

Ethical Declaration: Ethical clearance was obtained from Rajiv Gandhi Center for Biotechnology (RGCB/IHEC/250/2022/65) and from St. Jones Research Institute (15D/2023).

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Section 2- Events

IACR Conference Poster presentation

Rudransh Singh

UNCOVERING THE ROLE OF RIBOSOME HETEROGENEITY IN HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC), which accounts for about 90% of primary liver cancers, often shows increased activity in the Mammalian Target of Rapamycin (mTOR) pathway. mTOR, a PI3K family kinase in eukaryotes, plays a central role in regulating cell growth and metabolism. mTOR pathway is elevated in roughly 50% of HCC cases. mTOR promotes protein synthesis and ribosome biogenesis in the presence of nutrients and growth factors, however, both processes require substantial energy, which can strain cancer cells that are already under chronic stress. It remains unclear how mTOR supports cancer cell translation under such stressful conditions. Ribosomal composition also plays crucial role in translation reprogramming however how its contribution in HCC is not studied.
Objective: Given mTOR's hyperactivation in HCC, we plan to examine how mTOR signalling in tumours modifies ribosomal composition and how ribosome-associated factors respond to stress, impacting mRNA translation in HCC.
Methodology: For this study Liver double K/O model for PTEN and TSC (mTOR repressors) in C57BL/6J mice were used, which had mTOR hyperactivation. After tumour development, translational status was assessed via polysome profiling and puromycin incorporation assays, followed by mass spectrometry to analyse ribosomal composition.
Results: Tumours showed significant translational deregulation, with reduced global translation compared to adjacent non-tumour regions and normal liver in both fed and overnight starved mice, as indicated by polysome profiling and puromycin incorporation. Mass spectrometry of ribosomal fractions in mTOR-driven L-dKO HCC mouse tumors revealed altered ribosome composition. Further studies are needed to clarify their role in HCC translation regulation.

Keywords: Hepatocellular Carcinoma (HCC), mTOR hyperactivation, L-dKO mice, Polysome Profiling, puromycin incorporation assay.
Ethical Declaration: IAEC protocol No – 025/2023
Acknowledgements: Doctoral Committee members, Lab members, ACTREC for infrastructure support and DBT for fellowship.
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Section 2- Events

IACR Conference Poster presentation

Saumya Ranjan Satrusal

DEVELOPMENT OF A FIRST-IN-CLASS DUAL INHIBITOR TARGETING EZH2 AND EGFR AGAINST TRIPLE-NEGATIVE BREAST CANCER

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Introduction: TNBC has huge unmet medical need in India due to its high prevalence and mortality with no targeted therapies and aggressive metastasis. Simultaneous inhibition of multiple targets through a single inhibitor seems a lucrative anti-cancer strategy, considering TNBC's multifactorial pathophysiology. Concomitant overexpression of EZH2 and EGFR selectively in TNBC patients correlates with poor prognosis, which provides strong rationale for dual inhibition.
Objectives: As multiple clinical trials are on-going with EZH2 and EGFR inhibitors separately in TNBC, here, we have developed a strategy to target both proteins with a single molecule.
Materials and Methods: To address the above objective, we have synthesized 33 small molecules for dual inhibition of EZH2 and EGFR proteins and assessed for cell based dual target binding (CETSA) followed by downstream signal inhibition, cytotoxicity in normal versus cancer cells (SRB), migration inhibition (Invasion assay). In vivo efficacy was determined by Luc tagged allograft models of TNBC **via BLI.**
Results and Conclusions: Our lead compound, S-023-0996, displays strong dual inhibition of EZH2 and EGFR and robust antiproliferative potential against TNBC cell lines (IC_{50}~2.5 µM), while being less cytotoxic to non-cancerous cells (IC_{50}>50 µM). It also poses significant cytotoxicity against Indian TNBC PDX-O model. S-023-0996 (100mg/kg) demonstrated significant TGI along with inhibition of metastasis assessed by in vivo bioluminescence imaging in allograft mice models. Collectively, these pre-clinical findings suggest that S-023-0996 could be a promising drug candidate for further development.
Keywords: TNBC, EZH2, EGFR, Dual inhibitor, Metastasis
Ethical Declaration: Human tissue samples of TNBC were provided by King George's Medical University (KGMU), Lucknow, India. Written informed consent was obtained from above patients and complete study protocol was approved by the Ethics Committee of KGMU (Protocol Number: 116th ECM IIA/P16) and CSIR-CDRI (Protocol Number: CDRI/IAEC/2022/22).
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Section 2- Events

IACR Conference Poster presentation

Sulagna Rath

POST-TREATMENT AFTERMATH: ROLE OF IMMUNE CELL INFLUX DYNAMICS IN THE PTT-TREATED TUMOR MICRO-ENVIRONMENT

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Background: Globally, photothermal therapy (PTT) is actively being pursued as a promising hyperthermia approach for treating solid tumors. Intratumoral gold nanomaterial injection followed by 3-5 minutes of low-dose NIR laser (750 nm, 650 mW) demonstrated an effective ablation of 0.8-1cm² sized tumors. Due to hyperthermia, cancer cells release DAMPs into the tumor microenvironment, triggering immunogenic cell death.
Objectives: Considering the dynamicity of the tumor micro-environment during wound healing, we intend to investigate tumor-immune cell cross-talk after PTT treatment.
Methods: Syngeneic orthotopic breast cancer model in BALB/c mice was established using engineered 4T1-Firefly luciferase mouse breast cancer cell line. PTT treatment was done by combining Au-SLN nanomaterial with 750nm 650mW laser incidence. Control and treated tumor tissue samples and serum samples harvested at various time intervals were analysed by immunohistochemical, mass-spectrometry and cytokine array analysis.
Results and Conclusion: Compared to untreated control, significant tumor reduction and tissue integrity loss was observed at the PTT treated site of tumor. Overnight, the tumor microenvironment (TME) shifted to an anti-tumorigenic state, characterized by increased presence of pro-inflammatory M1 macrophages, reduced immunosuppressive M2 macrophages, and greater infiltration of both CD4 and CD8+ve T lymphocytes and dendritic cells (CD11c). However, by day 11, immune cell infiltration had significantly decreased ($p<0.05$), suggesting the TME had reprogrammed to evade anti-tumor effects. Serum cytokine analysis revealed arise in Th1 cytokines and chemokines, indicating increased anti-tumor activity. Together, these temporal immune cell dynamics helped to determine an optimized time window of immune reactivation after PTT, based on which a combinatorial immunotherapeutic approaches like macrophage polarisation or cytokine therapy and enhance the survival benefit further
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Keywords: Photothermal Therapy, DAMPs, Immunogenic cell death, Tumor micro-environment, Immunotherapy
Ethical Declaration: IAEC Protocol No-029/2021
Acknowledgments: ACTREC for infrastructure support and PhD fellowship to Sulagna Rath

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Section 2- Events

IACR Conference Poster presentation

Sunny Kumar

GLIOMA NANOTHERAPY: DELIVERY OF DUAL-DRUG LOADED NANOFORMULATION ACROSS BBB

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Background: Glioblastoma multiforme (GBM) remains one of the deadliest and most treatment-resistant brain tumors, largely due to the challenges of crossing the blood-brain barrier (BBB) and the tumor's adaptive resistance to conventional therapies.

Objectives

1. Development of dual-loaded nanoformulation.
2. Efficacy determination and validation of nanoformulation in *in-vitro* and *in-vivo* orthotopic glioma model.

Materials and Methods

1. Automated Stereotactic instrument for glioma orthotopic model generation
2. Pharmacokinetic study
3. Drug delivery across BBB
4. Solvent evaporation method
5. Drug-drug synergy
6. Mass spectrometry and FTIR
7. Bioinformatics

Results and Conclusions

In response to these hurdles, we have developed a cutting-edge nanotherapeutic platform using PLGA-based nanoparticles to co-encapsulate Temozolomide (TMZ) and the EGFR inhibitor 3,3′-diindolylmethane (DIM). This innovative dual-loaded nanoparticle system enhances the targeted delivery and bioavailability of both drugs, offering a promising solution to improve therapeutic outcomes. Preclinical *in vitro* and *in vivo* studies reveal that the synergistic interaction between TMZ and DIM significantly boosts TMZ's cytotoxicity, resulting in increased DNA damage, apoptosis, and a pronounced reduction in tumor growth. The nanocarrier not only optimizes drug delivery to the tumor site but also mitigates systemic toxicity, extending survival in GBM models. By overcoming key limitations of standard GBM treatments, including poor drug penetration and resistance, this novel combinatorial nanotherapy represents a transformative approach with the potential to reshape GBM treatment strategies, moving closer to more effective, targeted options for patients.

Keywords: Stereotactic instrument, Glioma, Dual-Loaded Nanoformulation, BBB, Apoptosis

Ethical Declaration: All animal procedures were performed under the guidelines of the institutional review board and the ethics committee of CSIR-Indian Institute of Chemical Biology.
Acknowledgements: We acknowledge Department of Science and Technology (DST), Council of Scientific and Industrial Research-Indian Institute of Chemical Biology (CSIR-IICB) and AcSIR.
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Section 2- Events

IACR Conference Poster presentation

Supriya Varsha Bhagat

UNRAVELLING THE UNDERPINNED GENETIC AND EPIGENETIC LANDSCAPE OF TOBACCO-RELATED ORAL CANCER IN SOUTHERN INDIA

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Background: India accounts for nearly one-third of cases of Oral Squamous Cell Carcinoma (OSCC), majorly affecting the gingiva-buccal region. In southern India, there is a female preponderance of oral cancer due to a unique betel quid (Kaddipudi) chewing habit. Our study focuses on unravelling the genetic and epigenetic mechanisms for the manifestation of habit-related oral cancer in the context of the Indian population.

Objective: Based on the female preponderance, we sequenced 48 female OSCC patients with unique tobacco chewing habits and identified several unique mutations in the TP53 and CASP8 genes. We aim to decipher the cross-talk between them to understand their synergism in oral cancer pathophysiology. OSCC is a heavily epigenetically regulated cancer. We wish to investigate the epigenetic landscape in these patients. Using the orthotropic mice model, we aim to evaluate the efficacy of selected inhibitors of p300 KAT and PRMT4/CARM1 arginine methyltransferase activity.

Materials and Methods: The mutations were identified using whole exome sequencing. Site-directed mutagenesis was used to generate the p53 mutants and stable cell lines were generated in the UMSCC-1 (p53-/-) background. We have quantitated the expression levels of p300, CARM1 and their associated histone marks. Using in-vitro assays and cell line assay treatments, we have screened CARM1 inhibitors.

Results and Conclusions: We identified five novel mutations in the TP53 gene and the highest mutation frequency in the CASP8 gene. We are characterizing some of the unique TP53 mutations for their GOF property for driving oral carcinogenesis. Additionally, the tumor suppressor p53 (both wildtype and specific mutants) also promotes p300 autoacetylation. We observed increased arginine methylation and lysine acetylation mediated by CARM1 and p300, suggesting a complex epigenetic landscape in tobacco-related oral cancer. Using in-vitro assay and cell line treatment, we have identified CARM1 specific inhibitor.

Keywords: Oral Cancer, TP53, CASP8, p300, CARM1, trans- autoacetylation, epigenetics, Inhibitors.

