Issue 48 June 2024

THE DOSSIER

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

From the Editor's Desk

Dr. Balagopalan and I discuss the agenda for the new edition of the Dossier

Dear Readers and Authors,

It gives me immense happiness and a distinct honor to welcome you all to the June 2024 Issue of the Dossier, which is the first edition for which I have served as Editor-in-Chief. First, thanks to my predecessor Dr. Lakshmi Balagopalan, who has done a fantastic job over the past five years for uplifting and maintaining the high standard of this newsletter.

I sincerely appreciate the hard work and dedication of all the Editors and Editorial Board members for the success of the Dossier. I am excited to introduce Dr. Ling Zhang, our new Section Editor for the Author Corner. In this issue, we have an encouraging message from the CCR's new Acting Co-Directors Dr. James Gulley and Dr. Glenn Merlino; an informative Tech Transfer article that highlights the importance of intellectual property protection, (particularly the what, why and how to begin a patent process); the available Advance Biophysics Resources for NCI researchers in the Core Corner section; and a spotlight on a Staff Scientist's research in the Author Corner.

Many of us attended the 20th Annual CCR and DCEG Staff Scientists and Staff Clinician's retreat that took place on April 26th, 2024, at the NCI Shady Grove Campus, which was a very well received meeting. I had the privilege to Co-Chair the retreat with Dr. Duane Hamilton. I sincerely thank all the retreat committee members for working tirelessly behind the scenes so we could fully benefit from the thought-provoking talks, table discussions on various research topics, networking and celebrating award winners. You can read more about the retreat in the Event Report in this issue and the award winners in the Congratulations Section.

I hope everyone is having a great time and enjoying the beautiful weather. School summer breaks are approaching soon and many of us are looking forward to it, and I believe everyone will take some family time to enjoy it before temperatures soar. I wish you all a fun-filled summer and hope you all will find some time to appreciate the research community we have here at the CCR, make mutually beneficial new collaborations, and be proud of your accomplishments.

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

A Message From The Acting Co-Directors, CCR

Dear Staff Scientist and Staff Clinicians,

We are humbled to have been selected to serve as Acting Co-Directors by NCI Director Kimryn Rathmell, M.D., Ph.D., and we are committed to leading CCR during this interim period with care and transparency. We know that we are writing to you during a time of many changes.

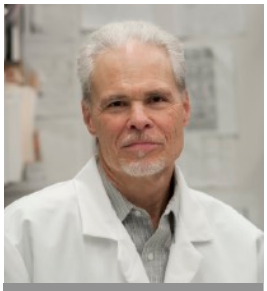
We would like to thank Dr. Tom Misteli, whose energy and dedication over the past eight years have inspired us and given us an incredible path to follow. In his eight years as CCR Director, we know he was a staunch supporter of the Staff Scientists and Staff Clinicians, who are the engine of scientific research in the CCR. Like him, we strongly believe that these positions, and you who fill them, are critical to the performance of our research program.

In addition to a leadership transition, we also find ourselves in a difficult financial situation. Due to a confluence of events over the last couple of years, the FY24 budget allocation is not enough to cover all of NCI's commitments. We want to stress that the belt-tightening is being felt across all of NCI's intramural and extramural programs. One immediate impact of this situation is a hiring freeze across all of NCI. Exceptions to the hiring freeze will be made on a case-by-case basis for reasons of mission-criticality, funding source, TTI status and laboratory size.

The NCI and CCR — and in fact the entire federal workforce — have been through this before, and we will come out stronger. We encourage you to speak to your peers as well as leadership about your concerns.

Regardless of these challenges and changes, we are fortunate to have access to remarkable resources that allow us to make unique and life-saving contributions to cancer research and treatment. The Staff Scientists and Staff Clinicians are an integral part of our mission.

Despite this transition, our research thrives.



Dr. Glenn Merlino
Acting Co-Director

Dr. James Gulley
Acting Co-Director

THE DOSSIER

Getting to know our new SS/SC

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

Bahman Afsari, Ph.D., M.Sc., SS
HIV and AIDS Malignancy Branch

Research focus:
My research focuses on helping biologists in the HAMB with bioinformatic analysis of cancer-related molecular data, especially cancers induced by viruses. The data can come from cancerous tissue or blood, generated by bulk, single-cell, or spatial technologies, and include gene expression measurements, genomic, epigenomic variations, or proteomics measurements.

How did you choose your career?
Since a very young age, I have been fascinated by mathematics, algorithms, and genetics. Finally, in my Ph.D., I found bioinformatics, allowing me to work on all these fields simultaneously. Since then, I have been developing algorithms to analyze and detect cancers from tissue and blood in academic and industrial settings. For almost a decade, I was involved with early cancer detection from blood.

What could be the impact of your research?
Our research can result in better treatments for patients with cancers caused by viruses, especially Kaposi Sarcoma. We may also have a better understanding of how viruses cause cancer. Moreover, I hope the bioinformatics tools we develop for our research can help cancer and virus researchers in their research.

Jibran Ahmed, MD, SC
Developmental Therapeutics Clinic

Research focus:
Early phase clinical trials, cancer immunotherapy

How did you choose your career?
I became interested in clinical research during my oncology training. I found the process of designing and conducting clinical trials fascinating, along with the collaborative opportunities. I became aware of the potential these clinical trials offered patients who might otherwise lack treatment options. After two years as a gastrointestinal (GI) oncologist, I decided to pursue this career path. My decision was influenced by the limited availability of treatment options to patients with advanced GI cancers.

What could be the impact of your research?
The early phase clinical trials offer an opportunity for patients with advanced, and often rare, cancers to explore the safety and efficacy of new agents and combinations. Many of our patients have progressed through several lines of treatment. These trials investigate pharmacodynamic biomarkers associated with drug activity. Assessing these biomarkers helps provide early insights into the targeted effects of new drugs or combinations, potentially shedding light on why certain treatments may be more or less safe and effective for specific individuals.

