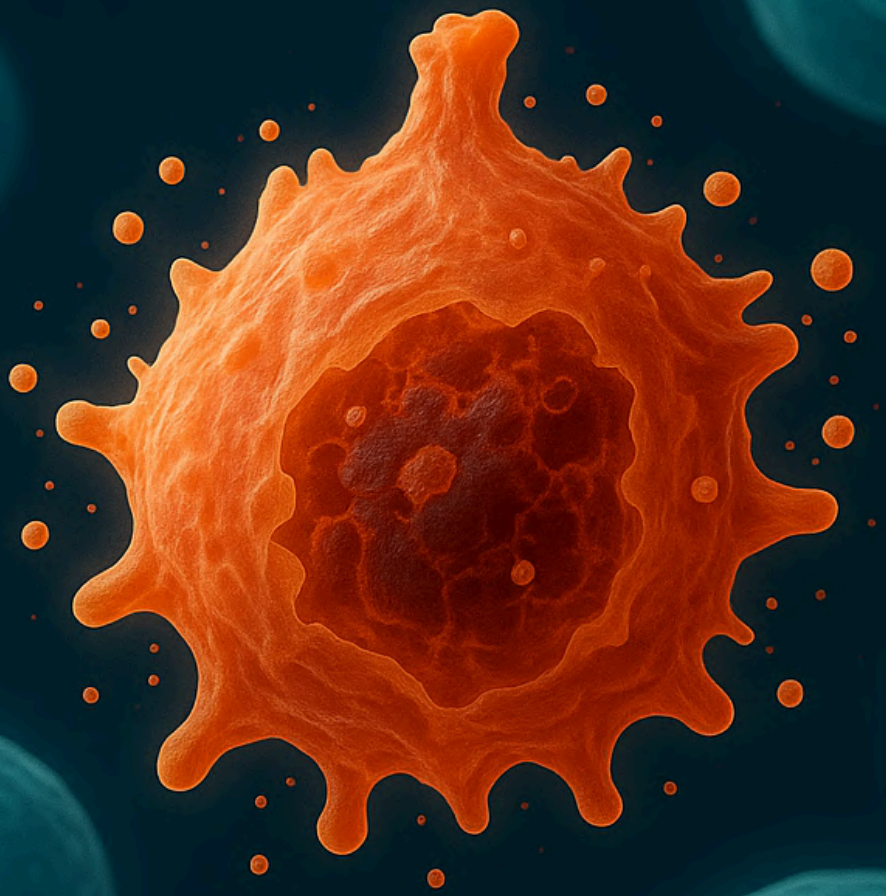
InScight

THE IISER KOLKATA SCIENCE MAGAZINE

#5 | SEP 2025



CELL DEATH MAKES LIVING EASIER

Chandrima Shaha

AT THE INTERSECTION OF PHYSICS AND BIOLOGY

Tamal Das on Forces & Cells

FROM CANCER RESEARCH TO PARADIGM SHIFTS

Interview with Sushanta Roychoudhury

WHY THERAPIES FAIL?

Ofer Reizes on cancer, collaboration, and curiosity

We are deeply saddened by the untimely passing of **ANAMITRA ROY**, a PhD student and BS-MS alumnus of IISER Kolkata. A passionate scientist, he understood the importance of science communication and always found time alongside his research to engage in outreach.

Through his popular science writings in various publications and his volunteering for outreach activities at IISER Kolkata, we are confident that he inspired many with his infectious passion for science. We at InScight shall fondly remember his quiet encouragement and appreciation of our work as IISER Kolkata's science magazine, and we will continue to draw inspiration from him.

May his soul rest in peace.

We share here a photograph he took of IISER Kolkata's victory in IICM, which captures the spirit and enthusiasm he brought to every walk of life. May it stand as a reminder of the passion he inspired in those around him.

Behind The Pages

We are back with another fascinating issue of *InScight*, where we celebrate biology not only as a field of study but also as a metaphor for how science itself should evolve—through courage, adaptability, cooperation, and a readiness to prune.

In the living world, survival is not merely about clinging to existence—it is about knowing when to let go. Biology teaches us this in the quiet, orchestrated drama of apoptosis, as explained by Prof. Chandrima Saha, senior scientist at IICB Kolkata. A cell willingly embraces death so that the organism may thrive. By removing what is damaged or dangerous, life safeguards its integrity.

This self-cleansing is not limited to cells. In epithelial tissues, neighbors sense a cell gone astray—mutated or invasive—and preserve harmony by pruning it.

Science, too, must adopt this wisdom. Just as tissues expel threats, society must shed dogma and superstition. Just as apoptosis clears the path for renewal, scientific inquiry must have the courage to discard outdated certainties and embrace curiosity.

Biology also teaches adaptability. As Prof. Nagraj Balasubramaniam from IISER Pune points out, cancer cells survive across a wide range of tissue stiffness. To defeat them, we must first understand how they rewire themselves. Their resilience, unsettling as it is, also teaches us a lesson: progress requires versatility, the ability to grow across both rigid and fluid terrains. Paradigm shifts of the kind Dr. Sushanta Roychoudhury from IICB envisions are possible only then.

Institutions, too, can embody this principle. TIFR Hyderabad is thriving by weaving together disciplines, as highlighted by Dr. Tamal Das in an interview with us. Much like cells coordinating in a tissue, chemists, physicists, and biologists engage in constant dialogue, allowing ideas to fuse and evolve. This interdisciplinary networking sparks creativity—mirroring the collective intelligence of living systems. Science should be done like that: not in isolation, but in vibrant, communicating networks—like Prof. Ofer Reizes' group at the Cleveland Clinic Lerner Research Institute, where surgeons and oncologists collaborate to tackle uterine cancer.

However steep the road, let us keep hope alive. To quote Darwin: "It is those who know little, and not those who know much, who so positively assert that this or that problem will never be solved by science."

And if life and science can evolve, why not us? *InScight*, too, is maturing. With each issue, it adapts and refines itself—much like the living systems it seeks to illuminate. As it grows, it prepares to widen our view, sharpening our collective vision of what science can be and what it must become.

Let us keep evolving.

Happy Reading,
Budhaditya Banerjee
Editor, *InScight*

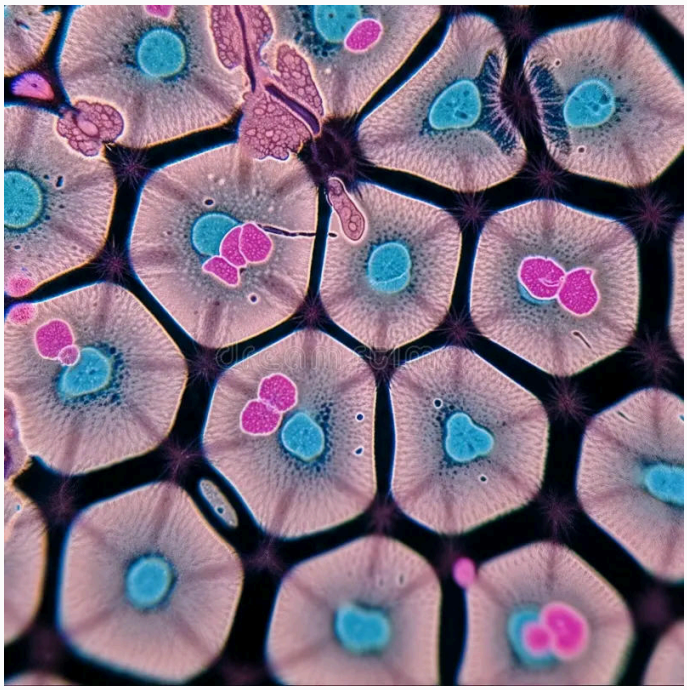


FIG 1 : "... there's a movie called The Matrix ... which plays on a similar idea: there's this unseen system all around you that shapes everything. In biology, the extracellular matrix functions the same way. It's present everywhere and affects how cells behave and how they interpret their surroundings." - Prof. Balasubramanian. Read his interview.

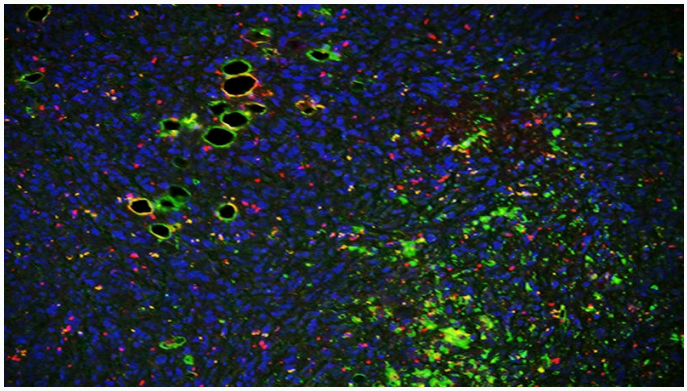


FIG 2 : Breast cancer cells stained with six primary antibodies to show areas of tumor. A research team led by Ofer Reizes and Justin Lathia designed a peptide therapeutic that disrupts the molecular processes behind aggressive cancer growth when delivered into cells. The study was highlighted in the January issue of Molecular Cancer Therapeutics. Learn more in his interview.

Frontiers in Biomedical and Sustainable Science

Foreword by Prof. Amitava Das

It gives me great pleasure to present this issue of *InScight*, a forum for discussing the frontier issues in contemporary science. True to its spirit, *InScight* reflects the diversity of inquiry that defines our institute and the larger scientific community. Contemporary science is increasingly interdisciplinary, requiring contributions from every branch—physics, chemistry, biology, mathematics, earth sciences, and beyond—to address the grand challenges of our times. From health and disease to sustainability and climate, progress depends on dialogue and collaboration across disciplinary boundaries.

Among the most dynamic areas of present-day research is biomedical science, where new ideas emerge at the interface of chemistry and biology. A compelling example is the study of disease biology and the therapeutic potential of short peptides. Recent publications highlight how these versatile biomolecules are not just fragments of larger proteins but highly functional agents capable of modulating protein–protein interactions, serving as enzyme inhibitors, receptor modulators, or drug carriers. Chemical innovations such as stapling and conjugation have enhanced their stability and efficacy, opening avenues against cancer, neurodegeneration, antimicrobial resistance, and other complex diseases. This exemplifies how fundamental molecular science converges with medicine to generate solutions with transformative impact.

In keeping with this interdisciplinary ethos, IISER Kolkata recently hosted the Bioanalytical Workshop 2025, which brought together researchers, students, and industry experts to share cutting-edge methods in biomedical analysis. Such platforms foster exchange across domains, ensuring that our students and young scientists remain well-equipped to push the frontiers of knowledge.

To promote and nurture interdisciplinary learning, IISER Kolkata has introduced a two-year MS program in Sustainable Science. The faculties of various departments of IISER Kolkata have come together in developing this course with the aim of addressing unmet challenges in Sustainable Ecosystems and emphasising our commitment to society.

This issue of *InScight* thus celebrates the synergy of disciplines—from molecular medicine to sustainability—while showcasing the creativity and commitment of our community. I hope these pages will inspire readers to appreciate the richness of interdisciplinary science and to envision new collaborations that advance both knowledge and societal well-being.

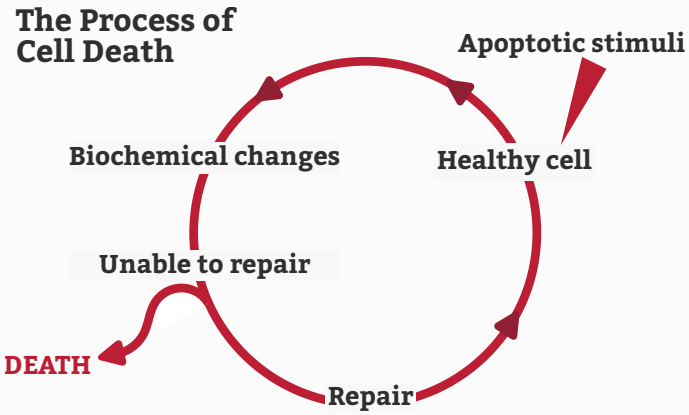


FIG 1 : A schematic representation of the process of cell death. Read the article by Prof. Chandrima Saha to find out more.

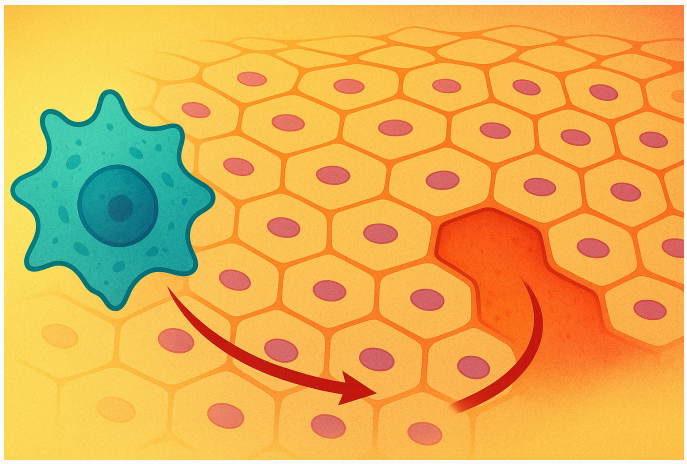


FIG 2 : Epithelial cells work together like a neighborhood watch, sensing when one of their neighbors turns abnormal and pushing it out before it can cause harm. This captures the essence of homeostasis that constitutes one aspect of Prof. Das's research. Read his interview here.

In This Issue

Academic Listings: Internships, PhDs, Post-docs

INTERNSHIPS

DoS/ISRO Internship & Student Project Trainee Schemes
⏰ Deadline: ⚠️
📎 Website

Research Internship at OIST
⏰ Deadline: 2025-10-15
📎 Website

Visiting Student Research Program at KAUST
⏰ Deadline: ⚠️
📎 Website

Training as a Material Tester
⏰ Deadline: 2025-12-30
📎 Website

PHD POSITIONS

Max Planck Institute for Informatics - PhD Applications
⏰ Deadline: ⚠️
📎 Website

IMPRS – Solar System Science (Astrophysics) – Göttingen & Braunschweig
⏰ Deadline: 2025-10-01
📎 Website

The International Max Planck Research School on Astrophysics at the Ludwig Maximilians University Munich
⏰ Deadline: 2025-11-01
📎 Website

UC Berkeley's Physics Graduate Program
⏰ Deadline: 2025-12-15
📎 Website

Exoplanet Characterisation Predictions via Gravitational Microlensing: Competition Funded PhD Project
⏰ Deadline: ⚠️
📎 Website

Princeton University PhD Graduate School Programme
⏰ Deadline: 2025-11-16
📎 Website

University of Chicago Graduate School Programme
⏰ Deadline: ⚠️
📎 Website

University of Texas at Austin Graduate School Programme
⏰ Deadline: ⚠️
📎 Website

University of Utah Graduate School Programme
⏰ Deadline: ⚠️
📎 Website

The Cologne Graduate School of Ageing Research (CGA)
⏰ Deadline: 2025-11-03
📎 Website

PhD Student (f/m/div) in the Field of Physiology and Food Chemistry
⏰ Deadline: 2025-09-14
📎 Website

Doctoral positions available at the Graduate School Life Science Munich	⏰ Deadline: ⚠️ 📎 Website
PhD positions at the International Max Planck Research School for Living Matter	⏰ Deadline: 2025-10-08 📎 Website
Max Planck doctoral positions in computer and information science	⏰ Deadline: 2025-09-15 📎 Website
Fully funded PhD Positions (Doctoral Researcher m/f/d) | Condensed Matter Science	⏰ Deadline: 2025-09-30 📎 Website
Anhalt University of Applied Sciences PhD position (m/f/d), no. 441	⏰ Deadline: 2025-09-15 📎 Website
2 Research Assistant (PhD) positions (m/f/d) Two-Phase Flow at the Chair of Turbomachinery	⏰ Deadline: 2025-09-15 📎 Website
PhD in Economics (m/f/d)	⏰ Deadline: 2025-09-14 📎 Website
PhD positions at the Cologne Graduate School of Ageing Research	⏰ Deadline: 2025-11-03 📎 Website
University of North Carolina at Chapel Hill PhD Programme	⏰ Deadline: 2025-12-16 📎 Website
University of North Carolina at Charlotte PhD Programme	⏰ Deadline: 2025-12-01 📎 Website
Louisiana State University PhD Programme	⏰ Deadline: ⚠️ 📎 Website
PhD Position - EPFL	⏰ Deadline: ⚠️ 📎 Website
Fully Funded PhD Position in Microbiology | Quorum Sensing & Host–Microbe Interactions	⏰ Deadline: 2025-09-30 📎 Website
Scientific Researcher (m/f/d) Adjoint Monte Carlo Simulation for Inverse Problems	⏰ Deadline: 2025-10-09 📎 Website

POSTDOCTORAL AND OTHER SHORT-TERM POSITIONS

John S. Foster, Jr. Postdoctoral Fellowship and the Harold Brown Postdoctoral Fellowship	⏰ Deadline: 2025-11-08 📎 Website
Coupled ionosphere-thermosphere modelling	⏰ Deadline: 2025-09-15 📎 Website
HARRY HESS FELLOWS PROGRAM 2026-2027	⏰ Deadline: 2025-10-12 📎 Website

Postdoctoral Scholar in Planetary Sciences and Astrobiology	⏰ Deadline: 2025-10-10 📎 Website
HRDG- Nehru Science Postdoctoral research Fellowship	⏰ Deadline: ⚠️ 📎 Website
Postdoc Position in Multi-messenger Astronomy and Data Science at Johns Hopkins University	⏰ Deadline: 2025-09-30 📎 Website
Postdoctoral Research Fellow at KICP Postdoctoral Research Fellow Chicago	⏰ Deadline: 2025-10-31 📎 Website
Postdoc position in Gravitational Waves at Nikhef	⏰ Deadline: 2025-09-15 📎 Website
Maria de Maeztu Postdoctoral position in Gravitational Waves Astronomy at the ICCUB	⏰ Deadline: 2025-11-30 📎 Website
PostDoc f/m/d – Investigation of the interfacial material growth of bioceramics using atom probe tomography (APT)	⏰ Deadline: 2025-10-31 📎 Website
Assistant/Associate/Full Professor, Marine and Geological Carbon Dioxide Removal	⏰ Deadline: 2025-09-28 📎 Website
Postdoctoral Research Associate - Environmental Earth & Atmospheric Sciences	⏰ Deadline: 2025-09-29 📎 Website
Faculty Position, Earth Science, Khalifa University, Abu Dhabi, UAE	⏰ Deadline: 2025-09-20 📎 Website
Assistant Professor - Energy Science and Engineering (Geothermal and/or Hydrogen Subsurface Eng)	⏰ Deadline: 2025-10-31 📎 Website
Post Doctoral Position at Institute of Physical Chemistry, Polish Academy of Sciences	⏰ Deadline: 2025-12-31 📎 Website

BAW 2025

Shaping the Next Generation of Biomedical Scientists

— Bishal Hazra,
Prof. Jayasri Das Sarma
(IISER Kolkata)

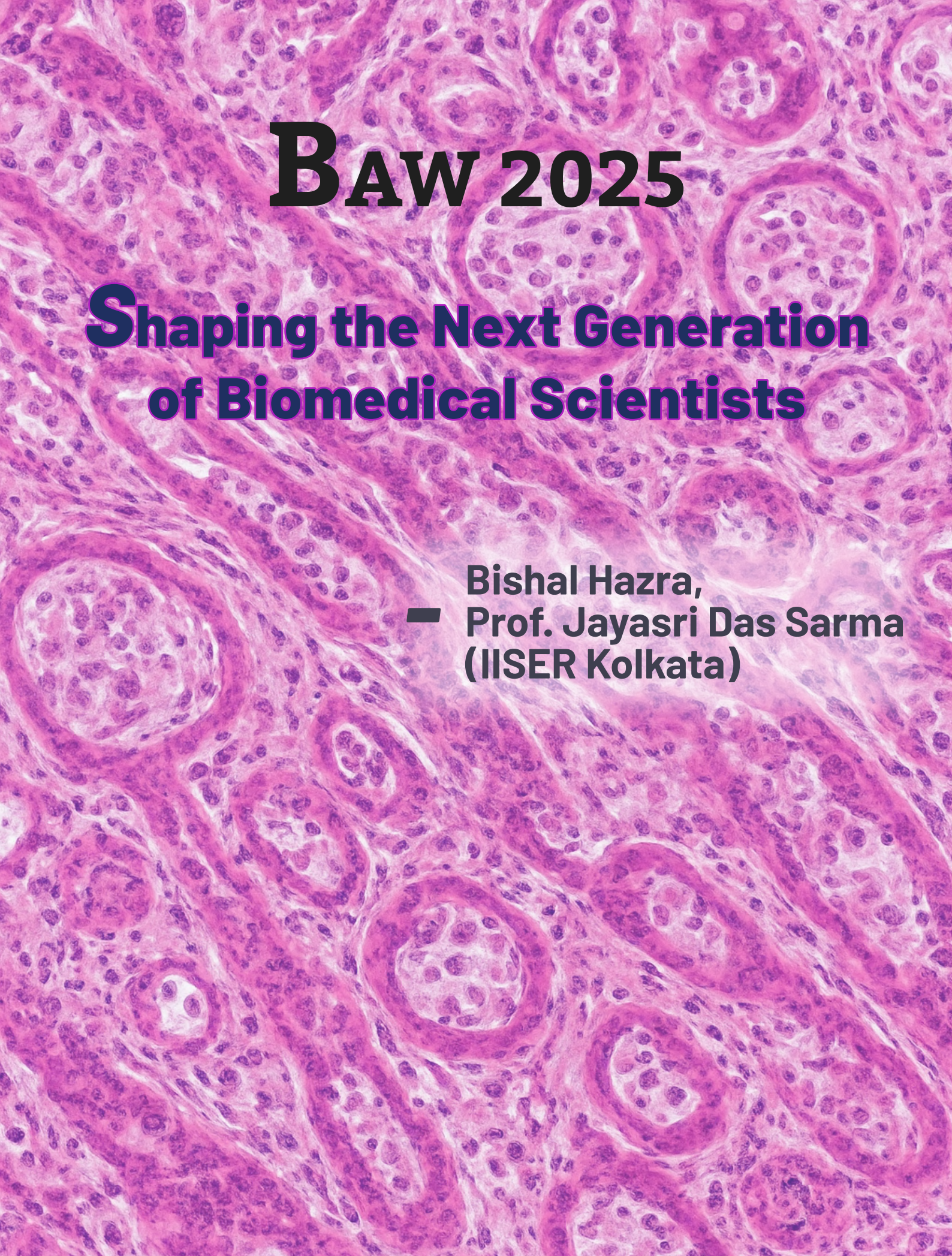


Image depicts microscopic view of stained tissue in a histopathology study – one of the core hands-on modules at BAW 2025 that trained participants to recognize cellular changes underlying disease, bridging classroom learning with real biomedical research.

***Prof. Jayasri Das Sarma**'s research at IISER Kolkata spans neurovirology, neuroimmunology and neural Cell Biology of Diseases among other things. She has been a leading figure in advancing understanding of virus–host interactions in the nervous system.*

***Bishal Hazra** is her fourth-year PhD student. His doctoral research focuses on the neuroimmunological aspects of viral pathogenesis.*

Genesis Of The Conference

The Bioanalytical Workshop (BAW) is a specialized conference organized by the Department of Biological Sciences, IISER Kolkata, that integrates hands-on training and interactive learning, aimed at strengthening expertise in the field of bioanalysis. Designed primarily for students and early-career researchers, the workshop focuses on advanced analytical techniques with a strong emphasis on translational research. Its core objective is to enhance scientific competence and equip participants with the tools necessary to contribute meaningfully to cutting-edge biomedical research.

BAW typically attracts participants from diverse backgrounds, including life sciences, medical sciences, pharmaceutical sciences, clinical research, and related disciplines. The program provides both theoretical knowledge and practical experience, thereby fostering technical proficiency and innovation among attendees. The inaugural edition of BAW was held in 2018 in Gangtok, drawing 67 national and international participants. Building on the success of its previous editions, BAW 2025: Frontiers in Disease Biology was scheduled to take place from June 27th to July 1st, 2025, combining a scientific conference with a hands-on workshop focused on preclinical animal models. The overarching goal of BAW 2025 is to align with the pace of evolving research technologies and methodologies. By offering immersive, skill-based training, the workshop aims to empower young scientists with practical expertise in high-demand areas.

About BAW 2025

The Indian Institute of Science Education and Research (IISER) Kolkata conducted the BAW 2025: Frontiers in Disease Biology, a premier five-day conference dedicated to advancing the understanding of disease mechanisms and innovative research approaches in biomedical sciences. Held from 27th June to 1st July 2025, the event brought together leading national and international scientists, early-career investigators, and researchers to share groundbreaking insights into disease biology. The conference featured a dynamic format, blending didactic lectures and hands-on workshops to offer a comprehensive learning experience.