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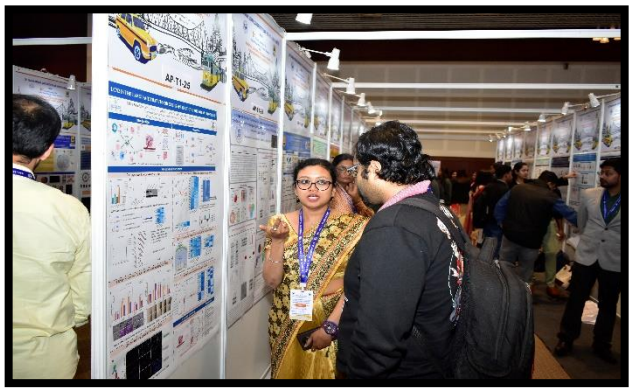
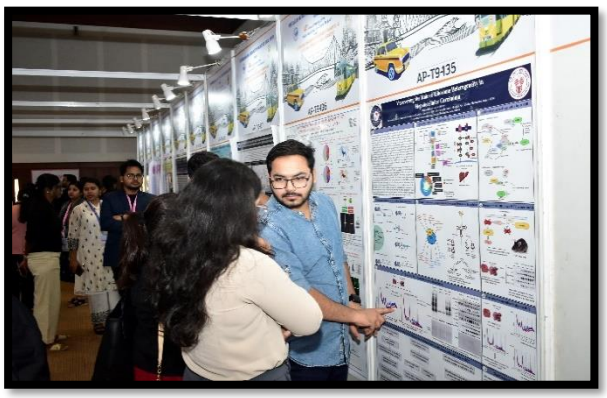
# Equal Contribution.

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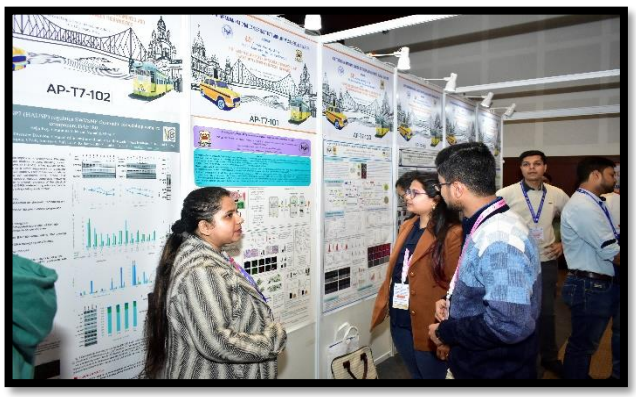
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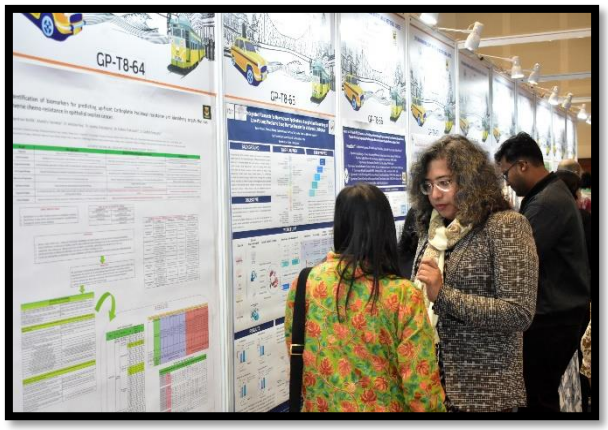
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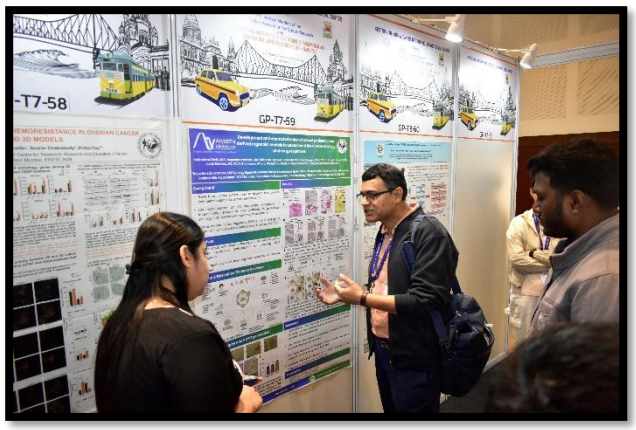
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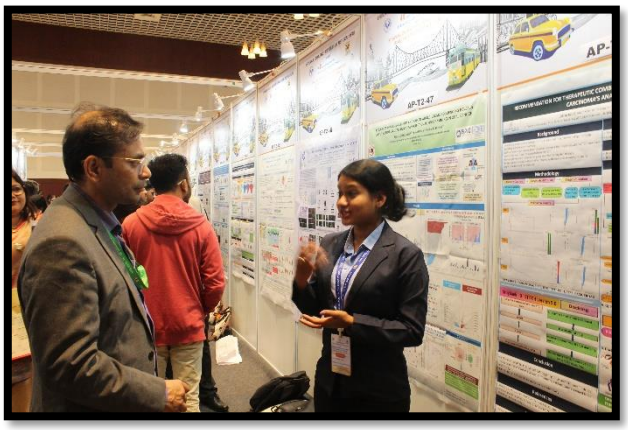


Section 2- Events

Winners of Annual Essay Competition

Essay Topic: Systems biology and bioinformatics: Advances and applications in cancer research and management

Divya Janjua

Unveiling the Molecular Secrets of Circulating Tumor Cells:

Revolutionizing Liquid Biopsy with Single-Cell RNA Sequencing (scRNA-seq)

-Divya Janjua (ST-228)

Cancer continues to be one of the primary concern worldwide with a total of 19,976,499 new cases coupled with 9,743,832 deaths. Among all, cervical cancer (CaCx) is the fourth most common cancer in women worldwide and stands as the major contributor with an estimated annual incidence of 662,301 cases (6.9%) and 348,874 deaths (8.1%). India alone accounts for 17.7% of the global burden, making CaCx the second most common cancer affecting Indian women. Alarmingly, the mortality rate in India stands at 17.9% **[1]**. This substantial contribution to the global burden is primarily driven by socio-economic challenges and cultural beliefs, which limit the accessibility and effectiveness of screening programs while deepening inequities in the health system **[2]**. Despite this, the treatment landscape for clinical management of CaCx remains relatively unchanged **[3]**. Radical oncosurgery and concurrent chemo-radiotherapy (CCRT) continue to be regarded as the backbone of curative treatment for locally advanced CaCx patients **[4, 5]**. The reported 5-year disease-free survival (DFS) rates are 62% for Stage II, 45% for Stage III, and the 3-year DFS is only 4% for Stage IV **[6]**. As the cancer progresses and metastasizes, the prognosis worsens, with a median survival of 8–13 months and a 5-year survival rate of just 16.5% **[7]**.

Unlike early-stage or locally advanced CaCx, which has established treatments like surgery, chemotherapy, and radiotherapy, metastatic CaCx lacks standard treatment due to its heterogenous manifestations **[9]**. Lack of appropriate screening for effective patient stratification hampers appropriate treatment decisions **[10]**, as there is no definitive criteria for accurately diagnosing recurrent or residual disease **[11-13]**. This makes it challenging to guide subsequent therapy **[14]**. Around 40% of CaCx patients experience recurrence with distant metastases post-treatment **[15]**. The mechanisms underlying tumor cell metastasis from the primary site to secondary locations are still poorly understood **[7, 16]**. As a result, detection of malignancy in advanced stages often leads to indiscriminate aggressive chemoradiotherapy. This underscores the urgent need for early detection of metastatic CaCx, enabling better patient stratification and more tailored therapeutic approaches.

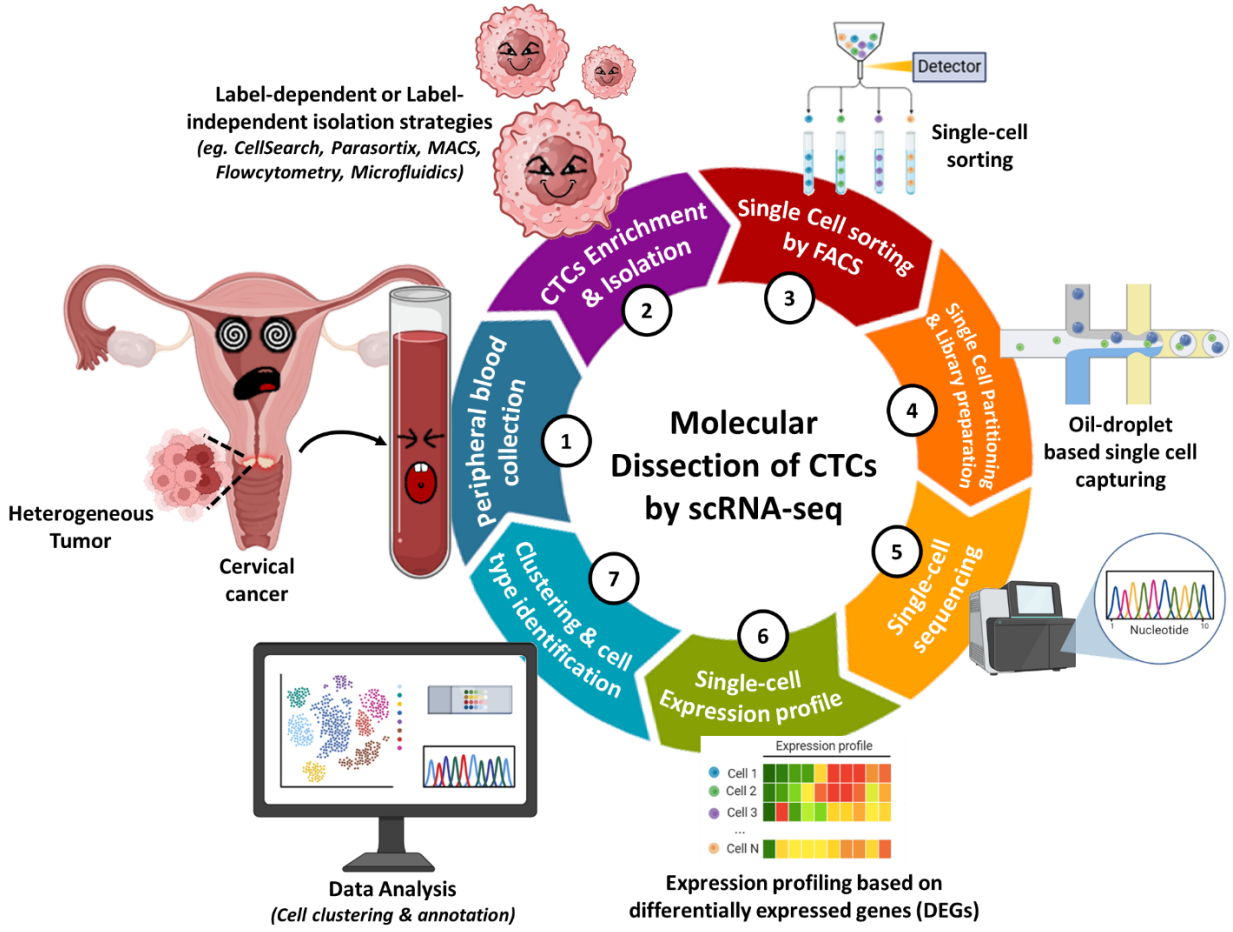
A number of evidences suggest that metastasis is an early event in carcinogenesis, occurring in approximately 60-70% of cancer patients, often before the primary tumor becomes clinically detectable **[17-20]**. During this process, tumor cells are sloughed off from the primary tumor and enter into circulation as disseminated tumor cells (DTCs) or circulating tumor cells (CTCs) **[21]**. Prior to seeding themselves at secondary target sites, these cells can undergo an extended period of proliferative dormancy **[17]** to acquire additional somatic mutations required for neoplastic expansion **[22]**. Hence, CTCs serve as the first indication for the onset of cancer metastasis, highlighting their clinical potential in timely detection of aggressive cancers **[23]**. CTCs have been established as eminent predictive and prognostic biomarker in a number of cancers such as gastric cancer **[24, 25]**, pancreatic cancer **[26]**, lung cancer **[27, 28]**, prostate cancer **[29-31]**, colorectal cancer **[32-34]**, hepatocellular carcinoma **[35]**, and breast cancer **[36-38]**. However, their clinical role in CaCx remains largely unexplored. The sporadic CTC-specific studies in the field of CaCx

[39-41] fail to address key aspects such as intra-tumor heterogeneity and self-seeding capacity. This highlights the need for further exploration of clinical potential of CaCx-CTCs.

