CCR Fellows & Young Investigators Newsletter

Center for Cancer Research

Volume 23, Issue 1 **Summer 2024**

Special newsletter edition: **24th CCR FYI Colloquium**

Happy July, CCR fellows! This issue of the newsletter is packed with articles summarizing the CCR-FYI Colloquium, held in late April! Please mark in your calendars the dates for next year's Colloquium (our 25th), to be held 15-16 May 2025. I strongly encouraged you to get involved in the planning of next year's Colloquium. In the meantime, I hope that some of our authors' insights in this issue are useful and inspirational. Thank you to the team for their work in assembling the newsletter!
– Riley Metcalfe, Editor-In-Chief

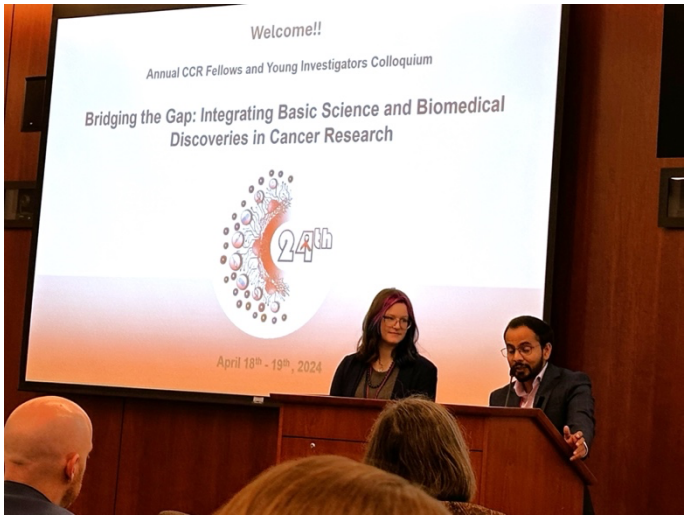
Table of Contents

Thank you to Gabrielle Sterns, Monika Chandravanshi, Alida Palmisano, Erika Ginsburg, and Kristen Fousek for providing photographs for the newsletter.

The CCR-FYI Association is supported by the Center for Cancer Training (CCT) and CCR Office of the Director, National Cancer Institute.

Reflections from Colloquium Co-chairs

By: Kathleen Reed (Colloquium co-chair, Bethesda) and Ramesh Chingle (Colloquium co-chair, Frederick)



Events like the CCR-FYI Colloquium are the highlight of my time at the NIH – a chance to meet with other trainees across the CCR, share their inspiring research, and connect with leaders in the field who are dedicated to mentorship and outreach. This year marked the 24th annual event, providing an avenue for scientists to come together to share ideas, foster collaborations, gain knowledge, and to hone professional development skills. Held in-person at NCI Shady Grove, this year's theme, "Bridging the Gap: Integrating Basic Science and Biomedical Discoveries in Cancer Research" was selected by the Colloquium Planning Committee members to be inclusive to researchers throughout the CCR, while also highlighting one of many great strengths of the NCI: the combination of clinical and fundamental approaches to better understand and treat cancer. Many talks and posters throughout the two-day event highlighted the advantages of close collaborations between labs and even institutes that have made tremendous developments possible.

For many months starting in the summer of 2023, Colloquium Planning Committee members worked tirelessly to make this Colloquium possible. We are incredibly thankful for all of those who contributed by suggesting speakers, workshops, and panels, coordinating invitations, designing an exciting and packed agenda, judging talks and abstracts, and handling logistics. Getting to know everyone throughout the year, and then to meet in-person at the event itself was an absolute honor and delight, and I couldn't possibly recommend it enough to other fellows. We are always looking for excited volunteers who can offer any amount of time or ideas to help shape future events. For anyone interested in joining the team for next year's landmark 25th Colloquium, please don't hesitate to reach out to the CCR-FYI leadership, especially the two co-chairs for next year's Colloquium, Kristen Fousek (Bethesda, kristen.fousek@nih.gov), or Riley Metcalfe (Frederick, riley.metcalfe@nih.gov).