Major scientific disciplines covered in the conference

The BAW conference encompassed rich and interdisciplinary themes that brought together diverse areas of cutting-edge biomedical research. It focused on Infection Biology, exploring host-pathogen interactions and mechanisms of immune evasion. Secondly, Stress Biology and Physiology examined how cells and organisms responded to various stressors and the physiological consequences of such responses. Thirdly, Pathways to Pathogenesis: Molecular Triggers of Diseases highlighted the signaling disruptions and molecular events that initiated and drove disease processes. The conference also addressed Neurodegeneration and the Neurobiology of Diseases, offering insights into the mechanisms underlying neural dysfunction and progressive neurodegenerative disorders. Mechanobiology featured prominently, emphasizing the influence of mechanical cues on

FIG 1: *The success of this event was made possible by the tireless dedication of volunteers across the Department of Biological Sciences, led by Prof. Jayasri Das Sarma, who served as the Organizing Secretary. Students, including PhD scholars and BS-MS students from various laboratories, contributed with remarkable enthusiasm to ensure the smooth execution of the program.*

cellular behavior and disease progression. In addition, the theme included Tissue Microenvironment and Cancer Biology, investigating how the local cellular and extracellular environment shapes tumor development and metastasis. Lastly, the conference emphasized Translational Frontiers in Human Health, focusing on how basic research findings could be translated into clinical innovations to improve human health outcomes.

Speakers of BAW 2025

The conference featured an exceptional lineup of speakers, including both distinguished national and international scientists who delivered insightful and thought-provoking talks across a broad spectrum of topics.

International Speakers

- Ofer Reizes - Cleveland Clinic Lerner Research Institute (LRI), USA
- Yasuyuki Fujita- from Graduate School of Medicine and Faculty of Medicine, Kyoto University
- Yusuke Toyama- Mechanobiology Institute, National University of Singapore

National Speakers

- Partha Pratim Majumder
- Susanta Roychoudhury
- Sushanta Dattagupta
- Chandrima Shaha
- Arup Banerjee
- Prasenjit Guchhait
- Srimonta Gayen
- Partha Pratim Datta
- Rupak Datta
- Ellora Sen
- Anirban Basu
- Pankaj Seth
- Tamal Das
- Abhijit Majumder
- Nagaraj Balasubramanium,

Chairpersons of various sessions

- Jayasri Das Sarma
- Rupak Datta
- Snehasikta Swarnakar
- Biswanath Maity
- Shubhra Majumder
- Malancha Ta
- Subhas C Biswas

FIG 2 : *The BAW attendees, including professors, speakers, and directors, came together to ensure the success of the event.*

FIG 3 : *Students getting hands-on experience in Animal Handling and Mouse dissection in the conference. Animal models helps us to study various diseases because of their close association with humans. In an aim to become a researcher in animal studies, Animal Handling and Dissection module proved to be a very valuable module to the students/participants.*

- Bidisha Sinha
- Siddhartha Jana,

The hands-on workshop on pre-clinical mouse models

The BAW conference offered students a unique and enriching opportunity to engage directly with fundamental experimental techniques widely used in biomedical research. Through dedicated hands-on sessions, they learned essential skills such as Animal Handling, which provided insight into the use of preclinical models for studying disease mechanisms and therapeutic interventions. The Histopathology module introduced them to the microscopic examination of tissues, enhancing their understanding of disease-associated changes at the cellular level. In the Flow Cytometry sessions, students gained experience with high- throughput cell analysis techniques crucial for immunological profiling and disease characterization.

FIG 4 : *Theory behind Histopathology being taught to the students by the volunteers. Histopathology module helped the students/ participants to understand about the diagnosis and study of diseases of the tissues, as it involves examining tissues and/or cells under a microscope.*

FIG 5 : *The volunteers of BAW, comprising students from IISER Kolkata.*

Additionally, Microscopy training familiarized them with advanced imaging tools used to visualize cellular and molecular structures in detail.

The Spirit of BAW: Student Initiative, Scientific Excellence, and Cultural Expression

What truly sets BAW 2025 apart is its collaborative and student-driven foundation. Unlike conventional scientific conferences, BAW thrives on the passion, dedication, and teamwork of its student organizers. The event reflects the commitment of faculty mentors and the tireless efforts of an exceptionally enthusiastic group of student volunteers who take responsibility for everything. They manage accommodation and travel arrangements, host and anchor events, oversee food and hospitality, capture the moments through photography, and even lead live laboratory demonstrations. Their involvement goes far beyond logistics. It gives them a rare opportunity to develop leadership, organizational, and communication skills that will serve them throughout their careers.

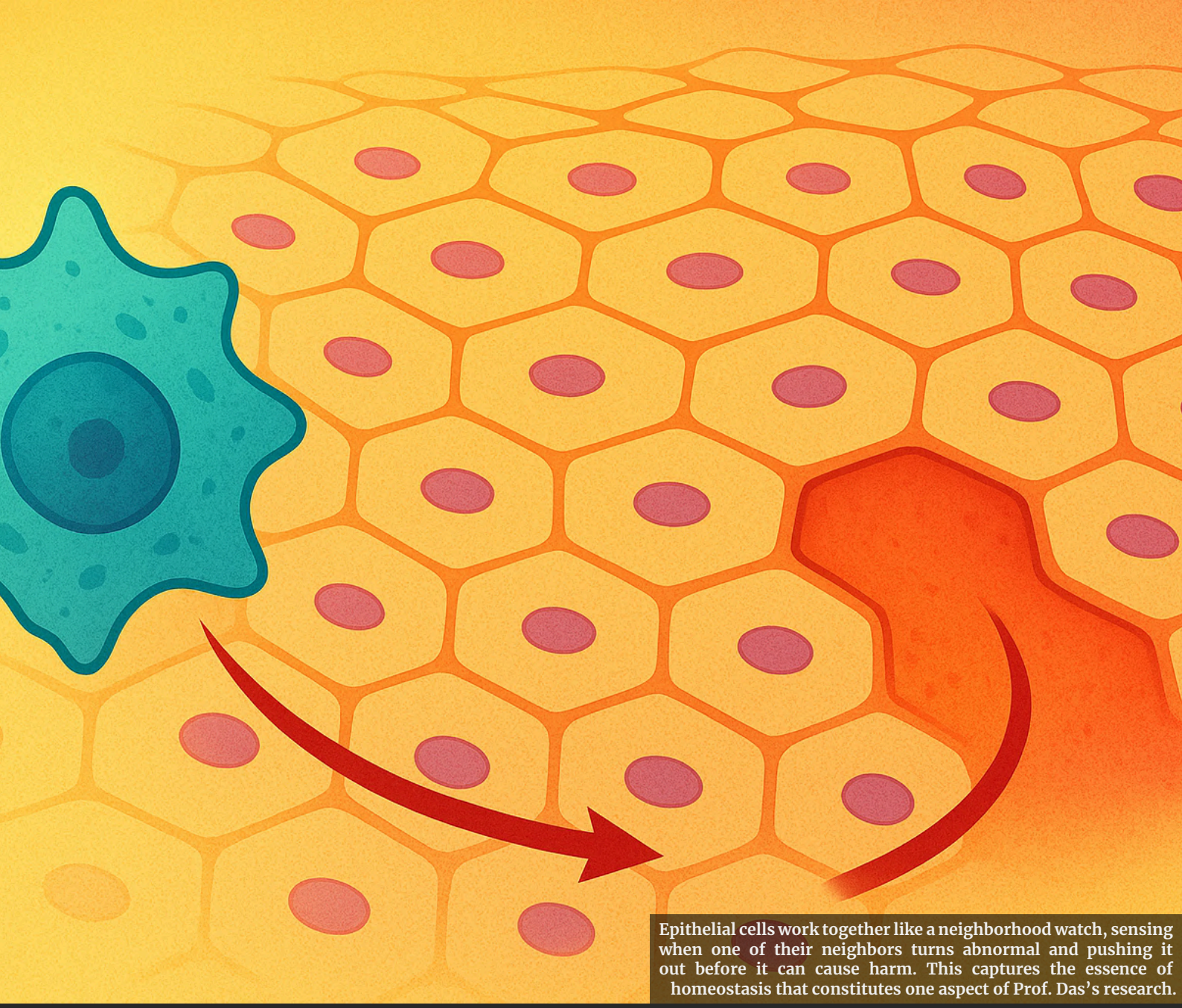
The conference also provides a stage to showcase IISER Kolkata's state-of-the-art research facilities to national and international participants, strengthening the institute's presence in the global scientific community. Adding warmth and vibrancy, BAW ends each year with a cultural evening. This is a celebration of art and camaraderie where faculty, students, and participants come together to share their talents in music, dance, drama, and poetry. This unique blend of science and culture creates an atmosphere that is as inspiring as it is welcoming.As BAW continues to grow in scale and reputation, it is set to evolve into a recognized scientific society that will nurture the next generation of bioscience professionals.

Conclusion

Since its inception in 2012, the Bioanalytical Workshop has grown remarkably, attracting an increasing number of applicants each year. About 250 students took part in the 2025 edition, which reflects both the program's credibility and the transformative experience it offers. One of BAW's defining features is its student-led model, where young

scholars are not just attendees but active contributors. They take charge of organizing and leading the hands-on demonstrations that form the core of the event. Over time, the workshop has expanded well beyond its early focus on neurobiology to embrace multiple areas of disease biology. This year's theme, "Frontiers in Disease Biology," reflects that broader vision. Beyond technical training, BAW has become a vibrant platform for networking, professional growth, and peer-to-peer learning. It creates opportunities for meaningful connections that often lead to collaborations shaping the future of biomedical research.

The workshop also ensures that participants feel at home. Each year, they are treated to delicious meals, and 2025 was no exception. The variety, flavor, and quality of the food earned praise from both students and distinguished speakers, adding a thoughtful and memorable touch to the scientific program. The cultural evening provided the perfect conclusion. It was a time to relax, celebrate, and showcase creativity through art and performance. Altogether, BAW 2025 was far more than just a workshop. It was a transformative experience that shaped skilled researchers, encouraged leadership, and fostered a dynamic and close-knit scientific community.



Epithelial cells work together like a neighborhood watch, sensing when one of their neighbors turns abnormal and pushing it out before it can cause harm. This captures the essence of homeostasis that constitutes one aspect of Prof. Das's research.

At the Intersection of Physics and Biology: Tamal Das on Forces, Cells, and Curiosity

Suman Halder (IISER Kolkata)

Dr. Tamal Das shares his journey from Howrah Zilla School to Tata Institute of Fundamental Research - Hyderabad. He discusses his laboratory's focus on the collective dynamics of epithelial cells, their applications in cancer prevention and wound healing, and the importance of interdisciplinary collaboration, with our correspondent Suman Halder.

Also available online, at scicomm.iiserkol.ac.in

SH: Welcome, sir, to InScight. I am Suman Halder, your host for the day. To start, could you please introduce yourself and tell us about your current role at TIFR?

TD: At TIFR, our lab works primarily in cell biology with an interest in developmental biology. We study biological problems from an interdisciplinary perspective, looking at biophysical aspects such as extracellular matrix (ECM) tension, cell–cell forces, and the physical state and geometry of cells. These are areas a typical molecular biologist may not focus on, but they complement conventional molecular signaling studies.

Our main focus is on the collective dynamics of epithelial cells—where many cells behave as a single unit. Epithelial tissue, which forms protective coverings like the skin, and lines organs such as the gastrointestinal tract, kidneys, and lungs, is ideal for studying such collective behavior. These cells are tightly connected, so any activity by one cell involves coordination with its neighbors.

Epithelial cells are also under constant tension, attached both to neighboring cells and to the ECM, somewhat like a "cellular Spider-Man" pulling on its surroundings. This allows us to measure forces and understand how they support collective behavior. Alongside this biophysical view, we also study how organelles—such as mitochondria, lysosomes, the endoplasmic reticulum, and the nucleus—change in relation to tissue-level behaviors. In short, we connect processes inside a cell to tissue-level phenomena through force transmission and molecular signaling.

SH: So, you are mainly working experimentally?

TD: Yes, we are primarily an experimental lab. However, we also analyze our data computationally. For example, in studying nuclear dynamics, we track fluctuations in the nucleus and use Fourier analysis to examine their decay across spatial frequencies. While we do not perform simulations ourselves, we collaborate with soft matter physicists who handle modeling, while we focus on experiments.

FIG 1 : *Dr. Tamal Das and other members of the Collective Cellular Dynamics (CCD) Laboratory at TIFR Hyderabad research the collective cell dynamics of epithelial tissues.*

SH: For the benefit of our readers, could you explain what TIFR is and its role in India's research ecosystem?

TD: TIFR Hyderabad has a unique structure—there are no departments. Physicists, chemists, and biologists work under one umbrella, which promotes interdisciplinary collaboration. For students, this means great flexibility: even if they join through the biology board, they can work in any lab, including those focused on simulations or molecular dynamics.

This structure avoids pigeonholing researchers into narrow categories and encourages cross-disciplinary culture, which is rare in India.

Another key point is our focus on fundamental research. Many modern applications—like lasers—originated from purely fundamental scientific questions. Lasers, now an applied technology, began with the simple idea of collimating light, backed by theory long before practical use emerged.

While translational research is essential and rightly receives funding to directly benefit society, it should not come at the cost of fundamental science. TIFR's mandate is to lead in fundamental research, ensuring that breakthroughs can later fuel impactful applications. Without such foundational work, progress in applied research would be only incremental.

SH: Now, can you tell us about some of the projects you are currently leading at TIFR and their broader impact?

TD: As I mentioned earlier, our lab focuses on the collective dynamics of epithelial cells. We have two broad objectives:

First, to test how much of what we read in textbooks truly holds in real biological systems and whether there's more beyond those established ideas. For instance, we are studying how cells behave under dynamic situations such as during migration or when the tissue removes a harmful, mutated cell.

Within a cell, there are organelles—like the endoplasmic reticulum, Golgi complex, mitochondria, and the nucleus. A basic biology textbook will tell you their primary functions: the endoplasmic reticulum in protein synthesis, mitochondria as the "powerhouse" of the cell, and so on. But we are discovering that beyond these canonical roles, these organelles are also involved in signaling processes that help coordinate such dynamic events.

One specific project in our lab examines how "good" cells in the body identify and eliminate potentially cancerous cells. This is a vital, ongoing process—mutations occur continuously due to random errors, UV exposure, or toxic chemicals, and the body must constantly remove these faulty cells to maintain health. Understanding this could contribute to cancer prevention strategies.

Another line of research looks at wound healing. When there's a gap or injury in epithelial tissue, cells migrate to close it. If we understand the exact mechanisms of how they do this, we might be able to design better wound-healing approaches.

So, on one hand, our work addresses fundamental biological questions like how intracellular structures influence collective cell behavior. On the other hand, it has potential applications in health and medicine, including cancer prevention and tissue repair.

SH: Could you briefly describe your academic journey, starting from your school years?

TD: I am from West Bengal and grew up in Howrah, where I studied at Howrah Zilla School. After Class 12, I joined IIT Kharagpur for an Integrated B.Tech–M.Tech in Biotechnology and Biochemical Engineering. I never attempted medical entrance exams; I was focused on engineering and initially aspired to be a physicist.

During IIT JEE counselling, I was curious about research opportunities. I asked what field had good prospects, and was told biotechnology was "the next big thing." That's how I entered the field.

I always had an inclination towards research. In my third year, a friend introduced me to Professor Suman Chakraborty from the Mechanical Engineering Department (now the Director of IIT Kharagpur). He was simulating DNA hybridization in a microchannel and needed input on the biological aspects. I joined him as a side project, and his intellect and mentorship inspired me.

Eventually, I pursued a PhD under his co-supervision, along with Prof. Tapas Maity from the Biotechnology department. This gave me the unique experience of working in two labs: the biochemistry lab in biotechnology and the microfluidics lab in mechanical engineering.

Professor Chakraborty's physicist's mindset influenced my thinking profoundly. For example, when I described a cell as having cytosol inside and media outside, he immediately framed it as a "two-fluid problem" and asked about interfacial tension—concepts rarely addressed in standard biology courses.

My PhD focused on bio-microfluidics, particularly how cells behave when confined in channels with heights comparable to the cell's own height. I studied two main effects: high shear stress from fluid flow, and local concentration buildup from secreted factors.

After my PhD, I did a short postdoc (10 months) at the Institute for Cancer in Montreal, affiliated with the University Hospital of Montreal. There, I worked on ovarian cancer, designing microfluidic channels to trap spheroids—spherical aggregates of cancer cells—from patients. We tested different chemotherapy combinations on these "mini-tumors" to predict which regimen would work best for each patient.

Although impactful, I wanted to return to more fundamental research. I joined the Max Planck Institute for Intelligent Systems in Germany, in Joachim Spatz's lab, initially proposing to study collective migration of cells in confined microenvironments. Ironically, in the next five years, I never touched microfluidics again.

This shift was deliberate. I often advise PhD students to identify their core niche and avoid staying too close to their doctoral topic out of comfort. Many researchers continue their PhD work as faculty, which is safe but can limit innovation. I decided to move towards biology, bringing in my physics and fluid mechanics background, rather than competing directly with established experts in microfluidics.

At that time, microfluidics research had two main tracks: Either you choose the pathway where theoretical fluid mechanics is applied to microfluidic systems, requiring deep expertise and mastery of the field. Or, you choose the track where Sophisticated multi-layer microfluidic "lab-on-a-chip" devices are used, which demand major infrastructure only a few institutes possess.

I realized I couldn't compete in the first area and didn't want my work to be restricted by the facility-intensive nature of the second. Staying in microfluidics risked producing only incremental progress, so I chose to focus on biology.

Joachim's lab was the perfect environment—over 100 people, immense resources, and cutting-edge equipment. I decided this was my chance to redefine my career. I began focusing more on biological problems and less on engineering. This led to a discovery involving the protein Merlin, which plays a role in coordinating collectively migrating cells. That work was eventually published in Nature Cell Biology in 2015, and it has been central to my subsequent research objectives.

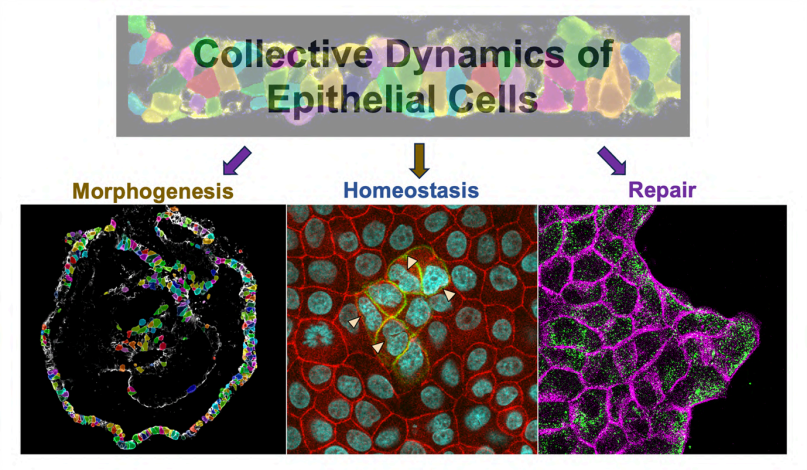


FIG 2: *Dr. Das' group studies how epithelial tissues - cell layers that line and protect our organs - use collective cell dynamics to drive development, defend against cancer, and heal wounds. They investigate (i) how individual cells coordinate to form organ structures during development (**morphogenesis**), (ii) act as a barrier to detect and remove potentially cancerous cells (**homeostasis**), and (iii) work together to close injuries through coordinated movement and structural changes (**repair**).*

That transition from engineering to biology was challenging but rewarding. While I still value physics deeply, I recognize my own limitations in it. I collaborate with physicists for simulations and modeling, while I focus on designing the most precise experiments possible—a key responsibility for any experimentalist.

This is my niche: bridging biology and physics, maintaining collaborations across disciplines, and using my interdisciplinary background to ask unique research questions.

SH: So can you mention your collaborators also? And they are mostly biophysicists?

TD: Yeah, so the person right now with whom I am collaborating most, I mean from the physics side. It is Max Bi. He is at Northeastern University. So Max is my collaborator for many projects as such. We have projects related to the cell competition and also morphogenesis, we are currently working on 3–4 projects. My group and Max's group are working.

Then I have collaborated and also collaborated with a mathematician in the University of Birmingham, Fabian Spiel. We have a work in Nature Cell Biology, where we looked at what endoplasmic reticulum morphology, how it undergoes the morphological changes during the wound healing and so. And Fabian provided a physical explanation underlying the morphological changes. It turns out that certain endoplasmic reticulum structures are energetically more favorable in one configuration than the other configuration. Within India, I have collaborated with two people.

One is Mohit Jolly, who is a Systems Biologist at IISc. We have so far collaborated in one project, but I wish to collaborate with him going ahead. And then within the institute, there is Saroj Nandi, who works on jamming and active matter.

SH: It has been quite a while since you completed your PhD. In your view, how has the experience of conducting doctoral research changed since then?

TD: Some things about a PhD never change—one of the most important is working with smart people. I've been fortunate to work with several, starting with Professor Suman Chakraborty.

He has an exceptional ability to grasp concepts in new fields at remarkable speed, draw analogies from other areas, and import those ideas effectively.

My postdoctoral advisor, Joachim Spat, was another influence—deeply insightful, with a clear vision for where science is heading.

One thing Professor Chakraborty told me has stayed with me: you only realize how good your PhD was about 10 years after finishing it. The real measure is what you are doing a decade later, because a PhD's value lies in the skills and judgment it gives you, not just the techniques you learn.

For me, one of those key skills is the ability to distinguish good science from bad—ordinary research from extraordinary. At the start of a PhD, you're naïve: you read a paper and get excited without fully understanding the context or significance. Over time, you should learn how to filter, to see what's worth pursuing.

This filtering skill has become more important because of how research has changed. My PhD years (2006–2010) were pre-social media for science. We had internet access, but slower, and less information bombardment. I still visited the IIT Kharagpur library to browse journals. Today, with platforms like Twitter, I can see research updates from across the world instantly—but this flood of information makes it harder to focus.

Earlier, the challenge was getting information; now, it's filtering it. You can realistically read at most a paper a day, so you have to choose wisely.

Another lesson from my PhD is the value of patience when chasing a big scientific story. It's tempting to split findings into smaller publishable parts for quick output. But if you want a complete, mechanistic, and impactful narrative—from first discovery to underlying process—you must invest years.

FIG 3 : *Dr. Das obtained his Ph.D. degree from IIT Kharagpur in 2010. His research work under the title of* ***Stress Responsive Dynamics of Mammalian Cells in Microconfinements*** *was carried out under the supervision of Prof. Suman Chakraborty (Mech.) and Prof. Tapas K. Maiti (Biotech.)*

FIG 4 : *From 2010 to 2011, Dr. Das was a postdoctoral research at the* ***Institut du Cancer de Montréal, Centre Hospitalier de l'Université de Montréal*** *(CHUM) in Montréal, Canada.*

SH: What emerging trends in biotechnology are you most excited about?

TD: One area I find particularly exciting is synthetic biology, which sits at the interface of biology and chemistry. Different people define it differently. For example, in iGEM competitions, teams design synthetic genomes. In Europe, my postdoc advisor Joachim is involved in a large project called SynCell, where they build artificial vesicles and add components step-by-step to determine the minimal composition needed for them to behave like cells.

My own interest lies in programming the internal structure of cells or even entire tissues to control their morphogenesis. This is something we haven't started yet, but I'm eager to explore it.

Another growing area is the integration of biophysics and principles of physics of matter into biology. Mechanobiology has been developing for over a decade now, so it's not entirely new, but synthetic biology remains the most exciting frontier for me.

SH: You've worked as a scientist in multiple countries. How would you compare the research cultures and professional norms in these different environments?

TD: I've worked in India, Canada, and Europe.

In North America, research is very grant-driven. PIs are constantly writing proposals, and that pressure is passed down to students. You're pushed hard - sometimes it's "swim or drown."

In Europe, the pace is calmer. This works well if you're self-driven, as I was, but it can also lead to complacency. Some people settle into technical positions without ever returning to the pressures of academia. Institutions like the Max Planck Society offer vast resources, but it's easy to get comfortable.

In India, the culture is somewhere in between. At top institutes like TIFR and IISc, we're doing fine, but pressure and resources vary widely.

SH: Have you had any experience working in industry? How do skills and expectations compare with academia?

TD: Not directly. My only exposure came during my PhD at IIT, which has strong industry links. While working on microfluidic systems, I collected data on how surface roughness affects fluid flow and heat dissipation, which was valuable for a chip-making company.

Their problem was cooling increasingly small semiconductor chips, which generate more heat. My findings on heat and mass transfer proved useful for their designs. That was my only real taste of industry collaboration. Other than that, I can't recall any other.

SH: In recent times, PhD graduates in India are facing a shortage of career opportunities. What can be done at the institutional level to address this?

TD: This is a difficult question, and I have two perspectives. The common answer is, of course, to create more institutes. But I believe PhD students themselves need to be proactive. Before starting a PhD, survey the available opportunities and ask whether you are exploring all possible career paths or narrowing yourself into a niche. The more niche your research, the fewer options you'll have.

