Issue 50 June 2025

THE DOSSIER

The Digest On CCR Staff Scientists and Staff Clinicians: Information, Employment and Research

From the Editor's Desk

Dear Colleagues,

It is with pride and gratitude that I welcome you to the June 2025 Issue of *The Dossier*, which is the 50th edition, and a milestone that marks 15 years of our shared journey. This achievement would not have been possible without the unwavering support of our readers, contributing writers, and the dedicated team of section editors and editorial board members. I would like to express my sincere appreciation to the entire editorial team for their hard work, commitment, and enthusiasm for putting this commemorative issue together, which reflects on the path we've traveled and looks ahead with renewed purpose. In this special edition, you will find remarkable contributions by many scientists, including important messages from NCI Principal Deputy Director Dr. Douglas Lowy and CCR's Acting Co-Directors Dr. James Gulley and Dr. Carol Thiele, an article co-authored by my predecessors and me that describes the progress of *The Dossier* from its inception near an elevator entrance to its arrival in your inboxes, and an insightful article that illustrates how technology transfer enables the NIH turn discovery into health. This issue also features the available CCR Genomics Core for NCI researchers, a spotlight on cancer research by two staff scientists in the Author Corner, and conversations with two CCR senior investigators in the PI Corner.

A significant number of CCR and DCEG Staff Scientists and Staff Clinicians (SSSC) attended the 21st Annual SSSC Retreat, held on April 18, 2025, at the NCI Shady Grove Campus. A detailed summary of the event's proceedings is available in the Event Report section and the SSSC award winners are recognized in the Congratulations section. With summer break just around the corner, many of us are eagerly looking forward to spending time with family and friends. I hope everyone finds time to relax and recharge. On behalf of the entire editorial team, I extend our best wishes for an enjoyable summer. I also encourage everyone to take a moment to appreciate the vibrant research community we share at NCI and to take pride in your contributions and achievements.

Brajendra Tripathi, Ph.D.
Editor-in-Chief

Douglas R. Lowy: 50 Years @ NCI and Counting

Dear Colleagues,

It is difficult to believe that my lab has been part of the NCI Intramural Research Program (IRP) for 50 years. The freedom of the IRP and encouragement to conduct high-risk research have remained constants throughout, despite many administrative and organizational changes during this period. In 1975, when I started my lab, I went to my boss, Dr. Alan Rabson, to ask whether there was particular research he wanted me to do. He replied, "Doug, just make it good." With those marching orders in mind, that's what I have tried to do.

I have surrounded myself with colleagues who are smarter than I am, which has been a tremendous benefit for me. John Schiller and I started doing research together more than 40 years ago. We initially worked on the genetics of the bovine papillomavirus (BPV), which was easier to determine than with human papillomaviruses (HPVs) because we had a source of infectious virus and an in vitro quantitative cell transformation assay, unlike HPVs. When HPVs were identified as the main cause of cervical cancer, which is one of the most common female cancers worldwide, we decided to see if we could develop a preventive HPV vaccine against. We were able embark on this project, despite lacking any experience with vaccines, thanks to the freedom of the IRP and the willingness of Reinhard Kirnbauer – a dermatologist from Austria who was a post-doc in the lab – to devote his research time to this risky project. Several extramural labs in the United States and abroad had a similar goal. We succeeded in large part because we first used BPV as our model system, thanks to its advantages described above, and only subsequently turned our attention to HPV, using BPV as our positive control. The clinical trial work led to a long-term collaboration with colleagues in DCEG, who have ably led several vaccine efficacy trials. The most recent vaccine results have validated our hypothesis that a single HPV vaccine dose can confer long-term protection. We anticipate regulatory bodies such as the CDC ACIP (Advisory Committee on Immunization Practices) and the World Health Organization will be considering the possibility of recommending a single dose, which could enable greater vaccine uptake, as well as being the first sub-unit vaccine with such a recommendation.

The lab, which is part of the Laboratory of Cellular Oncology (LCO), also conducts research on oncogenes and tumor suppressor genes. Associate Scientist Xiaolan Qian and Staff Scientist Brajendra Tripathi, with critical contributions by Bioinformatician Dunrui Wang and Biologist Marian Durkin, together with several outstanding post-bacs – Sophia Sahin most recently - continue to make unexpected, biologically relevant observations. Some recent findings from the lab include the first identification of a role for the mutant RAS oncoprotein in the export of nuclear proteins (Tripathi et al., *Nature Cancer*, 2024), a discovery with potential translationnal relevance, and the first identification of cancer-associated mutant RAS and RHO proteins that are biologically active when bound to GDP, in contrast to the widely held belief that these proteins must be bound to GTP in order to be biologically active (Qian et al., manuscript in preparation).

The continued productivity of the lab reflects staff scientists' initiative and follow-through, especially given my administrative responsibilities. More broadly, they exemplify the leadership roles played by many staff scientists and staff clinicians in carrying out the CCR/NCI mission.

I congratulate the entire editorial team for 50th Issue of *The Dossier* and hope *The Dossier* will continually deliver valuable information to our staff scientists and staff clinicians.

Douglas Lowy, M.D.
Principal Deputy
Director, NCI

Facing Challenges Together

A Note From The CCR Acting Co-Directors

Dear Staff Scientists and Staff Clinicians,

Dr. Gulley really enjoyed attending the SSSC retreat, and was happy to address your many thoughtful questions, especially about the current budget situation and appointment renewals. Many new policies and procedures have been put in place recently, and information has been changing quickly. We welcome the opportunity to update you here.

Communications

We are doing our best to communicate quickly and clearly to all of you. We realize CCR staff may first hear of changes from other institutes or outside media sources. While sometimes such rumors may turn out to be true, we must follow organizational communications channels before sharing information. Official guidance flows from the Department of Health and Human Services (DHHS) to NIH to NCI and then to CCR. We communicate policies as soon as they are conveyed to us from NCI leadership.

As a reminder, we monitor the AskCCR email box daily to provide CCR staff with resources to answer common questions. Also, our "all staff" email messages are archived on CCR Central. This is a great source to check before seeking more information. And we continue to publish our internal newsletter, Sixty-Second Update.

Budget and Purchasing

As discussed at the retreat, CCR continues to face unprecedented budget challenges, and we expect this to continue in FY26. Until Congress passes an appropriation, we won't know what CCR's budget will be. However, we have been strategically preparing for various scenarios and closely assessing our spending to identify cost-saving efficiencies.

We've had a lot of help from many in the CCR community. CCR's Scientific Cores Working Group, led by Dan McVicar and Tim Greten, provided recommended strategies to ensure the type of core services provided are those most scientifically important and are the most efficient to provide centrally. Their methodic analysis relied on budget data, input from CCR users, and benchmarking with outside vendors.

We also relied on input from labs and branches to meet our portion of the mandated 35 percent reduction in NIH contract expenditures. This reduction, along with purchasing restrictions, reductions in force (RIF) of NCI purchasing staff, and freezing of purchase cards have been extremely challenging for CCR.

However, we do see some hopeful signs of improvement. For example, purchase cards are no longer frozen, and training has opened to expand the number of cardholders and approvers. Also, purchases may now be made for research projects started after January 20, 2025, and Cardholders may purchase items in support of research without restriction, provided they are within their cardholder limit of $10K per item and meet normal p-card regulations.

Pay Adjustments

Taking a fresh and deep look into CCR spending has uncovered some ways that we can make CCR more equitable to ensure that all have access to resources and compensation that is consistent and fair. For example, in assessing CCR's historical approach to compensation, we found examples where some SSSC received spring pay adjustments or cost-of-living adjustments (COLAs), and others did not yet quadrennial pay adjustments were not reduced to account for these differences.

We have implemented what we hope will be a more consistent, equitable and transparent approach to discretionary pay adjustments for staff that considers differences across a variety of hiring authorities, under

Title 5 and Title 42. The new policy considers three factors when deciding upon a quadrennial pay adjustment:

- Quad rating
- Base pay increases received over the past four years (COLA and/or spring pay adjustments)
- Equity with similarly situated CCR staff

Note: one-time performance bonuses do not factor in base pay decisions. Also, the quad-reviewed staff members will receive a minimum pay adjustment of 2% for outstanding and 1% for outstanding-excellent, even if the four-year average was above the target.

We are working very closely with NCI and NIH leadership to address the challenges you are facing every day. Our SSSC community contributes in vital ways to our research advances, and we value each one of you and the hard work you do to support the CCR mission. Thank you for your dedication and persistence during these difficult times.

James Gulley, M.D.
Acting Co-Director

Carol Thiele Ph.D.
Acting Co-Director

15 Year Journey of *The Dossier*: Reflecting and Progressing Forward

Congratulations on the 15th Anniversary and 50th Issue of *The Dossier*! What better opportunity to appreciate your incredible work and celebrate how far we've come together? We are delighted to bring together this very special issue of *The Dossier* containing articles by members of the editorial board as well as past and present Editor-in-Chief, to mark and celebrate our first 15 years and the 50th Issue.