We would also like to thank all those involved in organizing and running the 2024 Colloquium:

Colloquium Planning Chairs

- Katie Reed
- Ramesh Chingle

Colloquium Planning Vice Chairs

- Monika Chandravanshi
- Sophia Varriano

Steering Committee Chairs

- Shivalee Duduskar
- Kristen Fousek

Planning Committee Members

- Vinutha Balachandra
- Christine Carney
- McKenna Crawford
- Priyanka Desai
- Sarah Dremel
- Kelcie Foss
- Katie Hebron
- Sophie Kang
- Arfa Moshiri
- Anna Newen
- Gauri Prasad
- Chathuranga Rathnamalala
- Josh Rich
- Ashlie Santaliz Casiano
- Shalu Sharma
- Julia Medina Velazquez
- Geraldine Vilmen
- Kaustubh Wagh

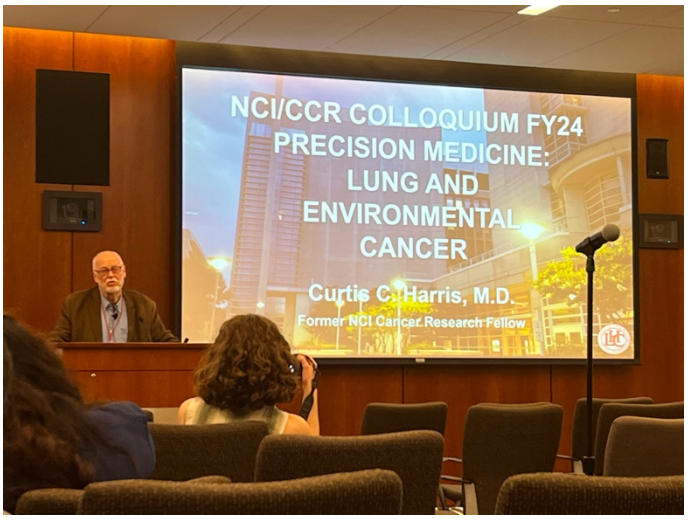
Center for Cancer Training

- Erika Ginsburg
- Maria Moten
- CCT Communications Team

Thank you to all of them, and I hope that you get involved next year!

Intramural Keynote: Innovations in Cancer Detection: Dr. Curtis Harris' Keynote Insights

By: Fiona Flynn



Dr. Curtis Harris, the co-Chief of the Laboratory of Human Carcinogenesis in the CCR delivered the first intramural keynote address, "Precision Medicine of Lung and Environmental Cancer," at the 24th Annual Center for Cancer Research Fellows and Young Investigators (CCR-FYI) Colloquium.

Harris received his medical degree from the University of Kansas Medical School and completed his clinical training in internal medicine at the University of California, Los Angeles. He conducted his residencies at the Washington, DC Veterans Affairs Hospital and at the National Cancer Institute (NCI). Dr. Harris has since served as chief of the Laboratory of Human Carcinogenesis since 1981 and is the head of the Molecular Genetics and Carcinogenesis section for the NCI. He has received many awards and accolades throughout his career, including the American Association for Cancer Research-American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention (2014), the Distinguished Service Medal, and the NCI Outstanding Mentor Award in 2007 and 2013.

Dr. Harris is renowned for his contributions to molecular and integrative epidemiology of human cancers. His groundbreaking work includes identifying the molecular link between the environmental carcinogen aflatoxin B1 and a mutation in the TP53 tumor suppressor gene. His laboratory also revealed that secondhand smoke exposure is associated with increased lung cancer risk among non-smokers. These findings have significantly advanced understanding of cancer pathogenesis and early detection strategies.

In his keynote address, Dr. Harris, a former NCI fellow himself and now a pioneer in the field of cancer research, shared valuable insights into the evolving landscape of precision medicine, specifically in the context of oncology. During his talk, he noted that the concept of precision oncology gained prominence during the Obama presidency. He discussed the significant milestones, including the Precision Medicine Initiative, whose mission is to provide a tailored approach to health care that considers individual differences in genes, environment, and lifestyle.