For example, my first PhD student always wanted to work in industry. I advised her to do a postdoc in a city with many startups — places like Boston, the Bay Area, Paris, Frankfurt, or Singapore — and ideally in a lab collaborating with those startups. In India, much of the industry is still service-oriented rather than innovation-driven, which limits opportunities for scientists. This is especially true in biology and biotechnology, though pharma does slightly better, mainly hiring chemists.

Many people treat a PhD as just the next step after an MSc, without considering the reality that science, like sports or the arts, is a creative field with very few top positions. In cricket, for example, countless people play at the club level, but only a handful make it to the national team — the same applies to research. The government could expand funding and facilities, but there will always be limits. Students should be aware of these constraints and be open to alternative career paths.

SH: As a working experimental biologist in India, what barriers do you face in your research compared to other countries?

TD: Rules and regulations can slow things down, especially procurement. The "lowest bidder" rule in tenders is meant to prevent financial wrongdoing, but it can also delay essential purchases. That said, things have improved a lot. During my PhD at IIT Kharagpur, ordering chemicals could take months. At TIFR Hyderabad, purchase orders are processed in a week's time, and common chemicals often arrive within days, similar to my experience at the Max Planck Institute.

Also, where you work matters. At TIFR, all PhD positions are funded by the institute through the Department of Atomic Energy, so I don't have to secure individual grants to pay students during their regular tenure. In most Western institutions, PIs must fund their students through grants, and without one, the student may have to leave. Both systems have advantages and disadvantages, and you need to understand how to work within them.

SH: Sir, I want to shift the topic of our discussion a bit and just ask you about this, that biophysics is at the interface of biology and physics. So, how do you see the future of this field evolving and also, will artificial intelligence become like an indispensable tool for a researcher in this field?

TD: Yes, in many ways I believe AI - especially large language models (LLMs) like ChatGPT and Google Gemini - has made my work faster and more convenient. Until recently, I was the one writing most of the analysis codes in my lab, as many of my students come from biology or biochemistry backgrounds.

Previously, if a student gave me data and asked for a custom analysis script, I knew exactly what to do but

struggled to find a continuous block of time to start from scratch. It could take months before I finally sat down to code. Now, I can ask an LLM to draft a basic version in MATLAB, then quickly refine it myself—allowing me to respond to students much faster.

For literature surveys, AI-based tools like Undermine AI and ChatGPT's research mode can quickly gather relevant papers and even give preliminary interpretations. Of course, these outputs must be verified, as AI sometimes generates incorrect or fictitious references. Still, it feels like interacting with a knowledgeable collaborator who speeds up the initial stages of research.

AI has also transformed image analysis. Ten to fifteen years ago, segmenting cells in tissue images was challenging without high-quality images, and standard algorithms like watershed had clear limitations. Now, tools like CellPose, trained on millions of examples, can match human-level segmentation accuracy.

A growing frontier is integrating multimodal datasets—combining imaging data, transcriptomic or genomic sequences, and medical imaging such as MRI—to build better predictive models. In physics, similar AI approaches are being used to tackle previously intractable problems.

The real question, however, is about AI's limits: distinguishing between automated analysis and genuine scientific insight. For instance, debates continue over whether AlphaFold's success is itself a discovery or merely a powerful tool enabling further discoveries. Regardless, I view these technologies as disruptive—in the positive sense—because they fundamentally change how we approach scientific problems.

SH: Despite the large number of students in our country, it often seems that the research output being generated from here is not the highest quality compared to the other countries like US and Europe and what do you think is the system we are using for this? So, that doesn't depend, in my opinion, on the business.

TD: It largely depends on the PI. While it's true that overall research output in India may lag behind some countries, there are many scientists here—physicists, biologists, chemists—whose work matches the best being done abroad. In my own lab, we have a couple of strong results coming out soon that, to my knowledge, no one else has achieved in our field.

The challenge is that the proportion of such high-performing researchers is small, and this is linked to funding. If a country spends 4% of its GDP on research and another spends only 0.4%, the difference will be visible in facilities, opportunities, and output. Of course, the relationship isn't perfectly linear, but resources matter.

That said, the quality of PhD students in India is on par with those abroad in terms of intelligence and capability. Many top labs in the US and Europe have a large proportion of Indian and Chinese researchers. The difference often comes down to vision. PIs abroad tend to be more ambitious, while funding constraints remain a persistent limitation here.

Your career path depends on your interests, but whatever your field - physics, chemistry, biology, mathematics - ensure that the questions you pursue are at the forefront of that discipline. Incremental questions will yield incremental answers. Aim for bold, high - impact problems. For example, instead of testing how a known reaction behaves with a slightly different salt concentration, consider introducing a completely novel element—such as a rare-earth salt—and exploring its entirely new interactions.

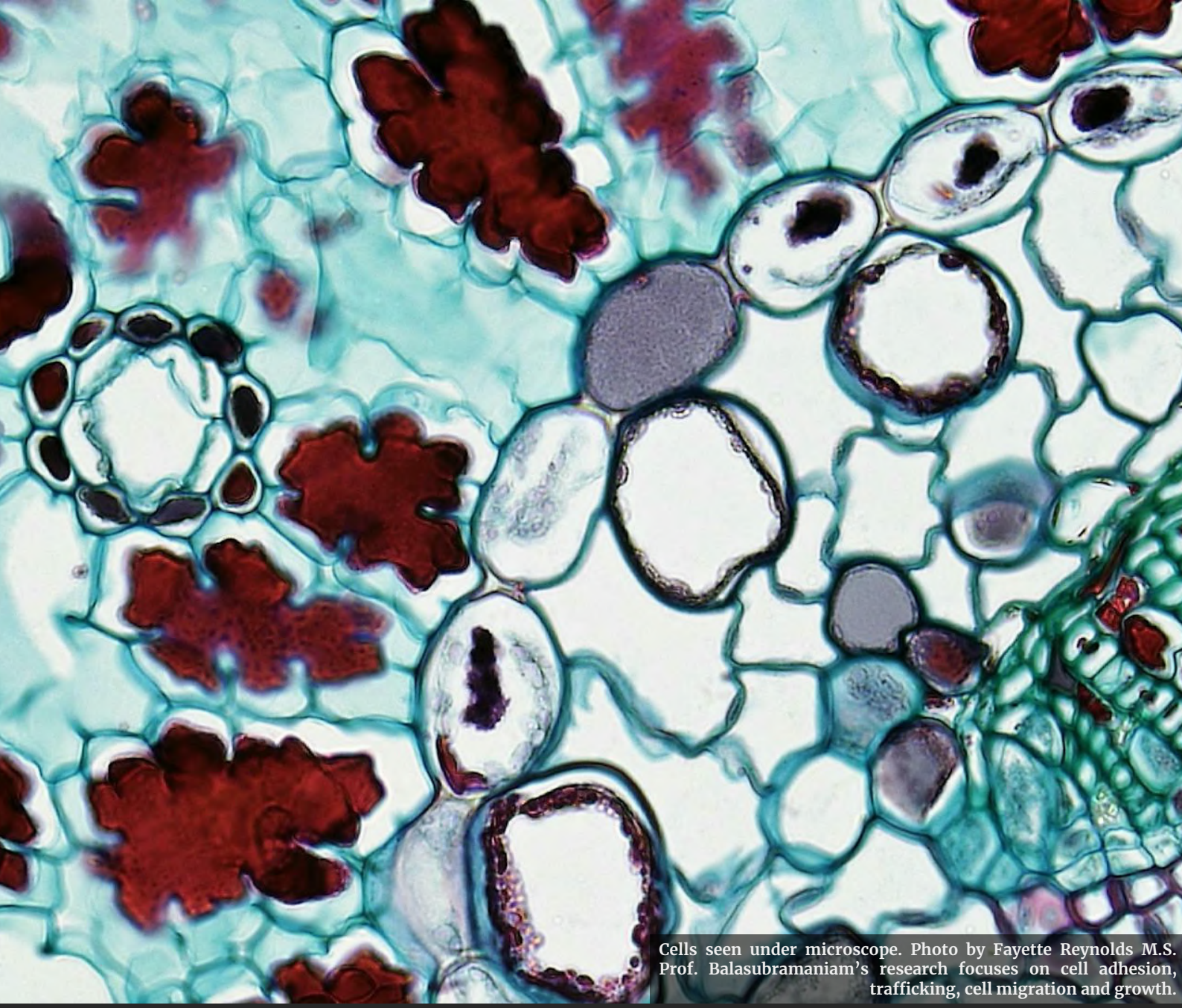
To reach that level, develop a regular habit of reading top journals in your field, even outside your immediate research area. Focus not on impact factors but on how influential work is structured and executed.

Attend high-quality conferences where the leaders in your field present. Listen carefully, engage with them if possible, and understand the direction in which the field is moving. This is a lifelong process—even as a PI, I still attend key meetings to track emerging areas and identify promising research directions.

SH: Thank you sir. It was my pleasure to have this chance to interview you.

FIG 5 : *From 2011 to 2016, Dr. Das was at the **Max Planck Institute for Intelligent Systems** in Stuttgart, Germany, where he served first as a postdoctoral researcher and later as a project leader.*

FIG 6 : *Since 2016, Dr. Das has been working at the **Tata Institute of Fundamental Research in Hyderabad** India.*



Cells seen under microscope. Photo by Fayette Reynolds M.S. Prof. Balasubramaniam's research focuses on cell adhesion, trafficking, cell migration and growth.

With Prof. Nagaraj Balasubramanian: On Cell Biology, Cancer, and the Joy of Doing Science

Sharanya Chatterjee (IISER Kolkata)

Prof. Nagaraj Balasubramanian (IISER Pune) talks about embracing uncertainty, the beauty of cell biology, and why enjoying the process matters more than rigid timelines. From cancer research to the rise of AI in science, he shares insights that remind us discovery is as much about curiosity as it is about perseverance.

🔗 *Also available online, at scicomm.iiserkol.ac.in*

SC: Today, we have with us Professor Nagaraj Balasubramanian from IISER, Pune. He is a cell biologist, and we're delighted to speak with him about his journey. Sir, when was the last time you visited IISER, Kolkata?

NB: This is actually my first visit. I've never been here before.

SC: Oh, is that so? How are you finding the conference?

NB: It's fantastic. The campus is beautiful, very green this time of year—thanks to the monsoon, I suppose. I'm glad to be here.

SC: And your thoughts on BAW?

NB: It's a wonderful initiative. I'm quite impressed by how a largely student-organized event has managed to bring together participants from all over the country. For students, it's a tremendous opportunity. The focus on hands-on training and peer-to-peer learning is commendable. It's great that students are involved in organizing and facilitating lab sessions too.

SC: Absolutely. Speaking of your journey, did you always aspire to be a researcher?

NB: Not really. I wasn't very academically inclined in my early years. But around the 8th or 9th standard, I began to enjoy what I was studying—especially biology. That shift was largely because of a teacher, Mrs. Pillai, who taught biology in a way that deeply resonated with me. She's no longer with us, but even after I completed my PhD and started my own lab, I would occasionally meet her.

Her influence stayed with me, and that's partly why I chose to work in an institution that emphasizes teaching.

FIG 1 : *Prof. Balasubramanian (right) with members of the Cell Adhesion Lab at IISER Pune. Their research explores how cell–matrix interactions regulate membrane trafficking, organelle architecture, and signalling, how these processes break down in cancers to enable anchorage-independent growth, and how targeting such pathways might restore normal anchorage dependence.*

When a teacher can impact a student's life so profoundly, there's a sense of responsibility—and privilege—to pass that on. That's when I began to seriously consider research, though it took time to find clarity and confidence in that path. I also had one or two family members in research, so I had some idea of what the journey involved.

SC: So, are they also from biology backgrounds?

NB: No, they were physicists. But having them around gave me some sense of what a research career demands—how much effort it takes, how smart you need to be. That awareness was both helpful and intimidating. Sometimes it's easier when you're starting from a blank slate. Otherwise, you end up comparing yourself: "**If this person is a scientist, am I good enough?**"

But ultimately, it's about getting the right opportunity at the right time. You apply to places, a door opens, and before you know it, you're doing something you enjoy. And if you're not overthinking it, you tend to just continue.

SC: So it all evolved organically?

NB: Yes, absolutely. Nothing was meticulously planned. It's more fun that way, honestly. Today, I see many students who crave structure—knowing what will happen three months or three years from now. But science doesn't always work that way.

To thrive, you need to be okay with uncertainty and still enjoy doing what you are doing. For me, it wasn't about planning a career or thinking about salaries or perks. I just kept doing it because I was having fun. And I still am.

SC: And we can all see where you are now.

NB: Exactly. Every step—PhD, postdoc, returning to India—happened naturally. You apply, the opportunity comes, you take it. Things fall into place. I still think it's a good approach, though I know it's harder these days.

SC: It's definitely more competitive now.

NB: Yes, and I understand why students feel the need to be more organized—earn degrees faster, have everything mapped out.

But my concern is: if you're under so much pressure to do everything "on time," are you even enjoying it? Because if you're not, it's hard to sustain. Structure helps with focus, but if it comes at the cost of joy, that's a problem.

SC: You forget why you started in the first place.

NB: Exactly. That's the key question I always ask students: **Are you having fun doing this?** If not, then none of the accomplishments matter in the long run. You can hit every milestone and still feel lost if the excitement is gone.

But if you remain enthusiastic, people notice. Whether you're applying for a PhD, postdoc, or a job, yes, your intellectual abilities matter—but people are hiring **people**. They want someone who brings positive energy to the lab, who's genuinely excited about their work.

So, while this approach may seem less structured, I believe it makes the journey more meaningful—and sustainable.

SC: So, why biology? What drew you to this microscopic world—especially as a cell biologist?

NB: I think it's largely because there's still so much to discover. There's something magical about looking through a microscope and witnessing an entire hidden world. Personally, I've always been drawn to art, and I find great beauty in the images we capture in cell biology. That aesthetic appreciation has shaped much of my scientific perspective.

When you observe cellular phenomena—some of which have evolved over millions of years—there's a sense of wonder that goes beyond just science. It's like standing in front of a Van Gogh painting. There's beauty and discovery coming together, which I think is quite unique to this field. That's what really pulled me into it.

SC: You started working in cell adhesion and trafficking at IISER, right?

NB: Yes, my PhD was in a lab focused on cell adhesion. I spent those years understanding that space in depth. But after finishing my PhD, I wanted to step away from that area and try something completely different—thinking I might return to cell adhesion later.

That idea, in hindsight, sounds naïve. In today's competitive environment, switching fields and then trying to return might seem like professional suicide. But I did it anyway.

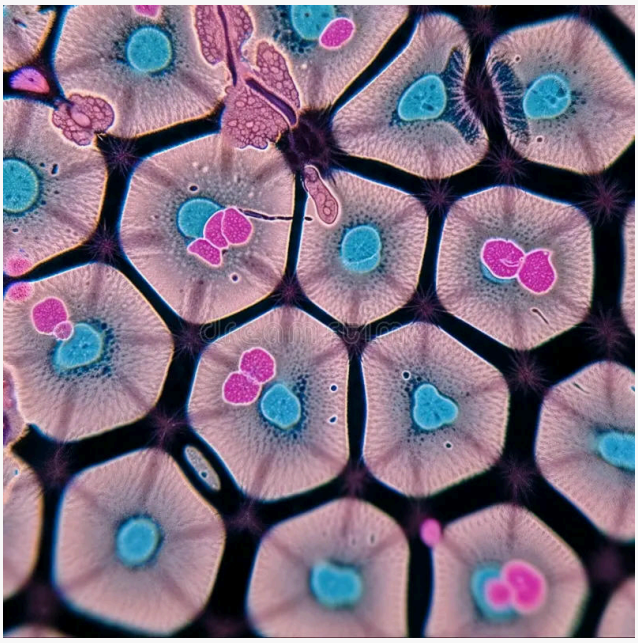


FIG 2 : *"... there's a movie called The Matrix ... which plays on a similar idea: there's this unseen system all around you that shapes everything. In biology, the extracellular matrix functions the same way. It's present everywhere and affects how cells behave and how they interpret their surroundings." - Prof. Balasubramanian*

SC: You were at the Cancer Research Institute at Tata Memorial Centre (TMC - now ACTREC) and then took a break from cancer biology, right?

NB: Yes. I moved to a lab that worked on **mammalian phototransduction**, which is worlds apart from traditional cell biology. It required me to learn new techniques and adopt a completely different way of thinking. Their questions and methods differed significantly from what I was used to.

At first, it was tough—new skills, unfamiliar concepts—but once I got through that, I gained not only new technical abilities but also a fresh mindset. That broader perspective eventually influenced my return to cell adhesion research.

When I decided to come back to that field, I identified a few top labs in cell adhesion and sent proposals. The first proposal I wrote was actually shaped by my experience in phototransduction—ideas about membranes that I had encountered there.

I sent the proposal to **Martin**, the top name on my list, not really expecting much. But within 15 minutes, I received a reply. I still remember the moment—I was too nervous to even open the email.

He wrote: "I've read your proposal. I have good news and bad news. The good news is, what you're proposing is true. The bad news is—we just submitted a paper proving it."

SC: Wow!

NB: Yes! But he added that they were working on other things and invited me to visit the lab if I was still interested. That experience changed everything.

What I learned is that stepping into a field you don't fully understand can be daunting, but also incredibly rewarding. That ability—to be comfortable with discomfort and still learn—is critical for anyone wanting to do science.

Many breakthroughs happen at the **interface of disciplines**, where different approaches meet. So yes, maybe I got lucky. But maybe that "luck" happened **because** I took the risk to explore something new—and brought that back into my core research.

SC: So that transition actually fueled your return?

NB: Exactly. It shaped my ideas and opened doors I hadn't imagined. That experience pushed us to explore areas we hadn't previously considered. Today, we work on organelles I never imagined studying and even do a fair amount of computational work—which was not something I expected.

What made that possible was the confidence to say, **"This looks interesting. I don't know enough about it yet, but I can learn."** That mindset is incredibly important. It allows you to bring new knowledge into your primary field of interest, creating fresh insights and connections.

For students and young researchers, it's critical to be comfortable stepping into unfamiliar territories. The most exciting science often happens when you bring two different areas together. You won't be an expert in both, but being willing to learn the second is what expands your perspective—and your possibilities.

SC: Exactly—and once you do, your entire vision broadens.

NB: Right. The willingness to learn, and the confidence that you **can** learn, makes all the difference.

SC: I loved your talk today—especially the part on mechanosensing. Could you explain for our audience how mechanosensing is related to cancer?

NB: Sure. Cells are not just biochemical entities—they are also **biophysical** entities. Every tissue The Matrix in your body has a certain stiffness and structure. A liver feels different from a heart because of these physical properties.

Now, if you remove all the cells from a tissue, what remains is the **extracellular matrix**—a kind of structural shell that defines the architecture of that organ. This matrix influences not just the shape, but also how cells behave within it.

You know, there's a movie called **The Matrix**—a classic from over 25 years ago—which plays on a similar idea: there's this unseen system all around you that shapes everything. In biology, the extracellular matrix functions the same way. It's present everywhere and affects how cells behave and how they interpret their surroundings.

It gives **biochemical cues**, yes—but also **biophysical** ones. Its architecture, shape, and stiffness all influence cellular behavior. So, it's quite brilliant: the body uses not only chemical signals but also physical ones to regulate cells.

SC: And how does that relate to cancer?

NB: In cancer, this becomes very relevant. I used to work at Tata Memorial Hospital, and surgeons there would often say: when you physically hold a tumor, its **stiffness** often gives you clues about its aggressiveness. Over time, they've noticed correlations—harder tumors are often more advanced.

So, cancer changes the mechanical environment. Tumor cells grow and alter the surrounding matrix, often making it stiffer. But what's more fascinating is how **cancer cells adapt**.

FIG 3 : *For his doctoral research in Biochemistry, Prof. Balasubramanian worked at the Cancer Research Institute (now ACTREC) at the Tata Memorial Center.*

Unlike normal cells, which need a very specific environment to survive—say, a liver cell won't grow in the lungs—**cancer cells can bypass that restriction**. They adapt to survive in environments with different biochemical and biophysical properties. They essentially override the usual requirement for adhesion and compatibility with the surrounding matrix.

One way they do this is by tolerating or even thriving in a **broader range of stiffnesses**. A normal cell will only grow within a narrow stiffness range—too hard or too soft, and it fails. But a cancer cell? It can grow just about anywhere—on soft or stiff substrates, or even on top of other cells.

SC: That adaptability is terrifying, but fascinating.

NB: It really is. That's why we study not just the **cell itself**, but also the **biomechanical properties** of the **environment** it's in. And it's a two-way street.

The **cell** has its own stiffness too—it can be soft or stiff depending on what's happening inside. And that cellular stiffness can influence how the surrounding matrix organizes and responds. It's not just the environment acting on the cell, but the cell reshaping the environment.

So, this dynamic interaction between **cell stiffness** and **matrix stiffness** plays a critical role in determining how cells behave—especially in diseases like cancer.

SC: I have a follow-up: stiffness is a biophysical property—but how is it translated biochemically within the cell?

NB: That's a great question. The key is that many **receptors respond to both biochemical and biophysical cues**—they don't fall into neat separate categories.

Take **integrins**, for example. These are receptors that bind to extracellular matrix proteins—so, they clearly participate in **biochemical interactions**. But the same integrin, when binding to a **stiffer matrix**, can trigger a **different response**. It's not about having a completely different mechano-specific receptor. Instead, the **same receptor behaves differently depending on mechanical context**.

SC: So it's the receptor behavior that makes the process mechano-responsive?

NB: Exactly. There **are** some receptors or channels—like **Piezo**, a mechanosensitive calcium channel—that are distinctly responsive to mechanical stimuli. But most of the time, it's about how **regular signaling molecules and pathways integrate mechanical input** alongside biochemical cues.

The key thing to understand is: **the same pathway** can respond to **both types of inputs**.

SC: So both the stiffness and the chemical environment affect the same pathway?

NB: Yes. In fact, many experiments that study cells on a matrix assume they're only looking at biochemical

signaling. But that matrix—especially on a plastic or glass dish—is extremely **stiff**, and that stiffness itself can activate signaling pathways.

So, when a pathway is activated, it might not be responding only to a chemical cue—it might also be reacting to the **mechanical properties** of the environment. Both cues converge on the same set of signaling proteins. You're not activating one "biochemical pathway" and one "biomechanical pathway"—you're activating **one integrated response**.

SC: And how do you observe the outcome of this dual signaling?

NB: All the cellular changes you typically associate with biochemical signaling—like **protein phosphorylation**, **gene expression changes**, **receptor clustering**, **localization**, or **signaling duration**—can also be triggered by **biophysical cues** like stiffness.

In fact, when cells are in their natural environment, they're constantly exposed to both cues at once. The cell doesn't consciously separate them—it just integrates the input and responds.

So, for example, if you expose a cell to a certain biochemical signal on a **soft** matrix, you may get one kind of response. On a **stiff** matrix with the same signal, the response may change—perhaps more intense or sustained. This is because the cell is integrating both types of information.

SC: But we're the ones who try to deconstruct it as two different types of input?

NB: Exactly. We separate them **experimentally** to understand their individual contributions. But the cell doesn't make that distinction—it just responds based on what it "feels." And everything we study—whether it's apoptosis, proliferation, migration—**has a biomechanical dimension**, because cells live in a mechanically dynamic environment.

That's what's so fascinating. Think about it—your **bone** is orders of magnitude stiffer than your **skin**. And yet, both support living cells. But if you **swap the environments**, say, place skin cells in a bone-like stiffness—they won't survive. The same goes for normal liver or kidney cells in an unfamiliar environment.

FIG 4 : *After completing his Ph.D., Prof. Balasubramanian carried out postdoctoral research on mammalian phototransduction at the University of Miami.*

SC: But cancer cells can?

NB: Yes, and that's part of what makes them so dangerous. **Cancer cells bypass adhesion-dependent regulation**. Adhesion involves receptors like integrins, which "read" both chemical and mechanical cues from the environment. When cancer cells lose that dependence, they gain the ability to grow in new places, even if the **stiffness and composition** are drastically different.

That adaptability is what enables **metastasis**—and makes cancer so difficult to treat. These cells don't care if the environment is soft or stiff—they just **find a way to survive and grow**.

SC: That's incredibly moving. Was there a specific turning point when you knew for sure that research was what you wanted to pursue?

NB: It was more of a gradual realization. I had some exposure to research early on because I had one or two relatives who were in the field, so I had some idea of what a research career looked like. But it took me some time to gain clarity. During my undergraduate years, I was still figuring things out. Eventually, I got into a Master's program where we had to do short research projects, and that's when things started to click. I realized I really enjoyed asking questions and trying to find answers—that process of discovery appealed to me. That's when I began seriously considering a research career.

SC: So I think a very simplified way to understand this is similar to the STRING analysis we currently use.

NB: Yes, absolutely. That's definitely part of it. But now imagine scaling that up to the level of an entire cell—not just one pathway or one molecule, but the full complexity of a cell. We're getting closer to having that capability. Right now, maybe only certain institutions with high-end computing power can do this, but very soon it'll be available to anyone.