In March 2010, a chance meeting between Dr. Anuradha Budhu (*SAS*) and Dr. Ofelia Olivero (former *SS*) at the elevators of Building 37, included a discussion about the upcoming NCI Staff Scientists and Staff Clinicians (SSSC) retreat and the notion that it would be a good idea to start a newsletter focused on the SSSC community. An outline for the newsletter was quickly drafted on a piece of paper at the elevator entrance. With no previous editorial experience and with only a month to the publication date of the first issue to coincide with SSSC retreat, Dr. Budhu formulated the mission and vision of the newsletter and assembled the content and writers, coordinating the effort with the CCR Office of the Director (OD), NCI Office of Communications, NCI Center for Cancer Training, and the SSSC organization. The next task was to come up with a name for the newsletter! Given the target audience and the purpose of the publication, Anuradha coined, "*The Dossier*" (The Digest on Staff Scientists and Staff Clinicians: Information, Employment and Research).

The first issue of *The Dossier* was published in April 2010, in print and electronic versions, with Dr. Budhu as Editor-in-Chief, with articles from the OD (Drs. Bob Wiltrout and Lee Helman), a CCR PI (Dr. Barbara Vonderhaar), the SSSC Co-Chairs, as well as information on the SSSC Quadrennial Review, Core Facilities and Bioinformatics Resources, and of course, the upcoming 6th SSSC retreat! The issue was a success and now, the task was set to prepare for future publications. An Editorial Review Board was established, and the publication timeline was set for quarterly issues with routine sections and the opportunity to add new sections/information of interest to the SSSC community as needed. As such, *The Dossier* has evolved over the years, including sections highlighting new SSSC, overviews of the published work of SSSC, career/professional development information, guest editorials and congratulations on accolades received by SSSC. In June 2011, after a few more issues were published, *The Dossier* welcomed two *SS* (Drs. Anne Gegonne and Caterina Bianco) as its first Section Editors, focusing on the Core and PI Corners, respectively. Since that time, many SSSC have joined *The Dossier* team as Section Editors *(Former: Cristina Bergamaschi*, *Takashi Furusawa*, *Brunilde Gril*, *Liu-ya Tang*, *Alexandra Zimmer, Lekha Mikkilineni and Majda Haznadar; Current: Yoshimi Greer, Lisa Jenkins, Sabina Kaczanowska, Andaleeb Sajid and Ling Zhang)* to share vital information with the SSSC community and gain editorial experience. *The Dossier* is now an all-digital format with current and all former issues available on the SSSC website (***The Dossier***).

After 9 years leading *The Dossier*, Dr. Budhu stepped aside and became the Senior Editor and handed the helm to Dr. Lakshmi Balagopalan *(AS)*, who had joined the team as a Section Editor in 2011. Dr. Balagopalan's first issue was published in March 2019. She revamped the newsletter with a modern take, updated the template and added the "Getting to know our new SSSC" and "Congratulations" sections. With the continued support from the CCR leadership, publications were sustained, even during the COVID-19 pandemic. At a time when in-person gatherings were on hold, *The Dossier* continued to keep the community informed and engaged.

In 2024, Dr. Brajendra Tripathi *(SS)*, who had joined the team as a Section Editor in 2022, became the new Editor-in-Chief. He implemented several new initiatives to enhance *The Dossier's* visibility and impact across NCI. He introduced the SSSC Author Corner to feature two SS and SC in each issue of *The Dossier* to recognize their outstanding research,

significant scientific contributions and achievements, career path, and interests. Dr. Tripathi also reduced the number of issues from four to two per year to help improve the quality of *The Dossier* by allowing the section editors to dedicate more time and resources to each edition. His quality-driven approach is expected to elevate the effectiveness of *The Dossier* by fostering deeper engagement with contributors and curating impactful articles, thereby increasing its relevance and resonance with readers.

As we celebrate our 50th issue and 15th anniversary, it has been our distinct privilege to consistently provide the SSSC community with valuable information and resources, including important messages from NCI leadership, PIs, highlighting outstanding SSSC research, introducing newly hired SSSC, summarizing clinical trials of SCs and availability of technology/methods at NCI Core facilities, recapping the SSSC retreat and professional development, career workshops, and scientific meetings as well as SSSC awards and achievements. We thank all *The Dossier* team members, including our former and current section editors, all the contributors who have written fantastic articles along the years as well as a special thank you to NCI and CCR leadership for their continued support.

A final thanks to our readers, ALL OF YOU, who have encouraged and furthered the progress of *The Dossier* from its beginnings at an elevator entrance to your inboxes. We aim to continue to steadfastly provide SSSC community with pertinent and useful information to promote the success of our SSSC community.

Anuradha Budhu, Ph.D.; Brajendra Tripathi, Ph.D.; Lakshmi Balagopalan, Ph.D.

Getting to Know Our New SSSC

Section Editor: Yoshimi Greer, M.D. Ph.D. (SS)

Christopher A. Febres-Aldana, M.D., SC

Laboratory of Pathology

Research focus:
Application of tumor profiling technologies for discovering novel biomarkers for precision oncology, studying tumor resistance, improving current tumor classification systems, and fully characterizing rare cancers.

How did you choose your career?
Pathology is the bridge between clinical medicine and translational sciences. I've always been interested in understanding how neoplastic diseases develop at structural and molecular levels. As a pathologist, working on real clinical cases allows me to see under the microscope features for designing comprehensive and well-balanced research that can be effectively translated into practice changes. Pathology combined my interest in diagnostics, problem-solving, and working behind the scenes to support patient care.

What could be the impact of your research?
We need efficient profiling strategies to guide the management of cancer patients. By characterizing tumor histopathology, genomics, and epigenomics, we can build a tissue-based digital platform that can classify and predict tumor pathobiology with great accuracy, helping in choosing the most effective targeted therapy and preventing the emergence of resistance.

What about you might be surprising?
I'm a guitar lover. I have played the guitar since childhood and enjoy improvising on fusion instrumentals. Progressive rock, fusion, jazz, and blues are my "jams."

Syed Abbas Bukhari, Ph.D., SS

**Genetics Branch,
Oncogenomic Laboratory**

Research focus:
I use multi-omics, gene regulatory network modeling, and computational approaches to study tumor progression, immune evasion, and therapy resistance. My work integrates genetic data with both bulk and single-cell transcriptomic profiles to identify key regulators and pathways that drive disease. A major focus of my research is on pediatric solid tumors, with the goal of informing precision oncology and developing more effective, targeted therapies.

How did you wind up in your current field?
I have always been drawn to both biology and computing since high school. During graduate school, I realized the potential of bioinformatics to bridge basic biology and translational research. This intersection became the foundation of my career—using computational tools to uncover the molecular underpinnings of disease and to translate complex data into biological insights

What could be the impact of your research?
By reconstructing tumor and microenvironment regulatory networks, my research aims to predict therapy responses, uncover mechanisms of resistance, and guide the development of personalized therapies. Ultimately, the goal is to enable more precise and durable treatment strategies that can shift cancer toward a more manageable disease.

Raju Chelluri, M.D., M.S., SC

Urologic Oncology Branch

Research focus:
I am a surgical oncologist focused in managing urothelial malignancy of the bladder and ureter. The patients we see and care for will form the basis of studying the metabolic and genomic drivers of urothelial cancer progression.

How did you choose your career?
I was honored to be a part of the Medical Research Scholar's Program here at NIH in 2014, after my third year of medical school. My mentor in medical school had been a surgeon-scientist here at NIH before becoming Chairman in Urology, coincidentally at almost the same exact time I started medical school. My mentor and my time at NIH convinced me to pursue a surgeon-scientist career focused on urologic malignancies.

What could be the impact of your research?
The overall goal is to study the biology of bladder cancer using human specimens obtained from surgery. Some concepts, such as the genomics of bladder cancer progression, are described but not actionable clinically. Others, such as the changes in metabolism in bladder cancer, have been only nascently described. We aim to characterize urothelial malignancies in a fashion that translates into clinically actionable tools or therapies to improve care for patients with bladder cancer.

Brian Pennarola, M.D., SC

Pediatric Oncology Branch

Research focus:
Development of high-quality advance care planning interventions for pediatric, adolescent, and young adult patients.

How did you choose your career?
While completing a pediatric hematology-oncology fellowship in the joint National Cancer Institute/Johns Hopkins program, I worked with Dr. Lori Wiener in the Pediatric Oncology Branch's Psychosocial Support and Research Program. Through my clinical and research work, I recognized the incredible privilege and responsibility it is to care for children and families in their most difficult times and cultivated an interest in the cross-over between pediatric oncology and palliative care. Following a 1-year fellowship in hospice and palliative medicine at Johns Hopkins Hospital, I returned to the POB to launch my career as a dually appointed pediatric hematologist-oncologist and pediatric palliative care physician and researcher.

What could be the impact of your research?
My research aims to improve communication for children, adolescent, and young adult patients through the use of novel interventions which both implement existing evidence-based practices and pilot new techniques and tools developed by our research group. We hope to highlight the benefits of honest and empathic communication about patient/family values, hopes, worries, and goals as these patients/families navigate clinical trials and life with serious illness.

Cem Sievers, Ph.D., SS

Surgical Oncology Program

Research focus:
Cancer immunology in the context of neoadjuvant/pre-operative immunotherapies. We are trying to understand the molecular and cellular factors that determine response to immunotherapies with a particular focus on tumor-infiltrating immune cells. Our research is mostly based on tissue samples we collect in the context of clinical trials.