Brynn B. Duncan, MD, SC
Pediatric Oncology Branch

Research focus:
Improving CAR T-cell therapies for children, adolescents, and young adults with leukemia and lymphoma through translational and clinical approaches.

How did you choose your career?
I was first introduced to cell therapies and CAR T-cells as a post-baccalaureate student in the POB back in 2010. I was fascinated by the concept of CAR T-cells, which were quite new at that time, and their efficacy against aggressive pediatric leukemias.

What could be the impact of your research?
I hope that my research will allow us to improve our use of CAR T-cells so that patients may derive additional benefit from the CARs that are currently in use commercially and allow researchers to better understand the function of novel CARs in clinical trials.

Christina Ferrone, Ph.D., SS
Laboratory of Pathology

Research focus:
I am a Clinical Genomics Scientist with the Molecular Diagnostics Laboratory (NCI COMPASS), Laboratory of Pathology, which provides state-of-the-art clinical sequencing services to CCR principal investigators. My interests include the molecular pathogenesis and genomic features of myeloid malignancies, integrated precision diagnostics and monitoring of various neoplasms, and personalized oncologic patient care.

How did you choose your career?
An impromptu 4th year undergraduate thesis project studying breast cancer ignited my passion for cancer research. From there, I went on to study myeloid malignancies, with my PhD focusing on molecular genomics of these diseases. My current career in cancer molecular genomics took shape over many years of chasing after the topics and research questions that really intrigued me, leading me to a role that is equally challenging and rewarding today.

Would you like to tell us something else about yourself?
This passion for molecular genomics has led me to pursue further studies in the field, and I will be beginning an ABMGG Laboratory Genetics and Genomics Fellowship through NHGRI in July, in parallel with my current role with NCI/Laboratory of Pathology.

Jeffrey Gagan, MD, Ph.D., SC
Laboratory of Pathology

Research focus:
My research focuses on identifying DNA and RNA biomarkers for rare tumor diagnosis.

How did you choose your career?
Many labs across the country have been capturing much more information than they can interpret and apply to patient care. I want to see increase the amount of wisdom that we can extract from all of that information.

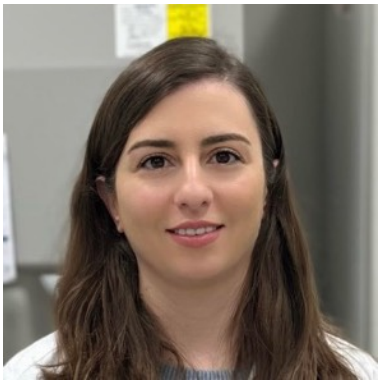
Would you like to tell us something else about yourself?
I am a big believer that what keeps you sharp is constantly teaching yourself new things and new skills. In the last 10 years, I have taught myself how to build my own gaming PC, how to program in Python, wilderness photography, and I'm now learning how to do Olympic weightlifting.

Chang-Sook Hong, Ph.D., SS
Laboratory of Pathology

Research focus:
My research focuses on investigating extracellular vesicles (EVs) in cancer. We analyze molecular profiles of EVs isolated from cancer cells and cancer blood samples to develop cancer diagnostic markers and predict prognosis and metastasis.

How did you choose your career?
I used to study viruses for developing cancer gene therapies. Then I learned that virus-sized (30-150nm) vesicles are secreted normally from cells, which are called as exosomes. I thought that was very fascinating and then joined EV research lab at University of Pittsburgh. At that time there were not many researchers working on EVs. So, the first thing I had to figure out was how to purify exosomes. Since then, numerous researchers have shown that EVs have essential roles in intercellular communication and disease progression. I was very excited to recently join Dr. Jennifer Jones' laboratory at Translational Nanobiology Section in CCR where cutting-edge technologies to analyze EVs have been developed.

What could be the impact of your research?
Since EVs are carrying molecules from parental cells and circulating in the systems, analysis of EVs has special advantages as a liquid biopsy in monitoring disease progress and therapies. Therefore, understanding how cancer derived EVs affect healthy cells including immune cells would be very important in cancer research, which could eventually lead to EV-based cancer therapies.



Meghri Katerji, M.Sc., Ph.D., SS
Laboratory of Cell and Developmental Signaling

Research focus:
My research is focused on cancer-associated kinases of the dark kinome. I investigate novel molecular mechanisms of tumorigenesis, with the overarching goal of identifying new therapeutic targets and developing precision cancer treatments.

How did you choose your career?
While I've always had an inherent passion for science, it was my father's diagnosis with stage IV pancreatic cancer that steered my focus towards cancer research. Watching him suffer from the adverse effects of chemotherapy transformed my academic interests into a heartfelt mission, with the hope of developing more tolerable treatments to improve the quality of life of patients and their families.

Would you like to tell us something else about yourself?
Many scientists believe that you must choose between career and personal life, and that work-life balance is an impossible feat. My non-scientific goal is to change this mindset and educate the younger generation that balance between their professional and personal lives is both possible and crucial. I had two children during graduate school. While challenging, the experience taught me resilience, time management, and the importance of prioritizing what truly matters. Now my kids look up to me with pride. My daughter wants to be a scientist herself. Knowing that I've influenced her in such a positive way makes all the challenges worthwhile.

Jessica Lake, MD, MPH, SC
Pediatric Oncology Branch

Research Focus:
Developing innovative cellular and other immunotherapy clinical trials for pediatric and young adult patients with relapsed/refractory solid tumors.

How did you choose your career?
I knew from a young age that I wanted to study oncology. The tremendous advancements that had taken place since the 1950s were inspiring but not enough. I knew more had to be done and that I wanted to be a part of it. Pediatrics came later when I realized that every volunteer experience, I signed up for in college was always with kids!

What could be the impact of your research?
My hope is that we will start to see responses to cellular therapy in our solid tumor patients akin to CAR T-cell therapy in leukemia with durable remissions.

David E. Milewski, Ph.D., SS
Genetics Branch

Research Focus:
My research interest is to apply basic science to develop effective cell therapies against pediatric solid tumors. Much of this is centered around mechanisms of both active and passive immune evasion in pediatric tumors. We rationally design and test multiple therapies including chemical, biological, or gene-engineering approaches and use multiomics to understand their effects mechanistically.