A graduate student sitting right here at IISER Kolkata could type in a well-framed query—specifying certain pathways or molecular players of interest—and the system could pull out all the processes and pathways likely to be perturbed or affected. Then the challenge becomes: how do you decide what to prioritize? What do you choose to study, and why?

In my opinion, any research aiming toward drug discovery is going to be **dramatically** influenced by this kind of integrative, AI-assisted analysis.

SC: That's fascinating. I'm currently working on chemoresistance in breast cancer. Initially, I was assigned a different project, but I ended up exploring questions and directions that weren't originally part of the plan.

NB: And that's great. That's exactly what research is about—being curious and following questions that matter. But let me ask you: in the context of chemoresistance in cancer, how do you decide **which** molecule to work on?

I assume it's mostly based on your lab's focus—you're told, "We're interested in this molecule, can you explore it?"

SC: Yes, exactly. That's how it started. But it made me ask a deeper question—why are we even studying this particular drug in the first place? Why this one, and not another?

NB: That's an excellent question. And I think the way you ask that question will look very different even just a year from now.

For instance, you can already go to platforms like **DeepSeek** and input a structured query: "I know A happens, I know B happens, and I suspect C might be important. Is there a pathway or process that connects these three observations?" DeepSeek will attempt to answer that, and the best part is—it **shows** you how it's thinking.

It has a feature that reveals its internal reasoning—similar to what companies like Google **DeepMind** have demonstrated. It tells you: "Okay, based on your input, here's how I'm connecting A, B, and C. Here's what I looked at first. Here's the network I'm building. Here's how I'm linking these molecules."

If you realize you've made a mistake—for example, that those three molecules are specific to breast cancer—you can recontextualize your query, and it recalculates based on that input. It's incredibly intuitive.

SC: That sounds game-changing.

FIG 5 : *"There's something magical about looking through a microscope and witnessing an entire hidden world. Personally, I've always been drawn to art, and I find great beauty in the images we capture in cell biology. That aesthetic appreciation has shaped much of my scientific perspective." - Prof. Balasubramanian on what drew him to the microscopic world of cell biology.*

NB: It absolutely is. In many ways, it **democratizes** data analysis. You and I, sitting here at IISER, can use these tools. But so can a tenth-standard student in Rourkela—anyone, really—if they can frame the question well.

That's the key skill going forward: the ability to **frame questions correctly and in the right context**. These tools can then provide the kinds of insights that used to take years of manual study. It's not that the data wasn't available before—it was. But now the effort to parse, connect, and extract meaning from it is drastically reduced.

So, the way we ask scientific questions is going to evolve rapidly—and I think that's a very exciting shift for researchers everywhere.

SC: That's how you frame questions—and the more you ask, the better you get at it.

NB: Exactly. Over the past 6–8 months of using AI, I've realized that how you phrase a question really determines the direction it takes. You can push it to think harder or more creatively. That means your interaction with it is shaping the answers you get.

As students, I think it's crucial to engage with this now—it's inevitable and already reshaping how we think and how we choose what to work on. Say you're working on molecule X—if the AI can access and connect all existing information on it, regardless of when or where it was published, that's incredibly powerful. How you frame or tweak the query becomes key.

Your insight then comes from understanding the players involved—evaluating each component independently before connecting them. We've done this in the lab. A couple of years ago, we had an idea and only recently generated the data to support it. The interesting question is: if we had framed that idea as a query back then, could the AI have pointed us in this direction? It's a useful exercise—it helps us learn how to shape better questions that lead to meaningful exploration.

So just like we're looking for new targets, pathways, or drug processes, AI is already influencing how we do science—and will do so even more in the future. This could help us select better candidates or ask questions we might have overlooked before.

SC: Or we might end up neglecting questions we would have otherwise asked.

NB: That's true. The challenge is to streamline this—so if you move from one refined question to the next in a structured way, the answers you get will be more meaningful. I think AI will remain a tool, but companies will emerge saying, "We've figured out the smarter way to ask questions to get the best answers." They'll validate these systems—maybe show that their method leads to successful outcomes 80% of the time.

So it becomes about funneling the vast information efficiently to quickly arrive at something worth pursuing. That could change how we approach research entirely.

SC: And maybe in a few years we'll see if that has a negative effect?

NB: Honestly, I don't know yet. It's definitely going to have an impact. Whether that's positive or negative will take time to understand.

SC: Maybe we won't even realize it—because we'll be channelled into one dominant way of thinking.

NB: That's a real possibility. But what's certain is that it will change how we think. Right now, if you have three drug candidates and want to evaluate them under different contexts—say four parameters—and tell the AI, "These are the conditions I care about," it can give you a well-reasoned answer. But you'll still need to validate it. That part won't go away. So, I believe, going forward, this ability to process vast data and narrow it down meaningfully is going to override almost everything. The science—yes, it's important—but the way AI allows you to refine what you're asking will change everything.

People like Demis Hassabis, who shared the 2024 Nobel Prize in Chemistry for AlphaFold — the protein structure prediction AI developed at DeepMind (Google's AI division), predict that by 2030, we'll see intuitive AI —systems that learn how you think and anticipate your patterns. That's big. It means it may one day understand your style of reasoning.

SC: Do you think that's too much power for the world to handle?

NB: It's coming, whether we like it or not. So we'd better learn to work with it—and use it creatively, to push forward what we're trying to do. Yes. And you're also not sure you'll get there. In many ways, it's like blind faith—you believe you'll learn the method, that you'll get there eventually. But there's no guarantee.

And it's not for everyone. Some people will make it, some won't. But when someone does achieve something, you can tell—it feels elusive and remarkable. That's the interesting parallel I see between science and art.

There's a huge amount of uncertainty in both. For example, when you submit a paper—even if you're a Nobel laureate—there's always a question: will it be accepted, will it be understood the way you meant it? Sometimes ideas take decades to be appreciated.

Like in art—Van Gogh didn't sell his work, didn't get recognition in his lifetime. Maybe if people had acknowledged his genius, it would have changed his life.

FIG 6 : *Prof. Balasubramanian's second postdocral stint was at the University of Virginia, focusing on cell adhesion and trafficking.*

But it took 50 or 100 years for the world to understand what he had created.

He died not knowing how impactful his work would become. That's true in science too—you do your work with good intention, publish it, and move on. Who knows? A century later, someone might look at it and say, "This is incredible—they were ahead of their time." But you'll never know.

SC: That's beautiful.

NB: So I think the parallel between science and art is very real. And when something remarkable happens—whether in art or science—for me, it feels like lightning striking. It's magic, built on years of training, experience, and effort. But even the creator didn't fully know they were capable of it.

That's what I feel when an experiment yields something extraordinary. You follow the method, trust your instincts, and do the work with care. You hope it leads to something unique. Sometimes it does, sometimes it doesn't.

Many artists and scientists have lived their whole lives dedicated to their work without ever being recognized. But they still did it—for exploration, for the belief that it mattered. That, to me, is the connection between the two worlds.

SC: Have you pursued any other creative interests beyond academics?

NB: I used to paint. I still sketch occasionally, but these days I mostly do photography. So yes, I've always kept a creative pursuit alive.

I think it's important for scientists to have something creative outside of their research. You may not always see it that way, but the very act of doing science requires creativity. I don't think there's a single scientist out there who is completely devoid of it. It's about discovering and nurturing that part of yourself.

We are wired to think creatively—that's what makes scientific exploration possible. So having a creative outlet helps. It has always helped me.

SC: Sir, moving from that—many people outside the world of science often feel estranged from it. What would your approach be to bring science closer to the general public?

NB: I think, first and foremost, we scientists have to be approachable. Science, much like art, is a deeply isolating pursuit. When you're building an experiment or crafting a research narrative, it often happens in solitude. Others may support you, but the core of the work is yours alone.

Many scientists are comfortable being alone, lost in their thoughts. That's part of the reason why we may appear aloof or uninterested in engaging. People often hesitate to approach scientists, partly because of the perception that we're intellectually distant or hard to relate to. If we also come across as unapproachable, that only reinforces the gap.

That's why the onus is on us to change that perception. If people feel you're open to answering their questions, they're more likely to ask. It's important, especially today, for the general public to understand what goes into scientific work—the persistence, the setbacks, the drive. It's not just about funding. Yes, money matters, but the personal investment, the dedication of the scientist—that's what truly drives discovery.

But people outside the field won't know this unless we talk about it. Every interaction is an opportunity to bridge that gap. You meet someone on a train, and they ask what you do—that's a moment to connect. Just like this conversation: I could be doing something else right now. But if even two people listen and come away with a deeper understanding of science and what it takes, then it's worth the hour or hour and a half.

Everyone connected to science has a responsibility to communicate not just what we do, but how we do it—and why it matters. People celebrate athletes as national heroes, but how often is a scientist publicly recognized or celebrated? That needs to change.

If we're out there telling our stories—sharing the challenges, the breakthroughs—then people will start to see science differently. The excitement of discovery, the thrill of overcoming obstacles—if that's communicated well, people will feel connected to it.

That's why athletes resonate. You saw Suryakumar Yadav take that incredible catch, and it made you feel something powerful. So naturally, if you met him, you'd want to shake his hand. Science should aim to evoke that same feeling—that awe, that thrill of achievement. If we can make people feel that about science, then maybe one day someone will shake a scientist's hand and say, "I read about what you did. It was incredible." That's why this kind of communication matters.

SC: One last question, can you tell us more about the International Conclave on Citizen Science happening in July?

NB: Sure. It's being organized by the Pune Knowledge Cluster, and I believe this is the first time they're holding such an event. There are many citizen science initiatives across India—and globally—like **iNaturalist**, which I use a lot. You can upload photos of plants, moths, or birds, and it identifies them using existing databases. It even shows distribution data and other nearby sightings.

So, the idea of the conclave is to bring together various citizen science projects and talk about how these initiatives contribute to scientific understanding. It's also a platform to share ideas and experiences from different regions and disciplines.

FIG 7 : *At IISER Pune, Prof. Balasubramanian leads the Cell Adhesion Lab, working on "cell adhesion-mediated regulation of trafficking and organelle function and its implications for cell migration and anchorage dependence".*

SC: Oh, like an exchange of ideas?

NB: Exactly. It's about sharing how these projects work and how citizen involvement can support scientific research. There are such initiatives in India too, and I think it's important we talk about them. It's an exciting first-time effort. Where did you come across it?

SC: Sir, thank you so much. This was a really amazing session. Any final thoughts or a message for us research students?

NB: Enjoy the process. You're in a very privileged space - to be able to ask questions that you're curious about, and with some luck, even make a profession out of answering them. That's rare.

It won't always be smooth. Things won't always go according to plan. But if you truly enjoy what you're doing, you'll always find a reason to keep going. And that's what makes this sustainable.

Don't pressure yourself too much with timelines. I see a lot of students telling themselves, "If I don't get here in five years, I'm a failure." That's not true. Even ten years can feel short if you enjoy the journey. But if you don't, even six months can feel unbearable.

It's like someone learning music saying, "If I train for ten years, will I sing like Kishori Amonkar?" No one can promise that. Not even Kishori Amonkar knew she'd become who she was. All we can do is teach you the tools, and if you enjoy the journey, maybe you'll go even further. But it's the joy in the process that matters most.

SC: Yes, it might or might not happen.

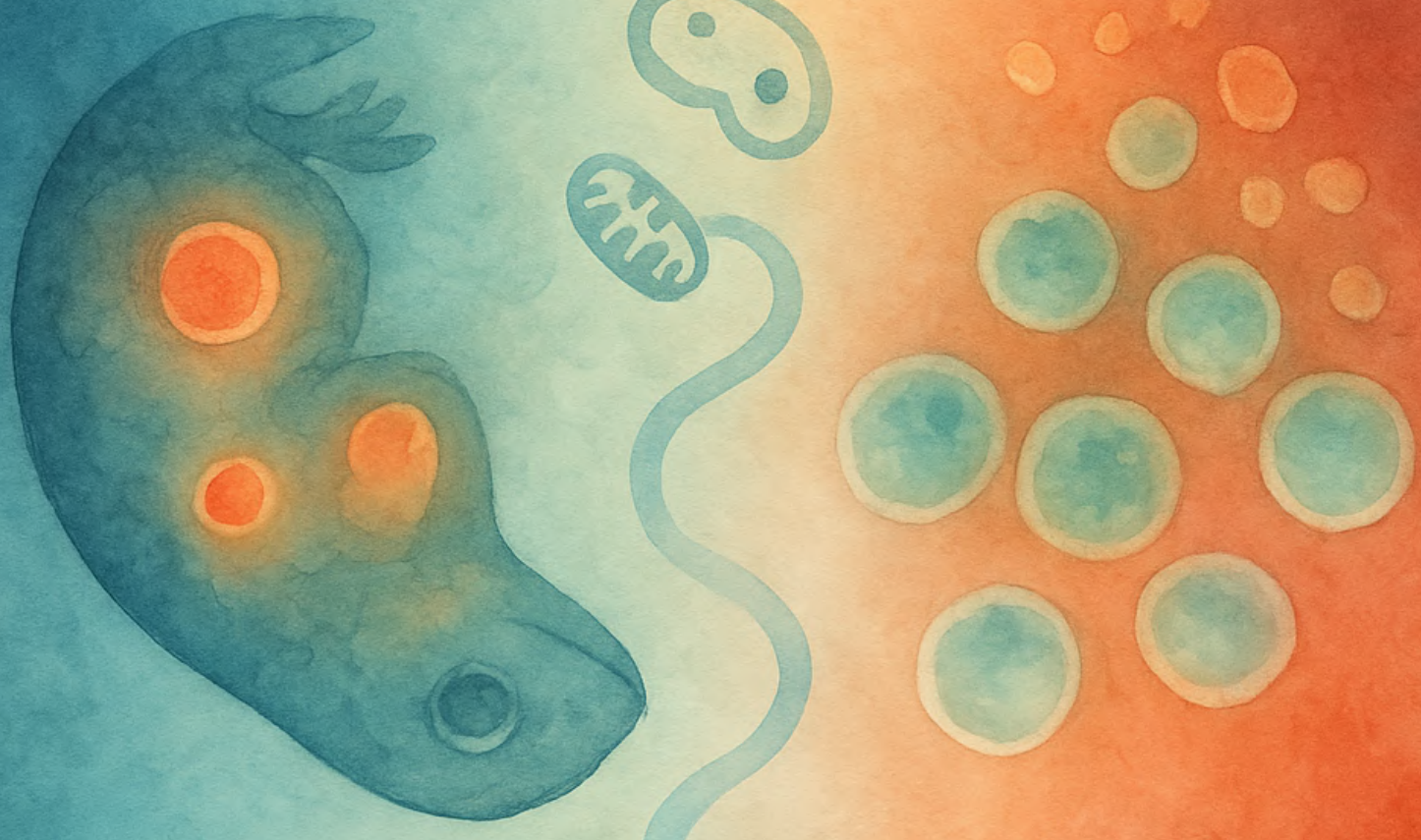
NB: Exactly. That uncertainty is part of the journey. If you let that uncertainty weigh you down every day, it'll stop being enjoyable—and then it's not sustainable. So, find a way to enjoy what you're doing. Everything else will follow.

SC: Thank you so much. This was truly inspiring.

NB: Thank you.

Chandrima Shaha (IICB, Kolkata)

Cell Death Makes Living Easier



Why do cells choose to die? From shaping embryos to protecting cell communities, programmed cell death is one of nature's quiet survival tricks. Prof. Shaha explores how life depends on death - even in the tiniest organisms.

Progress in science depends on new techniques, new discoveries, and new ideas, probably in that order.

— **Sydney Brenner**

Introduction

All living beings eventually die. Cells, as the fundamental units of life, became the primary focus of research to understand cell death. Over the past one and a half centuries, research on cell death has expanded, aided by groundbreaking advances in microscopy and biochemistry. The main focus has been on the **possible origins** and mechanisms of death when a cell dies either because it is aged or because it could not recover from injury (Fig 1). Because death paradoxically supports survival, questions about the process continue to fascinate biologists, chemists, and philosophers alike. This article will examine the intriguing questions and debates that dominate the field.

Scientists in the early and mid-19th century were interested in exploring how nature functions, because much was unknown. It was the time when **Charles Darwin** took the famous voyage of the Beagle and started working on the theory of evolution. His observations were published as a book titled "The Origin of Species" in 1859, and the theory of evolution by natural selection became the cornerstone of modern biology [1]. Around this time, **Carl Vogt**, a German scientist, who was studying the remarkable transformation of tadpoles into toads, put forth the theory that cells die to aid in the development of an organism from the embryo. Just over a century later, in the mid-1960s, a landmark paper was published by **William Lockshin** and **Caroll Williams**, describing cellular changes during insect metamorphosis, where cell death was necessary for shaping the organism. Importantly, they coined the term "Programmed Cell Death" (PCD), indicating the existence of a genetically programmed death process [2]. By then, immense advances in microscopy had allowed both macro and micro viewing, providing opportunities for great discoveries.

About seven years later, in 1972, three Australian scientists, **Kerr, Wyllie, and Currie**, published a landmark paper on cell death where they coined the term 'apoptosis' (Fig 2). It was inferred that complex biochemical processes brought about multiple morphological changes necessary for disposal of the dead cells or cellular corpse, by the macrophages. They defined a series of common cellular alterations, like cell

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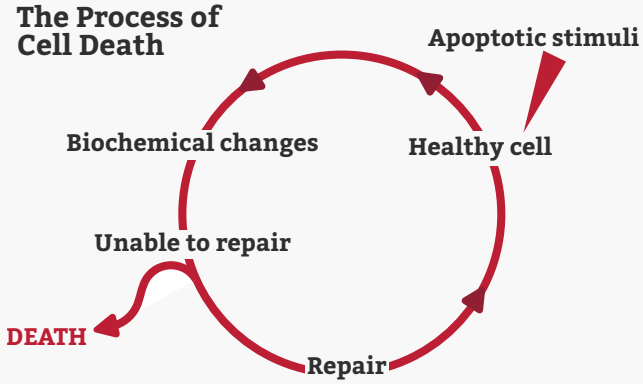


FIG 1 : *A schematic representation of the process of cell death.*

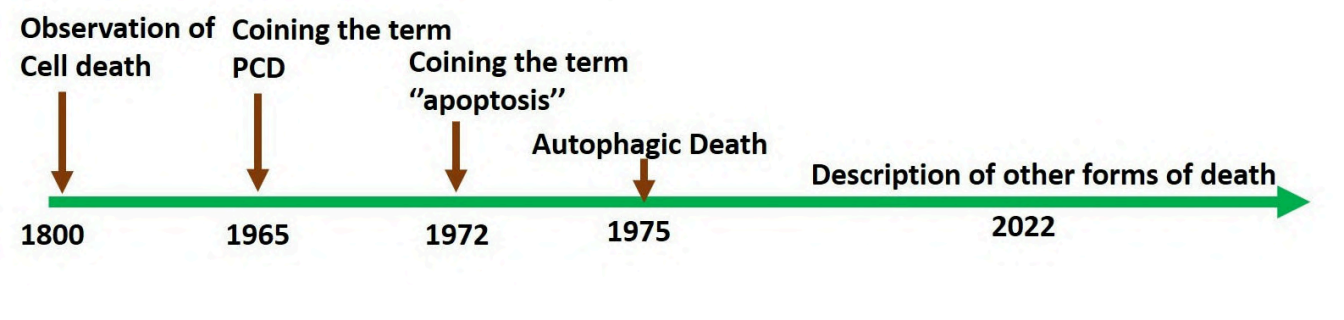


FIG 2 : *The timeline of landmarks in cell death research.*

shrinkage, nuclear fragmentation, membrane blebbing, and the formation of apoptotic bodies, that came to be recognized as the hallmarks of apoptotic death (Fig. 3). **Apoptotic death** is a subset of PCD that also includes other forms of death, with apoptosis being the most widely researched [3]. Between 1980–1990, genetic and molecular mechanisms related to apoptosis began to emerge, with the mapping of molecular pathways described between 1990 and 2000, and the therapeutic potential of the process and translational application trials started from 2000 onwards. Functionally, cell death supports cell survival by removing sick, damaged cells and cells with genetic errors to maintain homeostasis and is the major form of death during organismal development.

The symphony of apoptosis

The apoptotic process can be viewed as a symphony of signaling, like an orchestrated process with multiple players each having their specific roles, much like an intricate musical composition. The concert is required because when cells are eliminated from the body, the process needs to be precise to avoid damage to other cells. Therefore, the most important feature of the energy-dependent process of apoptosis is a **clean form of death**, in which cellular contents do not leak out during elimination. The apoptotic bodies that are generated, are membrane-bound forms picked up by phagocytes, the sentinels of the immune system, thereby preventing leakage of harmful lytic enzymes. Since the development of protein crystallography, the **information on molecular interactions** during the apoptotic process has led to a greater understanding of the molecular processes that regulate apoptosis. There are two main pathways of apoptotic death: the intrinsic pathway, mediated through the mitochondria, and the receptor-based pathway, where signals are received and transmitted by cell surface death receptors. For each of these pathways to induce apoptosis, specific enzymes called caspases are required to cleave substrates.

Caspases are a family of cysteine-aspartic acid proteases that are essential at various stages to complete the death process. They are produced as inactive pro-enzymes that are cleaved and activated as needed by the cellular machinery; otherwise, unnecessary cleavage could damage the cell. Functionally, two types of caspases exist: the initiator caspases activate another set of enzymes called effector caspases, responsible for digesting cellular components. The intrinsic pathway of apoptosis is mediated through the mitochondria via a complex interaction of pro- and anti-apoptotic molecules located on the mitochondrial membrane. When stress signals such as DNA damage, radiation, toxins, or oxidative stress are received, **pro-apoptotic molecules like Bax and Bak** and others form pores on

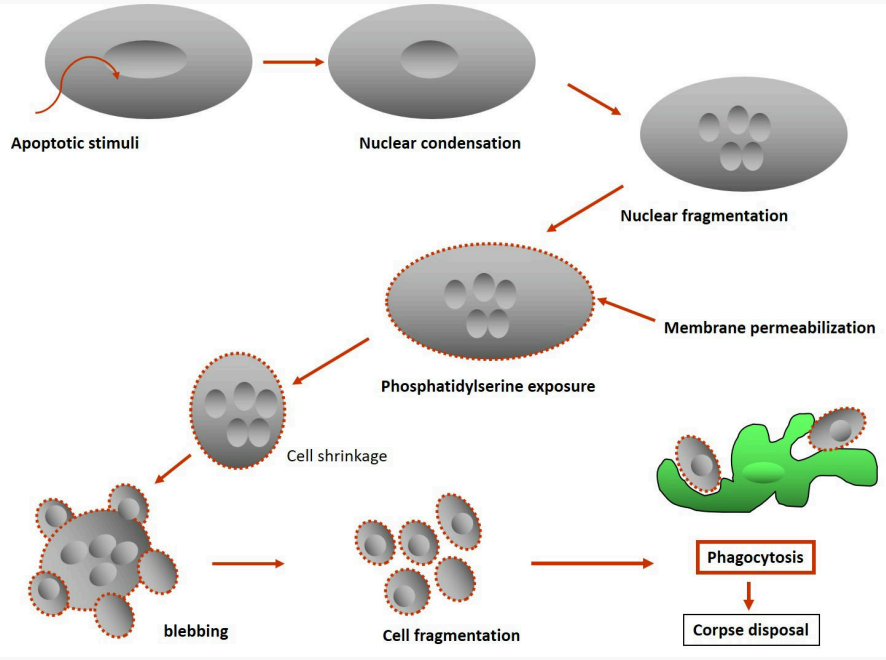


FIG 3: *A schematic representation of the morphological changes that occur during cellular apoptosis.*

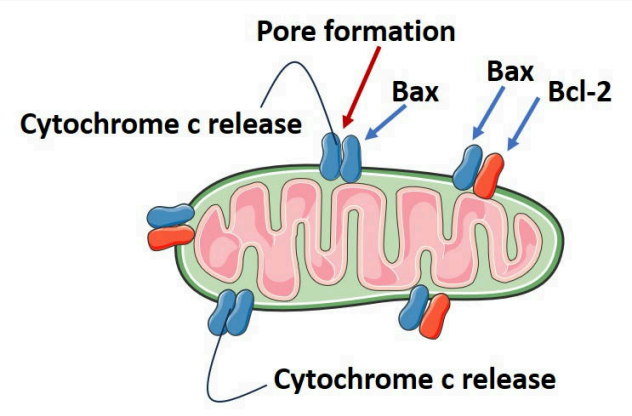


FIG 4 : *The interaction of pro and anti-apoptotic proteins on the mitochondria leading to the release of cytochrome c.*

the mitochondrial membrane. The formation of these pores, which is harmful to cellular processes, is normally prevented by the interaction of anti-apoptotic proteins like Bcl-2, BcL-xL, and MCL-1 with the pro-apoptotic proteins. As a result of pore formation, the release of cytochrome c, a component of the mitochondrial respiratory chain, occurs, initiating the dismantling process of the cell (Fig. 4). Cytochrome c release into the cytosol triggers the cytoplasmic protein Apaf-1 (apoptotic protease activating factor-1) to bind to it, forming the **"apoptosome" complex**. This complex recruits pro-caspase-9 and activates it to active caspase-9.