A substantial portion of his presentation was dedicated to comparing methodologies of cancer detection. He contrasted fragment-based cell-free DNA analyses from blood with mass spectrometry analysis of urine, noting that urine tests could achieve comparable levels with a

lower rate of false positives, particularly crucial for early-stage detection in both high and low-risk populations. Throughout his talk, Dr. Harris explored various facets of cancer research including the role of the metabolome in cancer prognosis, the interactions between the microbiome and cancer, as well as the influence of inflammation on cancer progression highlighted by the presence of specific bacteria like *Acidovorax* in lung cancers of smokers.

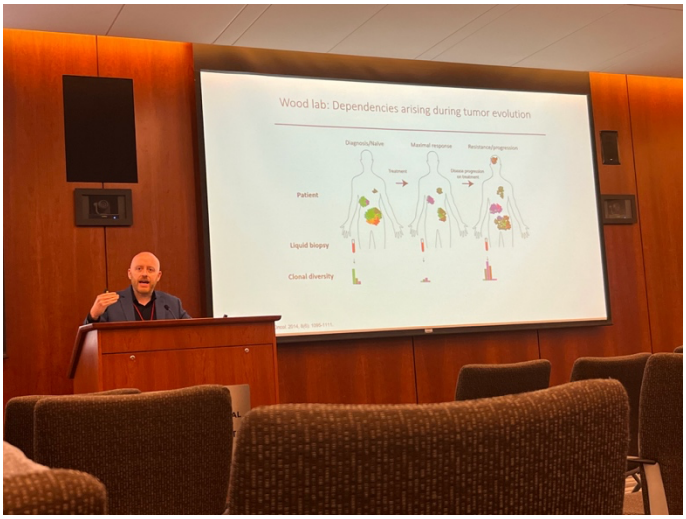
Additionally, Dr. Harris highlighted his influential research on p53, a tumor suppressor gene that his and other groups discovered could be mutated by environmental carcinogens, marking the early days of molecular epidemiology. His discussion extended to recent advancements by researchers like Dr. Bert Vogelstein, who have developed methodologies to detect fragmented DNA signatures of cancer in blood, enhancing early detection and potentially improving patient outcomes.

Dr. Harris also addressed the economic and health impacts of cancer, specifically lung cancer, which is not only the most expensive in terms of treatment but also leads to significant mortality. He emphasized the importance of a multi-disciplinary strategy in precision medicine, which has recently incorporated health disparity and prevention research to its objectives, aiming to improve clinical medicine and inform biomedical research across diverse populations.

In concluding his presentation, Dr. Harris underscored the importance of mentorship, especially at the NCI where he has worked with over 300 fellows, who have now mostly gone on to pursue careers as physician-scientists. He spoke passionately about the necessity of passing on knowledge, encouraging collaboration among young researchers, and fostering a community that not only advances cancer research but also integrates findings into other diseases. His call to the research fellows and young investigators was clear: leverage the community to deepen understanding across diseases and think beyond conventional boundaries to innovate and advance healthcare. This emphasis on mentorship and community serves as a cornerstone for nurturing the next generation of scientists in the challenging yet rewarding field of cancer research.

Extramural Keynote: Evolution of Tumor Dependencies

By: Ishan Rathore



Dr. Kris Wood is an associate professor in the Department of Pharmacology and Cancer Biology at Duke University. He received his PhD in chemical engineering from the Massachusetts Institute of Technology, where he developed self-assembling homomeric systems for controlled gene and drug delivery. While working as a postdoc at the Whitehead Institute for Biomedical Research and the Broad Institute of Harvard and MIT, he focused on developing functional genomic tools to study determinants of anti-cancer drug sensitivity. In 2012, he relocated to Duke University to begin his independent research group. His research team employs functional genomic technologies to mechanistically characterize cancer subtypes defined by biomarkers and discover new molecular targeted therapies for their treatment. His work also aims to define strategies to control long-term tumor evolution. Dr. Wood's research has been recognized by awards and has inspired the design of multiple ongoing clinical trials and the creation of three independent biotechnology companies, Celldom, Tavros Therapeutics, and Element Genomics.