A major bottleneck lies in the reliance on epithelial cell adhesion molecule (EpCAM)-based technologies, which continue to dominate the current landscape of CTC detection and isolation **[42]**. Among these, CellSearch® (Veridex LLC, Raritan, NJ, USA) remains the only FDA-approved technology for clinical CTC isolation **[43-45]**. However, EpCAM-based approaches inherently bias the isolation process, focusing predominantly on epithelial CTCs **[46]** while overlooking the rare but critical mesenchymal EpCAM-negative subset. This limitation becomes more pronounced during epithelial-to-mesenchymal transition (EMT), where epithelial markers are downregulated, leading to an underestimation of the total CTC population **[47]**. Such methods risk missing biologically significant EpCAM-negative CTCs **[42, 48-50]** that play crucial role in carcinogenic progression. In addition, assessing tumor cells directly in patient blood samples and standardizing markers for their detection presents significant challenges **[51]**, particularly given the scarcity and value of these samples.

With the advancement in technologies, the dissection of CTCs is no longer limited to their detection, isolation, and enumeration at bulk-level. The inherent heterogeneity of CTCs, magnified by limited knowledge of phenotypic markers, further complicates their accurate characterization **[52, 53]**. To address this, transcriptomic analysis at single-cell resolution holds promise to offer valuable insights into tumor classification, metastasis dynamics, disease progression, chemo-resistance mechanisms, and the potential for personalized adjuvant therapies as reported in gastric cancer **[54]**, breast cancer **[55]**, neuroblastoma **[56]**, and other solid tumors **[57]**. The magnification of CTCs at single-cell level can help in examining both inter- as well as intra-tumor heterogeneity. The single cell resolution can provide an insight into the rare metastatic population of CTCs to

target the physiologically relevant sub-population responsible for cancer metastases. Today, a single cell can be analyzed to have a better insight into the molecular mechanisms and the transcriptional programs active within the cell in a real-time manner.



Schematic representation of general workflow used for molecular profiling of CTCs using scRNA-seq.

Hence, the utilization of single-cell multi-omics approach provides a minimally-invasive yet maximally informative analysis of CTCs to distinguish the metastatic sub-population of CTCs based on genomic as well as phenotypic alterations acquired during circulation. The analysis of such CTCs will aid in characterizing different stages of carcinogenic progression. Also, using such CTCs as unique biomarkers will facilitate highly metastasis-directed therapeutics to combat cancer.

A recent shift from bench to bedside has been observed, with researchers increasingly focusing on single-cell sequencing to dissect the molecular landscape of CTCs. scRNA-seq has provided major insights into understanding the science of CTCs in various cancers, explaining their heterogeneity and molecular characteristics. For example, in lung adenocarcinoma, single-cell expression profiles differentiated CTCs from background noise of different blood cells by using markers like EpCAM **[58]**. This level of detail allowed for more precise identification and characterization of CTC sub-populations. Studies have shown that CTCs can exhibit different rate of proliferation, which can have prognostic implications. For instance, 35% of 105 patients with metastatic breast cancer showed CTCs with elevated Ki-67 expression, which is linked to a poor prognosis **[59]**. Additionally, scRNA-seq dissected the heterogeneity among CTCs at single-cell resolution, including EMT and MET like states, as well as cancer stem cells (CSCs) like phenotypes. Furthermore, single-cell dissection of CTCs can aid in identifying different subset of CTCs that participate in key signaling pathways driving metastasis and treatment resistance **[60]**. For example, in prostate cancer, activation of non-canonical Wnt signalling was observed in anti-androgen resistant patients. Experimental evidence using mouse models demonstrated the role of Wnt5a in mediating resistance to androgen receptor inhibitors, suggesting potential therapeutic targets **[61]**. In colorectal cancer, transcriptomic profiling of CTCs identified 410 genes including BMP6, TGFβ-1, and TLN1, which were associated with cellular movement and cell adhesion. Other CTC-specific genes identified were linked with cell death and cell proliferation such as clusterin and TIMP1 **[62]**. Interestingly, one group investigating the causes of liver metastases in colon cancer patients using single-cell exome sequencing reported the polyclonal origin of CTCs and highlighted the TRSP1 mutation as a potential therapeutic target **[63]**. Another study analyzing paired peripheral blood and bone marrow samples from 73 individuals, including myeloma

patients, employed 5' scRNA-seq and single-cell B-cell receptor sequencing (scBCR-seq) (10x Genomics). This study identified eight differentially upregulated genes in CTCs that enhanced their circulatory potential **[64]**. Similarly, transcriptomic profiling of single gastric CTCs revealed the expression of platelet-specific genes such as PF4 and PPBP, that enhanced the shelf-life of CTCs in circulation, thereby, promoting EMT **[54]**. In CaCx, limited efforts have been made to molecularly subtype cervical exfoliated cells using scRNA-seq, uncovering significant immune remodeling during disease progression **[65-68]**. These findings collectively demonstrate the immense potential of scRNA-seq and next-generation sequencing (NGS) approaches in advancing our understanding of CTC biology. They provide valuable insights into their role in disease progression. Overall, single-cell sequencing of CTCs articulates the way for the development of targeted personalized therapies to improve survival outcomes **[69].** However, to the best of our knowledge, there is no such report unraveling the molecular fingerprint of CTCs in CaCx. Therefore, applying advanced single-cell 'omics' technologies to CaCx-derived CTCs is essential to unlock their prognostic and therapeutic utility.

Ultimately, the rare and heterogeneous nature of these cells continues to pose a major challenge in their isolation, detection, and characterization. Improvements in several isolation and detection strategies with time have enhanced the clinical utility of CTCs. As a result, CTCs have emerged as robust biomarkers for diagnosis, prognosis, and therapeutic monitoring among different malignancies. Still dynamic nature of CTCs stemming from EMT prevents their effective utilization. Integrating multi-omics approaches into traditional strategies will aid in dissecting the molecular profile of CTCs without any marker-based selection bias. As the scRNA-seq technologies and bioinformatics pipelines continue to mature, CTCs are set to become an integral

component of precision oncology, offering hope for more effective and personalized cancer treatments.

REFERENCES

1. Globocan, *International Agency for Research in Cancer. World Health Organization.* 2022.
2. Sankaranarayanan, R., Ramadas K., and Cindy L., *Socioeconomic factors and cancer prevention in India.* World cancer report 2020. Cancer research for cancer prevention. , ed. E.W. Christopher P. Wild, and Bernard W. Stewart. 2020: Lyon (FR): International Agency for Research on Cancer.
3. Grau-Bejar, J.F., et al., *Advances in immunotherapy for cervical cancer.* Ther Adv Med Oncol, 2023. **15**: p. 17588359231163836. doi:10.1177/17588359231163836
4. Sun, H.Y., et al., *Cisplatin concurrent chemoradiotherapy vs adjuvant radiation in stage IB/IIA cervical cancer with intermediate risk factors, treated with radical surgery: a retrospective study.* Onco Targets Ther, 2018. **11**: p. 1149-1155. doi:10.2147/OTT.S158214
5. Waggoner, S.E., *Cervical cancer.* Lancet, 2003. **361**(9376): p. 2217-25. doi:10.1016/S0140-6736(03)13778-6
6. Chopra, S., et al., *Locally advanced cervical cancer: A study of 5-year outcomes.* Indian J Cancer, 2018. **55**(1): p. 45-49. doi:10.4103/ijc.IJC_428_17
7. Zhou, S. and F. Peng, *Patterns of metastases in cervical cancer: a population-based study.* Int J Clin Exp Pathol, 2020. **13**(7): p. 1615-1623.
8. Li, J., et al., *Cervical cancer prognosis and related risk factors for patients with cervical cancer: a long-term retrospective cohort study.* Sci Rep, 2022. **12**(1): p. 13994. doi:10.1038/s41598-022-17733-8
9. Li, H., X. Wu, and X. Cheng, *Advances in diagnosis and treatment of metastatic cervical cancer.* J Gynecol Oncol, 2016. **27**(4): p. e43. doi:10.3802/jgo.2016.27.e43
10. Safaeian, M., D. Solomon, and P.E. Castle, *Cervical cancer prevention--cervical screening: science in evolution.* Obstet Gynecol Clin North Am, 2007. **34**(4): p. 739-60, ix. doi:10.1016/j.ogc.2007.09.004
11. Teh, J., et al., *Concurrent chemoradiotherapy incorporating high-dose rate brachytherapy for locally advanced cervical carcinoma: survival outcomes, patterns of failure, and prognostic factors.* Int J Gynecol Cancer, 2010. **20**(3): p. 428-33. doi:10.1111/IGC.0b013e3181d4a0d1
12. Chen, S.W., et al., *Concurrent weekly cisplatin plus external beam radiotherapy and high-dose rate brachytherapy for advanced cervical cancer: a control cohort comparison with radiation alone on treatment outcome and complications.* Int J Radiat Oncol Biol Phys, 2006. **66**(5): p. 1370-7. doi:10.1016/j.ijrobp.2006.07.004
13. Mazeron, R., et al., *Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy.* Radiother Oncol, 2015. **114**(2): p. 257-63. doi:10.1016/j.radonc.2014.11.045
14. Schubert, M., et al., *Challenges in the Diagnosis and Individualized Treatment of Cervical Cancer.* Medicina (Kaunas), 2023. **59**(5). doi:10.3390/medicina59050925
15. Gennigens, C., et al., *Optimal treatment in locally advanced cervical cancer.* Expert Rev Anticancer Ther, 2021. **21**(6): p. 657-671. doi:10.1080/14737140.2021.1879646
16. Quinn, M.A., et al., *Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer.* Int J Gynaecol Obstet, 2006. **95 Suppl 1**: p. S43-103. doi:10.1016/S0020-7292(06)60030-1
17. Schmidt-Kittler, O., et al., *From latent disseminated cells to overt metastasis: genetic analysis of systemic breast cancer progression.* Proc Natl Acad Sci U S A, 2003. **100**(13): p. 7737-42. doi:10.1073/pnas.1331931100

18. Hu, Z. and C. Curtis, *Looking backward in time to define the chronology of metastasis.* Nat Commun, 2020. **11**(1): p. 3213. doi:10.1038/s41467-020-16995-y

19. Hanin, L. and S. Bunimovich-Mendrazitsky, *Reconstruction of the natural history of metastatic cancer and assessment of the effects of surgery: Gompertzian growth of the primary tumor.* Math Biosci, 2014. **247**: p. 47-58. doi:10.1016/j.mbs.2013.10.010

20. Hartung, N., et al., *Mathematical modeling of tumor growth and metastatic spreading: validation in tumor-bearing mice.* Cancer Res, 2014. **74**(22): p. 6397-407. doi:10.1158/0008-5472.CAN-14-0721

21. Ashworth, T.R., *A case of cancer in which cells similar to those in the tumours were seen in the blood after death.* Australas. Med. J., 1869. **14**: p. 146–149.