The receptor-mediated death process is triggered by the interaction of the death ligands with the cell surface death receptors like **TNF-alpha and Fas receptor**. This binding triggers FADD (Fas-associated death domain protein) to bind to the cytoplasmic part of the receptor and recruits procaspase-8 to form a structure named **DISC** (death-inducing signaling complex). Here, the activation of procaspase-8 is completed. Both caspase-8 and -9 are initiator caspases and activate the executioner caspases-3 or -6, or -7 to cleave cellular components like the cytoskeletal proteins, DNA repair enzymes, nuclear lamins, and DNA (Fig 5). As a consequence of these enzyme activities, the cell shrinks and breaks into small fragments called the apoptotic bodies, which are engulfed by phagocytes, the sentinels of the immune system, ensuring clean removal of cellular debris as referred to earlier. Apart from the above two pathways using caspases, there is a **caspase-independent death pathway** where cells undergo apoptosis using a mitochondrial protein, the Apoptosis-Inducing Factor (AIF), that travels from the mitochondria to the nucleus to degrade DNA after the cell has received a death signal [4].

Elegant models for apoptosis research

For any research program in biology, suitable cell systems or model organisms are necessary. These can be selected based on the research question, ease of technical manipulation, and similarity to the human system. Certain organismal models have been favorites for apoptosis research. A transparent worm, **Caenorhabditis elegans**, consisting of 1091 cells, where 131 cells die at a specific time during development by apoptosis, has been used in many studies [5]. Three collaborators, Sydney Brenner, Robert Horvitz, and John E. Sulston, used C. elegans as their model to study the apoptotic process. Their discoveries on programmed cell death were awarded the **Nobel Prize** in Physiology or Medicine in 2002. Their research revealed the involvement of four primary genes, EGL-1, CED9, CED4 and CED3, for apoptosis (Fig. 6). Genes with similar functions were identified in humans. Apart from C. elegans, other organisms used for apoptosis research include Drosophila melanogaster [6], Mus musculus, and Danio rerio [7]. Apoptotic pathways in **Mus musculus** are highly conserved with humans, making it a suitable model for studying mammalian apoptosis. Danio rerio is ideal for studying developmental apoptosis.

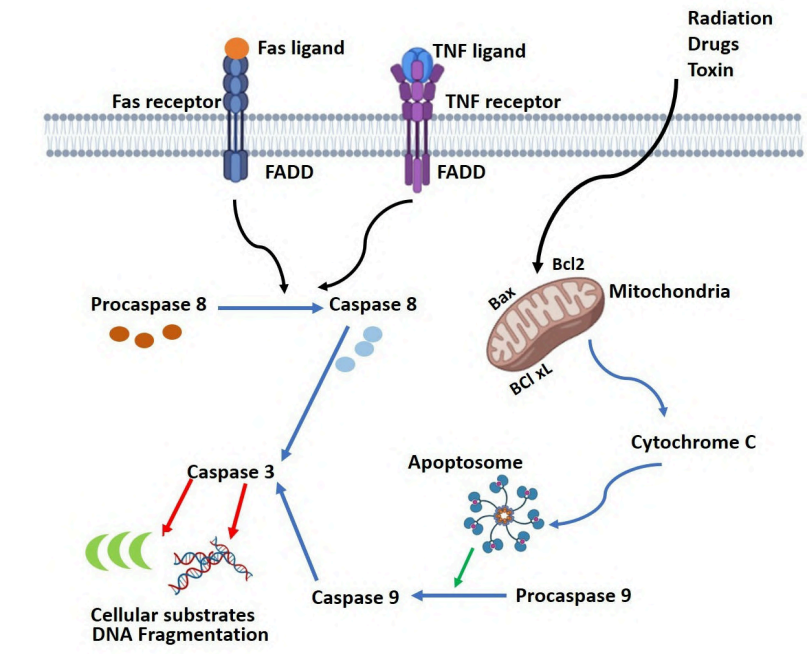
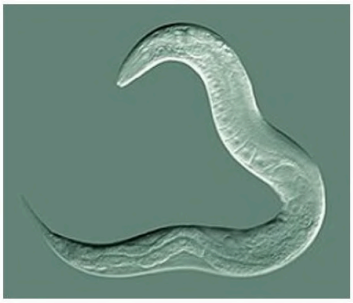


FIG 5: *Schematic diagram of the apoptotic pathways. Both the intrinsic pathway and the cell death-mediated pathway are shown, one mediated through the mitochondria and another through the death receptors on cell surface.*



131 cells out of the 1090 somatic cells formed during development undergo PCD. This cell death is a crucial part of shaping the final organism, ensuring the correct number and arrangement of cells in various tissues.

EGL-1, CED-9, CED-4, CED-3

FIG 6 : *Sydney Brenner, Robert Horvitz, and John E. Sulston, used C. elegans as their model to study the apoptotic process. Several genes linked to the apoptotic process were discovered. Their discoveries on programmed cell death were awarded the Nobel Prize in Physiology or Medicine in 2002.*

Why did selection choose apoptosis?

As developments in molecular and cell biology progressed, more and more new questions arose. Self-induced death as apoptosis was viewed as an **evolutionary puzzle** because selection is expected to favour the development of processes that help the individual to avoid death and propagate. Then how was the selection of the death process possible? At this juncture, ideas enforced the belief that the origin of PCD coincided with the emergence of multicellular organisms on Earth. The first multicellular organisms appeared around one billion years ago. Were they the first organisms whose cells were capable of self-destruction for the benefit of others? It was perceived that due to a close network of cells, **some members could undergo suicide** to protect others in their immediate niche. It was believed that selective pressure acted on the multicellular body to evolve cell death as a mechanism of survival because it is the evolutionary 'unit of selection.' Because biological systems are hierarchically organized, selection could operate at different levels, leading to cell death occurring at multiple levels without affecting the whole. Therefore, self-destruction through PCD could be seen as an extreme form of cooperation that is **costly to the lower level but beneficial for the higher level**, that is, at the level of the organism [8].

Is apoptotic death possible in unicellular organisms?

Apoptosis in unicellular organisms is a fascinating idea because, being single-celled, they do not need to act altruistically toward others. Or do they? In unicellular organisms, **"cell suicide"** or apoptosis through PCD may not be beneficial because, evolutionarily, death at the individual cell level could be considered a failure. Therefore, any gene that codes for death would be negatively selected. The notion that apoptosis evolved for the benefit of multicellular organisms started to shift around the mid-1990s when cell death was observed in unicellular organisms across various phyla. These included prokaryotes, phytoplankton, autotrophic and heterotrophic flagellates, yeasts, slime moulds, and ciliates. Studies investigating caspase homologues (metacaspase, orthocaspase, and paracaspase) containing the p20 domain—which includes the catalytic dyad formed by histidine and cysteine—revealed the presence of structural homologues widely spread across archaea, bacteria, and eukaryotes. This **indicated the presence of some form of apoptotic process** in these organisms.

However, para-caspases have not yet been shown to induce PCD functions. The question was, can death be a better strategy than survival for unicellular life forms? Who would benefit? The pursuit of answers regarding how cell death was selected in single-celled organisms and how it might benefit them led to multiple theories. It was suggested that, since unicellular organisms spend most of their lives in multicellular communities, they have developed **communication methods** through which they receive, detect, interpret, and respond to signals from others (Fig. 7). This behavior mimics multicellular functions. Examples include quorum sensing, where single-celled organisms respond to population density via signaling molecules; responses to chemical cues; electrical signaling; light-based communication; or horizontal gene transfer, as observed in bacteria.

Research suggests that cell death evolved in single-celled organisms due to their complex existence. Therefore, it is possible that cell fate, in terms of life and death, may also be influenced by an **evolutionary scenario** involving social control of death at the colony level. Unicellular populations that are mostly clonal share close genetic similarity. Also they stay in close communities, either as a community of the same species or a combination of multiple species (Fig. 7). Consequently, altruism expressed by individual members would benefit other members of the cell pool, but it would be **costly to the altruistic individual**. Possibly, mechanisms of kin selection are employed, where individuals support

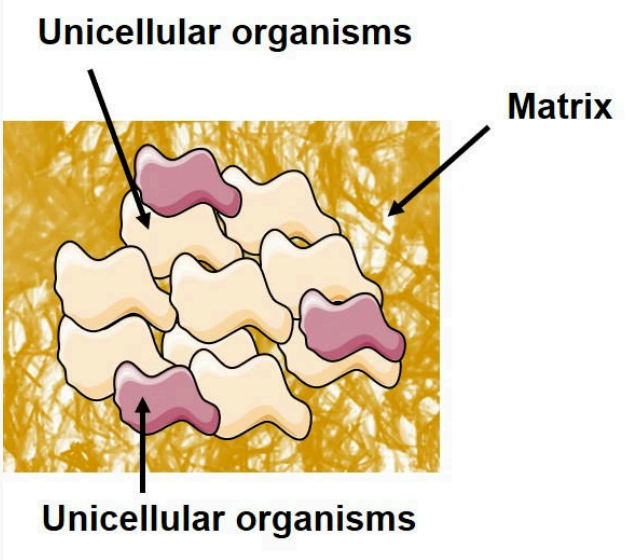


FIG 7 : *Sydney Brenner, Robert Horvitz, and John E. Sulston, used C. elegans as their model to study the apoptotic process. Several genes linked to the apoptotic process were discovered. Their discoveries on programmed cell death were awarded the Nobel Prize in Physiology or Medicine in 2002.*

relatives who share a significant portion of their genes, thereby enhancing their inclusive fitness. It appears that bacteria possess mechanisms that may influence internal death, mortality from an arms race, competitiveness, cooperation, selfishness, and altruism.

What benefit is it to the unicellular organisms of expressing apoptosis? Given that they live in close associations, they use apoptosis to discard unfit cells to help the colony to be healthy. Restriction in numbers is an important issue in any niche so as to not to create a stressful situation through overcrowding. Apoptosis is the preferred way because it happens **without the release of harmful agents** in a colony, therefore, a clean removal benefits others. This is also true for infectious agents, as they have to restrict their numbers so as not to kill the host. In this context, it is pertinent to mention that the infectious agents have developed an arsenal of mechanisms that have the potential to thwart the host's protective responses.

The same fundamental elements of the cell death program are activated in various cell types, whether they respond to developmental signals, immune signals, oxidative stress, injuries, or infections. The numerous components of cell death machinery are evolutionarily conserved from worms to humans; however, a lot needs to be researched for similarities and peculiarities of the cell death pathways in single celled life to understand the thread that exists between the uni and multicellular life [9,10]. Initial selection of the functional domains of molecular effectors that control death, aging, and adaptation might have favored their original selection, and this is true for both unicellular and multicellular organisms. Some of the molecules associated with cell death may have been associated with survival pathways that were later adapted for the death signalling. Cell death in unicellular organisms remains an attractive area for further research to understand an important component of the biology of survival.

References

1. Berry A, Browne J. PNAS. U S A. 26:119: 2022. doi: 10.1073/pnas.2122144119.
2. Lockshin RA, Williams CM. J Insect Physiol. 11:123-33. 1965 doi: 10.1016/0022-1910(65)90099-5.
3. Kerr JF, Wyllie AH, Currie AR. Br J Cancer. 26:239-57. 1972 doi: 10.1038/bjc.1972.33.
4. Yuan J, Ofengeim D. Nat Rev Mol Cell Biol. 25:379-395. 2024. doi: 10.1038/s41580-023-00689-6.
5. Zuryn S. Semin Cell Dev Biol. 15;154(Pt A):1-3. 2024. doi: 10.1016/j.semcdb.2023.07.006.
6. Zhou L. Adv Exp Med Biol. 1167:105-112. 2019. doi: 10.1007/978-3-030-23629-8_6
7. Costa B, Estrada MF, Mendes RV, Fior R. Cells. 2020 9:293. doi: 10.3390/cells9020293.
8. Ameisen JC. Cell Death Differ. 9:367-93. 2002. doi: 10.1038/sj.cdd.4400950.
9. Kulkarni M, Hardwick JM. Annu Rev Genet. 57:435-459. 2023 doi: 10.1146/annurev-genet-033123-095833.
10. Van Dyken JD, Zee PC. Am Nat. 204:468-481. doi: 10.1086/732199.

From Cancer Research to Paradigm Shifts: Dr. Sushanta Roychoudhury With InScight

Swarnendu Saha (IISER Kolkata)

From the Chittaranjan National Cancer Research Institute in Kolkata to postdoctoral work at a university in the USA, Prof. Sushanta Roychoudhury's career has spanned multiple laboratories, research fields, and continents. Visiting IISER Kolkata as a panelist for BAW 2025, Prof. Roychoudhury kindly took some time to speak with InScight.

Also available online, at scicomm.iiserkol.ac.in

SS: Hello Sir, I welcome you to this interview session with Team InScight. My name is Swarnendu Saha. My first question to you is: How did you get here? Could you briefly take us through your academic and research journey?

SR: Hello Swarnendu, thank you for having me. Well, my journey started with a BSc in Chemistry (Honours) at the University of Calcutta. At that time, I had very little idea about biochemistry as a subject.

Later, I joined the MSc program in Biochemistry at the same university. Once I entered the department, I found the subject truly fascinating. The way the courses were taught really helped us develop a research-oriented mindset. Biochemistry, as you know, is quite exploratory because we're constantly trying to understand the chemistry behind living systems.

During my master's, I realised that there were real opportunities to pursue research in this field. So, after completing my MSc, I looked for research institutes where I could do my PhD.

After earning my PhD, I went on to do postdoctoral research, and gradually, I was able to establish myself as an independent researcher. And that's how my academic and research journey unfolded.

SS: So where did you pursue your PhD, sir?

SR: I did my PhD at the Chittaranjan National Cancer Institute in Kolkata. I had a keen interest in cancer research, and at that time, it was the only dedicated cancer research institute in the city. So I joined there for my doctoral studies.

SS: Since it's essentially a hospital, right?

SR: Yes, it's a hospital-cum-research institute. There's a full-fledged research wing alongside the hospital. This structure is actually very advantageous because it allows you to experience both sides: basic scientific research and its direct clinical applications.

FIG 1 : *Dr. Sushanta Roychoudhury obtained his BSc. in chemistry and MSc. in biochemistry from the University of Calcutta. [Source: collegebatch.com]*

SS: Sir, in your days—or even today—how is research or a PhD done at institutes like the Chittaranjan National Cancer Institute fundamentally different from the same kind of research done elsewhere? For instance, I'm a student at IISER Kolkata, which primarily focuses on research with very little direct public interaction. And there are places like the University of Calcutta, where academics hold more weight than research.

How do these places differ from institutes that are closely linked to medicine and public service?

SR: That's a very relevant question. See, in biological research, we aim to understand the biology of living systems, and in humans, one important biological manifestation is disease. It depends on your research question. If you want to study a fundamental cellular function, institutes like IISER or university are ideal. However, if you want you to study disease mechanisms and ways to ameliorate it then places like medical institutions are ideal.

So if your research area focuses on disease—like cancer—then places like hospitals with dedicated research wings are actually more suitable. They naturally bridge basic research and clinical application.

In Western countries, large universities often have affiliated hospitals, which allows strong interaction between scientists and clinicians. Unfortunately, in our country, this integration isn't common. Research often happens in a disjointed manner, so even though we might study diseases in labs, we may lack direct clinical insight.

Personally, I realized this more strongly after retirement, when I joined Saroj Gupta Cancer Centre & Research Institute (also known as Thakurpukur Cancer Hospital), and saw firsthand how valuable it could have been if we had collaborated closely with clinicians right from the start. But systemic gaps still limit this synergy in India.

SS: I see. My next question is: Was your PhD research closely related to what you later did as an independent researcher at IICB? Or did you have to adapt to new directions after your PhD?

SR: I strongly believe in adaptation, and I actually enjoy the challenge of exploring new areas.

Although my broad background always stayed within cancer research, at different stages I focused on different aspects. For my PhD, I worked on drug–membrane interactions—studying how chemotherapeutic drugs interact with cancer cell membranes.

In my postdoc, I worked on growth factors—molecules that help cells proliferate. Then I shifted to research on the hepatitis B virus, which is known to cause liver cancer.

When I returned to India and started my own lab, I initially worked on Vibrio cholerae genome mapping—which had nothing to do with cancer—because genome mapping was an emerging area at the time. Later, I moved back into my interest area: cancer, focusing on cell biology, molecular biology, genetics, and genomics.

So, at each phase, I deliberately shifted gears. There are pros and cons to this, but I found it intellectually fulfilling.

SS: So your PhD topic—drug–membrane interaction—means once cancer is detected, the focus was on understanding how drugs behave with cancerous cells and how new drugs can be developed. Is that correct? I ask because I come from a physics background.

SR: Exactly. Chemotherapeutic drugs are small chemical molecules designed to interfere with essential cellular processes. While they target cancer cells, those same vital processes also exist in normal cells, which leads to toxicity and side effects.

My PhD focused on how these drugs pass through cell membranes and whether they also change the membrane properties of cancer cells, potentially making them more sensitive—or sometimes resistant—to treatment. That was the core idea of my research.

SS: Okay. But if I may ask a very fundamental question: Why is there cancer at all? And because of these underlying reasons, do you think it's ever possible to discover a method that can completely cure cancer—100%?

SR: That's a thoughtful question. At its core, cancer is the uncontrolled proliferation of our body's own cells. Normally, cells are programmed to know when to divide, how many times to divide, and when to die. But cancer cells defy these natural rules and keep dividing uncontrollably.

In fact, I often tell my students: If someone could live for 150 or 200 years, they would almost inevitably develop cancer. One reason we see more cancer cases today is simply that life expectancy has increased—people live long enough for cells to accumulate mutations and sometimes behave abnormally.

Apart from aging, external factors like radiation, diet, environmental chemicals, and lifestyle choices also increase the chance that cells may undergo harmful changes.

Now, it's also true that not everyone will get cancer. Our bodies have several defense mechanisms—like DNA repair and immune surveillance—to eliminate or control abnormal cells. Cancer develops when those defense systems fail or get bypassed.

So, in short: cancer arises partly from natural biological processes and partly from external triggers. And because the disease itself comes from our own cells evolving in unexpected ways, it's unlikely we'll find a single, universal cure for all cancers. Instead, we keep discovering better and more targeted ways to control, treat, or prevent specific types.

SS: Is smoking and chewing tobacco really the cause of cancer? Because even today, though tobacco consumption has decreased in some places, cancer cases still rise. So does tobacco definitely cause cancer, or does it just increase the chance?

SR: See, under normal circumstances, our cells grow and divide in a controlled way, guided by strict regulations. Those regulations can break when external agents—like chemicals from tobacco—interfere with our genetic material, the DNA.

Cigarette smoke and chewing tobacco contain thousands of chemicals, many of which are carcinogenic or mutagenic. This means they can directly damage or alter DNA. If such changes happen in critical genes that control cell growth and division, cancer can develop.

It's true that people often say, "My grandfather smoked his whole life but never got cancer," while someone else might get cancer at 40. That difference comes from many factors—like how efficiently each person's body can repair DNA damage, or whether the mutation hits a particularly vulnerable gene.

So, while smoking and tobacco use do not guarantee cancer in every case, they dramatically increase the risk. Over decades, data worldwide have repeatedly confirmed this link. So the question becomes: why knowingly take

FIG 2 : *Dr. Sushanta Roychoudhury obtained his PhD in drug-membrane interactions from the Chittaranjan National Cancer Institute (CNCI) in Kolkata. [Source: maps.google.com]*

that risk? That's why we advise quitting tobacco, even if someone you know avoided cancer despite smoking for years.

SS: Sir, did you spend time abroad, or was your academic journey mainly in India?

SR: After my PhD, I went to the University of Pennsylvania in Philadelphia, USA, where I did my postdoctoral research for about five and a half years.

SS: And you did only one postdoc?

SR: Actually, I did two postdocs there—both at the University of Pennsylvania. First, I worked on growth factors, and then I shifted to studying the hepatitis B virus, which is linked to liver cancer.

SS: Other than the US, did you spend academic time in other countries?

SR: No, my formal postdoctoral training was entirely in the US. Later, I visited other countries for conferences, meetings, and collaborations, but my postdoctoral work was done at Penn.

SS: These days, many students—after completing a bachelor's or master's in India—look to go abroad, mostly to Western countries and sometimes to the East. As someone who has experienced this yourself, do you see this trend as positive, or do you think it could be detrimental for India?

SR: Personally, I don't see it as detrimental. In fact, I think it can be very beneficial—not just for the individual, but eventually for the country too.

When I went abroad for my postdoc, the scientific culture and lifestyle were very different from what I had known in India. It taught me how to survive and succeed in a highly competitive, resource-rich research environment. That experience builds a lot of confidence and independence as a scientist.

At that time, research infrastructure in India wasn't as developed. But today, things have improved greatly—top Indian institutes now offer excellent training, facilities, and exposure.

Still, working abroad pushes you out of your comfort zone. Being alone in a different country, competing and collaborating at the global level—it shapes you in ways local experience sometimes can't. It teaches resilience, adaptability, and a broader way of thinking.

So, at some point in life, I think it's very valuable to go abroad, test yourself in a new environment, and then hopefully bring back that experience to enrich research in India.

SS: Sir, another thing I'd like to ask: In India, when someone wants to build a scientific career—say, as a professor in universities or as a scientist in national institutes like CSIR labs, the Department of Space, Department of Atomic Energy, ICMR, and so on—does having an academic background abroad really give an upper hand over colleagues who have done all their education in India, regardless of how strong those backgrounds are?

SR: Unfortunately, yes. Even today, students or scientists who have been trained abroad often get a bit of an advantage. But it really depends. I wouldn't say it's true in every case. If someone has done very good work in India and shows clear capability and contributions, I think the authorities do recognize that and consider it seriously. So, while an international background does help, it's not the only thing that matters.

SS: In contrast to the US, PhDs in Europe seem to be shorter—typically three and a half to four years, sometimes up to five at most. But in the US, it's almost always five years, and sometimes even stretches to six. Why do you think this difference exists? And do you feel that a PhD from one system has more value than from the other?

SR: I should say upfront that I have limited experience with the European system, so my view might be a bit skewed. But yes, you're correct: in Europe, most PhDs last around three to four years, and going up to five is rare.

FIG 3: *Dr. Sushanta Roychoudhury did his two postdocs in growth factors and hepatitis B virus from the University of Pennsylvania in Philadelphia, USA from 1985 to 1990. [Source: cntraveler.com]*

In the US, the PhD usually takes a minimum of five years. I think this comes from a difference in philosophy. In Europe, when you start your PhD, you often join a project that's largely predefined—you know quite clearly what you'll be working on from day one.

In contrast, in the US, the system tends to be more open-ended. Students have more freedom and are encouraged to develop their own questions and shape their projects, which naturally takes longer. For example, when you join as a postdoc in the US, you're expected to deliver quickly because you join a specific project immediately. But during a PhD, students get time to explore and refine their ideas.

Personally, I feel this approach in the US—where students learn to frame questions, develop projects, and navigate uncertainty—offers stronger training in independent thinking. But again, both systems produce very good researchers, and ultimately it's what the student does with that training that matters most.

SS: Now, shifting the discussion to your own professional life: after you became an independent scientist, did you still spend time in the lab yourself? Or did it become more about teaching, writing papers, and administrative work, while the lab functioned on its own?

SR: In my case, I worked at a research institute that mainly focused on research and accepted PhD students, so we didn't have a heavy teaching load—just a few classes that I would occasionally take, for instance at the University of Calcutta when they invited me.

So my primary focus always remained on my lab: spending as much time as possible with students and on research problems. Of course, as a scientist, I also had to do administrative work—being on committees, evaluations, and so on—which took time. But whenever possible, I prioritized being present in the lab and working closely with the students.

SS: I've observed different kinds of PIs. Some rarely come to the lab and leave students largely on their own, believing it helps students develop independence and passion. Others are very hands-on: they're in the lab early, stay until late at night, and are deeply involved in daily experiments. Some guide each step, while others only intervene when needed.

Given your own experiences, how would you describe your approach? And why did you choose that style rather than the others?

SR: That's a very important and interesting question. Let me explain with my own journey.

During my PhD, my supervisor gave us full freedom: we planned experiments, analyzed data, and kept up with literature on our own. While that taught me independence, I sometimes felt it would have been better if I had received more structured guidance—it might have improved my work.

In my first postdoc in the US, I had the opposite experience: every morning we had to meet our PI, who would write down exactly what experiments we had to do that day. In the evening, we had to report back with results. Honestly, that felt too controlling and made life quite stressful.

Then I moved to another lab for my second postdoc. There, the PI outlined the broad project area but let me design experiments, troubleshoot, and decide next steps myself. He was available if I got stuck, but otherwise trusted me to move things forward. I found this balance much healthier and more motivating.

So, when I became an independent scientist, I tried to combine these lessons. In my lab, I gave students freedom to explore and think, but I was always there to help them interpret data or troubleshoot difficult problems.