How did you choose your career?
I was always interested in molecular biology and epigenetics and since many pediatric cancers are driven by mutations or oncofusions in chromatin regulators, I was naturally drawn to the field. During my Ph.D., however, I also attended tumor board meetings and saw firsthand how challenging their clinical management is. This experience permanently changed the way I approach research. Even though I still have interests in tumor epigenetics, I've completely switched my focus to developing cell therapies against pediatric tumors due to the incredible responses we can achieve in our preclinical models.

What could be the impact of your research?
The majority of the research is focused on identifying effective adjuvant combinations for cell therapy and understanding how they influence the potency of therapy. The ultimate goal will be to translate our best combinations to clinical investigation here at the NCI.

Reyaz ur Rasool, Ph.D., SS
Laboratory of Pathology

Research Focus:
I am interested in understanding the epigenetic regulation of pediatric soft tissue cancer Rhabdomyosarcoma progression and treatment resistance.

How did you choose your career?
Choosing a career in cancer research started with a combination of curiosity and a desire to make a meaningful impact. I've always been fascinated by the complexity of the human body and the intricate ways diseases like cancer can affect it. So, to contribute in any way I could to the fight against this devastating disease fueled me to deepen my understanding and develop skills to further my career path to contribute to advancements in cancer research. After obtaining Ph.D. I joined Penn Medicine, University of Pennsylvania in 2018, as a postdoctoral fellow, where I complemented the lab's ongoing efforts in translational oncology with special focus on prostate cancer and Pediatric Ewing Sarcoma epigenetics. I then joined Barr Lab in the Laboratory of Pathology at NCI as a staff Scientist in Oct. 2023.

What could be the impact of your research?
Although the standard treatments cure most children with fusion-negative rhabdomyosarcoma, they don't offer much hope to those with fusion-positive tumors-an aggressive form of the disease. I hope that understanding the basic epigenetic mechanisms that govern rhabdomyosarcoma progression, especially the genesis of drug resistance mechanisms will pave the novel translational approaches.

Michelle Wright, Ph.D., RN, FAAN, SS
Neuro-Oncology Branch

Research Focus:
My research is centered on the intersection of translational omics and health outcomes. I analyze environmental, physiologic, and psychological factors to explore the biological basis of symptoms in people with brain and spinal cord tumors.
I also examine differences in health outcomes between patients with these tumors. By using approaches that also incorporate patient-reported outcomes, I aim to better understand differences in patients' clinical trajectories.

How did you choose your career?
Prior to joining NOB my research focused on women's health outcomes, but I interacted with the NOB on social media and was fascinated by their work. When I learned of the open position, I reached out to the PI to discuss the role and applied. I love that I can work directly with patients and focus on research that will impact their quality of life. Working directly with our patients ensures we don't lose sight of what outcomes are important to the patient to maintain their quality of life while in treatment and survivorship.

What could be the impact of your research?
The goal is to develop new approaches for improving patient outcomes and quality of life. Our approach is applicable across disease types and incorporating patient reported outcomes into translational research can ensure research and clinical interventions result in better outcomes that are most important to patients.

Welcome New Section Editor

Ling Zhang, Ph.D.
Section Editor: Author Corner

Ling Zhang, Ph.D., is a Staff Scientist and head of the cellular therapy translational group at the Center for Immuno-Oncology. Her research projects focus on discovering novel targets for T cell-based immunotherapy, enhancing the therapeutic efficacy of TCR-T cells using membrane-anchored cytokines, and providing rationale for translating these findings to clinical applications.

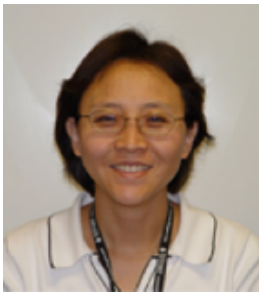
Ling joined the Dossier team to engage with the SS/SC organization, as the Dossier serves as an excellent platform for providing information and fostering collaboration within the SS/SC community. As a CCR SS/SC member, she has personally witnessed the valuable resources the Dossier offers and is eager to contribute further. As a Section Editor of the Author Corner, she will be highlighting ongoing impactful cancer research in the NCI-CCR community by our outstanding SS/SCs.

Congratulations

SS/SC Awards

Outstanding Mentor Awards

Lucas Horn, Ph.D., SS
Center for Immuno-Oncology



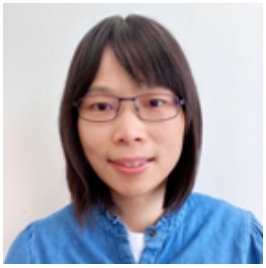
Binwu Tang, Ph.D., SS
Laboratory of Cancer Biology and Genetics

Best Oral and Poster Presentation Awards at the SS/SC Retreat

Best Talk

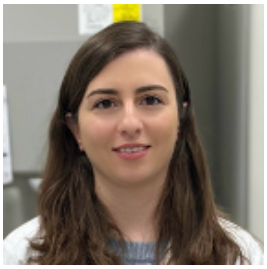
David E. Milewski, Ph.D., SS
Genetics Branch

Best Poster



Xiuxiu Lu, Ph.D., SS
Center for Structural Biology

Best Poster



Meghri Katerji, Ph.D., SS
Laboratory of Cell and Developmental Signaling

Best Poster

Wen-Yi Huang, Ph.D., SS
Metabolic Epidemiology Branch, DCEG

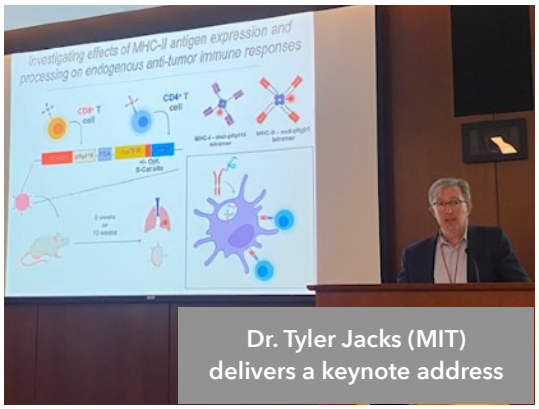
Event Report: 20th Annual SS/SC Retreat

The 20th Annual CCR and DCEG Staff Scientists and Staff Clinician's retreat took place on April 26th, 2024, at the NCI Shady Grove Campus.