How did you wind up in your current field?
My PhD work was at the intersection of epigenetics and computational biology exploring epigenetic gene regulation using computational methods. During my PhD I further developed an interest in cancer biology, as many chromatin regulators are altered during cancer development. Therefore, during my postdoc, I focused on epigenetic mechanisms underlying drug resistance in glioblastoma. Although my previous work mostly focused on the cancer-cell side, when I had the opportunity to join the head and neck cancer program at the NCI about five years ago (as a contractor), I was very excited about the possibility of working on and learning more about other cells that play a crucial role in cancer biology, namely tumor-infiltrating immune cells.

What could be the impact of your research?
An important goal of our research efforts is to characterize basic molecular and cellular mechanisms underlying the development of cancer that could enable us and others to develop more effective treatment strategies. At the Clinical Center we have the opportunity to integrate our findings into clinical trials with the aim to benefit cancer patients.

Omkar Singh, Ph.D., SS

Laboratory of Pathology

Research focus:
I am a trained Computational Biologist specializing in pathology-focused machine learning models for tumor classification. Currently, my work centers around developing predictive models utilizing DNA methylation data, a rapidly evolving and highly relevant area in cancer diagnostics.

How did you wind up in your current field?
I joined the Laboratory of Pathology in 2019 and have since been developing machine learning methods for tumor classification, with a particular emphasis on brain tumors. Our group successfully developed one of the most accurate brain tumor classifiers currently available, which is now actively integrated into daily clinical practice at NCI as well as utilized by multiple external clinical centers through an accessible online platform. We have applied for patent of our tool. Additionally, we are extending our methodologies to develop classifiers for other tumor types, including kidney and hematologic malignancies.

What could be the impact of your research?
My research directly addresses critical challenges in cancer diagnostics by applying advanced machine learning approaches to DNA methylation data. By improving the molecular classification of brain tumors, my work has contributed to more accurate, reproducible, and clinically actionable diagnoses, leading to better-informed treatment decisions. The adoption of our brain tumor classifier in routine clinical workflows underscores its real-world clinical value.

Varun Sood, M.S., Ph.D., SS
Laboratory of Receptor Biology and Gene Expression

Research focus: Identification of novel factors that regulate as stochastic transcriptional bursting, the inherent random pulses of transcription in vivo.

How did you choose your career?
My first lab internship during my Bachelors in India was the pivotal moment when I decided to make a livelihood out of research. Looking back, it was not the best lab or a successful project by any standards but the sheer joy that I derived from very small successes, like casting PAGE gene from scratch after 10 failed attempts, made it clear me that I had a dominant *LAB* gene. The next major event was coming to the USA for my Ph.D. at Northwestern University. I was blown away by the audacity of high-quality research that helped me develop a scientific temper. From intense focus on protein structural biology in my Master's I gravitated to genetics and transcription regulation as they felt more like interesting puzzles that could be probed with several perturbation tools. Thus, my research journey uniquely places me to investigate transcriptional regulation at the molecular level and leverage them for therapeutic ends.

What could be the impact of your research?
Transcription is at the heart of physiology and several disease etiologies; however, we still don't know a lot. Using a screening based mechanistic understanding of transcriptional bursting we can bridge our current gaps in understanding and improving current epigenetic based therapeutics.

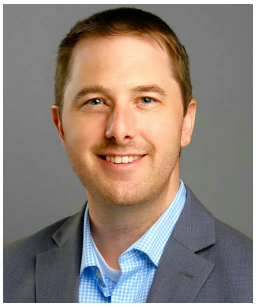
Congratulations

SSSC Awards

Outstanding Mentor Awards

Brajendra Tripathi, Ph.D.
Laboratory of Cellular Oncology

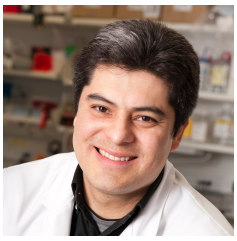
Chuen-Yen Lau, M.D.
HIV Dynamics and Replication Program



David E. Milewski, Ph.D.
Genetics Branch

Best Oral and Poster Presentation Awards at the SSSC Retreat

Best Talk



Julio Valencia, Ph.D.
Cancer Innovation Laboratory

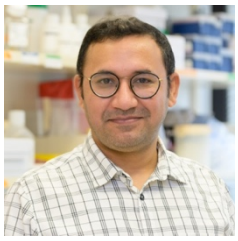
Best Poster

Francesco Ardori, Ph.D.
Mouse Cancer Genetics Program

Best Poster

Linh Bui-Raborn, Ph.D.
Laboratory of Translational Genomics

Best Poster



Imran Khan, Ph.D.
Women's Malignancies Branch

Event Report: Highlights from the 2025 Annual Staff Scientist and Staff Clinician Retreat

"We Must All Hang {In There} Together"

The annual NCI Staff Scientists and Staff Clinicians (SSSC) retreat is a quintessential example of a scientific meeting providing the SSSC community with a valuable forum to showcase their research. In continuation of this tradition, the 21st Annual SSSC Retreat was held in person on April 18th, 2025, at the NCI Shady Grove Campus as an NIH internal event. "Bridging the gap between basic and clinical cancer research in the era of digital transformation" was the theme for this year's retreat. By embracing this theme, our aim was to foster discussions about connecting mechanistic discoveries with therapeutic innovation and clinical practice. We hoped to learn about challenges that limit translation of scientific success into benefits for patients and how emerging technologies like artificial intelligence and machine learning could be leveraged to transform cancer diagnosis, treatment and prevention.

The Rockstar Team

As with any event, its success is heavily dependent on the effectiveness of the organizing committee. Our SSSC retreat organizing committee is composed of 35 members and follows the "highly aligned, loosely coupled" model popularized by a prominent streaming service and often seen in the context of biological systems as well. The committee is divided into small teams that cover different facets of retreat organization. Each subcommittee is dynamic, has self-direction and flexibility in execution yet is bound by the overarching goal of organizing a successful retreat. How our monthly conversations, different perspectives and layers of thinking evolved into concrete plans for the retreat was a perfect collaborative experiment.

Overview

The 21st Annual SSSC retreat had 154 registrants, two sessions with leadership participation, three keynote speakers whose work embodied the retreat theme, 8 SSSC oral presentations selected from submitted abstracts and 84 poster presentations. The retreat encompassed a broad spectrum of topics from basic biological mechanisms to innovative digital engagement to population-based cancer studies and epidemiological research.

The Morning Session

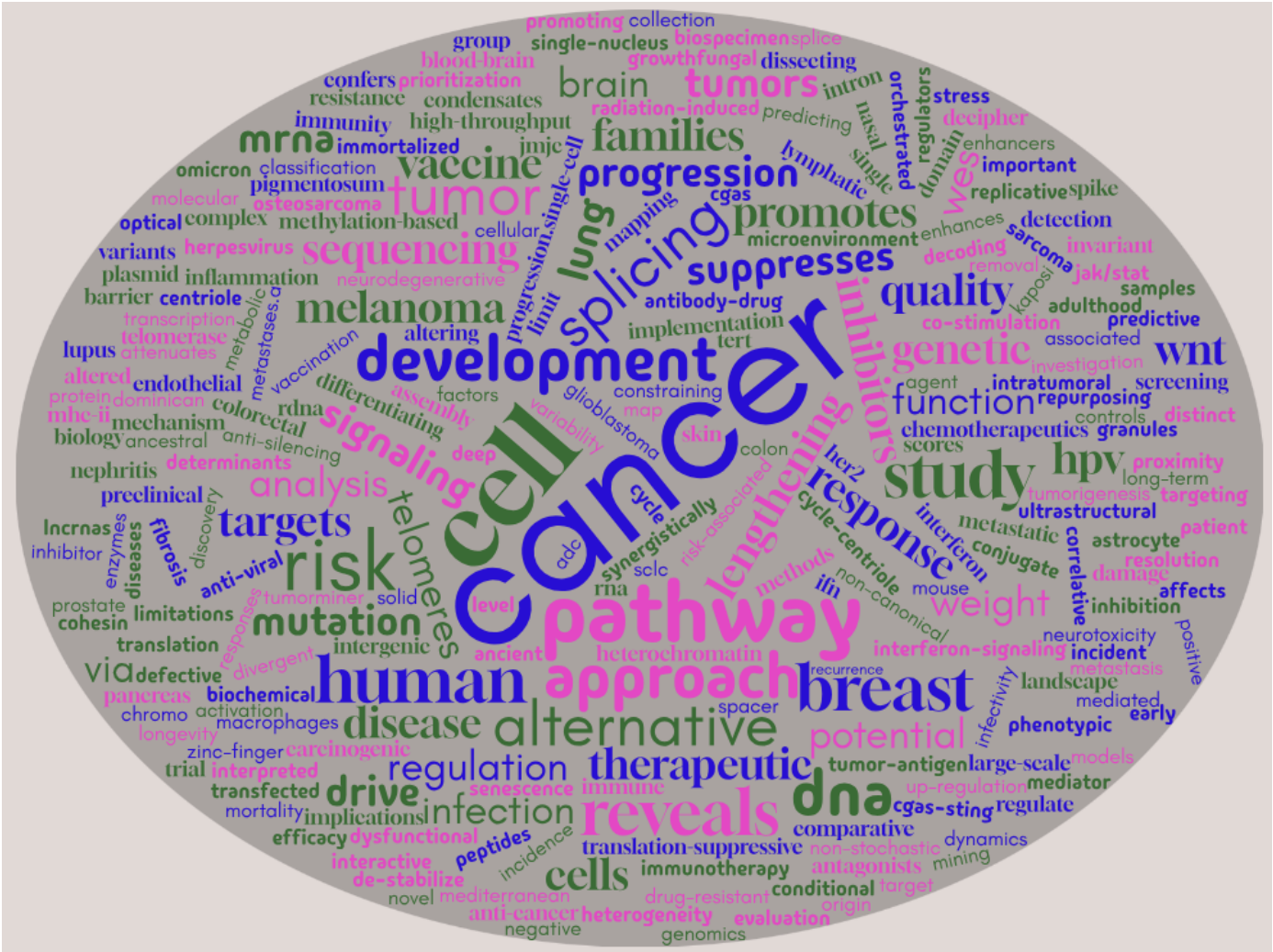
The retreat kicked off to an inspirational start with the Opening Remarks presented by Dr. Douglas Lowy, the Principal Deputy Director of NCI. Dr. Lowy spoke of how the Battle of Lexington shaped the course of our nation's freedom and values. He drew parallels to NCI's own cultural bedrock - to make a difference, to strive for excellence, to have an impact and to uphold our tradition of altruism. Dr. Lowy concluded with a quote attributed to Benjamin Franklin- "we must all hang together or assuredly we shall all hang separately" which became a symbol of the American Revolution. Dr. Lowy's words resonated deeply with the audience as evidenced by the murmurs of agreement that echoed throughout the hall.