22. Giancotti, F.G., *Mechanisms governing metastatic dormancy and reactivation.* Cell, 2013. **155**(4): p. 750-64. doi:10.1016/j.cell.2013.10.029

23. Baccelli, I., et al., *Identification of a population of blood circulating tumor cells from breast cancer patients that initiates metastasis in a xenograft assay.* Nat Biotechnol, 2013. **31**(6): p. 539-44. doi:10.1038/nbt.2576

24. Cheng, R., et al., *Circulating Tumor Cells as Diagnostic Markers of Early Gastric Cancer and Gastric Precancerous Lesions.* Oncology, 2023. **101**(8): p. 512-519. doi:10.1159/000531323

25. Qiu, Y., et al., *Circulating tumor cell-associated white blood cell cluster is associated with poor survival of patients with gastric cancer following radical gastrectomy.* Eur J Surg Oncol, 2022. **48**(5): p. 1039-1045. doi:10.1016/j.ejso.2021.11.115

26. Xing, Y., et al., *The clinical significance of circulating tumor cells and T lymphocyte subtypes in pancreatic cancer patients.* Bioengineered, 2022. **13**(2): p. 2130-2138. doi:10.1080/21655979.2021.2023800

27. Chen, F., et al., *The value of folate receptor-positive circulating tumour cells as a diagnostic biomarker for lung cancer: a systematic review and meta-analysis.* J Int Med Res, 2023. **51**(9): p. 3000605231199763. doi:10.1177/03000605231199763

28. Welsch, E., et al., *Prognostic significance of circulating tumor cells and tumor related transcripts in small cell lung cancer: A step further to clinical implementation.* Int J Cancer, 2024. **154**(12): p. 2189-2199. doi:10.1002/ijc.34886

29. Lian, S., et al., *Folate-Receptor Positive Circulating Tumor Cell Is a Potential Diagnostic Marker of Prostate Cancer.* Front Oncol, 2021. **11**: p. 708214. doi:10.3389/fonc.2021.708214

30. Cho, H., et al., *Impact of Circulating Tumor Cell-Expressed Prostate-Specific Membrane Antigen and Prostate-Specific Antigen Transcripts in Different Stages of Prostate Cancer.* Clin Cancer Res, 2024. **30**(9): p. 1788-1800. doi:10.1158/1078-0432.CCR-23-3083

31. Zapatero, A., et al., *Detection and dynamics of circulating tumor cells in patients with high-risk prostate cancer treated with radiotherapy and hormones: a prospective phase II study.* Radiat Oncol, 2020. **15**(1): p. 137. doi:10.1186/s13014-020-01577-5

32. Nursyirwan, S.A., et al., *Assessment of Circulating Tumor Cells in Colorectal Cancer as an Adjunctive Non-invasive Diagnostic Method.* Acta Med Indones, 2023. **55**(4): p. 385-395.

33. Yu, J., et al., *A Prospective Long-Term Follow-Up Study: The Application of Circulating Tumor Cells Analysis to Guide Adjuvant Therapy in Stage II Colorectal Cancer.* Ann Surg Oncol, 2023. **30**(13): p. 8495-8500. doi:10.1245/s10434-023-14168-x

34. Alsayed, A., et al., *Assessment of the Circulating Tumor Cells and Microsatellite Instability in Colorectal Cancer Patients: Prognostic and Diagnostic Value.* Onco Targets Ther, 2021. **14**: p. 1937-1951. doi:10.2147/OTT.S292551

35. Kocheise, L., et al., *EpCAM-positive circulating tumor cells and serum AFP levels predict outcome after curative resection of hepatocellular carcinoma.* Sci Rep, 2023. **13**(1): p. 20827. doi:10.1038/s41598-023-47580-0

36. Bai, S., et al., *Clinical diagnostic biomarker "circulating tumor cells" in breast cancer - a meta-analysis.* Front Oncol, 2023. **13**: p. 1137519. doi:10.3389/fonc.2023.1137519

37. Zhou, M., et al., *Correlation between the expression of CD24 on circulating tumor cells and prognosis in breast cancer.* Am J Transl Res, 2023. **15**(3): p. 1941-1952.

38. Wang, X.Q., et al., *Effect of CTCs and INHBA level on the effect and prognosis of different treatment methods for patients with early breast cancer.* Eur Rev Med Pharmacol Sci, 2020. **24**(24): p. 12735-12740. doi:10.26355/eurrev_202012_24172

39. Du, K., et al., *Circulating Tumor Cells Counting Act as a Potential Prognostic Factor in Cervical Cancer.* Technol Cancer Res Treat, 2020. **19**: p. 1533033820957005. doi:10.1177/1533033820957005

40. Tewari, K.S., et al., *Circulating Tumor Cells In Advanced Cervical Cancer: NRG Oncology-Gynecologic Oncology Group Study 240 (NCT 00803062).* Mol Cancer Ther, 2020. **19**(11): p. 2363-2370. doi:10.1158/1535-7163.MCT-20-0276

41. Chen, Z.Q., et al., *[Clinical Value of Peripheral Blood Circulating Tumor Cells Detection in Early Cervical Infiltrating Carcinoma Screening].* Sichuan Da Xue Xue Bao Yi Xue Ban, 2019. **50**(3): p. 415-419.

42. Konigsberg, R., et al., *Detection of EpCAM positive and negative circulating tumor cells in metastatic breast cancer patients.* Acta Oncol, 2011. **50**(5): p. 700-10. doi:10.3109/0284186X.2010.549151

43. Cristofanilli, M., et al., *Circulating tumor cells, disease progression, and survival in metastatic breast cancer.* N Engl J Med, 2004. **351**(8): p. 781-91. doi:10.1056/NEJMoa040766

44. Cohen, S.J., et al., *Isolation and characterization of circulating tumor cells in patients with metastatic colorectal cancer.* Clin Colorectal Cancer, 2006. **6**(2): p. 125-32. doi:10.3816/CCC.2006.n.029

45. Okegawa, T., K. Nutahara, and E. Higashihara, *Prognostic significance of circulating tumor cells in patients with hormone refractory prostate cancer.* J Urol, 2009. **181**(3): p. 1091-7. doi:10.1016/j.juro.2008.11.015

46. Hyun, K.A., et al., *Epithelial-to-mesenchymal transition leads to loss of EpCAM and different physical properties in circulating tumor cells from metastatic breast cancer.* Oncotarget, 2016. **7**(17): p. 24677-87. doi:10.18632/oncotarget.8250

47. Tai, K.Y., et al., *DNA methylation and histone modification regulate silencing of epithelial cell adhesion molecule for tumor invasion and progression.* Oncogene, 2007. **26**(27): p. 3989-97. doi:10.1038/sj.onc.1210176

48. Franken, A., et al., *Comparative analysis of EpCAM high-expressing and low-expressing circulating tumour cells with regard to their clonal relationship and clinical value.* Br J Cancer, 2023. **128**(9): p. 1742-1752. doi:10.1038/s41416-023-02179-0

49. Mikolajczyk, S.D., et al., *Detection of EpCAM-Negative and Cytokeratin-Negative Circulating Tumor Cells in Peripheral Blood.* J Oncol, 2011. **2011**: p. 252361. doi:10.1155/2011/252361

50. Nicolazzo, C., et al., *EpCAM(low) Circulating Tumor Cells: Gold in the Waste.* Dis Markers, 2019. **2019**: p. 1718920. doi:10.1155/2019/1718920

51. Marquette, C.H., et al., *Circulating tumour cells as a potential biomarker for lung cancer screening: a prospective cohort study.* Lancet Respir Med, 2020. **8**(7): p. 709-716. doi:10.1016/S2213-2600(20)30081-3

52. Park, S.M., et al., *Molecular profiling of single circulating tumor cells from lung cancer patients.* Proc Natl Acad Sci U S A, 2016. **113**(52): p. E8379-E8386. doi:10.1073/pnas.1608461113

53. Yu, M., et al., *Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition.* Science, 2013. **339**(6119): p. 580-4. doi:10.1126/science.1228522

54. Negishi, R., et al., *Transcriptomic profiling of single circulating tumor cells provides insight into human metastatic gastric cancer.* Commun Biol, 2022. **5**(1): p. 20. doi:10.1038/s42003-021-02937-x

55. Papadaki, M.A. and S. Agelaki, *Single-Cell RNA Sequencing Uncovers Heterogeneous Circulating Tumor Cell Subsets in Breast Cancer.* Cancers (Basel), 2022. **14**(5). doi:10.3390/cancers14051314

56. Kojima, M., et al., *Single-cell DNA and RNA sequencing of circulating tumor cells.* Sci Rep, 2021. **11**(1): p. 22864. doi:10.1038/s41598-021-02165-7

57. Xu, J., et al., *Using single-cell sequencing technology to detect circulating tumor cells in solid tumors.* Mol Cancer, 2021. **20**(1): p. 104. doi:10.1186/s12943-021-01392-w

58. Dong, Y., Z. Wang, and Q. Shi, *Liquid Biopsy Based Single-Cell Transcriptome Profiling Characterizes Heterogeneity of Disseminated Tumor Cells from Lung Adenocarcinoma.* Proteomics, 2020. **20**(13): p. e1900224. doi:10.1002/pmic.201900224

59. Magbanua, M.J.M., et al., *Expanded Genomic Profiling of Circulating Tumor Cells in Metastatic Breast Cancer Patients to Assess Biomarker Status and Biology Over Time (CALGB 40502 and CALGB 40503, Alliance).* Clin Cancer Res, 2018. **24**(6): p. 1486-1499. doi:10.1158/1078-0432.CCR-17-2312

60. Armstrong, A.J., et al., *Circulating tumor cells from patients with advanced prostate and breast cancer display both epithelial and mesenchymal markers.* Mol Cancer Res, 2011. **9**(8): p. 997-1007. doi:10.1158/1541-7786.MCR-10-0490

61. Miyamoto, D.T., et al., *RNA-Seq of single prostate CTCs implicates noncanonical Wnt signaling in antiandrogen resistance.* Science, 2015. **349**(6254): p. 1351-6. doi:10.1126/science.aab0917

62. Barbazan, J., et al., *Molecular characterization of circulating tumor cells in human metastatic colorectal cancer.* PLoS One, 2012. **7**(7): p. e40476. doi:10.1371/journal.pone.0040476

63. Cai, J., et al., *Single-cell exome sequencing reveals polyclonal seeding and TRPS1 mutations in colon cancer metastasis.* Signal Transduct Target Ther, 2024. **9**(1): p. 247. doi:10.1038/s41392-024-01960-8

64. Elizabeth D. Lightbody, D.T.F., Romanos Sklavenitis-Pistofidis, Junko Tsuji, Michael P. Agius, Ankit K. Dutta, Ting Wu, Hadley Barr, Mahshid Rahmat, Yoshinobu Konishi, Michelle P. Aranha, Michael Vinyard, Jean-Baptiste Alberge, Nang Kham Su, Cody J. Boehner, Laura Hevenor, Habib El-Khoury, Katherine Towle, Christian J. Cea-Curry, Erica Horowitz, Jacqueline Perry, Anna Cowan, Anna V. Justis, Daniel Auclair, Catherine R. Marinac, Gad Getz, Irene Ghobrial, *Single-Cell RNA Sequencing of Rare Circulating Tumor Cells in Precursor Myeloma Patients Reveals Molecular Underpinnings of Tumor Cell Circulation. .* Blood, 2022. **140 (Supplement 1)**: p. 602–603. doi:https://doi.org/10.1182/blood-2022-162851