In his talk, Dr. Wood shed light on recent research from his lab, covering three stages of cancer progression and the complexities of tumor dependencies and molecular mechanisms driving cancer growth. He describes how these dependencies change over time, from initial diagnosis to treatment response and eventual development of resistance. His lab seeks to identify potential targets for therapeutic intervention at each stage of cancer progression. His approach offers promising prospects for improving treatment outcomes and addressing the challenges of drug resistance in cancer therapy.

Tumor dependencies at early-stage cancer treatment

At early-stage cancer, he describes drugs as having both cell-detrimental and cell-beneficial effects. He and his team hypothesized if it is possible to separate these two effects to maximize the effectiveness of the drug. Their study focuses on a drug called Selinexor, which is approved for the treatment of certain hematological malignancies and is in advanced trials for AML. Selinexor is known for its role in blocking nuclear protein export and accumulating tumor-suppressive proteins in cancer cells. Dr. Wood presented their results which revealed the dual effect of the drug; it both impeded cancer cell fitness and triggered a pro-survival signal.

This discovery prompted the investigation of a combination therapy involving Selinexor and an AKT inhibitor. Their findings in a genetically engineered mouse model of AML suggest that this

combination outperforms standard chemotherapy regimens with potentially fewer side effects. The results of the study are quite promising, and a phase one clinical trial is underway in Paris.

Dependencies at the post-therapy phase of cancer

Next, Dr. Wood highlighted the residual disease phase, where cancer cells persist after treatment. This phase is critical as it harbors cells responsible for eventual resistance development. Residual disease cells exhibit distinct characteristics from parental cancer cells, including altered transcriptional states and convergent biological features. They also face constant drug pressure due to ongoing therapy, prompting an investigation into their unique survival dependencies. Targeting these cells could prevent long-term resistance evolution.

To support their point, his team studies epidermal growth factor receptor (EGFR) mutant cell lines treated with their cognate targeted therapy, focusing on the signaling pathways in residual surviving cells. They discovered that the residual cells in these model systems activated the ATM double-strand break repair pathway in response to drug treatment, uncovering a potential vulnerability, namely, their reliance on DNA repair mechanisms for survival. Furthermore, they demonstrated that treating residual cells with only an ATM inhibitor was ineffective. However, when exposed to continual pressure from EGFR inhibitors, these cells became sensitive to ATM inhibitors. Their research also indicated that patients with a rare co-occurrence of EGFR and ATM mutations responded better to EGFR inhibitors than those with wild-type ATM. Clinical observations in patients with EGFR mutant lung cancers further validated the therapeutic potential of targeting DNA repair pathways in residual disease. Patients with co-occurring loss-of-function mutations in ATM exhibited enhanced responses to targeted therapy. These findings offer a promising strategy to prevent the emergence of drug resistance and improve treatment outcomes for cancer patients.

He ended this part of the talk with a take-home message "…If we can take advantage of those induced dependencies, we can potentially kill off these cells before they have time to develop resistance. And so, a lot of work in our lab now is looking at how sublethal apoptotic signaling in residual cells can create new dependencies."

Tumor dependencies at the final stages of disease

Dr. Wood's talk further delved into the final stage of the disease, acquired resistance in cancer, a stage where tumors persist and grow despite therapy. When a patient acquires progressive resistant disease, it doesn't arise from a single drug resistance mechanism but by harboring multiple resistant clonal populations of cancer cells. Dr. Wood's work explores the concept that resistant clones that have acquired fitness advantage also incur hidden fitness trade-offs. This hypothesis stems from the understanding that evolutionary steps leading to a fitness advantage in one context often entail drawbacks in others, known as fitness trade-offs. Their work aims to identify those trade-offs and understand if there exists a commonality in those mechanisms.