FIG 4 : *Dr. Sushanta Roychoudhury serves as ICMR Emeritus Scientist and Honorary Advisor in the Saroj Gupta Cancer Center and Research Institute (Thakurpukur cancer hospital), West Bengal. [Source: mediniz.com]*

FIG 5 : *Dr. Sushanta Roychoudhury worked as a Chief Scientist at CSIR-Indian Institute of Chemical Biology, Kolkata from 1991 to 2015. [Source: iicb.res.in]*

We also had regular lab meetings, usually on Saturdays, where students presented what they had done, and we discussed challenges and next steps together.

At the same time, I made it clear that the experiment should guide the schedule: if your experiment needs you to come on a holiday or late at night, you must do it. But if you don't have critical work, you're free to take breaks, see a movie, or meet friends.

To me, that balance between freedom and mentorship is key. You let students think and develop, but you don't leave them completely alone when real problems come up.

SS: I understand. Could you please explain how your research has been aligned with the theme of BAW 2025?

SR: Actually, this was the first time I attended BAW, so initially, I didn't know very clearly what it was meant for. But I realized it mainly focuses on giving students some training in various laboratory techniques, and also on exposing them to modern research happening around the world.

So, in my talk, I tried to connect to that by discussing the title "Paradigm Shifts in P53 Research." This idea of "paradigm shifts" is actually something I personally believe in deeply.

In science, something you strongly believe today may change tomorrow as new data emerges. That's what makes science so dynamic and fascinating—you must always be open to change and rethink your understanding as fresh evidence comes in.

Through my talk, I wanted to convey this spirit: that science keeps evolving, and being part of that evolving process is what makes research so exciting. I hope I could give the students a sense of that energy and perspective.

SS: I understand, sir. As we come towards the end of this discussion, my last question would be: do you have any advice for the current students of IISER Kolkata, and for students in general?

SR: My advice would always be: whatever you do, do it because you love it—not just because you feel compelled to. Especially in research and academics, it's essential that you truly care about the questions you're exploring. You have to put your heart into it and really try to understand why what you're doing matters.

And then, do it passionately, and most importantly, with perseverance. That's something I always tell my students: perseverance is the single most important quality.

In research, especially in biological sciences, our systems are so complex and dynamic that often 95% of our experiments fail. Only around 5% actually give results. So, if your experiments fail, don't get discouraged or give up—that's part of the process.

It's that persistence through failure that ultimately leads to breakthroughs. That, I think, is the most important thing I've learned in my career.

SS: Thank you, sir. Thank you so much for your time.

SR: Thank you very much. And thank you for asking such thoughtful and important questions. I wish you all the best in your journey.

FIG 6 : *Dr. Sushanta Roychoudhury visited IISER Kolkata as a panelist for BAW - International Conference on Frontiers in Disease Biology 2025. [Source: facebook page of Neurovirology/ Neuroimmunology Lab of IISER Kolkata]*

Prof. Reizes (seated left) at The Ohio State University NSF I-Corps program.

Why Therapies Fail: Prof. Ofer Reizes on Cancer, Collaboration, Curiosity

Swarnendu Saha (IISER Kolkata)

Swarnendu Saha interviews **Prof. Ofer Reizes** of Cleveland Clinic of the United States to discuss American academia, his current focus on women's cancers and therapy resistance, and the vital role of collaboration between scientists and clinicians.

🔗 *Also available online, at scicomm.iiserkol.ac.in*

SS: Hello Sir, this is Swarnendu Saha from Team Insight. I'm a student here, and it's an honor for me to welcome you to this interview session. Likewise, it's an honor for me to have the opportunity to interview you.

Okay, so my very first question, which I generally like to start with, is: how did you reach here—meaning the position you are currently in?

Could you briefly share your academic and research journey, starting from your school days up to today?

OR: Can I do this in reverse? I'll start with where I am today and then walk you back to where I started, and why I became interested in science—not necessarily biomedical science.

I am currently a staff professor at the Cleveland Clinic Research Institute, which is part of the larger Cleveland Clinic, an international hospital system that has research as one of its main pillars. We are interested in studying and researching diseases. I joined the Cleveland Clinic almost 19 years ago with the goal of understanding the biology of diseases—essentially investigating what causes them.

The position I hold today, and the things I study now, are not necessarily the same as when I first joined the Cleveland Clinic. Before being recruited there, I actually worked in industry. I was at Procter & Gamble when they still had a pharmaceutical division. That company was focused on obesity and metabolic diseases. From that experience, I learned the process of what it takes to develop a drug and even gained insights into drug commercialization—knowledge that I later carried into my research at the Cleveland Clinic, where I now also teach courses on these topics.

In particular, I teach courses designed to help students understand what kinds of projects industry and commercial enterprises are likely to support, with a focus on whether the product being developed is truly necessary.

That brings us to around 2001. Going backwards from there, I completed my postdoctoral work at Harvard Medical School and Boston Children's Hospital. That period was really a time of free exploration, which allowed me to focus deeply on the type of scientific questions our lab was interested in. Specifically, this involved studies on obesity, including mouse model research. It was during this time in Boston that I really became more of an expert, as I gained clarity on the importance of defining and narrowing scientific problems.

Before that was graduate school. I pursued my PhD at the University of Texas Southwestern Medical Center in Dallas, which is still one of the premier health science centers in the U.S. There, I did my dissertation in molecular pharmacology. The work focused first on how to frame a meaningful research question, and second, on how to systematically address it.

Going back another step, that takes us to my college years at the University of Maryland. At the time, I initially intended to go to medical school—that was my main interest. But along the way, I caught the "research bug." I had the opportunity to work in labs both at the University of Maryland and at the National Institutes of Health as an undergraduate. That experience really switched on a light for me, and I realized I wanted to pursue research as my career.

I won't go further back into high school.

SS: So, at the University of Maryland, it was College Park?

OR: It was mostly College Park, although I also spent part of my time in Baltimore. The University of Maryland in Baltimore is designated an honors university. I moved there later in my college years because I wanted to study at a university that was well-known and heavily supported by the state, which had invested a lot of money to make it an elite institution.

It was a much smaller campus compared to College Park. College Park tends to be one of the largest schools in the country, probably among the top 10 in terms of size. Baltimore, on the other hand, was much smaller.

FIG 1 : *Ofer Reizes, PhD is professor and staff at the Cleveland Clinic Lerner Research Institute in the United States.*

One of the reasons I transferred there was a program that offered both a bachelor's and a master's degree. It was called Applied Molecular Biology. While not directly related to your broader question, it's relevant in the sense that the program provided strong technical training, though not much intellectual focus on developing into an independent investigator. I initially intended to spend an extra year there and complete a master's degree. But while I was there, I realized that wasn't what I wanted.

I decided, "You know what, this isn't going to get me where I want to be." So I finished my bachelor's degree as quickly as possible and went on to graduate school in Texas.

SS: Okay, I had the chance to visit the University of Maryland, College Park, for a day. I was in Washington D.C. this last December for the AGU conference.

OR: It's a beautiful campus.

SS: Yes, it was a beautiful campus. I went inside the student activity center and the football stadium. Nowadays, tram tracks are even being built across the campus.

OR: It was different when I went there, though.

SS: That didn't happen 30 years back.

OR: Was it 30? Yeah, I guess it was. Time flies when you're having fun.

SS: Yes. So, would you please briefly describe your research area and your research interests?

OR: The best way to describe my current research is that it focuses on cancer—specifically women's cancers—with an emphasis on understanding why our current therapies fail. In cases of breast, ovarian, or even uterine cancer, patients undergo surgery, but unfortunately the therapies they receive often stop working. The cancer cells become resistant to chemotherapy.

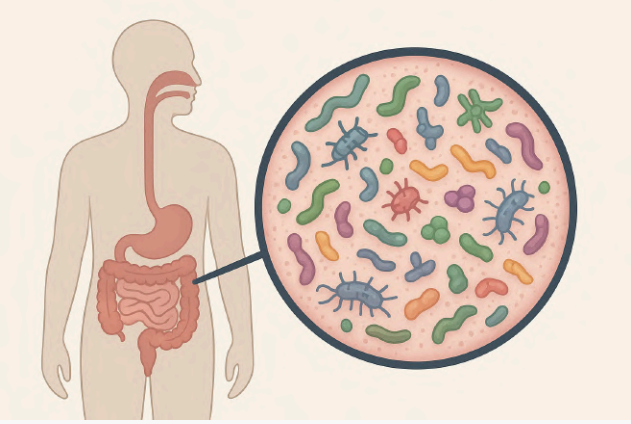


FIG 2 : *"We know the microbiome is critical for health ... also release chemicals that enter the body ... we did studies with ovarian cancer cells and found that a beneficial factor released by the gut microbiome actually inhibited ovarian cancer growth" - Prof. Reizes.*

There are many scientists investigating different mechanisms behind this, and we are among them. That's also something I'll be talking about here. The central idea is: can we understand why patients fail chemotherapy?

SS: You are not a physician.

OR: I'm not.

SS: So, you are dealing with human cancers—specifically cancers in women. How does a physician's approach differ in treating it? Because while doing research in this area, you also need regular checkups and datasets to check whether your methodology is working or not.

And since you mostly do lab work, data analysis, and theory based on past studies, how do the perspectives of a physician—someone with a medical background—and a scientist like you, from a research background, compare? Are they the same or different?

OR: Okay, that's an excellent question. My response is that we work as a team—and that's one of the advantages of being at the institution where I am, the Cleveland Clinic.

The majority of what the clinic does is treat patients, and we also have a very large cancer institute that focuses specifically on cancer patients. My work is closely connected to our clinical group. I collaborate with clinicians at various levels.

SS: By clinicians, you mean doctors?

OR: Yes, yes. So think of surgeons and think of medical oncologists—and I'm differentiating between them.

In some cancer fields, the same physician may do both surgery and treatment. In others, you have a surgeon and a separate medical oncologist. The oncologists are the ones who prescribe the drugs and monitor how the patient is doing.

Now, where do I fit into this continuum—which I sense is really the heart of your question? I fit in at the very beginning: the stage of trying to identify solutions that could eventually be implemented in the clinic. But the important point is, I don't do this in a vacuum.

A big part of my work involves discussions with my clinical colleagues to understand from them: what is the real problem? Why do patients still die? To put it bluntly, patients get diagnosed with cancer. Some do well, but others pass away very quickly. So the question we try to answer is: what is it that clinicians are unable to treat?

That's also why I love being where I am. At the Cleveland Clinic, I can have direct conversations with clinicians about their challenges. If I were at an institution without those connections, I could only rely on the literature—which is valuable, of course—but I'd miss the complexity of what actually happens when a patient walks in, gets diagnosed, receives treatment, and then fails that treatment.

Because I have that access, I can talk with clinicians and identify where in the patient journey we should ask questions, where we might intervene, and how we could improve outcomes.

Of course, there are other steps too—like translating discoveries into drugs and clinical trials. We're at the very early stages: understanding what goes wrong in treatment, developing therapeutics and strategies, and then passing those along to colleagues who can test safety and efficacy in clinical studies. We can do everything up until the point where it goes into a patient—but once it reaches that stage, you need a very different skill set.

SS: So, while doing this work, what kinds of scientific challenges do you face—the cons, the setbacks, the problems?

OR: That's a great question. One of the main issues is that biology is complex—it always finds a way around us.

For example, we may have a very specific direction and show that, in a particular cancer with certain characteristics, our drug works. But then, there are other cancer types that don't fit that pathway. They find ways to bypass the mechanism we're targeting. The frustration is that you end up with a very narrow solution.

Ideally, we want to disrupt the disease process at multiple levels, but in practice, our expertise may become focused on one very specific direction that doesn't apply universally.

Let me give you an example. One of our projects, which I'm not talking about today, involves the gut microbiome. We know the microbiome is critical for health and disease. The bacteria in our gut digest food but also release chemicals that enter the body.

Several years ago, we did studies with ovarian cancer cells and found that a beneficial factor released by the gut microbiome actually inhibited ovarian cancer growth. We thought, "Fantastic! If we understand this, and also how antibiotics disrupt those bacteria, this could be a real therapeutic strategy."

But when we tested the same approach in a different subtype of ovarian cancer, it didn't work.

FIG 3 : *Dr. Reizes earned a Bachelor of Arts in Molecular and Cellular Biology from the University of Maryland – Baltimore County.*

And that's the frustration: there is no single solution for every type of cancer. The disease will always find ways to evade treatment.

SS: Do history and geography play a role in this? How?

OR: Well, following up on what I just mentioned, geography has a major impact on the microbiome. The microbiome you have and the one I have are very different. So, patients here would probably respond differently to treatments, depending on how their microbiome interacts with the disease.

The microbiome I'm talking about is in our gut—it sits in our intestines and is critical for digesting food. But as a result, it also releases certain factors into the body. That much is well established. The key point is that your microbiome is going to be significantly different from mine. Can you modify it? We still don't fully know.

That's an example of how geography matters. Of course, genetics plays an important role too, but there's increasing evidence that the environment is a critical factor in determining how patients respond to disease and how they survive.

SS: Migration has always existed, but in today's world of globalization, it's happening even more. Don't you think that under such circumstances, the role of geography—or even history—goes down a little?

OR: I don't think so, because the environment doesn't necessarily change. The globalization you're referring to is really about the movement of people.

For example, we know that when individuals from one country move to another, their disease risks may change. Take obesity: individuals from Asia who move to the United States and adopt the American lifestyle are more likely to become obese. That's an environmental effect.

And the reverse is also true. If I come to your country, I may struggle with the food or the water because my microbiome isn't adapted to interact with what I'll be exposed to. That's why, whenever I come to India, I'm extremely careful about what I eat and drink.

SS: What do you eat and drink?

OR: Well, I only drink bottled water—or boiled water—or hot drinks, which probably inactivate harmful bacteria. Otherwise, I could end up with a very unpleasant battle inside my intestines, and that's an experience I'd prefer to avoid.

SS: Okay. What is the basic background of education in the USA right now?

OR: So, the way the U.S. system works—which has been extremely effective over the years—is this: there are four years of college, and then students decide whether they want to pursue a Ph.D., medical school, engineering, or any other path. In my opinion, it's been one of the top places for learning and research, as evidenced by the

international community that comes to the U.S. to study or advance their careers.

I also recently had a graduate student come from India who just started her Ph.D. in my group. So, I really like having an international community in my lab.

SS: As a guide, what factors do you look for? Or, what key words in recommendation letters help you decide whether to take someone or not?

OR: One word: Passion.

Passion for learning. Passion for research. Passion for motivation.

SS: Not exactly passion for the kind of work you do?

OR: Not necessarily. That's something I can help guide the student or trainee toward.

SS: Okay. In India, in most universities, students are graded by percentage. Each semester or year, they get a percentage in various papers, which is then calculated through a formula.

So, finally, you might get something like 75%, 80%, or 82%. Some institutes, like ours, use CGPA—Cumulative Grade Point Average. Each course is graded, then averaged into an SGPA (Semester GPA), and then all semesters together form the CGPA.

That's on a scale of 10. So, a student might get 7.5, 8.2, or above 9. Above 9 is generally considered very good.

However, different institutes have different professors, grading systems, and standards. In some institutes, getting 7.5 means you're an excellent student, while in others, unless you score 8.8 or above, it isn't considered outstanding.

So now, as a guide, when you're evaluating a student's transcript—say someone has a number out of 10, with individual course grades A, B, C, etc.—do those numbers strongly influence your decision to accept them or not?

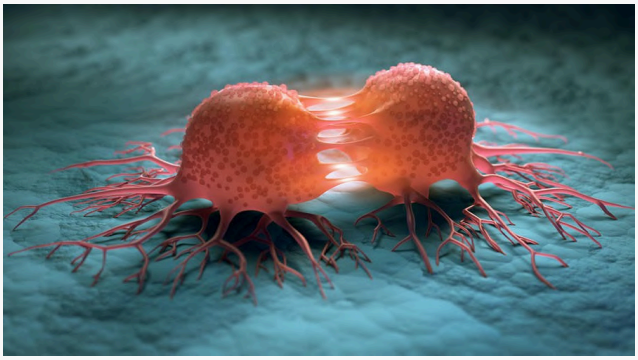


FIG 4 : *"In cases of breast, ovarian, or even uterine cancer … the therapies they receive often stop working. The cancer cells become resistant to chemotherapy. There are many scientists investigating different mechanisms behind this, and we are among them."*

OR: Yes. That's an excellent question.I understand what you're asking. The answer is—it's unpredictable. You really don't know until you put that person in a research environment, teach them techniques, and give them opportunities to apply their abilities.

That's when the difference shows—their passion for the work.

I could see someone who is an excellent test-taker and who did very well in classes, but maybe they only enjoy the "book" side of things, not the hands-on problem-solving that research requires.

So it's a difficult issue. For example, you could have one student with a 9 (on your grading scale) and another with an 8 excel once given that opportunity to really develop their scientific, you know, scientific focus.

SS: You said that's your personal approach.

OR: Yes.

SS: But how does the system look at it? Because you're also part of that system. There must be certain rules or norms of the institute, or the education department, that you have to follow. So how does it normally work?

OR: That's a good point. It really depends on where in the system you're trying to enter—as a student or as a trainee.

For example, when you think about graduate or undergraduate admissions, the school itself sets minimum requirements. You still have to show a certain academic level—good enough grades or test scores. A student with very low scores simply won't even be admitted. So that already excludes a percentage of applicants.

On my side, of course, I wouldn't take a student with extremely low scores because they wouldn't even make it into the institution in the first place.

Now, if you're asking what happens beyond that cutoff—who makes the actual selection? At the graduate level, that decision lies with the school. At the postdoc level, that decision lies fully with me.

SS: Fully?

OR: Fully—except for one thing. For international students, English is critical. They need to be able to read, understand, and discuss research in English.

We've had cases where a candidate looked great on paper—strong background, strong recommendations—but when tested on their English comprehension, they failed. That becomes a disqualifying factor.

So yes, there are institutional criteria that filter people out, but once those are met, the final decision for postdocs is mine, as the PI.

Now, if you're asking about medical school—that's a completely different process. There are standardized

tests, letters of support, and interviews that weigh heavily in those admissions.

SS: Okay. So, let's assume if I apply to you, I would first need to clear the English requirement.

OR: Yes.

SS: Should we discuss politics?

OR: If you want to discuss politics, that's fine. You may not learn anything from me, but sure. What aspect of politics do you want to ask about?

SS: The same thing the world is looking into — what is America currently doing?

OR: I don't know. Honestly, I don't know. It's... a sad situation.

SS: Sir, your research work has any connection, since you mentioned microbes, to what happened during 2019–2020 with COVID?

OR: Yes.

SS: Not in the sense of your research being interrupted by COVID, but scientifically — did the phenomena that came with COVID affect cancer in any way, directly or indirectly?

OR: Our direct studies don't link to COVID. As you pointed out, the other side of it is that COVID certainly affected our research. But it's not a research question that we are actively addressing.

SS: One more thing. During COVID, we all saw how doctors, sweepers, medical practitioners, and health workers were suddenly looked upon as heroes, even gods. Everyone looked up to scientists and doctors.

Normally, scientists don't get much recognition — it's seen as just another regular job, often thankless. But during that time, people treated scientists almost like celebrities. From your perspective as an American researcher, did you ever feel that being a scientist was or was not a good decision? Did you ever feel that if you had chosen another path, you might have earned more money, respect, or power — things that might be considered more necessary?

OR: I understand what you're asking. So the first part of my answer is: I've never looked back. I've never questioned my decision to go into research.

I've never thought of it only in terms of finances or the ability to make a living. And so I've never really been concerned about that. Let me pause on that for a moment.

Financially, I do pretty well. Could I make more money in industry or something like that? Probably. But I wouldn't be as happy with what I do for a living. What I mean by that is, I get to decide what questions I want to ask.

I mentioned earlier that I was, for several years, at Procter & Gamble in the pharmaceutical research division. I was brought there to study obesity and develop therapeutics. That was awesome—I learned a lot.

But at the end of the day, they were making decisions to go in other directions with their research. So the choice of which projects to pursue was totally out of my hands.

Now, in academic research, of course, there are still things beyond your control—like convincing the community that what you're doing is important. In order to get grants, you have to show that your work addresses a critical question. But beyond that, the decision about which questions we focus on—that's mine to make.

SS: Aren't there projects where your lab has to follow certain rules or directives? I don't mean administrative constraints, not in that sense.

I mean, suppose you're part of a big project, or your department is involved in one. You'd need to align with what others are doing, follow the project guidelines, and work under that system. Have you ever worked in that way?

OR: To some extent, yes. What you're describing is more of a team science type of project, where everyone has different components of the overall scheme.

Right now, for example, we've submitted a grant related to the microbiome with multiple PIs—principal investigators. Our overall goal is to understand the biology of the interaction between the microbiome and disease, in this case cancer.

We're all focused on cancer, and we teach each other what we're doing, helping one another ask bigger questions. So, to answer your question, in those cases, the overall direction is jointly decided.

FIG 5 : *After obtaining a PhD in molecular pharmacology from the University of Texas Southwestern Medical Center – Dallas, Dr. Reizes pursued a post-doctoral fellowship in developmental biology and metabolic disease from The Children's Hospital Boston/Harvard Medical Center.*

SS: Would it be possible for you to give us your impression of how research in India is progressing? And what differences do you see between the Indian system and the American system?

OR: A little. The only thing I can really comment on, from my outside observations, is that the research here is of very high quality and has a very high impact. The challenge is that India is such a large country population-wise, and there simply aren't enough positions for you and your colleagues to expand that research further.

I don't know what the grant success rates are in India, but I understand it's an interesting and different system. Many countries have their own structures that differ from the U.S. For example, when you're a professor here, your salary is provided directly by your institution. That's not the case in the U.S. In many academic institutions there, you have to write grants that partially support your salary.

It's also different in terms of how students are funded. In the U.S., students are funded through grants or fellowships. If they don't have those, the professor must support them through grants. I'm not fully versed in the Indian system, but I know excellent science is being done here, including through international collaborations.

The biggest challenge, as I mentioned earlier, is that many Indian fellows and trainees want to return to India after going abroad, but there are often no positions available for them. That makes it hard to retain or bring back talented researchers. But again, that largely comes down to the population size—you are a very populous country.

FIG 6 : *Dr. Reizes with Katie Crean-Tate at the SGO (Society of Gynecologic Oncology) Annual Meeting.*

SS: What funding opportunities are currently available in the U.S. for students from the Global South, or so-called third world countries? I've seen many of my friends going abroad this year, mostly in chemistry and biology. But in physics and mathematics, it seems like opportunities are shrinking.

OR: Yes, those areas have been struggling, regardless of the international community wanting to work in the U.S. They're inherently more difficult to break into here because there are fewer positions available. Historically, chemistry and biology have had a larger community due to demand, which has shaped the opportunities.

SS: Have you ever been to Europe, East Asia—Japan, Korea—or Australia?

OR: Yes, Europe multiple times. Asia and Australia as well.

SS: In the U.S., completing a Ph.D. usually takes five years. Sometimes it stretches to six or seven if you combine a master's along with it.

OR: For which discipline?

SS: Generally, in science. Students do some coursework equivalent to a master's degree and then continue with lab rotations.

OR: Yes, we call them rotations. I can speak specifically about the Ph.D. track.

SS: I'll come back to my main question. In Europe, Ph.D.s usually take about three to four years. Why this distinction? What are the pros and cons of the U.S. system from your perspective as an American scientist?

OR: That's a very interesting question. The U.S. system tends to emphasize the number and impact of papers a trainee produces, which often makes the process longer. Not always, but often.

There's also a leveling process at the start. Students coming from undergrad don't always have the same academic background, so the first year to year-and-a-half involves coursework to bring everyone up to speed. After that, the dissertation itself usually takes about three to three-and-a-half years. Publications are what ultimately earn you the degree.

In Europe, it's different. I've often heard it said that in the U.S., the quality of education improves as you move upward: high school may not be as strong, college improves, and graduate school is even stronger. In Europe, however, high school and college are often very rigorous, but Ph.D. training may not be as intensive. That's one reason why the U.S. has historically been seen as a superior place to pursue doctoral studies.

SS: Do you think someone earning a Ph.D. from Cambridge in the UK wouldn't have the same edge as someone from Princeton in the U.S.? Let's

assume the same field, same quality of work. The only difference is the country and institution.

OR: That's a loaded question. There are many aspects. If you're asking whether I'd pick someone from the U.S. versus the UK as a postdoc—well, it depends.

Honestly, citizenship matters. If two candidates are equal in terms of papers and quality, the American has an advantage because they can apply for U.S. fellowships and grants, which foreign nationals can't. For example, if an Indian student comes to me with an outstanding record but no independent funding, I'd need to find the money myself. But if they arrive with a fellowship from India or another source, that makes the process much easier.

So yes, sometimes the distinction isn't about the quality of the Ph.D. itself, but about access to funding and ease of hiring.

SS: What's your opinion about academic Ph.D.s versus industrial Ph.D.s?

OR: I can't really speak much about the industrial side.

SS: Alright. Let's move toward the conclusion. What would be your advice for students graduating now and heading out for their Ph.D. or postdoc?

OR: In the U.S. or globally?

SS: Globally, but the U.S. included.