After the Opening Remarks, our first Keynote Speaker was Dr. Ramaprasad Srinivasan, Deputy Director CCR, NCI. He took us through a remarkable exploration of his research on hereditary kidney cancer involving von Hippel Lindau (VHL) disease. He provided a riveting overview of the identification of the VHL gene and its mutations leading to Clear Cell Renal Cell Carcinoma, challenges in targeting the VHL pathway and endeavors leading to the idea of directly targeting HIF2-α with small molecule inhibitors.

NCI Principal Deputy Director Dr. Douglas Lowy and CCR Acting Director Dr. James Gulley address SSSC. Dr. Ramaprasad Srinivasan and Dr. Eytan Ruppin of NCI deliver keynote address. Scientists at the retreat discuss various important topics on cancer research.

His team's breakthrough efforts culminated in the second generation HIF2α inhibitor, Belzutifan, being approved by the FDA as the first agent to treat VHL patients. The enthusiasm for the subject matter was palpable with the scientific dialogue continuing into the Q&A session with Dr. Srinivasan and even spilling into the coffee break.

After a brief introduction to the SSSC organization by the Co-Chairs, the focus shifted to oral presentations from the SSSC. The talks showcased the variety of research ranging from dissection of dynamics of human centriole assembly by ultrastructural analysis to identification of new drug combinations that cooperate with the inhibition of nuclear export function to treat KRAS-driven pancreatic cancers. The session also included elegant work about engineering Natural Killer cells to express TCR and membrane tethered IL15/IL-21 that enhance their cytotoxic capacity and development of human genetically engineered myeloid cells for a first-in human-clinical trial. After an engaging audience discussion, the morning events concluded to allow for the first poster session. The posters spanned a broad range of topics across various fields as highlighted in the accompanying word cloud generated from the abstracts. Both the morning and afternoon poster sessions provided opportunities for scientific interactions and feedback.



The word cloud generated from the abstracts as part of the retreat narrative

Dr. Sharon Savage, Clinical Director, DCEG, NCI presents Outstanding Mentor, Best Oral and Best Poster Presentation Awards to SSSC

The Afternoon Session

The networking opportunities continued into lunch where the atmosphere was vibrant with banter, and intellectual exchange. Lunch was followed by a session engaging with leadership; Dr. James Gulley, the acting Co-Director of CCR, addressed the most pressing concerns and queries from SSSC. His presence provided assurance and was a confidence booster for the community.

The second Keynote presentation was delivered by Dr. Eytan Ruppin, Chief, Cancer Data Science Laboratory, CCR, NCI. His talk was an invaluable source of knowledge about novel digital approaches and their translational capabilities. He elaborated on a new machine learning platform with the potential to transform interpretation of traditional H&E images. His unique and humorous flair kept the presentation as entertaining as it was educational. His talk sparked a deeply interesting discussion about the current barriers in using digital techniques in the clinics.

The SSSC oral presentation session that followed led us on a journey encompassing novel splice mechanisms of the telomerase reverse transcriptase gene that influence cancer risk to exploring nuanced redundancies of the Interferon regulatory machinery to develop more targeted, less toxic immunologic therapies. This session also included presentations that embraced new technological developments, such as the use of machine learning platforms involving Raman spectroscopy to classify glioma subtypes and employing single-cell transcriptomics to reveal altered landscape of the blood-brain brain barrier in breast cancer metastases.

The final talk and Closing Remarks were delivered by Dr. Sharon Savage, Clinical Director, DCEG, NCI. Her talk connecting telomere biology to human disease captivated the audience. She took us through her pioneering journey of identifying the genetic causes, standardizing reliable methods for telomere length measurement, understanding the basic biology, elucidating the medical complications, and most importantly establishing collaborative resources and raising awareness about telomere biology disorders. In her Closing Remarks, Dr. Savage highlighted how the meeting showcased the breadth and quality of research undertaken in CCR and DCEG spanning fundamental, translational, clinical, and epidemiological studies.

A highlight of the retreat was the ceremony that continued the tradition of presenting awards to the best mentors (received by Dr. Brajendra Tripathi, Dr. Chen-Yen Lau, Dr. David Milewski), best oral presentation (Dr. Julio C. Valencia) and best posters (Dr. Francesco Tomassoni Ardori, Dr. Imran Khan, and Dr. Linh Bui-Raborn).

Concluding Remarks

After the event, about 35% of the attendees completed an online survey. The overall feedback was favorable with participants expressing satisfaction about the content and format. It was a pleasure to come together with friends and colleagues to exchange thoughts and ideas, to learn how massive data from experimental work has provided the impetus for developing cutting-edge digital tools, how the synergy in bench to bedside approaches is amplified by integration of digital technology, and what challenges are involved in the process.

Acknowledgements

We convey our gratitude to the Center for Cancer Training (CCT) team- Dr. Oliver Bogler, the Director of CCT for his guidance and constant support, Dr. Chanelle Case Borden, Ms. Maria Moten, Ms. Angela Jones and the web team for their exceptional support in the organization of the retreat. We also express our sincere thanks to Dr. Dale Lewis who photographed the event and provided incredible pictures.

Sukhbir Kaur, Ph.D. and Usha Acharya, Ph.D.
(Co-Chairs of 2025 SSSC Retreat Committee)

THE DOSSIER

Tech Transfer Corner

Section Editor: Sabina Kratzmeier, Ph.D., (SS)

How Technology Transfer Helps the NIH Turn Discovery into Health

NIH technology transfer is the process by which a scientific discovery becomes a product to benefit public health. The NCI Technology Transfer Center (TTC) is integral to the NIH mission by managing the technology transfer activities to foster collaboration, invention development, and licensing to advance today's discoveries into tomorrow's medical care. The TTC supports this mission through patenting, licensing, distribution of research materials, developing partnership agreements, and exchanging confidential information and data. Most people think of patents when they think of technology transfer, and protecting and licensing NCI's intellectual property is a key component of the TTC's mission. You can learn more about technology transfer in general, and the patenting process specifically, in the Tech Transfer Corner of the June 2023 and 2024 *Dossier* issues, respectively. However, the TTC facilitates many other critical technology transfer activities as well.

Beyond Patents

There are several focused legal agreements that need to be put in place for government laboratories to share reagents and ideas with outside parties while protecting their intellectual property (IP). These types of agreements include Confidential Disclosure Agreements (CDA), Material Transfer Agreements (MTA), Clinical Trial Agreements (CTA), Collaboration Agreements, and Cooperative Research and Development Agreements (CRADA). Their purpose is to define, document, and protect the confidentiality and use of materials and data developed by NIH researchers by providing specific guidelines as to who, what, when, where, why and how the shared material or information can be used. With the one exception of the CRADA, these technology transfer agreements do not allow for money to be received by NIH. The CRADA is the only technology transfer mechanism where a Federal laboratory can receive funding for the associated research and development activities.

Partnering with Industry in Your Research: Cooperative Research and Development Agreements

CRADAs are used for sharing research materials and ideas between an NIH research lab and an outside partner, which is most commonly a company but can also include a university, state/local government, non-profit, or other Federal laboratory, and performing a collaborative research project. This type of agreement can lead to a successful collaboration to advance the progress of a research project and perform key studies to develop an invention towards commercialization. In fiscal year 2024, the TTC managed 247 active CRADAs for the NCI and the nine other institutes that the TTC supports, demonstrating the demand for this unique mechanism.

To establish a CRADA, the scope of the proposed work must be clearly defined. The CRADA document includes a research plan that details the study objectives and proposed experiments that will be performed by each party and a budget for the outside partner to provide financial support to offset NIH costs. Further, the NIH retains the right to publish the findings from the work performed under the CRADA in accordance with the NIH's mission for dissemination of research findings.