Dr. Wood's lab conducted two parallel projects investigating resistance mechanisms to bromodomain inhibitors in AML and BRAF inhibitors in melanoma. They found that despite the differences in drugs and cancer types, both cancers led to activation of the Myc oncogenic transcription factor. This discovery suggests that Myc activation is a common downstream

effector of diverse pathways, even when resistance developed through different molecular mechanisms. This observation led to a simplified model of resistance evolution, where tumors can be categorized into two states: oncogene-driven and therapy-resistant with Myc dependency. With this knowledge, Dr. Wood's team explored the potential of targeting Myc-induced vulnerabilities to overcome therapy resistance. In one of their studies, they found that drug-resistant cancer cells with Myc hyperactivation exhibit more sensitivity to B cell Lymphoma 2 (Bcl-2) inhibitors, which activate the mitochondrial apoptotic pathway. In AML cells resistant to bromodomain inhibitors, they observed heightened sensitivity to Bcl-2 inhibitors. Their research showed that the sequence of drug administration is crucial and administering the bromodomain inhibitor followed by the Bcl-2 inhibitor was more effective than the reverse order. The data support the idea that sequential treatment selects resistance mechanisms that converge on Myc hyperactivation and sensitization to Bcl-2 inhibitors.

Dr. Wood's talk highlighted his research uncovering novel insights into cancer progression through different stages of the disease. Their focus on discovering tumor dependencies at the initial, treatment and resistance stage of cancer has provided new opportunities for development of innovative therapeutic approaches.

Outstanding Postdoctoral Fellow: “Camel Nanobody-based B7-H3 CAR-T Cells with High Efficacy Against Large Solid Tumors”

By: Gauri Prasad

This session highlighted the Outstanding Postdoctoral Fellow Award received by Dr. Dan Li, Research Fellow in Dr. Mitchell Ho’s lab at the CCR, NCI. Her research aims to develop a novel engineered antibody-based immunotherapy to treat liver cancer. Based on her work, the FDA approved a clinical trial of GPC3 CAR-T therapy at the NIH clinical center. Dr Li has also received several federal Technology Transfer Act awards in 2021, 2022 and 2023.

At the CCR-FYI colloquium, Dr. Li's research presentation titled "Camel nanobody-based B7-H3 CAR-T cells with high efficacy against large solid tumors," began by recounting the inspiring journey of cancer immunotherapy with the case of Emily Whitehead, the first pediatric patient to successfully receive CAR-T cell therapy for acute lymphoblastic leukemia at six years old. Emily's local medical team had exhausted all options until she participated in her first anti-CD19 CAR-T cell clinical trial. Ten years later, Emily celebrated a decade of being cancer-free by taking another photo to mark the milestone. Her story is a powerful testament to the potential of cancer immunotherapy.

CAR-T cells are engineered T-cells with chimeric antigen receptors (CARs) to specifically target tumor antigens expressed on cancer cells. The CAR structure includes a single-chain variable fragment (scFv) of an antibody, a hinge, a transmembrane domain, a costimulatory domain, and a CD3delta domain. CAR recognition of the tumor antigen triggers T-cell signaling, leading to the release of cytokines and chemokines which ultimately results in tumor cell death.

In clinical applications, T-cells are isolated from patients' peripheral blood mononuclear cells (PBMCs) and modified with a CAR virus to generate CAR-T cells. After expansion *in vitro*, these CAR-T cells are reintroduced into patients to target and eliminate cancer cells. While several CAR-T cell therapies have been approved by the FDA for blood cancers, none have yet been approved for solid tumors due to limitations in their ability to infiltrate and kill solid tumor cells. The obstacles to CAR-T cell therapy for solid tumors include barriers to infiltration such as: decreased tumor vasculature and dense extracellular matrix proteins hindering T-cell motility and function including presence of immunosuppressive cells, inhibiting molecules, and heterogenous expression of tumor-specific antigens.