OR: Okay. In the U.S., it's a complex environment right now. Many students are choosing to take time off after undergrad—what we call "gap years"—to work in labs, gain technical experience, and then apply to graduate or medical school. That's partly because the academic climate feels unstable at the moment.

Still, the opportunities in academic life are incredible. It's highly competitive—no doubt, in India even more so—but the rewards and the richness of the experience are very high.

I'll admit, I'm biased. But I believe the experience you gain in research is unlike anything else. My own children didn't choose science, but I always tell them the same thing: choose something you truly love and feel passionate about.

I've never regretted my decision to become a scientist. Yes, I get frustrated when a grant is rejected or when reviewers are harsh. But I've never looked back wishing I'd taken another path, like medical school.

SS: Okay, sir. With that, we'll end today's conversation. We hope our readers will enjoy it. Thank you.

OR: Thank you. It's been wonderful. You're a great interviewer.

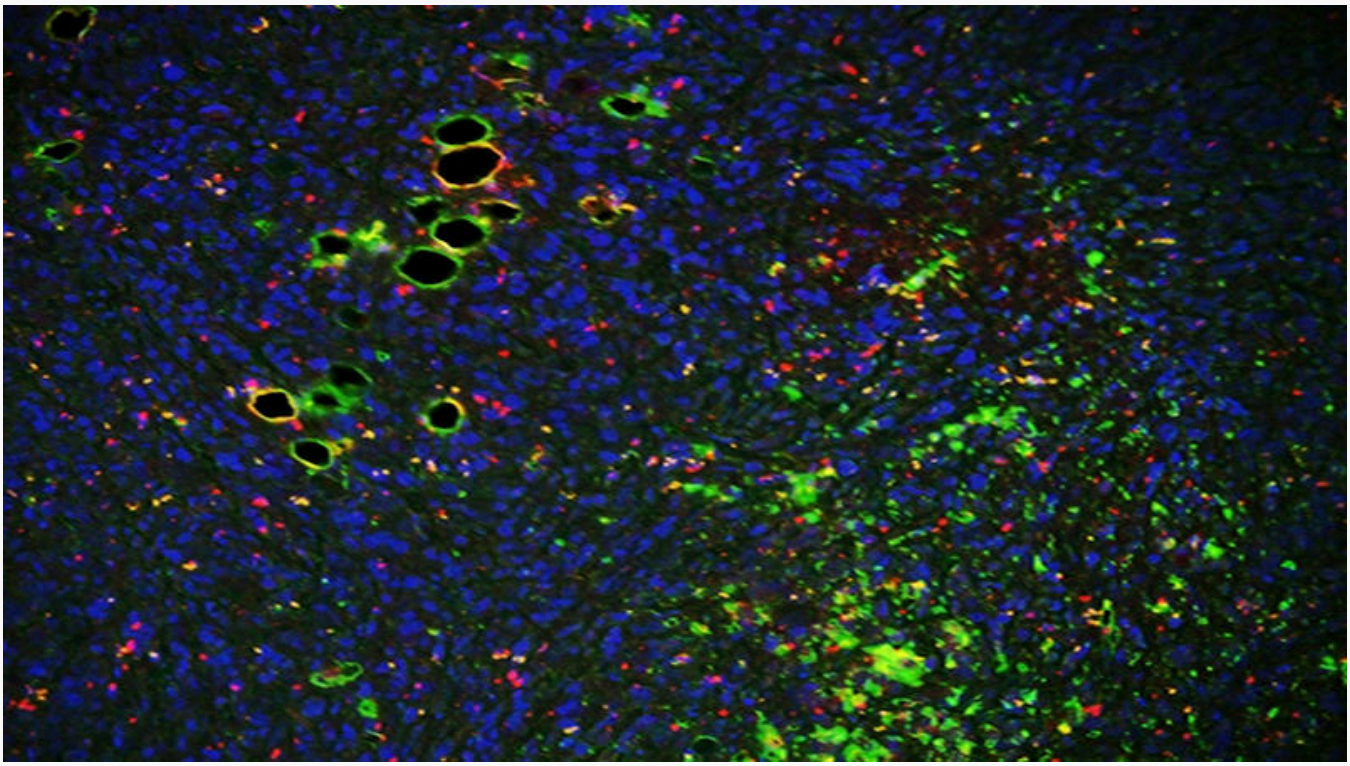
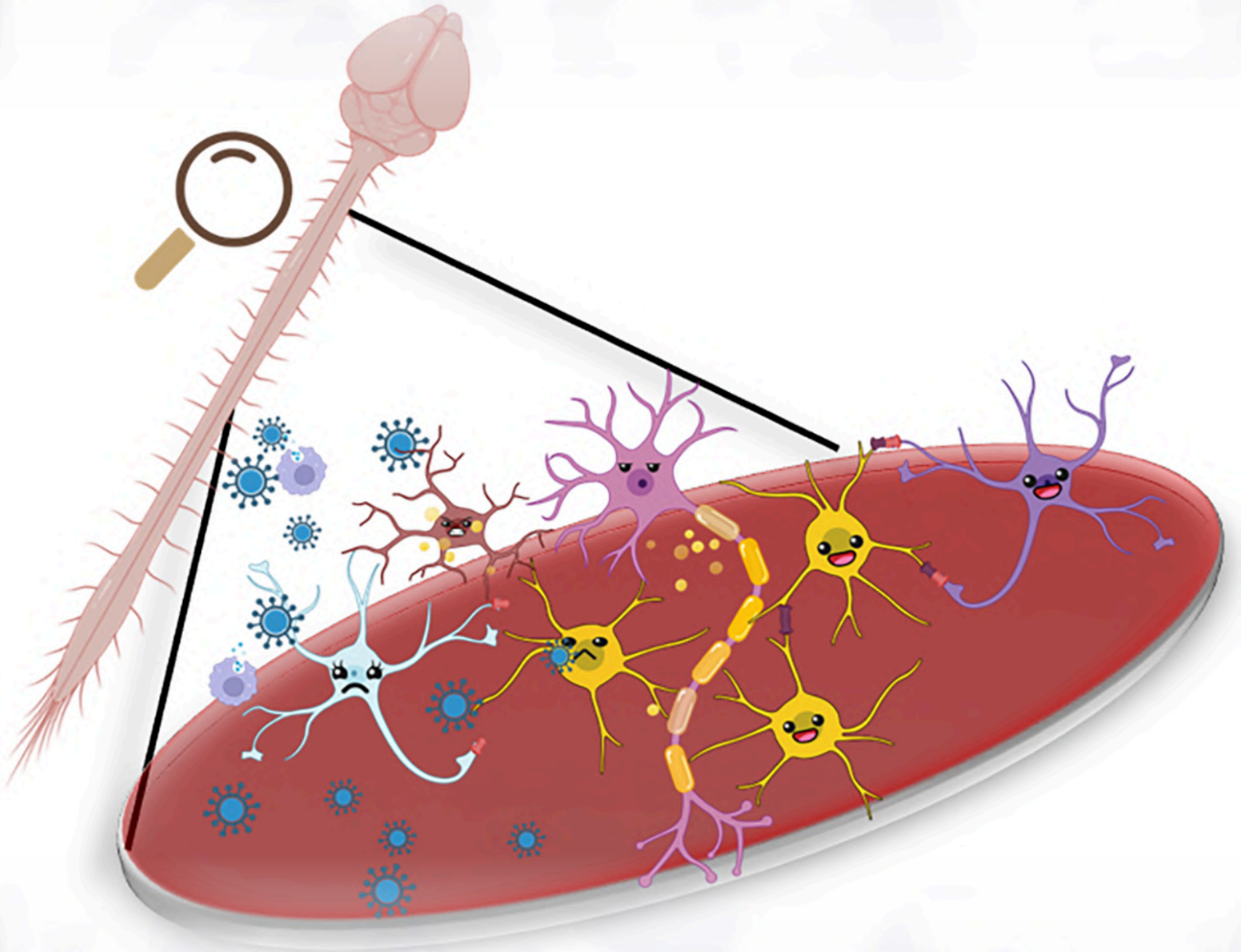


FIG 7 : *Breast cancer cells stained with six primary antibodies to show areas of tumor. A research team led by Ofer Reizes and Justin Lathia designed a peptide therapeutic that disrupts the molecular processes behind aggressive cancer growth when delivered into cells. The study was highlighted in the January issue of Molecular Cancer Therapeutics.*

A Stranger Crashes the Party

Decoding the White Matter Wipeout



— Mahua Maulik (BRIC-NIBMG)

Dr. Mahua Maulik, Fellow at the National Institute of Biomedical Genomics (NIBMG), India earned her PhD from University of Alberta, Canada and has since established herself as an independent investigator focusing on the molecular and cellular mechanisms of neurodegenerative and demyelinating disorders. Through her work, Dr. Maulik has achieved many awards across the globe over the years.

In the nervous system, myelin acts like insulation on electric wires - essential for fast, precise communication between neurons. But when viral infections invade the central nervous system (CNS), they can trigger immune attacks and cellular chaos that strip away this protective coating. Using single-cell analysis, uncovering how these "party crashers" disrupt myelin maintenance, reveals new paths to understand and potentially repair the damage in neuroinflammatory demyelinating diseases.

Do you know what gets on our nerves all the time?

Our friends, mostly! – Oligodendrocytes, the cells that form myelin in the CNS. They are our lifeline support system. How would you feel if they were stripped away from you by some strangers? Well, I can relate you with someone I know a bit closer – Neurons. You will be alone, drained of your refreshing communications and if you don't find new promising friends sooner or later you become depressed until your last breath just like them.

Demyelinating diseases of the CNS, such as multiple sclerosis (MS), are characterized by the destruction of myelin sheaths which are cytoplasmic extensions of oligodendrocytes around the axon of neurons and impaired remyelination (Fig 1). Chronic demyelination is often associated with neuroinflammation, glial dysfunction, and failure of oligodendrocyte progenitor cell maturation. While many studies focus on autoimmune or toxin-induced demyelination models, increasing evidence suggests that neurotropic viruses, including β-coronaviruses, the so called "strangers" can induce persistent CNS pathology characterized by chronic inflammation and impaired myelin repair [1-3].

Mouse hepatitis virus strain A59 (MHV-A59), a neurotropic β-coronavirus, serves as a well-established model to study virus-induced demyelination. Intracranial infection with MHV-A59 leads to acute encephalomyelitis, which refers to the inflammation of both brain and spinal cord. This is followed by a chronic phase marked by demyelination and immune cell persistence in the spinal cord [4-6] (Fig 2). However, the mechanisms through which viral infection leads to chronic demyelination and the cellular and molecular landscape of the affected CNS remain incompletely understood. In our earlier study, in a targeted approach using immunostaining methods in spinal cord tissue sections collected from MHV-A59 infected and control mice, we observed significant variations in the proportion of different oligodendrocyte lineage cells upon infection, which correlated well with the extent of demyelination. Further we have reported differential regulation of cell junction molecules, such as connexin 47 (Cx47), in different oligodendrocyte lineage cell populations over time following infection [7].

Sharing is Caring: The Inner Network that keep the CNS in Balance

We all know how sharing with friends helps us stay connected and build strong relationships. Turns out, our brain cells feel the same way! They build tiny bridges - like secret passageways - to pass messages and share what they need to stay in sync. This constant

exchange helps maintain balance and harmony in the CNS. Connexins constitute a large family of transmembrane proteins that are essential for the formation of gap junctions (GJs) - specialized intercellular channels that permit direct communication between the cytoplasm of neighbouring cells [8, 9]. Each gap junction channel is composed of two hemichannels (connexons), contributed by adjacent cells, with each connexon assembled from six connexin subunits. These channels facilitate the rapid and bidirectional exchange of ions, second messengers, metabolites, and small signalling molecules (typically <1 kDa), thereby enabling synchronized cellular responses. In the CNS, connexin-mediated GJs are critical for supporting neuroglial interactions, propagating calcium waves, and maintaining the ionic and metabolic balance required for brain homeostasis.

Disruptions in connexin function have been implicated in a range of neurological disorders, highlighting their importance in sustaining normal brain physiology and coordinated cellular behaviour. Our study revealed that Cx47 GJs are persistently lost in mature oligodendrocytes, not only in demyelinating lesions but also in surrounding normal appearing white matter areas during chronic demyelination (Fig 3). The loss of Cx47 in the oligodendrocytes is most likely triggered by an initial loss of its coupling partner, Cx43 in astrocytes, which occurs during acute viral infection. At later stages after viral clearance, astroglial Cx43 GJ expression re-emerge but mature oligodendrocytes mostly lack Cx47 GJ expression and thus fail to fully re-establish connections with the astrocytes. However, we observed appearance of Cx47 surface puncta in the oligodendrocyte precursor cells at this chronic demyelinating stage. This suggested of a plausible role of the Cx47 channels, modulated differently in the different oligodendrocyte lineage cells, in the demyelinating pathology induced by an initial viral

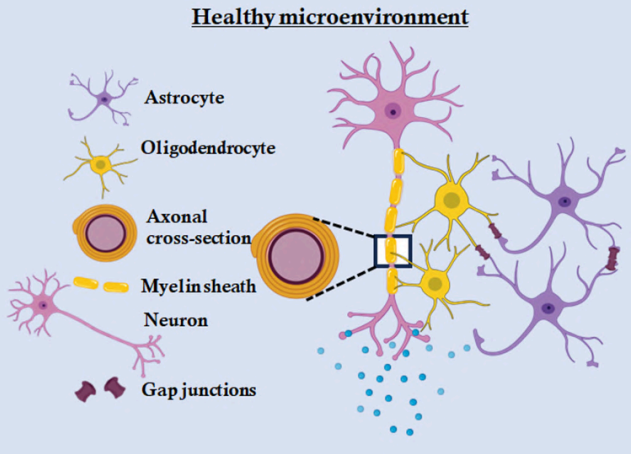


FIG 1 : *A cartoon depicting the interconnected network of various cell types comprising the spinal cord tissue (Image created in BioRender.com).*

infection. However, a key challenge remained to decipher how the individual cell states of the oligodendrocyte lineage cells interact with the other cell types in the tissue microenvironment upon an initial viral insult and contribute to the chronic pathological state.

It's crowded: Let's meet them in person

Imagine a stranger walks into your group of friends, who stirs things up. How would your friends react? Each one of them would have their own intrinsic reactions and opinions. It's hard to figure out everyone's reactions all at once. That's a bit like what happens in our body -

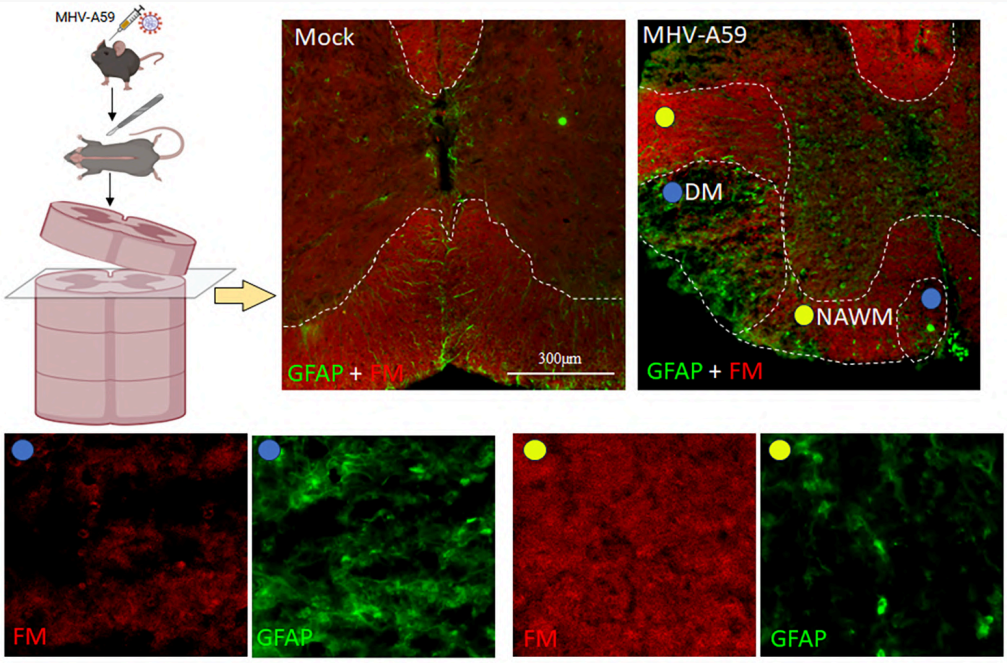


FIG 2 : *Representative images from spinal cord cross sections immunostained with anti-GFAP antibody (labelling astrocytes) and Fluoromyelin Red stain showing intense red staining in the white matter areas from mock-infected control and MHV-A59 virus infected mice. Demyelinated lesions (blue dots) exhibit loss of FluoroMylein red lipid stain and a higher intensity of GFAP-positive astrocytes indicating persisting neuroinflammation compared to the surrounding normal appearing white matter (yellow dot) regions of the infected spinal cord at chronic stage (30-days post-infection). [Modified from Das S et al, Molecular Neurobiology, 2025].*

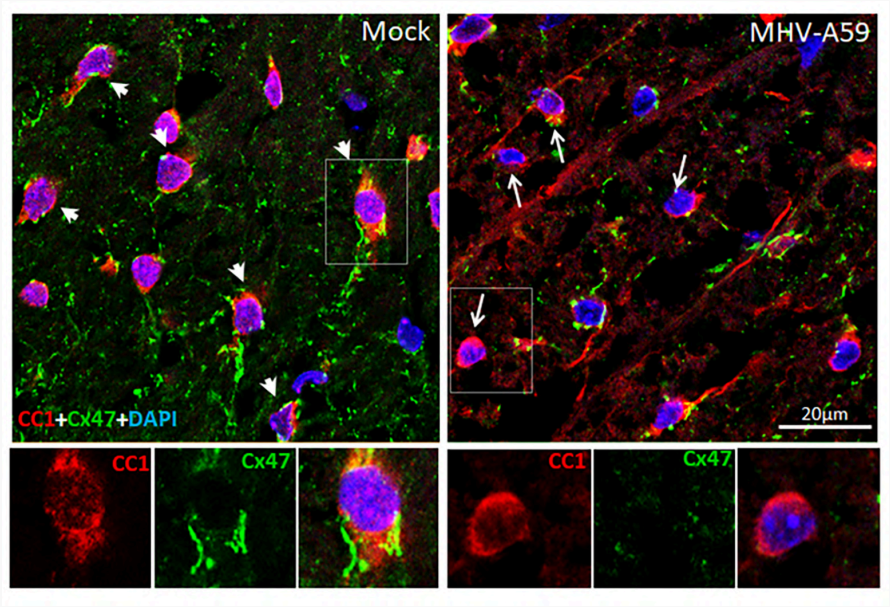


FIG 3: *Representative confocal images from control and MHV-A59 infected spinal cord showing expression of Cx47 gap junction puncta (green) in CC1-labelled (red) mature oligodendrocytes. Nuclei are stained with DAPI (blue). In mock-infected controls most of the CC1-labelled oligodendrocytes exhibit Cx47 punctate staining at the cell boundaries. In contrast, in the MHV-A59 infected tissues, Cx47 labelling is either lost or much reduced in majority of the mature oligodendrocytes (published in Das S et al, Molecular Neurobiology, 2025).*

different cells respond differently to the same event. The complexity of the CNS comes from its incredible variety of cell types and their ever-changing interactions in health and disease. While traditional bulk RNA sequencing approaches have provided foundational insights into gene expression changes in demyelinating diseases, they obscure cell type–specific transcriptional signatures and fail to resolve rare or transient cell states critical to understanding disease progression. Single-nucleus RNA sequencing (snRNA-seq), which profiles RNA transcripts directly from isolated nuclei, offers several distinct advantages when applied to CNS tissues, especially in models of neurodegenerative or inflammatory disorders [10-12]. Particularly, snRNA-seq enables the profiling of gene expression at single-cell resolution while circumventing challenges associated with dissociating fragile CNS tissues, which can introduce stress-related artifacts or lead to selective loss of certain cell types having complex morphology during enzymatic digestion. This approach is principally advantageous in spinal cord tissue, where myelin-rich architecture and inflammatory changes can complicate live cell dissociation.

Thus, in our study we adopted this high-throughput method of snRNA-seq to classify thousands of nuclei into canonical CNS cell types—including neurons, astrocytes, oligodendrocyte lineage cells, microglia, and infiltrating immune cells—based on gene expression profiles (Fig 4). Sub-clustering further revealed disease-associated cell states, such as reactive astrocyte phenotypes (A1 vs. A2), reactive microglia, and disease associated oligodendrocytes (DOLs). Furthermore, snRNA-seq also captured immune cell infiltration with a population of T cells detected only in the infected spinal cord. This is critical in post-viral demyelination, where persistent peripheral immune cell infiltration is a hallmark of disease. Profiling the transcriptomes of these immune populations alongside CNS glia would help the identification of distinct cell–cell interaction pathways that may drive neuroinflammation and glial dysfunction leading to a demyelinating pathology. Dysregulated processes within specific cell types can be understood from pathway enrichment and gene regulatory network analyses. Our results show distinct gene expression signatures regulating myelination, inflammation, and neuronal function. Notably, oligodendrocyte lineage cells exhibit marked state transitions and altered interactions with other spinal cell types, potentially underlying persistent demyelination even after clearance of active viral infection. These findings establish the first single-cell atlas of the spinal cord in virus-induced chronic demyelination and provide critical insights into cell-specific and network-level mechanisms driving disease pathology.

From Discovery to Hope: Charting the Future of Demyelinating Disease Research

Understanding how a viral infection triggers chronic damage in the brain and spinal cord is a critical step toward unraveling the complexities of demyelinating diseases like multiple sclerosis. By combining advanced tools like single-nucleus RNA sequencing with detailed molecular studies, we are beginning to chart the intricate web of cellular interactions that go awry after a viral assault on the nervous system. Our research not only sheds light on how glial cells—especially oligodendrocytes—respond and adapt in this environment but also opens new avenues for exploring why repair mechanisms fail in chronic conditions. Moving forward, integrating these insights with cutting-edge technologies like spatial transcriptomics and lipidomics may reveal how persistent changes in cellular networks contribute to long-term neurological disorders, including those linked to emerging viral infections like SARS-CoV-2. The hope is that such research will pave the way for targeted therapies that can truly modify disease outcomes by restoring the delicate balance of cell communication within the CNS.