65. Guo, C., et al., *Spatiotemporally deciphering the mysterious mechanism of persistent HPV-induced malignant transition and immune remodelling from HPV-infected normal cervix, precancer to cervical cancer: Integrating single-cell RNA-sequencing and spatial transcriptome.* Clin Transl Med, 2023. **13**(3): p. e1219. doi:10.1002/ctm2.1219

66. Sheng, B., et al., *Single-cell RNA sequencing of cervical exfoliated cells reveals potential biomarkers and cellular pathogenesis in cervical carcinogenesis.* Cell Death Dis, 2024. **15**(2): p. 130. doi:10.1038/s41419-024-06522-y

67. Cao, G., et al., *Single-cell dissection of cervical cancer reveals key subsets of the tumor immune microenvironment.* EMBO J, 2023. **42**(16): p. e110757. doi:10.15252/embj.2022110757

68. Liu, C., et al., *Single-cell RNA-sequencing reveals radiochemotherapy-induced innate immune activation and MHC-II upregulation in cervical cancer.* Signal Transduct Target Ther, 2023. **8**(1): p. 44. doi:10.1038/s41392-022-01264-9

69. Lin, D., et al., *Circulating tumor cells: biology and clinical significance.* Signal Transduct Target Ther, 2021. **6**(1): p. 404. doi:10.1038/s41392-021-00817-8

Section 2- Events

OINDRILA GHOSAL,

The premise of the tale of data-transmission relay in a simplistic setting can be the association of the nucleotide monomers by phosphodiester bond to form a stretch of deoxyribonucleic acid. In the eukaryotic nucleus, two complementary strands of nucleic acids, then, intertwine and wrap themselves around the histone octamers. Apart from the composition of the genes and the regulatory regions, depending on the epigenetic signatures of the nucleosomes, the assembly of the DNA and the histones, the decision to transcribe the content to another nucleic acid, ribonucleic acid sequence is taken. If positive, the latter translocates to the cytosol where it is acted upon by the translation machinery. Thus, the synthesised string of amino acids, protein, is a testament of the passage of information of struggle and survival.

The macromolecules, however, do not exist in isolation. In fact, the reciprocal cross-talks among the cellular, extracellular and environmental components ensure the viability of the higher order systems, including organisms. Despite the multitude of the communications in the bustling metropolis of the living systems, to maintain the fine balance between apoptosis and survival, the homeostatic mechanisms are employed. Additionally, to complement the feedback checkpoints, these biological entities are never bereft of the purview of the five-pronged aspects of Darwinism – evolution, common descent, multiplication of species, gradualism and natural selection. [6]

In essence, the complexity inherent to the biology of life, is the driving force behind the diversity and distribution of the biosphere constituents. While the complicated interactions are vital to the normal physiology, dysregulations of the same result in oncogenic pathologies. Starting from the anomalies in the genetic composition, formation of deregulated transcripts and proteins to the rewiring of the existing signal transduction networks (mainly to avert the therapeutic effects of the administered drugs), cancer is rarely a condition stemming from a single causative event [3]. Obviously, there are ample numbers of distinguishing factors between untransformed and transformed cells and yet the two share a common ground – conservation of Darwinian evolution [7]. Sub-clonal diversity and expansion highlight the same phenomenon [7]. On the contrary, some attributes in cancer evolution such as driving saltatory catastrophes (chromosomal chromoplexy, whole genome doubling and chromothripsis), genetic drifts, age-dependent changes and unequal distribution of centromere lacking extrachromosomal DNA (harbouring oncogenes) at each cell division are in striking contrast to Darwin's postulates [7].

What catenates physiology and pathology together is data. There is no dearth of data, or more precisely, processed information across the globe [10]. The genome with its charted and uncharted

territories can intuitively serve as the starting point. The analysis of each data point ultimately sepulchres the construction of biologically relevant inferences [2].

Experimental biology has been making huge strides for several decades now. Consequently, data-driven science at its pace, is constantly improvising to catalogue the inputs and attempt interpretation of the puzzles of nature. Multidisciplinary fields like systems biology and bioinformatics that amalgamate biology, chemistry, computational technology and mathematics, [11] are innovations toward comprehending the ever-evolving life from the deluge of data by building models and mathematical predictions along the lines of the interacting pathways and molecules [2][8].

For instance, any cell is an information databank. Before the advent of the Next Generation Sequencing (NGS) in the early 2000s, concurrent with the completion of the Human Genome Project, such a statement would be steeped in fiction [4]. The technology, relying heavily on the molecular biology of DNA polymerisation and computational biology for the sequencing and identification of variants, respectively, is currently a routine word in the clinical scenario [4]. The decoding of the nucleic acids, and their saga of mutations – the playground for the detection, characterisation and designing of therapeutic strategies – has impressively traversed the "bench to bedside" roadmap [4].

NGS has manoeuvred miles to bridge basic and translational research, nevertheless, several reports in the past few years have been paving the road to the ulterior motive of cancer biology research, personalised medicine [1]. Previously, targeted therapies with small molecule inhibitors and RNA interference have backfired due to rewiring of the targeted pathways [2]. Failures as these underscore the importance to shift from reductionist approach to eagle-eye map of the cellular circuits [3]. In a recent attempt to identify the key biomarkers in breast cancer, J Zheng *et al* have engineered a pathway network using GeneRank algorithm [1]. X Wu *et al's* investigation of the role of *HMGB1* in the initiation and progression of lung cancer [1] and Binary Differential Evolution Algorithm (BDEP) by Y. Liang *et al* [1] have shed light on the deducible targets. Mani *et al* [3] has unravelled the interactome in three kinds of Non-Hodgkin's lymphoma to pinpoint the pathways dysregulated in tumour related B-cells. Though only a few are highlighted, the literature otherwise is resplendent with cases that study the consequences of the oncogenic mutations, drug interactions, cellular phenotypes, pathogenic initiation and so on [3]. Apart from these experiments, integrated databases, namely The Cancer Genome Atlas (TCGA), Integrated Cancer Biology Program (ICBP), Human Protein Reference Database and Library of Integrated Cellular Signatures are also instrumental in research.

Another stalwart achievement in nucleic acid research has been NGS backed single cell transcriptomics (Galaxy [18] and Cytoscape [19]) which along with charting the expression profile of the genes has facilitated the detection of circulating tumour DNAs in the non-invasive liquid biopsy [12]. The complementary advantage is the profiling of the inherent heterogeneity in cancer

and planning a tailor-made treatment regimen [17]. For non-coding RNA analysis, miRbase [20] and LncRNAdb [21] are often explored.

Genomic research is incomplete without tracing the epigenetic markers. Tools like Bismark [13], Methykit [13] and ChIP-seq [14] capture a snapshot of these vital pieces of information.

On the other hand, the journey of proteins from sequence to structure prediction for 60 years had been stagnant [5]. Unlike DNA, proteins lack regularity and internal pattern [5]. The arbitrarily arranged helices in the three-dimensional structure of myoglobin cemented the notion [5]. Finally, the winner of CASP14 meeting, Google DeepMind's AlphaFold2, trained heavily on about 18000 protein sequences and structures, was successful at modelling structures with an impressive RMSD of 0.96 Å [5]. Though the marvel of machine learning is yet to report a direct translation in cancer research, together with the docking and simulation tools (HADDOCK [22] and Schrodinger [23]) it can add precision to structure-based drug designing. On a different note, efforts by Yifat Geffen *et al* have made analysis of post-translational modifications a reality [15].

Along with structural and functional modifications, cancers are also a study of mutations [3]. The computational branch of protein engineering, Ancestral Sequence Reconstruction (ASR) [9] poses optimism in targeting cancer. In a previous instance, it had elevated the pharmaceutical attributes of coagulation factor VIII [9].

The data from all the possible sources – genomic, epigenomic, transcriptomic, post-transcriptomic, translational and post translational – are the seeds of the compendium of holistic information. Not only is data collection important but also the processing and interpretation. The symbiosis between biology and technology is relentlessly scripting the lexicon of enriching the knowledge pool on both the sides [8]. To rephrase, technology educates itself on the systems of the living world and codes its learnings in bits and bytes. Feats as these lay the foundations for systems clinical medicine [16].

Yet, in the era where data is the currency, cancer thrives as an unbeatable malady. The problem is complicated because of intratumor heterogeneity, resistance and evolution [7]. Many leads in bench-side research succumb before becoming a clinical reality. Deciphering the pathways, identifying the anomalies, interpreting the exchanges and singling out the biomarkers have cleared much air about the enormity of the crisis and enhanced the diagnosis and druggability. While systems biology and bioinformatics have curated and analysed innumerable patient-derived and molecular data to sketch patterns in cancerous and normal conditions, a personalised silver bullet is still in the making.

Perhaps, coming years shall witness the co-evolution of experimental sciences and technology. Fresher ideas and approaches might join the list. Programs like Cancer Systems Biology Consortium [8] shall advance our understanding of the fundamental and translational aspects of the disease to chisel a nemesis. NGS might as well progress toward cost and time effectiveness.

Artificial intelligence might alleviate the lacunae in the therapeutic front. Also, inclusion of cohorts across all habitable geographies and their baggage of information in interactive and mineable platforms seems to be a parallel way to mitigate the gap.

Multivariate interventions from microbiology, parasitology, physics, chemistry, mathematics, statistics, biochemistry, molecular biology, bioinformatics and systems biology are surely going to supplement precision in clinical decisions. There are many milestones to cross from population studies to cellular studies to predictive models to therapeutic achievements. Until then, smoothening the edges of the puzzle-pieces of the picture of personalised medicine is absolutely essential.

REFERENCES

1. Cai, Y., Huang, T., & Yang, J. (2018). Applications of bioinformatics and systems biology in precision medicine and immunooncology. BioMed Research International, 2018.
2. Ram, P. T., Mendelsohn, J., & Mills, G. B. (2012). Bioinformatics and systems biology. Molecular oncology, 6(2), 147-154.
3. Kreeger, P. K., & Lauffenburger, D. A. (2010). Cancer systems biology: a network modeling perspective. Carcinogenesis, 31(1), 2-8.
4. Goodwin, S., McPherson, J. D., & McCombie, W. R. (2016). Coming of age: ten years of next-generation sequencing technologies. Nature reviews genetics, 17(6), 333-351.
5. https://www.arturorobertazzi.it/2023/09/60-years-in-the-making-alphafolds-historical-breakthrough-in-protein-structure-prediction/#:~:text=AlphaFold%2C%20this%20marvel%20of%20machine,grail%20had%20finally%20been%20unearthed. (Accessed on 01.12.24)
6. Peretó, J., & Català, J. (2012). Darwinism and the origin of life. Evolution: Education and Outreach, 5, 337-341.