The theme of this year's retreat was 'Interdisciplinary Collaborations in Cancer Research'.

NCI Director Dr. Rathmell addresses SS/SC

Dr. McCormick (USCF) delivers a keynote address



Dr. Tyler Jacks (MIT) delivers a keynote address

Staff Scientists and Staff Clinicians at the Retreat

Dr. Brajendra Tripathi introduces Dr. James Gulley

Dr. Stacy Doran (L) with Ms. Sue Scott (C) and her mother (R)

Dr. Brajendra Tripathi and Dr. Gulley after his remarks




Dr. Brajendra Tripathi and Dr. Tyler Jacks after his talk


Dr. Stephen Chanock, DCEG Director, addresses SS/SC




Scientists discuss various important topics on cancer research


Ms. Sue Scott shares her experiences

The exceptional turn-out was a testament to the collaborative spirit and intellectual vigor that characterizes the SS/SCs within the CCR/DCEG. The retreat began with a warm welcome address by Dr. Stephen Chanock, the Director of DCEG, followed by the remarks by the NCI Director Dr. Kimryn Rathmell who provided a strategic overview of the NCI's vision and ongoing initiatives. There were two keynote speakers this year. The first keynote address was delivered by Dr. Frank McCormick from UCSF, during which he delved into the molecular intricacies of RAS proteins and their implications in various human diseases, particularly in cancer. The second keynote speaker was Dr. Tyler Jacks from MIT, who shed light on a fascinating glimpse into the potential of mouse models in understanding cancer-immune interactions.

Dr. James Gulley, NCI Clinical Director, delivers the closing remarks

Dr. James Gulley, NCI Clinical Director, presents the awards

In a change from previous retreats, this year's organizing committee decided to have table discussions on several current topics of cancer research and highlight more of the amazing work performed by SS/SCs within the CCR/DCEG. We had eight oral presentations selected from the top-ranked abstracts submitted to the retreat. In the first session, Dr. Bing-Rui Zhou presented on the role of pioneer transcription factors in chromatin DNA exposure, Dr. Binwu Tang discussed a novel imaging approach that highlighted the significance of cancer stem cells in metastatic progression. Dr. James Madigan presented his work on epigenetic regulation in pancreatic neuroendocrine tumors, Dr. Phelan's provided key insights into the response to BTK inhibitors in aggressive lymphomas.

In the second session, Dr. Sofia Gameiro discussed the synergy of epigenetic modulation and tumor-targeted IL-12 in promoting regression of PD-1/-L1-resistant tumors. Dr. David Milewski's talk on engineered T cell transfer and TGFbeta signaling blockade offered promising insights into immunotherapy applications. Dr. Dimitris Stellas presented his work on the metabolic fitness of tumor-infiltrating CD8+T cells. We also had presentations from Dr. Lene Veiga who discussed her research on thoracic soft tissue sarcoma risk, while Dr. Masashi

Watanabe's presented findings from a Phase II trial on immune checkpoint inhibition in glioblastoma and gliosarcoma. Dr. Stacy Doran presented a clinical study performed within the CCR which utilized adoptively transferred tumor-infiltrating lymphocytes in patients with HPV-associated cancers and introduced a Cancer Survivorship Speaker, Ms. Sue Scott, who was enrolled onto this study, and subsequently achieved an objective complete response, and has now been cancer-free for over a decade. Ms. Scott shared her story of cancer diagnosis and her participation in this clinical trial. Demonstrating the real-world impact of the research performed by SS/SC within the CCR/DCEG. Dr. James Gulley, Clinical Director of CCR, provided the closing remarks and presided over the awards ceremony, during which the Outstanding Poster Awards were given to Xiuxiu Lu (Center for Structural Biology), Meghri Katerji (Laboratory of Cell and Developmental Signaling) and Wen-Yi Huang (Metabolic Epidemiology Branch). The Outstanding Oral Presentation was awarded to David E. Milewski (Cancer Genetics Branch). The Outstanding Mentor Awards were presented to Dr. Lucas Horn (Center for Immuno-Oncology) and Dr. Binwu Tang (Laboratory for Cancer Biology and Genetics).

Finally, Dr. Brajendra Tripathi, Co-Chair of the Retreat Committee, delivered a vote of thanks to the NCI/CCR leadership, the OITE team, all the speakers and participants for sharing their knowledge and important research findings, the judges for evaluating the abstracts, posters, and oral presentations, and all committee members for their hard work and dedication in organizing this successful event.

The day's events were capped off with a happy hour at Rio Lakefront in Gaithersburg, Maryland, providing a relaxed atmosphere for attendees to unwind and reflect on the day's learnings.

In summary, this year's retreat was a resounding success, showcasing the latest advancements in cancer research and fostering a collaborative environment for scientists to share their work and ideas. The event not only highlighted the cutting-edge research being conducted at the CCR and DCEG, but also underscored the importance of our work as we continue our battle against cancer.

Dr. Brajendra Tripathi and Dr. Duane Hamilton
Co-Chairs for the 2024 SC/SC Retreat Committee

Brajendra Tripathi, Ph.D.
Co-Chair, SS/SC Retreat

Duane Hamilton, Ph.D.
Co-Chair, SC/SC Retreat

Tech Transfer Corner

Section Editor: Sabina Kaczanowska Ph.D. (SS)

To Patent, or Not To Patent? That is the Question

The NCI Technology Transfer Center (TTC) implements the Federal Technology Transfer Act by using patents as an incentive for the commercial development of life-saving technologies and through executing research collaboration and licensing agreements. The NIH cannot commercialize or manufacture its discoveries. It therefore relies on its technology transfer offices to facilitate partnerships with outside organizations so that these discoveries can reach the public to fulfill the NIH mission of improving public health. TTC supports technology transfer on behalf of the National Cancer Institute and nine other NIH Offices and Centers.