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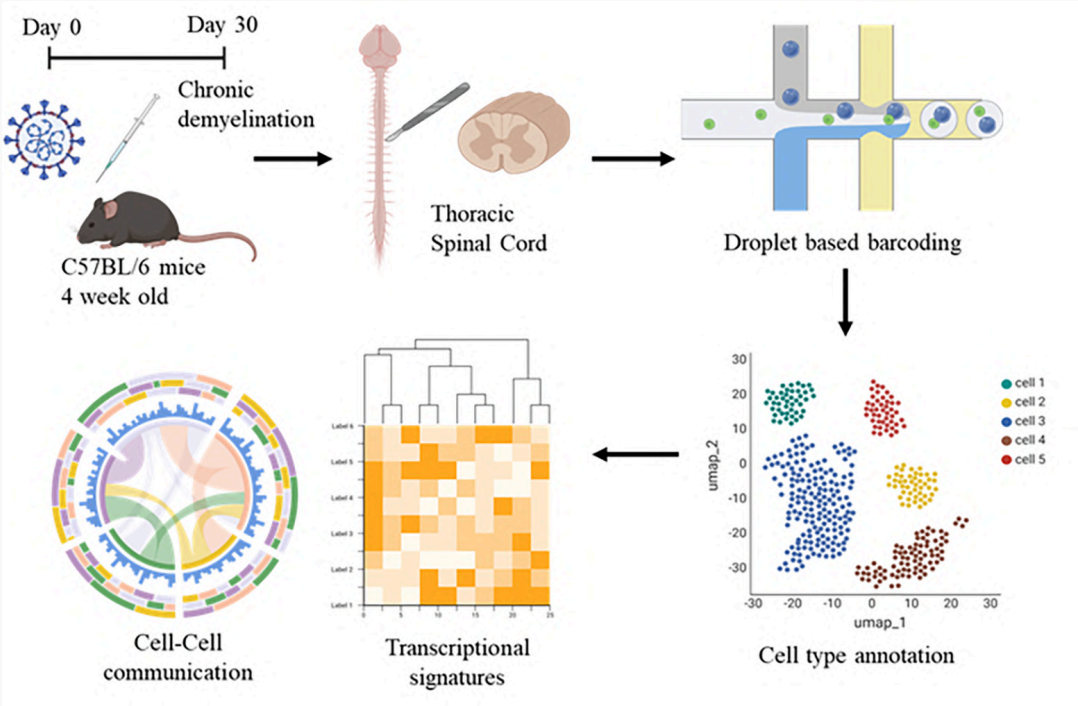

FIG 4 : *Schematic of single nucleus RNA sequencing experimental design and workflow. Thoracic spinal cord segments collected from mock-infected control and MHV-A59 virus-infected mice at 30 days post-infection were subjected to single nuclei isolation and droplet-based barcoding for RNA sequencing. Sequencing reads were aligned to mouse reference genome and analyzed to quantify gene expression levels for each nucleus. Bioinformatic analyses, including clustering, differential expression analysis, and cell-cell interaction analysis are performed to gain biological insights (Image created in BioRender.com).*

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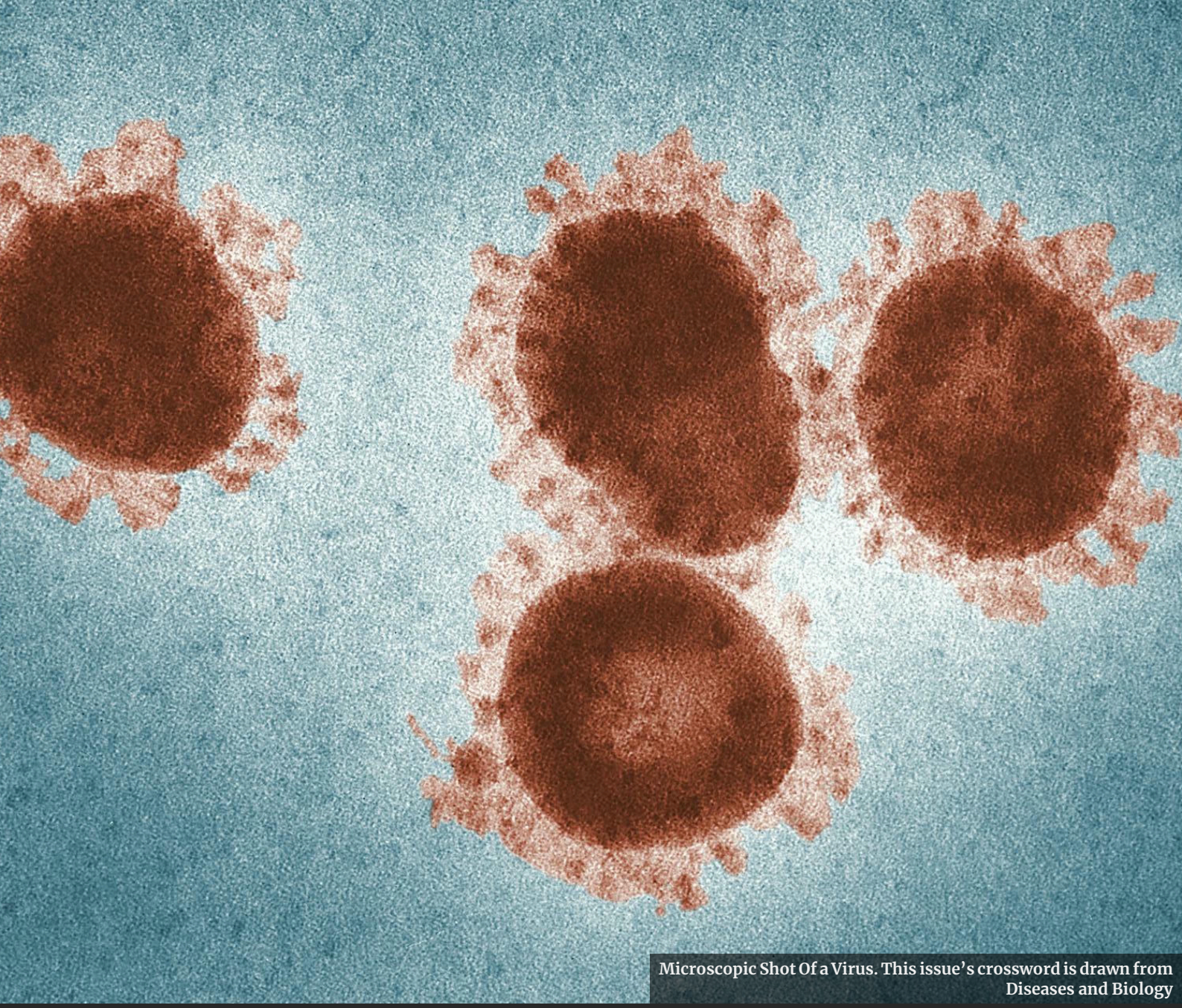
Image credit: Sai Gayathri R and Soubhik Das

References

1. Bergmann, C.C., T.E. Lane, and S.A. Stohlman, Coronavirus infection of the central nervous system: host-virus stand-off. Nat Rev Microbiol, 2006. 4(2): p. 121-32.
2. Brola, W. and M. Wilski, Neurological consequences of COVID-19. Pharmacol Rep, 2022. 74(6): p. 1208-1222.
3. Gasmi, A., et al., Neurological Involvements of SARS-CoV2 Infection. Mol Neurobiol, 2021. 58(3): p. 944-949.
4. Das Sarma, J., et al., Mechanisms of primary axonal damage in a viral model of multiple sclerosis. J Neurosci, 2009. 29(33): p. 10272-80.
5. Lane, T.E. and M.J. Buchmeier, Murine coronavirus infection: a paradigm for virus-induced demyelinating disease. Trends Microbiol, 1997. 5(1): p. 9-14.
6. Perlman, S. and A.A. Dandekar, Immunopathogenesis of coronavirus infections: implications for SARS. Nat Rev Immunol, 2005. 5(12): p. 917-27.
7. Das, S., et al., Neurotropic Murine beta-Coronavirus Infection Causes Differential Expression of Connexin 47 in Oligodendrocyte Subpopulations Associated with Demyelination. Mol Neurobiol, 2025. 62(3): p. 3428-3445.
8. Goodenough, D.A. and D.L. Paul, Gap junctions. Cold Spring Harb Perspect Biol, 2009. 1(1): p. a002576.
9. Laird, D.W. and P.D. Lampe, Therapeutic strategies targeting connexins. Nat Rev Drug Discov, 2018. 17(12): p. 905-921.
10. Lake, B.B., et al., Integrative single-cell analysis of transcriptional and epigenetic states in the human adult brain. Nat Biotechnol, 2018. 36(1): p. 70-80.
11. Rosenberg, A.B., et al., Single-cell profiling of the developing mouse brain and spinal cord with split-pool barcoding. Science, 2018. 360(6385): p. 176-182.
12. Russ, D.E., et al., A harmonized atlas of mouse spinal cord cell types and their spatial organization. Nat Commun, 2021. 12(1): p. 5722.



Microscopic Shot Of a Virus. This issue's crossword is drawn from Diseases and Biology

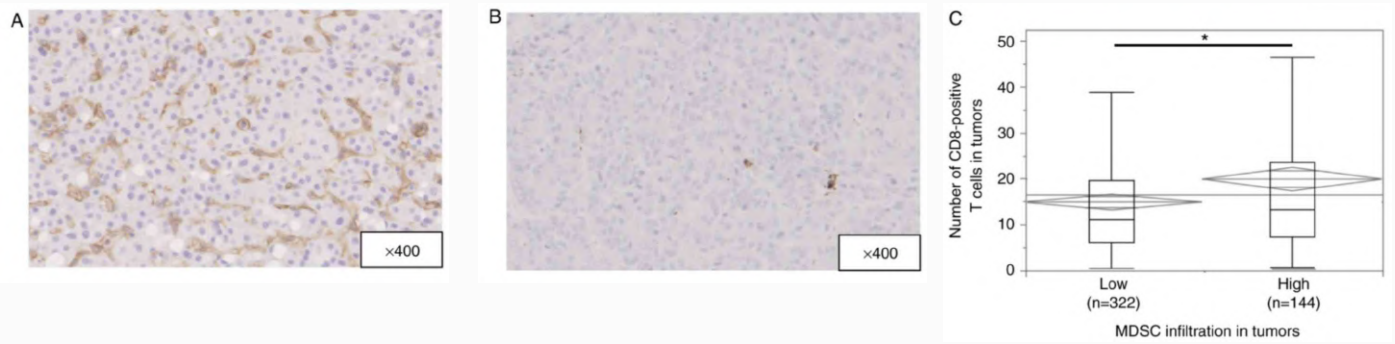
Science Games

Questions drawn from ideas of general science.
Science Quiz

The theme for this issue is Chemistry.
Themed Crossword

Link each term with the next, and complete the science word chain!
Linked List

Quiz: Diseases and Biology



Q1. The figure below shows an immunohistochemistry (IHC) image of a solid tumor section. The brown-stained cells represent an immune cell population that accumulates in the tumor microenvironment (TME) and is known for suppressing cytotoxic T lymphocyte activity, thereby promoting tumor immune evasion. **Which immune cell type is most consistent with this immunosuppressive role in the TME?**

I. CD8+ cytotoxic T cells
II. Natural killer (NK) cells
III. Myeloid-derived suppressor cells (MDSCs)
IV. B-lymphocytes

Q2. Chronic psychosocial stress has been repeatedly associated with increased risk for cardiovascular and metabolic diseases. A recent Frontiers in Physiology (2024) review emphasized the central role of neuroendocrine dysregulation in linking stress to long-term disease outcomes. In particular, one hormonal axis has been shown to mediate the release of glucocorticoids such as cortisol, which in turn dysregulate glucose metabolism, immune function, and cardiovascular physiology. **Which of the following pathways is most directly involved in this mechanism?**

I. Hypothalamic–pituitary–adrenal (HPA) axis leading to cortisol overproduction
II. Growth hormone axis leading to reduced IGF-1 release
III. Hypothalamic–pituitary–thyroid axis causing reduced T3/T4 secretion
IV. Pineal gland activity leading to suppressed melatonin levels

Q3. Artificial intelligence (AI) and machine learning are being rapidly integrated into healthcare to improve early disease prediction. A Frontiers in Medicine (2023) review showed that AI algorithms applied to radiological imaging have dramatically increased diagnostic accuracy in certain infectious diseases. **Among the following, which disease has seen the greatest progress in AI-based diagnostic imaging due to global prevalence and high chest X-ray availability?**

I. Alzheimer's disease via PET imaging of amyloid
II. Tuberculosis through automated chest X-ray screening
III. Type 1 diabetes via ultrasound imaging
IV. Sickle cell anemia via blood smear analysis

Q4. Parkinson's disease is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra. Beyond dopamine loss, recent studies in Nature Medicine (2024) highlight the contribution of neuroinflammation to disease progression. Clinical trials are now investigating therapies that specifically target inflammatory signaling pathways. **Which pathway is currently one of the most promising therapeutic targets for slowing Parkinson's progression?**

I. Inhibition of the IL-1β / NLRP3 inflammasome pathway
II. Upregulation of dopamine transporters
III. Serotonin reuptake inhibition
IV. NMDA receptor antagonism

Q5. Recent research on SARS-CoV-2 (Cell, 2023) has highlighted that the viral spike protein is not only responsible for enabling viral entry into host cells through ACE2 binding but also plays an active role in disease severity. Studies have demonstrated that the spike protein can act as a signaling molecule that interacts with host immune sensors. **Which of the following findings best explains this additional role of the spike protein in infection biology?**

I. Acts as transcription factor in nuclei
II. Alters mitochondrial metabolism
III. Activates Toll-like receptor (TLR) pathways, inducing inflammation
IV. Blocks antigen presentation via MHC-I

Q6. Pathogenic bacteria often interfere with host cell processes to create a favorable niche for survival and replication. A Nature Microbiology (2024) study recently revealed that certain bacterial effectors delivered via secretion systems directly modify host chromatin, influencing transcriptional activity. This strategy allows the pathogen to silence host defense genes and promote infection. **Which of the following mechanisms best describes this form of epigenetic manipulation?**

I. Direct methylation of bacterial DNA by host enzymes
II. Secretion of bacterial proteins that modify histone acetylation
III. Interference with host mRNA splicing
IV. Enhanced ribosomal translation of host proteins

Q7. Advances in cancer diagnostics are shifting toward minimally invasive approaches that can detect tumors at earlier stages. According to Lancet Oncology (2024), liquid biopsy has emerged as one of the most powerful clinical tools in oncology, as it allows detection of tumor-derived genetic material in circulation. **Which of the following is the primary biomarker analyzed in liquid biopsy for cancer detection and monitoring?**

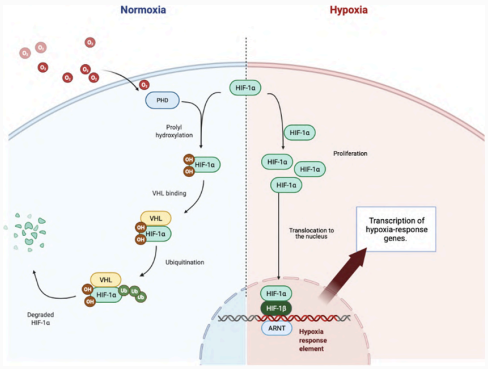
I. Circulating tumor DNA (ctDNA) fragments
II. Erythrocyte membrane proteins
III. HbA1c levels
IV. Synaptic vesicle proteins

Q8. Cognitive decline in Alzheimer's disease has long been attributed to amyloid plaque deposition, but recent Nature Neuroscience (2023) findings challenge this view by showing that synaptic dysfunction occurs much earlier than visible plaque accumulation. Researchers now argue that pathological mislocalization of a specific neuronal protein destabilizes microtubules and disrupts synaptic signaling before large aggregates form. **Which protein is primarily implicated in this early synaptic dysfunction?**

I. Hyperphosphorylated tau protein
II. Excess acetylcholine release
III. Dopamine imbalance
IV. Serotonin transporter reduction

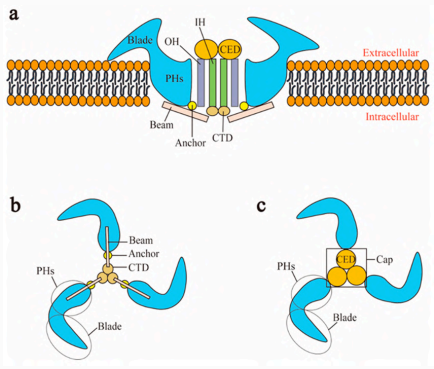
Q9. Refer to the diagram below showing the HIF-1 signaling pathway under normoxic and hypoxic conditions. **Which process occurs as a direct consequence of HIF-1α stabilization under hypoxic tumor conditions?**

I. HIF-1α is hydroxylated by PHDs, leading to degradation
II. HIF-1α complexes with HIF-1β, inducing VEGF and glycolytic genes
III. HIF-1α activates p53-mediated apoptosis
IV. HIF-1α triggers NF-κB inflammatory signaling



Q10. Refer to the schematic diagram above illustrating the structure and activation of the Piezo1 mechanosensitive ion channel. Under mechanical stimuli such as changes in substrate stiffness or shear stress, **which of the following correctly describes the role of the Piezo1 channel in stem cell fate regulation?**

I. Permits selective chloride influx, inhibiting differentiation
II. Forms propeller-shaped channel for Ca2+ influx and mechanotransduction
III. Recruits NAD+/K+ ATPase pumps
IV. Interacts with CFTR to regulate glutamate transport



Answers can be found at the end of the issue. For an interactive version of the quiz, check out our ***website***

Who Am I? – Natural Laws & Processes Edition

Identify the natural laws and biochemical processes from the hints.

Which law of nature am I?

- Discovered in the early 19th century, I explain why carbon dioxide stays trapped in your soda until the cap is opened.
- I describe how the amount of gas dissolved in a liquid depends on the pressure above it, keeping soft drinks fizzy under a sealed lid.
- Beyond beverages, I also govern how gases like oxygen dissolve into the bloodstream, maintaining nature's delicate balance of exchange.

Which natural process am I?

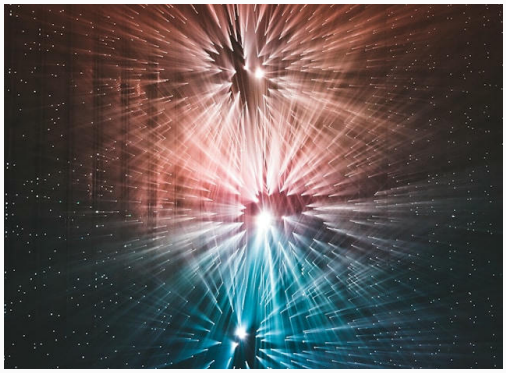
- I transform fallen leaves, dead plants, and animal remains into simpler building blocks that enrich the earth.
- Driven by microbes like bacteria and fungi, I break down complex organic matter and release nutrients that help plants thrive.
- Beyond nourishing the soil, I also influence the planet's carbon balance, subtly shaping the air we breathe.

Which scientific principle am I?

- Formulated in 1908, I describe how a population's genetic makeup can remain in balance when no external forces act upon it.
- Named after two mathematicians, I predict that allele frequencies stay constant unless altered by mutation, selection, or migration.
- Beyond representing stability, I provide a baseline for detecting shifts in genetic variation, helping scientists trace how populations evolve over time.

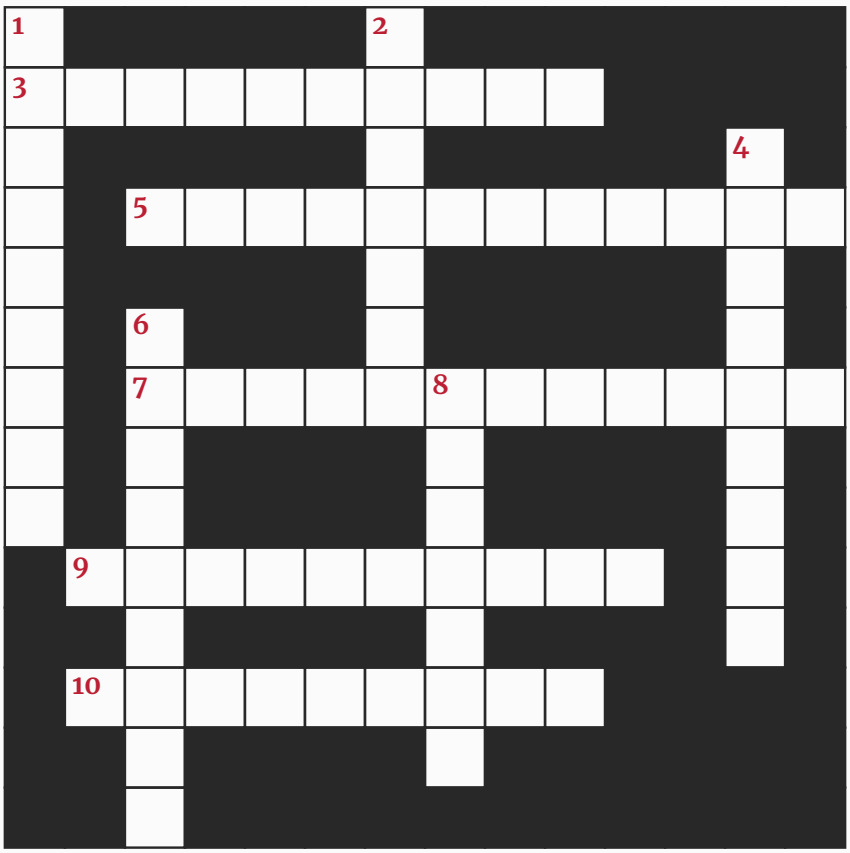
Which fundamental constant of nature am I?

- I am reported to have been measured for the first time by the Danish astronomer Ole Christensen Rømer.
- I connect electricity and magnetism, quietly emerging from Maxwell's equations in the 19th century.
- By remaining finite, I ensure that the past and the future remain distinct.



Themed Crossword

This issue's crossword is based on **Diseases and Biology**.



Across

3. Star-shaped support cells in the brain that nourish neurons, maintain homeostasis, and turn harmful when reactive in disease. (10)
5. Formation of new blood vessels that feed tumors and support their growth and spread. (12)
7. A bodily response to infection or injury, often causing redness and swelling. (12)
9. The process of achieving stability through physiological or behavioral changes in response to stress. (10)
10. Cell surface receptors that anchor cells to the extracellular matrix and relay mechanical signals inside. (9)

Down

1. A neurodegenerative disorder marked by tremors and dopamine depletion. (9)
2. Low oxygen zones inside tumors that trigger survival, angiogenesis, and therapy resistance. (7)
4. Brain's resident immune cells that protect neurons but can drive chronic inflammation in disease. (9)
6. The degree of pathogenicity or ability of a microbe to cause disease. (9)
8. Infectious, misfolded protein that causes healthy proteins to misfold, leading to fatal neurodegenerative diseases (7)

*Solution can be found at the end of the issue. For an interactive version of the crossword, check out our **website**.*

Linked List — Indian Defense Research Edition

Linked List is a general science-based word game. The rules are straightforward:

1. The goal is to guess eleven words that have been drawn from science.
2. The first word (the seed) will be provided to you, and hints and number of letters will be provided for the remaining words.
3. You are also informed that the first letter of any word is the last letter of the previous word. So the first letter of the second word will be the last letter of the seed word, the first letter of the third word is the last letter of the second word, and so on.
4. This property goes all the way, so that the last letter of the last (eleventh) word is also the first letter of the seed word.

Find all the words!

Today's seed: **SHUBHANSHU SHUKLA**

1. Director of the Bhabha Atomic Research Centre, Trombay from 1996 to 2000, champions India's self-reliance on thorium as a fuel for nuclear energy (13)

A												

2. Hyderabad-based DRDO laboratory specializing in missile systems and advanced defense technologies. (22)

3. Renowned Indian scientist, known as the "Missile Woman of India," and key figure in the Agni missile program. (12)

4. India's first unique manned ocean mission under the Deep Ocean Mission, aiming to send three people in a specially designed submersible, the MATSYA 6000, to explore the deep sea up to 6,000 meters. (11)

5. Premier Indian engineering institute engaged in Odisha, as a Regional Engineering College (12)

6. Family of solid-fuel, road and rail-mobile, surface-to-surface ballistic missiles developed by DRDO. (4)

7. India's apex body for biomedical research, instrumental in combating Covid-19 (4)

8. Indian physicist and key architect of India's nuclear program, contributing to post-1991 nuclear and defense science initiatives. (12)

9. Indian scientist and former DRDO official who led development of missile and defense technologies in the post-1991 era, receipient of Padma Bhushan and Order of Friendship, Russia. (19)

10. Series of multipurpose, geostationary satellites launched by the Indian Space Research Organisation (ISRO) that provides telecommunications, broadcasting, weather forecasting, and search and rescue services for India, Since its establishment in 1983. (5)

11. India's indigenous supersonic light combat aircraft, inducted into the Air Force in 2016. (5)

				S

*Solution can be found at the end of the issue. For an interactive version of this game, check out our **website**.*

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We feature science-themed games such as crosswords, quizzes, and word-link challenges. If you have content for these or ideas for new games, please email us at *scicomm@iiserkol.ac.in*.

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To showcase cutting-edge research, we publish short summaries (350–400 words) of recently published scientific papers. The summary should broadly outline the research questions and highlight the key findings.. Submit your research stories **here**.

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More importantly, we would love to hear any feedback that you might have about this endeavour, so please send us your comments at *scicomm@iiserkol.ac.in*.

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Suman Halder

Social Media

Sayan Saha

Science Games

Alekhya Kundu

The Last Page

Crossword

Across

3. ASTROCYTES
5. ANGIOGENESIS
7. INFLAMMATION
9. ALLOSTASIS
10. INTEGRINS

Down

1. PARKINSON
2. HYPOXIA
4. MICROGLIA
6. VIRULENCE
8. MALARIA

Who Am I?

1. Henry's law
2. Decomposition
3. Hardy–Weinberg principle
4. Speed of light

Linked List

1. ANIL KAKODKAR
2. RESEARCH CENTRE IMARAT
3. TESSY THOMAS
4. SAMUDRAYAAN
5. NIT ROURKELA
6. AGNI
7. ICMR
8. RAJA RAMANNA
9. A. SIVATHANU PILLAI
10. INSAT
11. TEJAS

Quiz

1. Myeloid-derived suppressor cells (MDSCs)
2. Hypothalamic–pituitary–adrenal (HPA) axis leading to cortisol overproduction
3. Tuberculosis through automated chest X-ray screening
4. Inhibition of the IL-1β / NLRP3 inflammasome pathway
5. Activates Toll-like receptor (TLR) pathways, inducing inflammation
6. Secretion of bacterial proteins that modify histone acetylation
7. Circulating tumor DNA (ctDNA) fragments
8. Hyperphosphorylated tau protein
9. HIF-1α complexes with HIF-1β, inducing VEGF and glycolytic genes
10. Forms propeller-shaped channel for Ca2+ influx and mechanotransduction

You made it to the end! While we cook up the next issue, here's a random photo dump.

79th Independence Day

As light diffracts into its vibrant spectrum, the tricolour unfurled at IISER Kolkata, symbolizing the diverse yet united spirit of our nation. *Credit: IISER Kolkata*

The Moon in Eclipse

Bathed in Earth's shadow, the Moon turned into a canvas of cosmic beauty. The Total Lunar Eclipse witnessed at IISER Kolkata, brought closer through a telescope session by Singularity: The Astro Club. *Credit: Susnata Chattopadhyay*

Kabaddi Showdown: IISER K vs IISER TVM

In one of the most intense matches of IISM-2024, IISER Kolkata clinched victory over IISER Thiruvananthapuram in Kabaddi after four thrilling tie-breakers. *Credit: Madhura Theng*