7. Vendramin, R., Litchfield, K., & Swanton, C. (2021). Cancer evolution: Darwin and beyond. The EMBO journal, 40(18), e108389.
8. https://www.cancer.gov/about-nci/organization/dcb/research-programs/csbc (Accessed on 02.12.24)
9. Zakas, P. M., Brown, H. C., Knight, K., Meeks, S. L., Spencer, H. T., Gaucher, E. A., & Doering, C. B. (2017). Enhancing the pharmaceutical properties of protein drugs by ancestral sequence reconstruction. Nature biotechnology, 35(1), 35-37.
10. Mitra, S., Das, S., & Chakrabarti, J. (2013). Systems biology of cancer biomarker detection. Cancer Biomarkers, 13(4), 201-213.
11. Chowdhary, M., Rani, A., Parkash, J., Shahnaz, M., & Dev, D. (2016). Bioinformatics: an overview for cancer research. Journal of Drug Delivery and Therapeutics, 6(4), 69-72.
12. https://sapac.illumina.com/areas-of-interest/cancer/clinical-cancer-research/somatic-mutations/ctdna-sequencing.html#:~:text=Circulating%20Tumor%20DNA%20Analysis%20with%20NGS&text=Next%2Dgeneration%20sequencing%20(NGS),tumor%2Dderived%20alterations%20in%20ctDNA. (Accessed on 30.11.24)
13. Yassi, M., Chatterjee, A., & Parry, M. (2023). Application of deep learning in cancer epigenetics through DNA methylation analysis. Briefings in bioinformatics, 24(6), bbad411.
14. Bock, C., & Lengauer, T. (2008). Computational epigenetics. Bioinformatics, 24(1), 1-10.
15. Geffen, Y., Anand, S., Akiyama, Y., Yaron, T. M., Song, Y., Johnson, J. L., ... & Zhou, D. C. (2023). Pan-cancer analysis of post-translational modifications reveals shared patterns of protein regulation. Cell, 186(18), 3945-3967.

16. Wu, D., Rice, C. M., & Wang, X. (2012). Cancer bioinformatics: A new approach to systems clinical medicine. BMC bioinformatics, 13, 1-4.
17. Kaur, P. (2022). Next-Generation Sequencing in Cancer Research. In Biomedical Translational Research: Technologies for Improving Healthcare (pp. 155-166). Singapore: Springer Nature Singapore.
18. Giardine, B., Riemer, C., Hardison, R. C., Burhans, R., Elnitski, L., Shah, P., ... & Nekrutenko, A. (2005). Galaxy: a platform for interactive large-scale genome analysis. Genome research, 15(10), 1451-1455.
19. https://cytoscape.org/what_is_cytoscape.html (Accessed on 01.12.24)
20. Griffiths-Jones, S. (2006). miRBase: the microRNA sequence database. MicroRNA Protocols, 129-138.
21. Amaral, P. P., Clark, M. B., Gascoigne, D. K., Dinger, M. E., & Mattick, J. S. (2011). lncRNAdb: a reference database for long noncoding RNAs. Nucleic acids research, 39(suppl_1), D146-D151.
22. Dominguez, C., Boelens, R., & Bonvin, A. M. (2003). HADDOCK: a protein− protein docking approach based on biochemical or biophysical information. Journal of the American Chemical Society, 125(7), 1731-1737.

https://www.computabio.com/applications-of-schrodinger-software.html (Accessed on 02.12.24)

Section 2- Events

Essay Topic: Systems biology and bioinformatics: Advances and applications in cancer research and management

Preeti

"Computers are incredibly fast, accurate, and stupid. Humans are incredibly slow, inaccurate, and brilliant. Together they are powerful beyond imagination" – Albert Einstein

Across the vast expanse of time, from its inception to its evolution, life has continually devised strategies to adapt and endure. This intricate symphony of existence sparks profound questions: Is there a grand conductor orchestrating its harmony, or does life function as a self-organizing system, emerging from the spontaneous interactions of its fundamental parts? Through interconnected molecular networks, adaptive homeostasis responses, feedback mechanisms, biological systems respond to environmental changes and overcome obstacles to ensure survival of fittest which is the core theme illustrated in systems biology. Systems biology provides a holistic view which states that diseases are not merely isolated to genetic alterations but dynamically influenced by interactions between various genes, proteins, interconnected biological networks and to their environment. The traditional research approaches focus on identifying the role of individual genes and proteins functions in diseases, a detailed high-throughput integrated and iterative 'systems biology' approaches are vital for the advancement and execution of effective treatment solutions. A data-driven stratagem which requires large amounts of high-quality data, unbiased analysis, crossing multiple scales to develop robust predictive models which are refined by testing through continuous experimental validations. Such vigorous advents assist in understanding the emergence of drug resistances, identifying potential predictive biomarkers, increasing therapy efficacy to enhance the life quality and secure a long run cure against fatal diseases [1].

Now, let's explore a different dimension and step into the life of cancerous cells which carries potential to exploit the dynamic adaptability of cellular system to hijack and reprogram the molecular networks for destructive progression. Cancer being a deadly disease globally with an estimated 20 million new cases and 9.7 million deaths in 2022. World Health Organization (WHO) asserts 1 in 5 individuals succumb to cancer at some point in their lives which highlights the widespread impact and an urgent need of advancements in diagnosis, prevention and treatment strategies [2]. Cancer, driven by genetic disruptions where mutations, chromosomal rearrangements, epigenetic reprogramming, inactivated tumor suppressors and hyperactive oncogenes leads to cascade of abnormalities. Although the cellular DNA repair system tries to correct these errors and later immune surveillance eliminates the precancerous cells before they interfere with normal pathways. However, a subset of genetic alterations called 'driver' aberrations which represent the potential biomarkers, can bypass these safeguards conferring normal cells a transformation into cancerous situations. There are 'passenger' mutations as well which do not

affect cancer cells but can occur in cancer genes thus are not effectual targets. Although in an extreme cellular heterogeneity and impure samples it is difficult to identify the low frequency mutations which can be directly correlated with the tumor progression and treatment resistances [1]. Till now, subclonal events investigations in cancer relied on non-standard experimental approaches where shared clonal events are analysed across multiple metastases sets from different patients employing ultra deep sequencing. Other approaches are sequencing few single cells using whole genome amplification (WGA), and next generation sequencing [3,4]. On the other hand, major cancer genomic initiatives as The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC) routinely sequence thousands of tumors for whole genomes where an accurate detection of clonal and subclonal mutations in these sets require highly sensitive and specific detection techniques. Though, experimental validation enhances specificity, it remains an expensive and labor-intensive process. Advanced system-based computational tools, such as MuTect address these challenges by applying a Bayesian classifier that requires only a few reads. This approach employs finely tuned filters to detect low-frequency subclonal drivers with high specificity where evaluation relies on sequencing depth, base quality and allelic fraction. Studies of subclonal mutations facilitated by such methods contribute to a deeper understanding of tumor evolution and help uncover the mechanisms underlying resistance to therapies [5].

High-throughput, data-driven analyses of RNA expression, protein levels, and metabolite profiles enable the examination of vast datasets generated across diverse platforms. On one hand, research networks such as Stand Up to Cancer (SU2C), TCGA, and ICGC focus on collecting tumor samples, performing molecular profiling, and linking these findings to patient outcomes. Such approaches are versatile, can be applied from single cells and tissues to primary tumors and metastases samples or combination of all. However, gathering a high-quality clinical data spanning pathology, treatments, and outcomes is still a major obstacle here. Ahead, the CCLE (Cancer Cell Line Encyclopedia), LINCS (Library of Integrated Network-based Cellular Signatures), and ICBP (International Cancer Bioinformatics Partnership) platforms are dedicated towards obtaining an inclusive molecular categorisation of how cancerous lines respond to various perturbations, such as drug treatments, genetic modifications, and environmental changes. The multi-omics data at genomic, transcriptomic, proteomic and metabolomic levels from these platforms are being used to build algorithms which can be used to reveal intricate relationships between various cellular signaling pathways and gene expression changes triggered by different compounds. The main aim is to identify key molecular drivers which can influence cancer cell behaviour, including their sensitivity or resistance to drug regimens. Other computational resources and online databases are GeneCards, UniProt and STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) which offer detailed data on gene sequences, proteins sequences, protein-protein interactions and functions [1].

To understand the dynamics of cellular pathways during cancer, Metabolomics plays a unique role by capturing the end products of cellular processes which are metabolites. In case of cancerous situations where metabolic reprogramming is a hallmark, metabolomics serves as a powerful tool to know tumor progression intensely. Using altered metabolic pathways as increased glycolysis (Warburg effect) or enhanced lipid metabolism, cancer cells support rapid

growth, adapt to stress and resist apoptosis. A major challenge for System biology for today is integrating metabolomics with other omics platforms. The incorporation of these diverse datasets is a complex task because the data types not only vary in terms of their dimensionality as metabolite levels vs. gene expression but also in terms of their time scales and resolution. Genomic data is inherently static, while metabolomic data offers dynamic, real-time variations in cellular metabolism. Moreover, merging large-scale datasets from several omics layers involves overcoming concerns as well such as data noise, missing values and heterogeneity. Currently, HMDB (Human Metabolome Database) and METLIN are the prominent databases which provides detailed information on human metabolites, their functions and associated diseases. KEGG (Kyoto Encyclopedia of Genes and Genomes), Cytoscape, Metabolomics Workbench and MetaboAnalyst are the online computational tools for visualizing and analyzing large, multi-dimensional datasets generated in cancer research. These platforms provide a crucial link between metabolites and their respective genes and proteins, intricate pathways in which they are participating and predicts how variations and one molecular layer can impact others. Collectively, these platforms and tools serve as pillars in current cancer research to develop robust, comprehensive models for personalized medicine, interpret metabolic profiles in tumors, in identification of new biomarkers and novel therapeutic discoveries [6].

Despite significant advancements, systems biology and bioinformatics face key challenges in cancer research. Standardizing, integrating, and interpreting vast multi-omics datasets remain difficult due to the heterogeneity of cancer, with variations among patients, tumor types, and even within individual tumors complicating analysis. Moreover, these complex datasets require substantial computational resources and advanced algorithms, which may not be accessible to all research teams. Translating computational findings into clinical practice remains another challenge. Predictive models and discoveries must undergo rigorous experimental validation and clinical trials to ensure accuracy, reproducibility, and efficacy. Effective collaboration between computational scientists and clinicians is critical but often hindered by differences in expertise and priorities. The future of cancer research depends on the seamless integration of multi-omics data - encompassing genomics, proteomics, transcriptomics, and metabolomics into unified frameworks. Artificial intelligence and machine learning will play a pivotal role in analyzing these datasets, identifying therapeutic targets, and predicting patient-specific responses, while dynamic models will provide insights into tumor progression and resistance mechanisms.

In conclusion, the advancement in the area of bioinformatics and systems biology have revolutionized the research for cancer and management. Researchers are able to untie the complexities of cancer at unprecedented dimensions, unveiling novel biomarkers, therapeutic targets, and unique personalized cure strategies. The evolving technology will undoubtedly drive future discoveries, eventually improving patient outcomes and getting a long-run cancer cure, in this data-driven field. However, with every great expectation from anything comes inevitable stories of failures and setbacks. In the path of scientific discoveries and evolving cancer, scientists must be prepared to combat such challenges. The advancement in tools of bioinformatics and computational biology may not always lead to instant victory, but they can deliver the foundation for understanding, adapting, and refining. The real failure lies in deserting the search. A search for cure against the devastating menace of cancer to human life. So, we must never give up and

continue our pursuit to find solutions, as ultimately, one day with the combination of technology, persistence, and human determination will find a way to defeat the monster.

"The cure for cancer is in the data."
– Leroy Hood

References:

1. Werner HM. et al. (2014) Cancer Systems Biology: a peek into the future of patient care? *Nat Rev Clin Oncol.* 11(3):167.
2. World Health Organization- who.int
3. Campbell PJ, et al. (2010) The patterns and dynamics of genomic instability in metastatic pancreatic cancer. *Nature.* 467(7319):1109.
4. Navin N, et al. (2011) Tumour evolution inferred by single-cell sequencing. *Nature.* 472(7341):90.
5. Cibulskis K, et al. (2013) Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. *Nat Biotechnol.* 31:213.
6. Palermo A, et al. (2023) Metabolomics- and systems-biology-guided discovery of metabolite lead compounds and druggable targets. *Drug Discov Today.* 28(2):103460.