What is a Patent? The United States Patent and Trademark Office (USTPO) defines a patent as a type of intellectual property that gives the right to temporarily exclude others from making, using, selling, or importing an invention. This constitutional right to temporarily exclude others from practicing your invention provides the incentive for a company to develop and benefit from your invention without others "stealing" your idea. Patents are subject to property law, and as such, they can be bought, sold, and rented (which is referred to as licensing). A patent protects the invention to make it worth it for a company to invest the time and money needed to commercialize the technology without another company swooping in at the end to copy the final product. Without intellectual property protection, a company would not be financially viable, and the technology will not be developed for public use.

What Can You Patent? You cannot patent a discovery of something that exists in nature, for example, the sequence of a naturally occurring gene. You can patent an invention based on Innovation, or something that did not previously exist in nature. The most common patent used in the biomedical field is a utility patent that protects, "a new or improved and useful process, machine, article of manufacture, or composition of matter". This can include a material, device, or method to improve patient care. Common examples include therapeutics, diagnostics, research tools, devices, software, and vaccines. The NIH owns the right to any invention developed as part of your official duty.

Your patent must meet the defined patentability requirements:

1. **Novelty**: the idea is different from "prior art from you or from others, meaning that it has not been done before and is not publicly disclosed
2. **Non-Obviousness**: you must provide evidence to support "unexpected superior" properties
3. **Utility**: the invention must serve a purpose
4. **Enablement**: you must provide a detailed description and demonstrate that the invention works as claimed, such that that an expert in the field could make and use the invention
5. **Definiteness**: the scope of claims is clear, so the public is informed of the boundaries of what constitutes infringement of the patent

When Should I Report an Invention?

Timely reporting of inventions is critical because either failing to report your discovery prior to public disclosure, or submitting your Employee Invention Report (EIR) at the last minute or immediately before disclosure may result in loss of important patent property rights that could prevent your invention from being developed and used to benefit the public.

In general, a "public disclosure" is the release of information about the discovery in sufficient detail to allow a fellow scientist in the field to

make, use, or apply the invention to their research.

Public disclosures include:

- Talks, presentations, seminars, posters
- Publications, including abstracts on websites
- Internet postings
- Graduate student theses, job interviews
- Discussions with non-NIH personnel without a Confidential Disclosure Agreement (CDA) in place

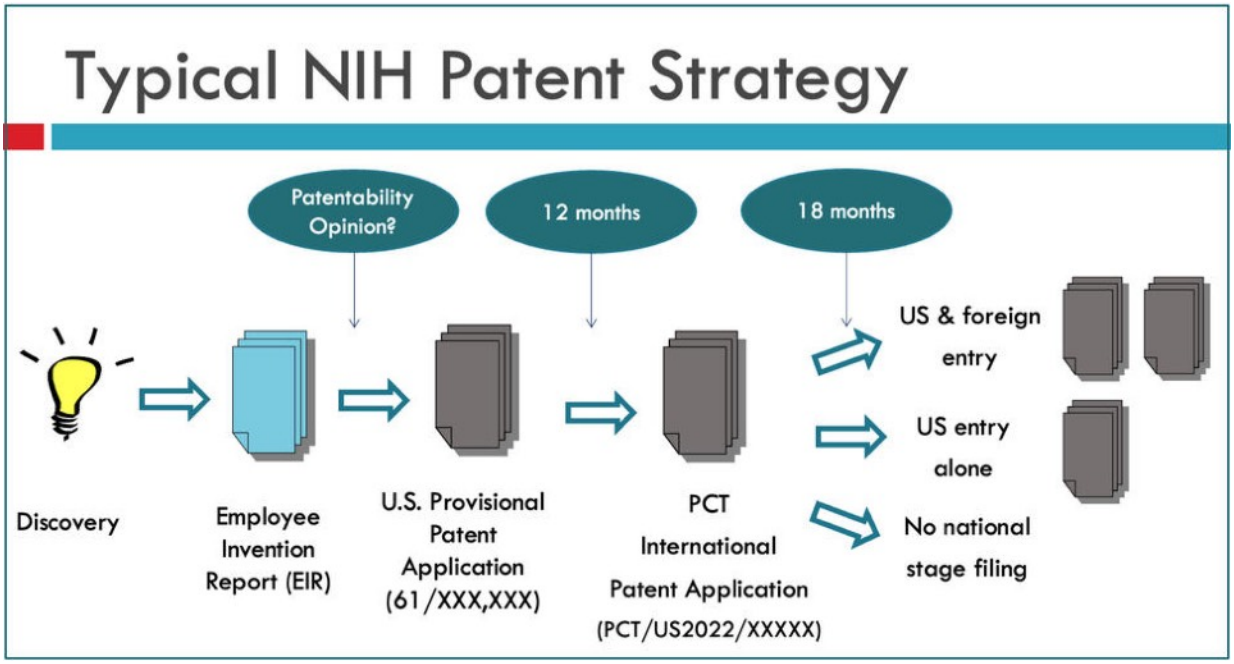
How to begin the patent process?

The first step is to reach out to your TTC Technology Transfer Manager (TTM) to submit an Employee Invention Report (EIR) to document your invention. TTMs work with a contracted law firm to help determine if your invention is patentable, and if so, recommend that the NCI file a U.S. provisional patent application with the USTPO.

The TTC recommends that you submit an EIR at least 12 weeks prior to any public disclosure of your invention to allow time for the necessary paperwork to be filed.

In the U.S., your invention is protected from the time of the provisional patent application filing, referred to as the "priority date." However, since each country has its own patent office, to preserve international patent protection, you must wait until the U.S. PCT patent application is filed to publicly discuss your invention without compromising its intellectual property. Learn more about the patent process at NCI.