In return, the outside CRADA partner gains access to the unique reagents, resources, and scientific and regulatory expertise of the NIH investigators, as well as rights to the specific data and materials generated within the scope of the CRADA. One of the key benefits of a CRADA to the outside partner is that they have the right of first refusal to any new IP developed under the CRADA Research Plan, meaning that they will have the option to commercially license any resultant CRADA Subject Invention before anyone else. Importantly, the government maintains the rights to the NIH-generated IP.

To learn more from an insider's perspective, I invited Dr. Lucas Horn, a Staff Scientist in the CCR Center for Immuno-Oncology, to share his thoughts on his experience working with CRADA partners in the laboratory:

"During my time at the Center for Immuno-Oncology I have worked on numerous projects that involved a CRADA. In my case, these CRADA partners have all been small or medium sized pharmaceutical companies who work with us for the goal of developing novel immunotherapy approaches that can be translated into the clinic and help treat cancer patients with an unmet need. These CRADA collaborations between NCI laboratories and the private sector are facilitated by the NCI Technology Transfer Center. Our CRADA partners typically provide their own novel agents that can be used in preclinical studies and, ultimately, in clinical studies, and in some cases, additional funding for experiments, personnel, or in the clinic to support the CRADA research. This saves the lab and the NCI millions of dollars every year. A potential downside to consider when entering a CRADA would be that companies will occasionally change leadership or direction and pull a reagent you are working with from further use. I have been fortunate to have co-authored multiple peer-reviewed papers with our CRADA partners which have then provided the scientific rationale for the development of clinical trials now taking place here at the CCR. My experience of working on a project involving a CRADA has been very positive. These collaborations have been very impactful for my scientific career, and I look forward to continuing to work closely with them in the future."

More information on CRADAs can be found on the TTC CRADA Information Sheet. If you are interested in initiating a CRADA or other technology transfer agreement, please reach out to your Technology Transfer Manager (TTM)

Core Corner

Section Editor: Lisa Jenkins, Ph.D. (SS)

Discovery-based genomic analyses have a tremendous value for hypothesis generation. Understanding the changes in transcript level on a global scale upon stress, in tumor cells, or when a gene is knocked out can give critical insights into functional effects within cells. Established in 1997, the CCR Genomics Core has evolved from a dedicated sequencing service into a comprehensive genomics resource through its partnership with the CCR Office of Science & Technology Resources (OSTR) in 2014. Currently, the CCR Genomics Core, led by Dr. Madeline Wong (Genomics Lead) and Dr. Desiree Tillo (Bioinformatics Lead), supports seven different platforms across nineteen instruments, offering a broad range of genomics and sequencing services to researchers at the NCI and beyond. Operating on a cost-recovery, fee-for-service model, charging only for consumables, the Core supports CCR laboratories at both Bethesda and Frederick campuses, as well as users from across NIH institutes. To give an idea of how broad the reach is for the Genomics Core, in FY24 the staff processed over 32,000 samples from more than 3,200 requests, serving 418 users across 172 research groups, including 79% of CCR programs.

Located in Building 41 on the Bethesda campus, the CCR Genomics Core currently offers the following services:

Sanger Sequencing (ABI 3500xL): Standard plasmid region and PCR fragment sequencing. Turnaround time is typically within one business day.

Next Generation Sequencing on Illumina short read platforms (iSeq, MiSeq and NextSeq2000) as well as long read sequencing on the Oxford Nanopore Technologies GridION and P2solo platforms: For short read sequencing, only ready-to-sequence libraries provided by users are accepted, or the core can perform library preparation for certain applications (specifically RNASeq, ChIPSeq, Bacterial whole genome, Bruker Digital Spatial Profiling).

Whole Plasmid Sequencing (Oxford Nanopore Technologies platform): Obtain full length consensus plasmid sequence without the use of primers with 99% raw read accuracy. Currently, the assay is carried out once a week (Tuesdays) with results delivered the following day.

Analytical & Preparative Electrophoresis (Agilent TapeStation 4150 & 4200, Fragment Analyzer, QuantStudio RT-PCR system, Qubit, PippinHT): Analyze DNA/RNA size, quantity & integrity. Data is available within the same day.

Droplet Digital PCR (Biorad QX200 ddPCR System): Provides absolute quantification of target molecules without the use of standard curves. The Core offers both EvaGreen and Probes Assay for gene expression, mutation or copy number variation. Data is typically available within 24 hours and, often, in the same day.

Digital Gene Expression (Bruker nCounter System platform): Novel digital color-coded barcode technology (direct multiplexed measurement of gene expression) with high levels of precision and sensitivity. The platform uses color-coded oligonucleotide barcodes to detect and quantify up to 800 targets at a time from 12 samples in a single assay.

Digital Spatial Profiling on the Bruker GeoMx DSP (in collaboration with Spatial Imaging Technology Resource, SpITR Core): High-plex spatial profiling to assess protein and/or RNA within tissue samples from a single FFPE or fresh frozen slide for readout with nCounter or Next Generation Sequencing (NGS) platforms for both mouse and human panels.

The CCR Genomics Core is an open access facility that strives to provide efficiency and quality with rapid turn-around. No POTS orders are required, and data can be delivered for many applications within 24 hours. One of the unique aspects of the CCR Genomics Core is that it operates like a boutique hotel – as a relatively small facility, the core staff can work closely with investigators at each stage of their experiment. For

example, they provide initial consultations to assess experimental and analysis needs, offer guidance in available genomics methods, provide guidance at the data analysis stage, and are always willing to help with troubleshooting. Overall, the consultative approach offered by the CCR Genomics Core allows scientists to try new approaches quickly and cost-effectively, which enables optimization of experiments before moving to full-scale, production-ready sequencing projects.

In addition, the CCR Genomics Core can serve as a touchpoint between vendors and the researchers if needed. Staff frequently host events and seminars highlighting technologies that would be valuable for NCI researchers. In the past, vendors such as Illumina, Oxford Nanopore, Nanostring, Thermo-Fisher, Curio Biosciences, and BioSkrybe have been featured. These technical seminars provide scientists with the opportunity to learn about new methodologies and applications of existing technology and to speak with company experts about their own needs and concerns. As part of their efforts to maintain a high level of technical expertise, the CCR Genomics Core works closely with OSTR to identify, evaluate and make available new technologies as they emerge either through company partnerships, instrument loans, or through purchases. Doing so helps to ensure access to the most advanced genomic technologies and enriches the research environment for all CCR investigators.

Among all of the offerings of the CCR Genomics Core, core staff are currently very excited about long read sequencing on the Oxford Nanopore Long Read platform. A major limitation of short-read sequencing is that reconstruction and quantification of longer molecules (i.e., certain genomic regions, transcript isoforms) is difficult when using fragments that are much shorter than the molecule being analyzed. Longer read lengths allow for challenging regions, such as repeats, to be resolved and can identify more complex structural variations in genomic sequencing, e.g. duplications and large insertions. Additionally, this platform can sequence nucleic acids directly which enables the identification of base modifications in both DNA and RNA, as well as identification of full-length RNA transcript isoforms.

As this is one of the newer technologies offered, making it available to the intramural community has been a true team effort, requiring bench knowledge, IT support, and bioinformatics expertise. The platform is currently being used for whole plasmid sequencing and custom projects. For example, core staff have worked with investigators to use the platform to sequence viral and bacterial genomes, identify transcripts and base modifications with direct RNA sequencing, analyze single cell isoforms in a 10X single cell library, genotype long PCR amplicons, and detect mutations and DNA methylation in selected genomic regions via adaptive sampling. The ability to work with investigators to tailor the applications for the project and question to be addressed is part of the consultative approach offered by the CCR Genomics Core.

With all these possibilities available, the next step is to speak with members of the facility about your own needs. To start a project, simply email ncilecdnacore@mail.nih.gov for guidance on the specific technology that best fits your needs. You can also register and submit samples through their iLab website at: https://nci.corefacilities.org/account/login.

The CCR Genomics Core (pictured at left) combines bench researchers and bioinformatics support to assist researchers throughout the stages of a project.

PI Corner

Section Editor: Andaleeb Sajid, Ph.D. (SS)

Yamini Dalal, Ph.D.
Senior Investigator, LRBGE

In a unique discussion at the cutting-edge intersection of biochemistry, molecular biology, and genomics, a team of esteemed scientists shared their journey in scientific discovery and collaboration. This team, led by Dr. Yamini Dalal, has pushed the boundaries of their research for over a decade, breaking new ground in the study of centromere structure, chromatin biology, and cancer research. Dr. Dalal received her Ph.D. in 2003 from Purdue University and pursued her postdoctoral work at Fred Hutchinson Cancer Research Center. After years of hard work and numerous accomplishments, Dr. Yamini established her lab at NIH in 2008 and received tenure in 2018. Currently, she also serves as Senior Advisor for Faculty Development at the CCR Office of Scientific Programs.