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1. Introduction

Cancer remains a significant global health concern, accounting for a substantial share of morbidity and mortality worldwide. In 2024, International Agency for Research on Cancer (IARC) estimated, approximately 20 million new cancer cases were diagnosed, and 9.7 million deaths were attributed to cancer globally. Cancer cases are projected to increase to 35 million by 2050 [1]. This rising burden is driven by factors such as population aging, urbanization, and lifestyle changes, including increased exposure to carcinogens like tobacco, processed foods, and pollution [2,3]. The heterogeneity of cancer—marked by its diverse genetic, molecular, and cellular underpinnings—complicates both its study and treatment. Cancer progression involves multiscale processes, from genetic mutations to systemic effects, demanding a nuanced understanding and innovative approaches for its effective management [4].

Systems biology offers a revolutionary perspective by focusing on the interactions and dynamics within biological systems rather than isolated components. By integrating molecular pathways, gene regulatory networks, and cellular dynamics, it provides insights into emergent properties of cancer systems [5]. Meanwhile, bioinformatics plays a pivotal role in managing and interpreting the vast datasets generated by high-throughput technologies such as genomics, transcriptomics, and proteomics [6]. Together, these disciplines enable a comprehensive understanding of cancer biology.

The global cancer burden in 2024 underscores the pressing need for such interdisciplinary approaches, aligning scientific innovation with healthcare accessibility to address this growing challenge [7]. This essay aims to explore how systems biology and bioinformatics synergistically advance cancer research and management. By highlighting recent innovations and applications, it delves into their transformative impact on early diagnosis, personalized treatment, and improving patient outcomes.

2. Advances in Systems Biology for Cancer Research

2.1 Multi-Omics Integration

Multi-omics integration combines genomic, proteomic, and metabolomic datasets to provide a comprehensive understanding of cancer biology. By identifying novel biomarkers, such integration enhances early detection and targeted therapies. For instance, genomic sequencing can reveal mutations in cancer-driving genes, while proteomic analysis identifies protein-level changes linked to those mutations. Metabolomics offers insights into tumor metabolism, crucial for understanding the tumor microenvironment [8].

Epigenomic profiling further enriches this approach by mapping modifications such as DNA methylation and histone acetylation, which influence gene expression without altering the DNA sequence. Studies highlight the role of epigenetic changes in tumor evolution, including resistance to therapy and metastatic potential [9]. For example, methylation patterns in genes like BRCA1 provide prognostic information and influence treatment decisions in breast and ovarian cancers [10].

2.2 Systems-Level Modeling of Tumors

Systems biology uses computational models to simulate tumor progression and metastasis, enabling predictions about disease dynamics under different conditions. These models integrate data from multiple sources, such as gene expression and cellular signaling pathways, to replicate tumor behavior [11]. For example, agent-based modeling helps simulate interactions between tumor cells and their microenvironment, informing therapeutic strategies.

Moreover, in silico simulations allow researchers to test various treatment modalities before clinical trials. A notable example includes simulations of immune checkpoint inhibitors in melanoma, predicting patient-specific responses [12].

2.3 Network Biology in Cancer

Network biology examines molecular interaction networks to identify critical nodes, such as driver mutations and dysregulated pathways, that contribute to cancer progression. For instance, the analysis of protein-protein interaction networks has identified actionable targets in pathways like PI3K-AKT and RAS-MAPK [13].

These approaches are also pivotal in understanding drug resistance. Systems-level studies show how mutations in downstream effectors of the EGFR pathway lead to resistance in lung cancer, providing insights into combination therapy design [14].

2.4 Role in Drug Development

Systems biology accelerates drug development by identifying druggable targets through pathway analysis. For instance, inhibitors targeting the HER2 receptor in breast cancer emerged from pathway-focused studies [15]. Additionally, systems pharmacology integrates data on drug interactions and toxicity to design combination therapies. An example is the optimization of immune checkpoint inhibitors with chemotherapy for enhanced efficacy in lung cancer [16].

3. Advances in Bioinformatics for Cancer Research

3.1 Big Data and Artificial Intelligence

The surge in high-throughput technologies has generated massive datasets in cancer genomics. Artificial Intelligence (AI) and Machine Learning (ML) algorithms are pivotal for processing and extracting insights from these datasets. AI-driven models analyze genomic, proteomic, and clinical data to predict cancer susceptibility, progression, and treatment responses. For instance, ML-based tools like DeepGene and CancerNet classify cancer subtypes and predict survival outcomes with remarkable accuracy [17].

Predictive algorithms, such as those used in IBM Watson for Oncology, evaluate a patient's molecular profile to recommend tailored therapies. Similarly, AI aids in radiogenomics, linking imaging data with genetic mutations to refine diagnosis and prognosis [18, 19].

3.2 Next-Generation Sequencing (NGS) and Bioinformatics

NGS technologies enable high-throughput sequencing, generating comprehensive cancer genome profiles. Bioinformatics tools like GATK (Genome Analysis Toolkit) and Mutect2 analyze this data to identify actionable mutations, such as EGFR mutations in lung cancer or BRCA1/2 in breast cancer [20].

NGS-based methods have been instrumental in detecting rare variants and clonal evolution, enhancing our understanding of cancer heterogeneity. For example, the Cancer Genome Atlas (TCGA) leverages NGS data to provide a molecular taxonomy of cancers, guiding targeted therapies [21].

3.3 Biomarker Discovery and Validation

Bioinformatics accelerates the discovery and validation of biomarkers for cancer diagnosis, prognosis, and therapy selection. Computational tools analyze high-dimensional data to identify biomarkers such as circulating tumor DNA (ctDNA) and exosomal RNA, which are pivotal for liquid biopsies [22]. For instance, ctDNA analysis using platforms like Guardant360 offers non-invasive tumor profiling, enabling real-time monitoring of treatment responses and resistance mechanisms [23].

3.4 Personalized Medicine and Bioinformatics

Bioinformatics platforms integrate patient-specific molecular data to match individuals with personalized therapies. Tools such as cBioPortal and OncoKB provide actionable insights from genomic data to inform treatment decisions. For example, identifying HER2 amplifications allows the use of trastuzumab in HER2-positive breast cancer [24].

Moreover, bioinformatics facilitates the design of clinical trials, such as basket and umbrella trials, targeting specific mutations across diverse cancers. This integration of molecular data into clinical workflows exemplifies the transition toward precision oncology [25].

4. Applications in Cancer Research and Management

4.1 Early Detection and Screening

Computational tools have significantly advanced the ability to create biomarker panels for early cancer diagnosis. By analyzing large-scale genomic, proteomic, and metabolomic data, bioinformatics helps identify specific biomarkers that can detect cancer at its earliest stages [26]. For example, the use of machine learning algorithms on gene expression profiles has led to the development of diagnostic panels capable of identifying breast and ovarian cancer before clinical symptoms appear [27]. Additionally, liquid biopsy technologies, which analyze circulating tumor DNA (ctDNA) and RNA in blood samples, rely heavily on bioinformatics tools to process and interpret large datasets. These technologies have made non-invasive cancer screening a reality, improving early diagnosis and patient prognosis [28].

4.2 Precision Oncology

Precision oncology is a treatment approach that tailors therapies based on the molecular and genetic profile of individual patients. Integrating clinical data with genomic data using bioinformatics tools enables the design of personalized treatment plans that are more effective and less toxic than traditional approaches [29]. Systems biology plays a crucial role in understanding patient-specific tumor vulnerabilities by analyzing the interactions between tumor cells and their microenvironment. This approach can help identify druggable targets unique to the patient's cancer, enabling more precise treatment regimens [30].

4.3 Treatment Monitoring and Optimization

Bioinformatics-driven methods are increasingly being used to monitor real-time treatment efficacy in cancer patients. By analyzing longitudinal data, including genomic and transcriptomic profiles, bioinformatics tools can track the tumor's response to therapy, identifying potential resistance mechanisms early [31]. In combination with computational models, these methods enable the development of adaptive therapies, where the treatment plan is adjusted based on the ongoing analysis of tumor evolution and patient response [32].

4.4 Advancements in Immunotherapy

Immunotherapy has revolutionized cancer treatment, and computational prediction of neoantigens has emerged as a key tool for designing cancer vaccines. Neoantigens are tumor-specific mutations that can be targeted by the immune system, and bioinformatics tools analyze tumor sequencing data to predict potential neoantigens for personalized vaccine development [33]. Additionally, systems biology is crucial in studying the immune-tumor interactions, helping to understand the mechanisms by which tumors evade immune detection and identifying strategies to enhance the immune response [34].

4.5 Drug Discovery and Repurposing

Network pharmacology is a promising approach in drug discovery that integrates bioinformatics tools to analyze drug-target interactions within the context of disease networks. By studying how drugs affect entire biological networks, researchers can identify novel drug candidates for cancer treatment [35]. Furthermore, computational approaches are being used to repurpose existing drugs for cancer treatment by predicting the potential efficacy of non-cancer

drugs on cancer pathways. This method has accelerated the identification of alternative therapies that can be quickly brought to clinical trials [36].

4.6 Public Health and Cancer Epidemiology

Bioinformatics provides invaluable insights into population-level cancer risk factors, helping to identify genetic, environmental, and lifestyle factors that contribute to cancer incidence [37]. By analyzing large epidemiological datasets, bioinformatics tools generate predictive models that can identify high-risk populations and inform screening and prevention strategies. These models allow for the targeting of resources toward individuals most at risk, optimizing public health initiatives and improving early intervention efforts [38].

5. Challenges in Integrating Systems Biology and Bioinformatics in Cancer Research

5.1 Data-Related Challenges

The integration of systems biology and bioinformatics in cancer research faces significant data-related challenges due to the volume, variety, and complexity of cancer-related data. High-throughput technologies generate massive datasets, including genomic, transcriptomic, and proteomic information, which must be integrated and analyzed for meaningful insights [39]. However, these datasets often suffer from inconsistencies, which complicates interpretation and the development of reliable models. Moreover, data standardization and interoperability issues persist, as different research groups and institutions use varied formats, tools, and standards, hindering the seamless exchange of information [40].

5.2 Computational Challenges

Current computational models often struggle to capture the full biological complexity of cancer. Cancer is a dynamic, multifactorial disease, and traditional computational models are often

too simplistic to accurately simulate the intricate network of molecular, cellular, and environmental interactions that drive tumorigenesis [5]. Additionally, there is a growing need for scalable algorithms capable of processing vast datasets in real-time, which would enable continuous monitoring of treatment efficacy and the adaptation of personalized therapy plans [29].

5.3 Ethical and Privacy Concerns

The integration of patient data for cancer research raises significant ethical and privacy concerns. Handling sensitive genomic and clinical data requires careful adherence to privacy regulations such as the General Data Protection Regulation (GDPR) in Europe and the Health Insurance Portability and Accountability Act (HIPAA) in the U.S. [41]. Balancing the need for data sharing to advance research with the protection of patient privacy is a critical challenge in this field.

5.4 Resource Constraints

In resource-limited settings, access to high-performance computing infrastructure is often a barrier to the implementation of advanced systems biology and bioinformatics tools. High-capacity computational resources are required to process and analyze the large datasets generated in cancer research, which may not be available in low-resource environments [42]. Additionally, the training of interdisciplinary researchers who possess both biological and computational expertise is crucial to bridging the gap between bioinformatics and systems biology. Developing educational programs that equip researchers with these skills remains a challenge.