Why Patent? If your research is translational and has real-world applications for improving public health, a patent is necessary for your technology to be licensed, commercialized and developed into a product that can reach the public. This is the goal! Further, as an inventor on an NIH patent, you must report new inventions, including improvements of previously reported inventions to the TTM assigned to your Laboratory. TTC outlines guidance for NIH researchers and inventors including when an inventor might receive royalties on patented invention or patent application. Importantly, TTC's Technology Transfer Managers are available to support investigators through the entire process. If you do not already know the name of your Technology Transfer Manager, Contact TTC for help identifying a staff member for assistance.



The Core Corner

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

The Biophysics Resource: A Hub for Biophysics Experimental Support and Training

Have you ever wanted to measure the binding affinity of a small molecule inhibitor to a protein or determine the size of your nanoparticles? Do you need to check whether a mutation changed the overall conformation of a molecule? Would knowing the mass of your protein in different complexes to understand the stoichiometry of interaction advance your project?

The Biophysics Resource offers ten cutting-edge biophysical technologies for CCR researchers: circular dichroism (CD) spectroscopy; steady-state and time-resolved fluorescence spectroscopy; isothermal titration calorimetry (ITC); differential scanning fluorimetry (nanoDSF); liquid chromatography with mass spectrometry detection (LC-MS and LC-MS-MS); dynamic light scattering (DLS); microscale thermophoresis (MST); UV-Vis spectrophotometry with thermal scanning option; switchSENSE molecular dynamics technology; and mass photometry (MP). These technologies allow for characterization of individual biological molecules as well as characterization of their interactions. Users can get information about molecular mass, particle size, stability, structural details (e.g., secondary or tertiary structure), the strength of an interaction, and binding mechanism.

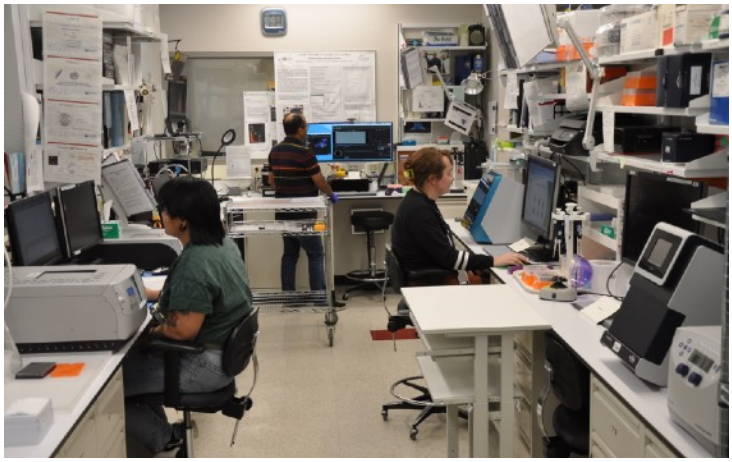
Mass photometry is one of the newest additions to the technologies offered by the Biophysics Resource, says Resource Manager Dr. Sergey Tarasov, “It has brought a “breakthrough in the measurement of the mass of single molecules in solution, in their native state and without the need for labels.”

This sophisticated method watches the landing of molecules on the microscopy slide and measures the interference between reflected and scattered laser light at the landing point; the resulting contract is directly proportional to molecular mass. This method does not require any sample preparation, is extremely fast (the result comes in a minute after sample loading) and allows for mass determination of molecules and their multimers. It also provides the fastest approach to detection and characterization of macromolecular interactions. Mass photometry analysis is suitable for measuring the mass of water-soluble molecules in the 30 kDa-5 MDa mass range, and though a lot of generally published work using it has been performed using proteins it has also been used to study nucleic acids, heteromolecular interactions such as DNA-protein complexes, vesicles and micelles, and polysarcosine star polymers for drug delivery.

The Biophysics Resource has a lot to offer, both in terms of technology and in terms of training. Unlike many other CCR cores and facilities, users of the Biophysics Resource learn to operate the instruments and conduct their own experiments. Dr. Tarasov and his associate Marzena Dyba train all first-time users and are available to consult with investigators on experimental design and analysis, as well as to collaborate with them on more complex studies. For SS/SCs, this poses an excellent opportunity to grow their expertise while pursuing their research. With nearly 600 users over the years, the Biophysics Resource is truly a “Hub for Biophysics Support and Training”.

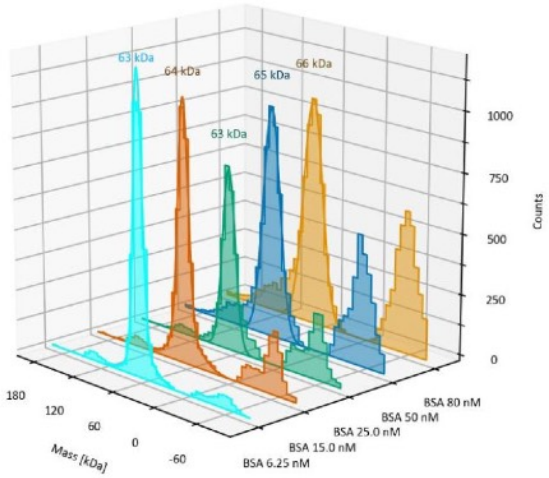
With so many options for experimental approaches, the best way to start a project is to contact Sergey Tarasov (tarasovs@mail.nih.gov) to arrange a visit to the lab. Sergey and Marzena will carefully listen to ideas and needs, offer suggestions for appropriate methods, and when feasible help run a quick pilot experiment to determine future steps.

The Biophysics Resource operates on a subscription model in which a PI pays a modest yearly fee that allows all members of the section unlimited access to all instrumentation in the Resource for the fiscal year, and the first trial is always free. Currently, the Resource has a partnership with thirty-five CCR, Leidos and NIH labs and, of course, they are always open to meet new people and new ideas!



Working with the Biophysics Resource

A typical day at the Biophysics Resource



Data from the mass photometry study of BSA monomer-dimer equilibrium at variable concentrations. The runtime for each concentration was only 60 sec.