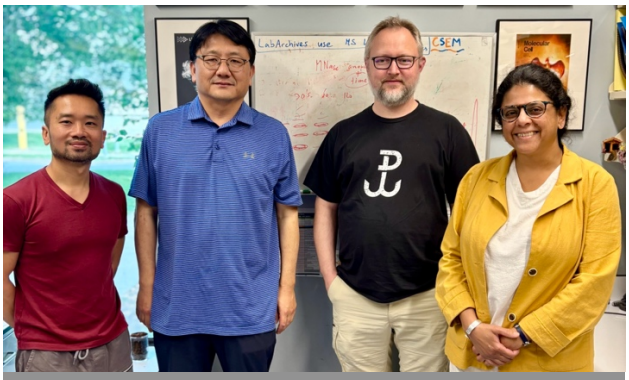
Within a short time after starting her lab, she recruited Dr. Minh Bui, a plant geneticist, as her first postdoctoral fellow. With all his hard work and accomplishments, Minh progressed well in the lab and currently works as a senior research assistant. Dr. Yamini fondly recalls the early days of the lab when Minh took the lead to organize the team and make it work efficiently, making him the hardest-working person in the room, which was an inspiration. He proved that people with diverse interests and backgrounds can contribute in unique ways to a research group. Dr. Dalal was quick to recognize Dr. Minh's pivotal role in ensuring the rigor and success of the lab, identifying him as a meticulous scientist who maintains a high level of precision, which is important not only while doing his own experiments but also while training other post-doctoral fellows and interns.

Soon, Dr. Daniël Melters joined the lab as a post-doctoral fellow, with a background in molecular biology and evolutionary genomics. He now works as a staff scientist. Having mastered his skills in Atomic Force Microscopy (AFM), Dr. Melters contributed significantly to the lab with several important publications, many of them featured on the journal covers. Amongst his several accomplishments, the adaptation of high-speed AFM for chromatin kinetics has the potential to change the way scientists' study molecular biology and map genomic dynamics.

Dr. Dalal believed in the importance of bringing together diverse expertise from various fields, including genomics, plant genetics, and biochemistry and insists that the diverse skill sets complement each other. With this, Dr. Songjoon Baek, a computational biologist and statistician, joined their lab as a staff scientist in 2009. Dr. Baek worked primarily with Gordon Hager's lab, and partly with Dr. Dalal from 2010-2020. He then also started working with Dr. Arda's lab, a tenure-track investigator in CCR, on studies of pancreatic dysfunction. Dr. Baek currently works as a combined team member with Dr. Arda and Dr. Dalal. Dr. Baek's work in computational biology and data analysis has also played a crucial role in the lab's success. Dr. Baek initially focused on sequencing data analysis and the integration of statistics with AFM data. Over time, Dr. Dalal saw the value of leveraging Dr. Baek's expertise to improve the lab's ability to quantify AFM data.

Emphasizing the importance of these three researchers, Dr. Dalal mentions the research breakthroughs that wouldn't have been possible if each of them were working alone: "Each person brings a different mindset, and they challenge each other to think better, in an interdisciplinary way." The lab's success isn't just reflected in their publications, but in the collaborative spirit and the mentorship that shapes the careers of every lab member. As Dr. Dalal notes, the success of the lab isn't simply about publishing papers, it's about answering meaningful scientific questions. And we do it as a team".

Dr. Dalal identifies a staff scientist as a permanent staff member who is not just a specialist but a researcher with deep expertise, contributing to the lab's success. She emphasizes that the success of any research project is not just the result of one person or the PI, but also the extraordinary contributions of staff scientists. These individuals, often not in the limelight, play a crucial role in driving innovation, building new technologies, and refining the methods that bring about groundbreaking discoveries. In discussing about the staff scientists, Dr. Dalal states that her lab operates not with a strict hierarchy, but with a focus on individual skills. This flexibility in structure allows staff scientists to teach and help each other based on their unique strengths. The team members are constantly challenging themselves to push boundaries and adapt to new methods. Whether it's incorporating the latest technologies or exploring entirely new scientific concepts, the team is united by a shared passion for discovery.



Members of Yamini Dalal's Lab

Dr. Yamini believes that one critical component of this success is mentorship. Staff scientists don't just contribute to their own research; they actively help guide and teach the next generation of scientists in the lab. The mentorship system ensures that all members, regardless of their experience level, have the resources and guidance needed to succeed. The PI, for example, relies on their staff to ensure that lab members are learning and using proper techniques, from Western blotting to statistical analysis. While the path forward for staff scientists is not always clear, with limited resources and space constraining career growth opportunities, there is a recognition that their work is indispensable.

A lab is more than just a place where experiments happen- it's a dynamic environment where ideas are born, nurtured, and transformed into groundbreaking research, Dr. Dalal states. In her lab, staff scientists are recognized as the backbone that supports every step of the research process. Staff scientists in this lab have demonstrated an exceptional ability to adapt, integrate new tools, and embrace new challenges. Whether it's developing cutting-edge imaging technologies or designing innovative biosensors, each member of the team brings a unique skill set to the table. While PIs are responsible for overseeing the overall direction of the lab and providing guidance with their vision, staff scientists help to provide day-to-day guidance, teaching lab members the essential skills they need to succeed. Staff scientists help to ensure that everyone in the lab is equipped with the knowledge and expertise to move their projects forward. This culture also ensures that lab members are constantly challenged to improve their skills and learn new techniques. Dr. Dalal encourages staff scientists to push boundaries of their knowledge, which ultimately benefits the entire team.

PI Corner

Section Editor: Andaleeb Sajid, Ph.D. (SS)

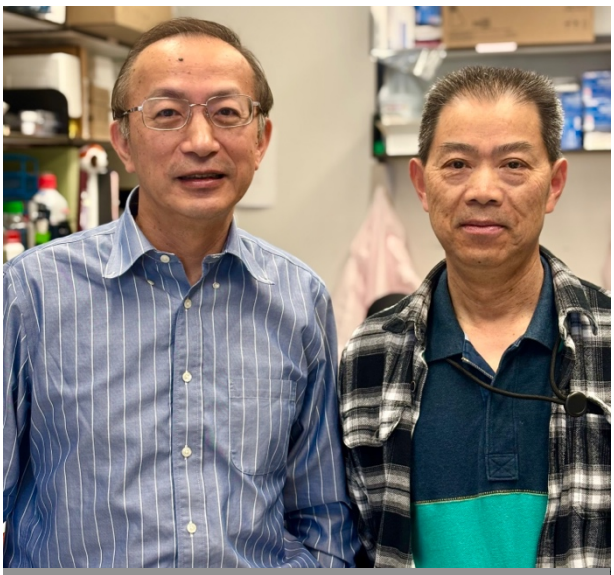
Mitchell Ho, Ph.D.
Deputy Chief, LMB

Dr. Mitchell Ho's career exemplifies the potential of translational science to move from basic research at the bench to clinical trials at the bedside. He is the Deputy Chief of the Laboratory of Molecular Biology and Director of the Antibody Engineering Program at the NCI, CCR. Trained in immunology and rooted in the rigorous research environments, Dr. Ho has built a multidisciplinary program at the NCI, which bridges basic biological discoveries with clinical applications, now initiating multiple early-phase clinical trials along with clinical groups at the NIH Clinical Center. Dr. Ho began his academic journey in China, where he developed an early interest in molecular biology. He later pursued a Ph.D. in Immunology at the University of Illinois at Urbana-Champaign. This laid the foundation for his versatility as a scientist, where he trained not only in project design and experimental techniques but also in grant writing as he successfully obtained a competitive NIH NRSA F31 predoctoral fellowship during his Ph.D. studies. These early professional experiences deepened his interest in biomedical research and set the stage for postdoctoral research focused on cancer-targeted immunotherapy.

In 2002, Dr. Ho joined the laboratory of Dr. Ira Pastan at NIH, a renowned lab where he worked on recombinant immunotoxins, including anti-CD22 fusion proteins designed for hematologic malignancies. "I was fascinated by the idea of guiding a bacterial toxin into a cancer cell with an antibody," Dr. Ho mentions. His research required a detailed understanding of receptor biology, internalization pathways, and cell death mechanisms. These experiences further strengthened his commitment to translational oncology. In 2008, he was appointed as a tenure-track principal investigator at the NCI, where he established his own laboratory focused on the development of targeted therapies for solid tumors using antibody engineering. His laboratory has centered its research on glypicans- specifically GPC3 and GPC2, the cell surface oncofetal proteins expressed during fetal development but re-expressed in various cancers including liver cancer and pediatric cancer, thus projecting as therapeutic targets. These efforts have culminated in four clinical trials developed in his laboratory, now implemented in collaboration with clinical branches at the NCI, representing significant milestones in the translation of laboratory discoveries to patient care.