6. Future Directions and Emerging Trends

6.1 Advances in Single-Cell Technologies

Single-cell RNA sequencing (scRNA-seq) has revolutionized our understanding of tumor heterogeneity by enabling the examination of gene expression profiles at the individual cell level. This technology allows researchers to identify rare cell populations, understand intra-tumor diversity, and uncover potential therapeutic targets [43]. Additionally, the integration of scRNA-seq with spatial transcriptomics holds promise for studying the tumor microenvironment in unprecedented detail. This combination enables the mapping of gene expression in the context of tissue architecture, providing insights into how tumor cells interact with their surrounding environment and facilitating the development of more targeted therapies [44].

6.2 AI and Quantum Computing in Cancer Research

Artificial Intelligence (AI) is poised to transform cancer research, particularly in drug discovery and personalized medicine. AI-driven tools can analyze vast datasets to predict drug efficacy, identify biomarkers, and design tailored treatment regimens [45]. Additionally, quantum computing offers potential breakthroughs in solving complex biological problems, such as protein folding and simulating molecular interactions at a scale and speed far beyond current capabilities. This could significantly enhance drug discovery and systems biology modelling [46].

6.3 Multi-Disciplinary Collaborations

The future of cancer research relies heavily on multi-disciplinary collaborations between biologists, clinicians, and data scientists. Such collaborations are essential for integrating systems biology and bioinformatics into routine clinical practice, enabling personalized treatment approaches and improving patient outcomes [47].

6.4 Expansion of Global Cancer Databases

The expansion of global cancer databases and open-access data repositories will accelerate cancer research by providing researchers worldwide with valuable data. However, ensuring equitable access to these resources and tools is crucial for advancing global cancer research and overcoming disparities in cancer care [48].

7. Conclusion

Systems biology and bioinformatics have revolutionized cancer research and management by integrating complex biological data to uncover critical insights. These disciplines enable the identification of biomarkers, pathways, and therapeutic targets, paving the way for innovations in early diagnosis, personalized treatment, and improved patient outcomes. Despite these advancements, challenges such as data heterogeneity, computational limitations, and the need for real-world clinical validation persist. However, continuous innovation in computational tools, artificial intelligence, and big data analytics offers immense potential to address these hurdles effectively.

As cancer remains a global health priority, achieving transformative progress demands sustained investments in research, interdisciplinary collaborations, and equitable access to technological advancements. The commitment of scientists, healthcare professionals, and policymakers is crucial to harnessing the full potential of systems biology and bioinformatics, ultimately reducing the burden of cancer worldwide.

References

1) International Agency for Research on Cancer (IARC). (2024). *Global cancer statistics 2024*. Retrieved from IARC Statistics. International Agency for Research on Cancer

(IARC). (2024). *Global Cancer Observatory: Cancer Statistics*. Retrieved from Global Cancer Observatory.

2) World Health Organization (WHO). (2024). *Cancer fact sheet*. Available at: WHO Cancer Overview.
3) UICC (2024). *The economic and social impacts of cancer globally*. Available at: UICC Reports.
4) Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell, 144*(5), 646–674.
5) Kitano, H., 2002. Systems biology: a brief overview. *Science*, 295(5560), pp.1662-1664.
6) Altman, R.B., 2018. Bioinformatics in support of precision medicine. *Genome Biology*, 19(1), p.228.
7) Union for International Cancer Control (UICC). (2024). *Global Equity in Cancer Control: Closing the Gap*. Retrieved from UICC.
8) Hasin, Y., Seldin, M., & Lusis, A. (2017). Multi-omics approaches to disease. *Genome Biology, 18*(1), 83.
9) Easwaran, H., Tsai, H. C., & Baylin, S. B. (2014). Epigenetic changes in cancer. *Cold Spring Harbor Perspectives in Biology, 6*(5), a019505.
10) Esteller, M. (2007). Epigenetics in cancer. *New England Journal of Medicine, 358*(11), 1148–1159.
11) Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell, 144*(5), 646–674.
12) Wang, E., et al. (2019). Predictive modeling of cancer immune checkpoint blockade. *Cell Reports, 27*(8), 2244–2255.e6.

13) Vidal, M., Cusick, M. E., & Barabási, A. L. (2011). Interactome networks and human disease. *Cell, 144*(6), 986–998.

14) Kobayashi, S., et al. (2005). EGFR mutation and resistance of non–small-cell lung cancer to gefitinib. *New England Journal of Medicine, 352*(8), 786–792.

15) Baselga, J. (2010). Targeting the phosphoinositide-3 (PI3K) pathway in breast cancer. *Oncology, 24*(2), 128–140.

16) Chen, D. S., & Mellman, I. (2017). Elements of cancer immunity and the cancer–immune set point. *Nature, 541*(7637), 321–330.

17) Esteva, A., et al. (2017). Deep learning in cancer genomics and oncology. *Nature Medicine, 23*(8), 999–1004.

18) Hosny, A., Parmar, C., Quackenbush, J., Schwartz, L. H., & Aerts, H. J. (2018). Artificial intelligence in radiology. *Nature Reviews Cancer, 18*(8), 500–510.

19) Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine, 25*(1), 44–56.

20) Van der Auwera, G. A., Carneiro, M. O., & Hartl, C. (2013). From FastQ data to high-confidence variant calls: The Genome Analysis Toolkit best practices pipeline. *Current Protocols in Bioinformatics, 43*(1), 11–10.

21) Weinstein, J. N., et al. (2013). The Cancer Genome Atlas Pan-Cancer analysis project. *Nature Genetics, 45*(10), 1113–1120.

22) Keller, L., & Pantel, K. (2019). Unravelling tumour heterogeneity by single-cell profiling of circulating tumour cells. *Nature Reviews Cancer, 19*(10), 553–567.

23) Wan, J. C. M., et al. (2017). Liquid biopsies come of age: Towards implementation of circulating tumour DNA. *Nature Reviews Cancer*, *17*(4), 223–238.

24) Zehir, A., et al. (2017). Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nature Medicine*, *23*(6), 703–713.

25) Herbst, R. S., et al. (2015). The biology and management of non-small cell lung cancer. *Nature*, *553*(7689), 446–454.

26) Reinhold, W.C., et al., 2015. Bioinformatics Tools for Cancer Biomarker Discovery. *Cancer Research*, 75(18), pp. 3678-3687.

27) Duffy, M.J., et al., 2018. Biomarkers for Early Detection of Cancer: A Bioinformatics Approach. *Clinical Cancer Research*, 24(1), pp. 11-20.

28) Manczak, M., et al., 2020. Liquid Biopsy in Cancer: Bioinformatics Insights and Technologies. *Journal of Clinical Oncology*, 38(2), pp. 123-132.

29) Mack, R.W., et al., 2014. Bioinformatics in Precision Oncology: Integrating Genomic and Clinical Data. *The Lancet Oncology*, 15(4), pp. 425-431.

30) Garofalo, M., et al., 2021. Systems Biology in Precision Oncology: Targeting Tumor Vulnerabilities. *Nature Reviews Clinical Oncology*, 18(1), pp. 12-26.

31) Yu, J., et al., 2017. Bioinformatics for Monitoring Cancer Treatment. *Cancer Research*, 77(15), pp. 4278-4287.

32) Yuan, Y., et al., 2017. Adaptive Therapy and Computational Models in Cancer Treatment. *Nature Cancer*, 3(6), pp. 220-230.

33) Yadav, M., et al., 2014. Neoantigens in Cancer Immunotherapy: A Bioinformatics Approach. *Journal of Immunology*, 193(4), pp. 1492-1500.

34) Moyron, R., et al., 2019. Immunotherapy and Systems Biology: Understanding Immune-Tumor Interactions. *Nature Reviews Immunology*, 19(2), pp. 72-84.

35) Zhang, R., et al., 2019. Network Pharmacology in Cancer Drug Discovery: Computational Approaches and Applications. *Journal of Cancer Research and Clinical Oncology*, 145(4), pp. 927-939.

36) Pushpakom, S., et al., 2019. Drug Repurposing for Cancer: Computational Methods and Bioinformatics Approaches. *Nature Reviews Drug Discovery*, 18(7), pp. 413-423.

37) Barker, P.M., et al., 2020. Global Cancer Risk Factors: Insights from Bioinformatics Analysis. *Cancer Epidemiology*, 61, pp. 30-40.

38) Siegel, R.L., et al., 2020. Cancer Statistics, 2020. *CA: A Cancer Journal for Clinicians*, 70(1), pp. 7-30.

39) Collins, F.S., et al., 2003. The Human Genome Project: Lessons from Large-Scale Biology. *Science*, 300(5617), pp. 286-290.

40) Liu, J., et al., 2020. Data Standardization in Cancer Genomics: Challenges and Solutions. *Bioinformatics*, 36(14), pp. 4310-4316.

41) Malin, B., et al., 2021. Ethical and Privacy Concerns in the Use of Cancer Genomic Data. *The Journal of Law, Medicine & Ethics*, 49(1), pp. 89-100.

42) Berglund, P., et al., 2020. Addressing Resource Constraints in Cancer Research: A Focus on Bioinformatics. *Journal of Cancer Informatics*, 9(3), pp. 56-63.

43) Navin, N.E., 2014. Cancer Genomics: One Cell at a Time. *Nature Methods*, 11(11), pp. 701-702.

44) Vickovic, S., et al., 2019. Multi-Omics Integration: Spatial Transcriptomics and Single-Cell RNA Sequencing in Cancer Research. *Nature Reviews Cancer*, 19(10), pp. 537-550.

45) Esteva, A., et al., 2019. Artificial Intelligence in Oncology: Current Applications and Future Directions. *The Lancet Oncology*, 20(4), pp. 349-362.

46) Arute, F., et al., 2019. Quantum Computing for Biological Applications. *Nature*, 574(7779), pp. 505-510.

47) Ramaswamy, S., et al., 2015. Integrating Systems Biology and Bioinformatics in Cancer Research: A Roadmap to Precision Medicine. *Clinical Cancer Research*, 21(8), pp. 1782-1792.

48) Zhu, Z., et al., 2019. Open-Access Data Repositories in Cancer Research: Towards Global Collaboration. *Lancet Global Health*, 7(1), pp. e40-e49.

Section 3- Programs
World Cancer Research Day Program

WORLD CANCER RESEARCH DAY

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RISE WITH EDUCATION
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WORLD CANCER RESEARCH DAY

23rd SEPTEMBER 2024

Organized by Indian Association Of Cancer Research (IACR) & SIES College, Sion West, Mumbai

The Seminar series on World Cancer Research Day (WCRD) jointly conducted by Indian Association for Cancer Research (IACR) and SIES College, Sion west, Mumbai on the 23rd of September, 2024 is open to teachers and students of local Mumbai colleges. Registration is free but we have limited space so please register if you wish to attend.

Dr Uma Shankar Principal, SIES College, Sion West, Mumbai	Organisers from SIES College,Sion West, Mumbai	Dr Satish Sarfare Vice-Principal, SIES College, Sion West, Mumbai

List of speakers

Dr Sanjeev Waghmare
Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai
Title - " Stem cells and cancer: challenges and prospects"

Dr Subir Biswas
Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai
Title - History, basics, and opportunities of cancer immunotherapy.

Dr Manoj B. Mahimkar
Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai
Title - "Molecular Genetic Alterations in Oral Cancer and their Prognostic Significance."

TIMINGS: 10.00 AM - 1.00 PM

Registration is free but participants should register at the link provided below by 15/09/2024

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What are stem cells?
Maintains tissue homeostasis throughout the life of an animal and repair the injured tissue
Self renewal property – Ability to go through numerous cycle of cell division without differentiation
Pluripotent – Capacity to form all the tissues
Adult stem cells- Tissue specific lineage
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