Author Corner

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

Dr. Zhihui Liu serves as a Senior Associate Scientist in the Pediatric Oncology Branch. His research is focusing on the understanding of the molecular mechanisms involved in neuroblastoma (NB) tumorigenesis and progression. His main focus is to investigate the transcriptional dysregulation that contribute to the malignancy of NB. We contacted Zhuihui to learn more about his current cancer research and implications of his findings into new cancer treatments.

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

I received my B.S. in biochemistry from Nanjing University and received my Ph.D. from the Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences in 2004. After graduation, I joined the Pediatric Oncology Branch of the NCI as a visiting fellow in Dr. Carol Thiele's laboratory. Currently, I work in the same lab as a Senior Associate Scientist. My interest in science began during college. I also have a few years of experience working in a pharmaceutical industry after graduation from college, where I realized that biological research could significantly impact the treatment of patients with various diseases. If I weren't a scientist, I would consider pursuing a career in a pharmaceutical industry.

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

My research is in cancer biology, in particular, pediatric cancer neuroblastoma and rhabdomyosarcoma. Research in our lab centers on uncovering the molecular mechanisms driving cancer initiation and progression, encompassing oncogenes, tumor suppressors, transcriptional dysregulation, and epigenetics. I have been using cutting-edge techniques such as ChIP-seq, ATAC-seq, HiChIP, Hi-C, and single-cell RNA-seq to identify dysregulated transcription factors and epigenetic regulators that contribute to tumorigenesis in pediatric cancers. One project I have been working on in the past few years is MYCN-focused. Amplification of MYCN is found in ~40% of high-risk NB patients, which correlates with poor prognosis. MYCN activates canonical MYC targets involved in ribosome biogenesis, and protein synthesis, and represses neuronal differentiation genes to drive oncogenesis in neuroblastoma. However, the mechanisms by which MYCN orchestrates global gene expression remain incompletely understood. Our study finds that MYCN binds promoters to upregulate canonical MYC targets but binds to both enhancers and promoters to repress differentiation genes. MYCN binding also increases H3K4me3 and H3K27ac on canonical MYC target promoters and decreases H3K27ac on neuronal differentiation gene enhancers and promoters. Further study indicates that WDR5 facilitates MYCN promoter binding to activate canonical MYC target genes, whereas MYCN recruits G9a to enhancers to repress neuronal differentiation genes (**Fig. 1**). Importantly, targeting both MYCN's active and repressive transcriptional activities using WDR5 and G9a inhibitors synergistically suppresses neuroblastoma growth. This study was recently published in PLOS Biology (DOI: 10.1371/journal.pbio.3002240).

Another project I am leading aims to understand the driving force behind neuroblastoma cell plasticity. Tumor cell heterogeneity significantly influences therapy responsiveness in neuroblastoma, which comprises two primary

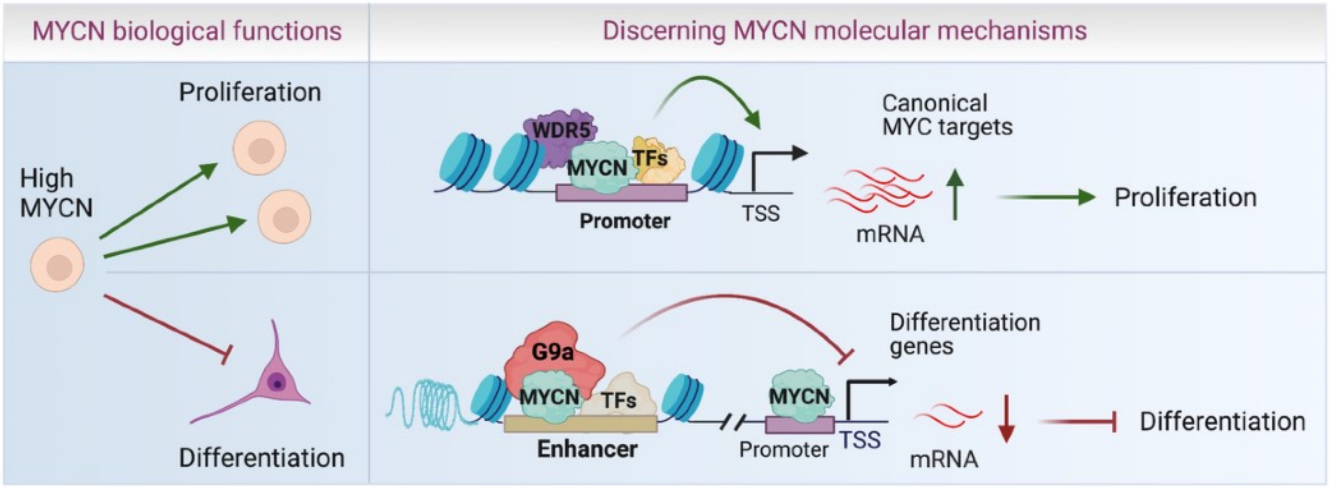


Figure 1. Schematic diagram of MYCN action. WDR5 assists MYCN to bind promoters and up-regulate canonical MYC target genes to stimulate cell proliferation, whereas MYCN recruits G9a to enhancers to down-regulate neuronal differentiation genes and inhibit cell differentiation.

subtypes: adrenergic (ADRN) and mesenchymal (MES). ADRN and MES phenotype is determined by core transcription factors. ADRN predominates in tumors, while MES becomes enriched post-chemotherapy or in relapsed tumors. The interconversion between these subtypes contributes to neuroblastoma lineage plasticity, but the underlying epigenetic mechanisms driving this phenotypic switching remain poorly understood. The SWI/SNF chromatin remodeling complex plays a vital role in nucleosome assembly and gene expression control. Our research found that SWI/SNF ATPases depletion through genetic silencing or PROTACs (proteolysis-targeting chimeras) degradation compacts cis-regulatory elements, diminishes enhancer activity, and displaces core transcription factors (MYCN, HAND2, PHOX2B, and GATA3) from DNA. This process suppresses transcriptional programs associated with plasticity. Notably, we discovered that SWI/SNF ATPases are essential for establishing an MES gene-permissive chromatin state in ADRN-type neuroblastoma. By reducing the epigenetic barrier, SWI/SNF ATPases facilitate lineage plasticity (**Fig. 2**). Targeting SWI/SNF ATPases with SMARCA2/4. dual degraders effectively inhibits neuroblastoma cell proliferation, invasion, and notably, cellular plasticity. Additionally, it sensitizes neuroblastoma cells to chemotherapeutic drug treatment. These findings underscore the pivotal role of SWI/SNF ATPases in driving intrinsic plasticity and therapy resistance in neuroblastoma, highlighting them as a promising target for combinational treatments in this cancer. Currently, this story is under revision.