Dr. Mitchell Ho emphasizes the importance of a diverse and collaborative lab environment. His team includes staff scientists, postdoctoral fellows, postbaccalaureate students, Ph.D. and M.D. trainees, clinical fellows, and summer interns. "It's a lot of fun to design projects based on individual interests and career goals- some researchers are excited by biological mechanisms and engineering, others by clinical applications. Everyone is at a different career stage, and they enjoy laboratory research to achieve their career goals" he notes. His approach to mentoring staff scientists is particularly robust. One former staff scientist, initially a postdoctoral fellow in the lab, developed a research portfolio on GPC2 and later transitioned to lead a drug development group in industry. Another staff scientist now leads a collaborative antibody engineering core, partnering with various CCR labs across the NIH campus. "The staff scientist's role is essential," Dr. Ho explains. "They perform critical experiments, train junior members, and often serve as scientific anchors in long-term projects. Many also participate in NIH committees and write grant applications, including NCI Director's Intramural Innovation Awards", secured

twice by his staff scientist. Dr. Ho underscores that mentoring and workforce development are central to NCI's mission. "It is important for staff scientists to enjoy doing experiments in the laboratory setting, working with other scientists, learning new knowledge and technologies to stay at the cutting-edge, and helping train the next generation of scientists," he says. His lab regularly hosts trainees from international institutions, including Oxford and Cambridge, and researchers from across the world. In recent years, his lab has hosted PhD students from Mahidol University in Thailand. The team's structure reflects the NCI's broader intramural mission: a blend of discovery-driven science with structured mentorship and opportunities for career advancement. "It's a unique ecosystem," he adds, "and it works best when we enjoy working with everyone in a lab and value every contributor- from interns to staff scientists."



Mitchell Ho, Ph.D. (L) and Yan Lin Yu, Ph.D. (R)
Laboratory of Molecular Biology

Now a decade since achieving tenure, Dr. Ho continues to guide a lab that integrates foundational research with clinical relevance. He received recognition for his efforts with multiple awards- the APAO Scientific Achievement Award and the Dr. Francisco S. Sy Award for Mentorship Excellence at the U.S. Department of Health and Human Services. Dr. Ho was elected a Fellow of the American Institute for Medical and Biological Engineering (2023) and 2024 Asian American Engineer of the Year. Dr. Ho's current focus remains on translating immunological insights into viable therapies while continuing to mentor the diverse team that drives the work forward.

Author Corner

Section Editor: Ling Zhang, Ph.D. (SS)

Azam Ghafoor, M.D.
Associate Research Physician

Q1. **Where did you graduate, and what led you to pursue a career as a Staff Clinician?**

I graduated from the Indiana University School of Medicine in 2013, earning my Doctor of Medicine. Following the completion of my internal medicine residency, I pursued a fellowship in medical oncology at the NCI from 2016 to 2018. During the final year of my fellowship at the NCI, I had the opportunity to conduct laboratory research, which deepened my curiosity about cancer biology and sparked an interest in clinical research. This experience catalyzed my decision to pursue a role as a Staff Clinician at the NCI, where I could continue bridging clinical practice with scientific discovery. The transition from fellowship to a Staff Clinician position at the NCI was natural because of the rigorous and immersive training I received at the NIH. This foundation provided me with exposure to novel cancer therapies, translational research, and clinical trials, aligning with my interest for improving cancer care through scientific innovation.

Q2. What is your general role as a Staff Clinician inside NIH?

As a Staff Clinician in the Thoracic and GI Malignancies Branch (TGMB) at the NIH, my role is to contribute to the branch's clinical research mission, which focuses on developing innovative therapies for thoracic malignancies. My responsibilities are multifaceted and span clinical care, research, protocol development, and institutional service. Clinically, I provide care to patients enrolled in NIH clinical protocols, ensuring the highest standards of patient safety and treatment compliance. I also play an active role in training and supervising medical staff and oncology fellows.

On the research side, I support the development and execution of early-phase, first-in-human clinical trials, serving as an investigator on several protocols. I am involved in the design of innovative studies that aim to translate laboratory discoveries into potential therapeutic options for patients with thoracic cancers. In addition to my clinical and research duties, I participate in various institutional initiatives, like chairing the NIH Thoracic Tumor Board, which facilitates multidisciplinary case discussions across departments. What makes this role especially rewarding is collaborative nature of the work. I can engage with a wide spectrum of professionals — from patients and clinical staff to bench scientists, pharmacists, and research nurses. This continuous interaction across disciplines keeps the work engaging, meaningful, and aligned with the goal of advancing cancer care.

Q3. What clinical studies are you currently engaged in, and what is next?

My research currently spans three interrelated domains: cancer genomics, immunotherapy, and precision medicine. As an investigator, I direct a large, prospective observational study involving over 200 patients, focused on the natural history and clinical outcomes of individuals with germline mutations in BRCA1-Associated Protein 1 (BAP1). BAP1 is a deubiquitylase that plays a critical role in regulating the cell cycle and DNA damage response. Germline BAP1 mutations predispose individuals to certain cancers such as mesothelio-

ma, cutaneous melanoma, uveal melanoma, meningioma, renal, bladder, and breast cancers. Our study at the TGMB/Hassan lab provides longitudinal clinical and imaging surveillance for these high-risk individuals, aiming to assess the benefit of early detection and improving outcomes.

In the realm of cell-based immunotherapy, I serve as an associate PI on translational efforts to evaluate mesothelin-directed adoptive cellular therapies, including chimeric antigen receptor (CAR) T cells, for solid tumors. These therapies, developed by Dr. Raffit Hassan and colleagues at the Thoracic and GI Malignancies Branch, are currently undergoing clinical evaluation.

Looking forward, I am launching a new clinical study in precision oncology, in collaboration with Drs. Brajendra Tripathi and Douglas Lowy at the Laboratory of Cellular Oncology. This work builds on their recent discoveries (Tripathi et al., *Nature Communications*, 2021; Tripathi et al., *Nature Cancer*, 2024) of a novel oncogenic mechanism involving mutant KRAS, which promotes export of nuclear cargo proteins to the cytoplasm. Their preclinical work further identified a novel therapeutic combination strategy to restore the activity of tumor suppressor DLC1 in KRAS-mutant cancers — an approach not previously explored and now poised for its first clinical translation.

Q4. Could you point out the steps and challenges of conducting a clinical study?

The initial step in conducting a clinical study is to identify an unmet clinical need within a specific patient population. This involves proposing a potential intervention aimed at assessing meaningful clinical outcomes. At its core, any clinical study must be "patient-centric", with a primary focus on participant safety and relevance to real-world patient care. From there, the investigator formulates a testable hypothesis and define specific, measurable objectives that will guide the study and evaluate the hypothesis effectively. One of the most critical decisions in the early stages is selecting an appropriate study design. The design must be well-aligned with the hypothesis and objectives — whether it's a randomized controlled trial, cohort study, or other model — to ensure valid, interpretable results. Once the fundamental design elements ("nuts and bolts") of a clinical study are established, the next critical step is to write and develop the clinical trial protocol. This document serves as the blueprint for how the study will be conducted and must satisfy scientific, regulatory, and ethical standards. The finalized protocol is then submitted for regulatory review (FDA) and ethical approval (IRB). Once all those hoops are cleared, the study proceeds to site preparation and enrolling patients.

One of the biggest challenges of conducting a clinical study is navigating through the complex regulatory requirements, that can delay study start and progress. However, having a well written protocol with feedback from peers and protocol support, can help with regulatory clearance. The key to a successful study and overcoming the challenges is executing the study in accordance with the protocol, timelines, safety, and endpoints. Ultimately the development and implement-tation of a clinical study is inherently a collaborative and multidisciplinary effort. No single individual can manage all aspects effectively and teamwork is involved at each stage.

Q5. Any advice for new clinicians or about collaboration between staff clinicians and staff scientists?

Be proactive in identifying mentors who align with your clinical and/or research interests. Don't rely on a single mentor — develop a network that covers multiple areas of your career, including clinical excellence, research strategy, career development, and work–life balance. Initiate

conversations with potential mentors, express your interests clearly and ask thoughtful questions about their experiences and guidance. Clear communication with your mentors allows them to tailor their advice, help set realistic milestones, and connect you with relevant opportunities, and collaborators.

Effective collaboration between staff clinicians and staff scientists is vital to advancing translational research. These partnerships thrive when built around shared goals, such as improving care for patients or understanding disease mechanisms. It is essential to recognize the unique expertise each party brings: clinicians offer direct patient insights and access to the clinic, while scientists provide deep technical knowledge and innovative approaches to discovery. To foster strong partnerships, establish regular communication through meetings or lab discussions. Encourage the exchange of perspectives, where clinicians can relay observations from the bedside, and scientists can share recent scientific advances or technologies. Finally, translate collaborative ideas into action by co-developing protocols, grant applications, or publications. Putting shared concepts into a formal, written plan can often be the catalyst that transforms ideas into impactful work.

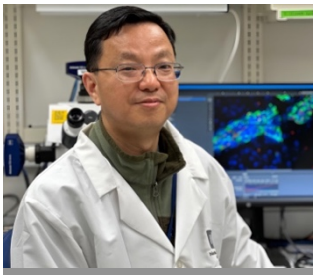
Q6. What activities or hobbies do you enjoy doing outside of work? Outside of work, I enjoy spending time with my wife and our 14-month-old daughter, Aasiyah. Much of my free time is centered around family activities such as visiting parks, attending library/reading clubs, and exploring new places together. Aasiyah has a love for animals, and a recent visit to the Smithsonian National Zoo was a highlight

Azam Ghafoor, M.D. with his daughter

- she especially enjoyed the elephant trails and the bird house exhibits. I'm also an avid sports fan, with a strong interest in both football and basketball. I follow the Washington Commanders during football season, and I'm a long-time supporter of the Indiana Pacers, a hobby that began during my medical school and residency. In addition, I have a passion for trying new foods and exploring different cuisines. My wife, who is from Northern Virginia, shares this interest, and we often seek out local restaurants and new culinary experiences. Our favorite types of cuisine are American and Persian, and we enjoy discovering unique takes on these foods.

Author Corner

Section Editor: Ling Zhang, Ph.D. (SS)



Wei Zhang, Ph.D.

Staff Scientist

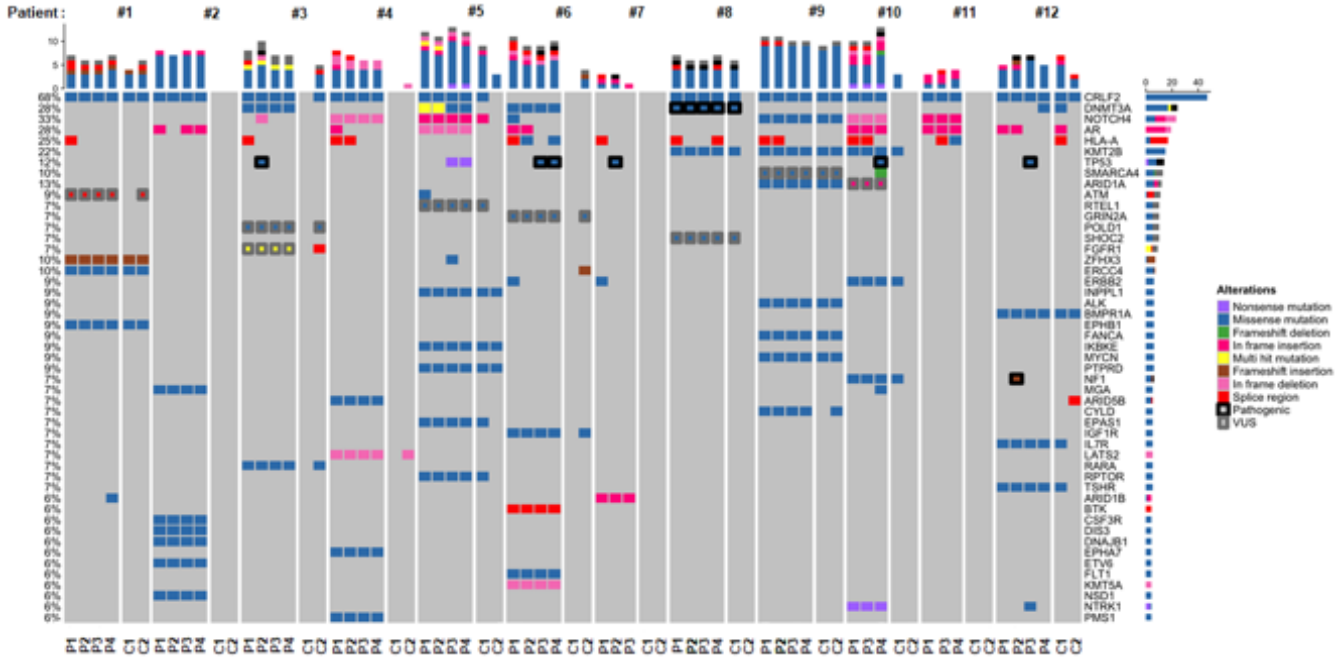
Q1. Where did you graduate, and when did your interest in science begin? What career would you choose if you were not a scientist?

I earned my Ph.D. from the Department of Biochemistry at Case Western Reserve University in Cleveland, where I focused on the role of transcription factors in development. Following this, I completed my postdoctoral training at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University in Baltimore, specializing in cancer epigenetics. My fascination with science began in childhood, sparked by a deep enthusiasm for reading science books. These books introduced me to the wonders of medicine, chemistry, and other scientific disciplines, and fueled my curiosity for my future scientific pursuits. My enriching biomedical research training under the mentorship of Drs. Michael Weiss and Steve Baylin has profoundly influenced my decision to pursue an academic research career. Their guidance and support during my Ph.D. and postdoctoral training were instrumental in shaping my career path. If I weren't a scientist, I would choose to be a biology teacher and dedicate myself to training the next generation of biomedical scientists.

Q2. What project are you currently engaged in, and what is next to you?

Brain metastases occur frequently in breast cancer patients with metastatic HER2 overexpressing (HER2+) or triple-negative breast cancer (TNBC). Currently, I am dedicated to the discovery of novel therapeutics for the prevention and treatment of breast cancer brain metastases, using both preclinical models and clinical studies. For example, I participated in a phase I clinical trial (NCT03190967) led by Drs. Alex Zimmer and Patricia Steeg evaluating the combination of the HER2-targeted therapy T-DM1 with temozolomide for the secondary prevention of brain metastases in HER2-positive breast cancer patients, particularly after prior treatment for brain metastases. This was the first trial aimed at preventing breast cancer brain metastases. Remarkably, during a median follow-up of 9.6 months, only two out of twelve patients developed new parenchymal brain metastases, a promising result compared to historical data.

As part of the study, I led a biomarker analysis using whole-exome sequencing of cell-free DNA (cfDNA) from plasma and cerebrospinal fluid (CSF). My analysis revealed cancer-associated mutations in CSF cfDNA at trial entry, despite recent local therapy—indicating ongoing brain metastatic colonization and a high risk for recurrence. I have also initiated a collaboration with Novartis to evaluate the efficacy of a small molecule inhibitor of the colony-stimulating factor-1 receptor (CSF-1R) in the prevention and treatment of brain metastasis in TNBC. This research utilizes our laboratory's established hematogenous brain-tropic animal models. Administration of a CSF-1R inhibitor resulted in a significant reduction in brain metastasis formation in both prevention and treatment settings. Notably, efficacy was achieved without the need for complete suppression of brain myeloid cells, suggesting that potential adverse effects associated with complete myeloid suppression can be minimized. These findings underscore the potential of CSF-1R inhibition as a therapeutic strategy in the treatment of TNBC brain metastases. Going forward, I am committed to staying at the forefront of emerging trends and



Cancer mutation profiling of cell-free DNA (cfDNA) from serum and cerebrospinal fluid in metastatic HER2+ breast cancer patients enrolled in a Phase I clinical trial (NCT03190967) for the secondary prevention of brain metastases.

tools to continue to address the translational and clinical aspects of cancer metastasis.

Q3. Do you plan to translate your fundamental discoveries into new cancer treatments? If so, how?

I am dedicated to translating basic scientific discoveries into innovative cancer diagnostics and therapeutics, striving to bridge the gap between laboratory research and clinical application. Based on my recent studies of cfDNA cancer mutations in patients' CSF, a follow-up clinical study has been proposed in the Women's Malignancies Branch at NCI to evaluate cfDNA cancer mutations in CSF as predictive biomarkers of brain metastasis in metastatic breast cancer. Through this work, we aim to contribute to the development of cfDNA-based liquid biopsy assays to enhance personalized treatment strategies and improve patient outcomes.

Q4. What have been the challenges you have encountered in your career so far?

During my more than 10 years of cancer research, I have published many scientific findings in peer-reviewed journals. One of the biggest challenges I've faced has been navigating the complexities of translational cancer research - bridging the gap between promising laboratory findings and clinical application. An important lesson I've learned is the value of aligning preclinical models with real-world patient scenarios and designing studies that are both scientifically rigorous and clinically relevant. Additionally, my academic research experience has shown that securing funding for high-risk, innovative projects—such as those aimed at preventing cancer metastasis—remains a consistent challenge. However, I have found that persistence, strategic collaboration, and a strong clinical vision have proven essential to advancing my research career.

Q5. What advice would you like to share with young scientists to build a successful career in research?

While hard work is a valuable virtue, I've come to realize that mentorship and collaborative teamwork are essential for achieving meaningful success and personal fulfillment. This insight has been shaped by the guidance of my Ph.D., postdoctoral mentors and committee members during my tenure at academic institutions and the NCI. During my graduate studies, I had the privilege of collaborating with a medical student, a senior research scientist in our lab, and a renowned geneticist at Stanford University to

investigate the role of a family of developmental transcription factors in both *Drosophila* and humans. Our collaborative efforts led to the publication of a series of research articles and culminated in the award of an NIH R01 grant to continue this pivotal study. While at UT Southwestern Medical Center prior to joining the NCI, I collaborated with a medical oncologist and a surgical oncologist to repurpose the antifungal drug itraconazole for the treatment of esophageal cancer. Our team was the first to demonstrate its potent anti-tumor activity through a novel mechanism involving the suppression of the HER2/AKT signaling pathway. This collaborative effort led to the successful completion of a Phase I clinical trial and progression to a Phase II trial. Notably, our translational and clinical studies were funded by a Merit Grant Award by the U.S. Department of Veterans Affairs. Since joining the Women's Malignancies Branch about three years ago, I have continued to benefit from collaborative partnerships with physicians and researchers within our branch, as well as with pharmaceutical companies outside of the NIH. These collaborations have been instrumental in advancing our translational research and enhancing the impact of our work.

Q6. What activities or hobbies do you enjoy doing outside of work?

I enjoy visiting museums, watching movies, and traveling with my family. There are a few countries on my list that I would like to visit soon. I also have a strong passion for science education. I find great fulfillment in working with local school science teachers to effectively engage students and facilitate their understanding of basic scientific concepts.

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