Next, I would like to employ a combination of molecular and cellular biology techniques, alongside high-throughput, unbiased screening approaches, such as CRISPR-seq screening, or barcoded opening reading frame libraries for pooled screening, to identify dysregulated genes that contribute to tumorigenesis and cancer progression.

Q3. How do you plan to translate your fundamental discoveries into new cancer treatments?

I aim to bridge the gap between basic research and real-world impact by exploring small molecules for precision therapy. We plan to evaluate SMARCA2/4 inhibitors used in preclinical neuroblastoma models. If successful, we will collaborate with the clinical team within the Pediatric Oncology Branch to develop clinical protocols to treat neuroblastoma patients.

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

As a scientist, I encounter research-related problems, including experimental setbacks. While it's exciting to make novel discoveries, it can be frustrating when outcomes don't meet expectations. Another challenge is the intense pressure to publish in reputable journals.

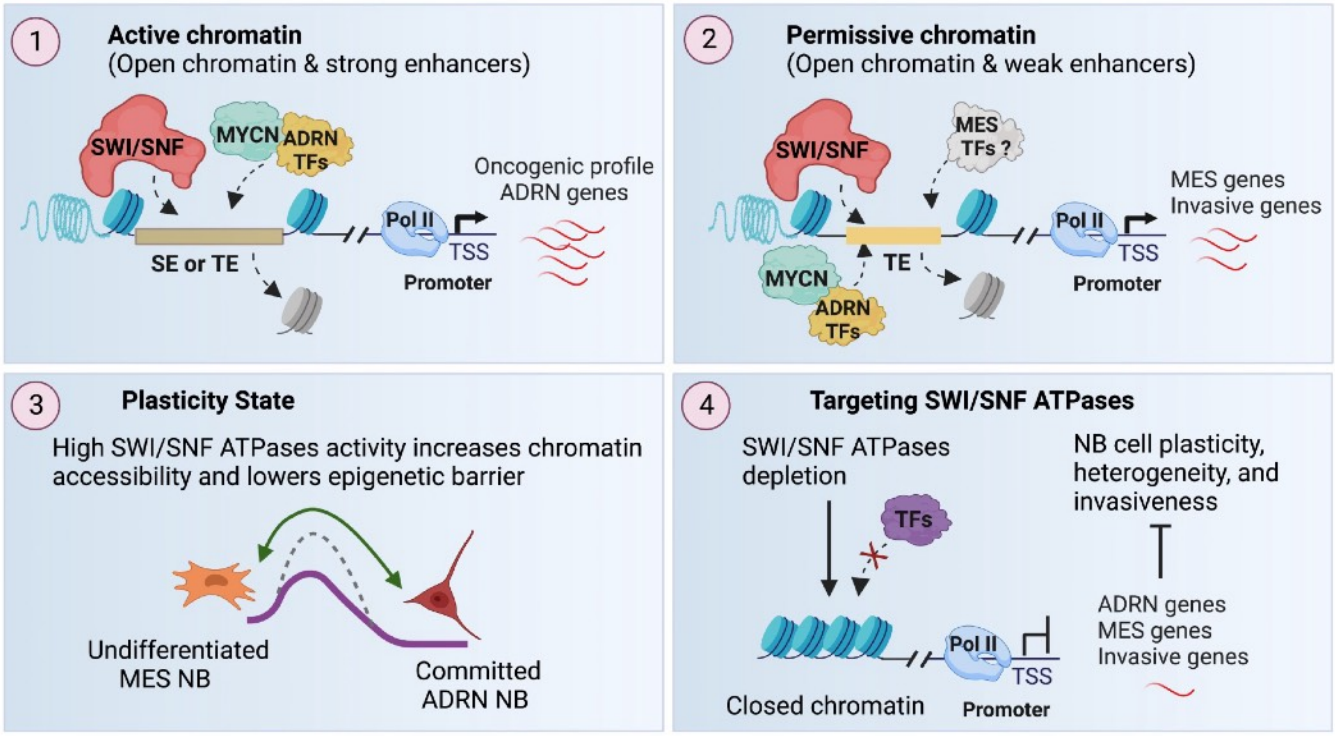


Figure 2. Schematic diagram illustrating the impact of SWI/SNF ATPases on ADRN-type NB cells. High SWI/SNF ATPases levels increase chromatin accessibility, enhance DNA binding of core TFs, reduce the epigenetic barrier, and promote NB cell plasticity, contributing to intra-tumor heterogeneity, highlighting their potential as appealing therapeutic targets (Created with BioRendere.com). Note: SE, super-enhancer; TE, typical enhancer.

However, I've learned that negative results can also benefit the field. Balancing quality with quantity ensures our work contributes meaningfully to the scientific community.

Q5. What advice would you like to share with your younger colleagues to build a successful career in research?

Your research should align with the lab's scope and the PI's interests. However, it's beneficial if you and your PI can find common ground and agree on mutually interesting projects. As a researcher, passion and curiosity are always essential for success. Additionally, staying updated on cutting-edge techniques, recent discoveries, and advancements in your field is crucial. Active involvement in the scientific community, like joining interest groups, reviewing papers and grant applications, and participating in editorial boards, will enhance your career. Writing successful grant proposals is helpful in building a thriving scientific career.

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

Outside of the lab, I like to read books, watch TV shows, and play table tennis.

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Contributors

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