Dr. Li's research focuses on the B7-H3 protein, which is highly expressed in multiple solid tumors but limited in normal organs and is thus a promising therapeutic target across multiple cancer types. She found that high B7-H3 expression correlates with poor overall survival in pancreatic cancer and neuroblastoma patients, leading to her further interest in developing CAR-T cell-based immunotherapy for these two challenging cancers.

To develop anti-B7-H3 immunotherapy, Dr. Li isolated nanobodies from a phage-displayed camel VHH library, screening for those specifically binding to B7-H3. Several nanobodies exhibited high affinity and specificity for B7-H3-positive tumor cells. She subsequently engineered CAR-T cells using these nanobodies, replacing the traditional scFv with high-affinity nanobodies. These nanobody-based CAR-T cells demonstrated potent antigen-dependent cytolytic activity against B7-H3-positive tumor cells in vitro and in mouse models, effectively regressing pancreatic tumors and inhibiting growth of large neuroblastomas. Further analysis revealed that nanobody-based CAR-T cells exhibited superior antigen-binding capacity and potent activation of T-cell memory phenotypes compared to scFv-based CAR-T cells, suggesting enhanced therapeutic efficacy.

A major innovation of Dr. Li’s research is using B7-H3, a tumor-associated antigen rather than a tumor-specific one. The advantage of utilizing a tumor-associated antigen lies in its potential clinical applicability across various cancer types, enabling this strategy to be used to treat different forms of cancer. Additionally, Dr. Li employed a nanobody sourced from camels. By aligning it with human VHH, her team discovered a significant sequence identity match of 77%. Previous studies have successfully utilized nanobody-based CAR-T cells for lymphoma treatment, gaining FDA approval. Interestingly, those studies also utilized non-humanized nanobodies derived from llamas. As humanization is deemed safer, Dr. Li and the team are currently working on the humanization of these nanobodies. Humanization involves altering the non-human nanobody sequences to more closely resemble human antibody sequences. This typically involves modifying the regions of the nanobody that are recognized as foreign by the human immune system. By making the nanobody sequences more like human antibodies, the likelihood of the human immune system recognizing the therapeutic nanobody as foreign is reduced. This decreases the potential for immunogenic responses, improves the safety profile, and enhances the therapeutic efficacy of the nanobodies. However, uncertainty remains regarding the humanization process, prompting them to explore alternative frameworks leveraging artificial intelligence-based analytical approaches.

Dr. Li's groundbreaking research highlights the potential of nanobody-based CAR-T cell therapy targeting B7-H3 as a promising approach for treating solid tumors. This work paves the way for future clinical trials and highlights the importance of interdisciplinary collaboration in advancing cancer immunotherapy.

Panel: Exploring Careers at the Bench: Academia and Beyond

By: Christine Muli

Making career choices can feel daunting, but the career panel at the CCR-FYI Colloquium offered great pieces of advice which reframed my perspective. The panel featured five professionals from various backgrounds, which spanned academia, industry and non-profits: Drs. Clara Bodelon (Senior Principal Scientist in Survivorship Research at the American Cancer Society), Jesse Boehm (Chief Scientific Officer at Break Through Cancer and Principal Investigator at Massachusetts Institute of Technology's Koch Institute for Integrative Cancer Research), Dmitry Galbrilovich (Chief Scientist in Cancer Immunology at AstraZeneca), Michael La Frano (Director of Metabolomics and Proteomics at University of Illinois Urbana-Champaign), and Evagelia Laiakis (Associate Professor at Georgetown University). Topics ranged from academic and pharmaceutical career paths to career transitions, and how to stand out in the job search.

Question: How did you choose whether the academic or non-academic career was for you?

The panelists had previous and current experience in academia. Dr. Evagelia pointed out that academia can offer career tracks beyond professorship and your own lab. In academia, you can be more focused on lecturing or join a research facility/core. Dr. La Frano was previously a tenure-track assistant professor, but six years into his role, he realized he needed something different. Now as the Director of Metabolomics and Proteomics at University of Illinois Urbana-Champaign, he's still in the academic world and enjoys the aspects of his job where he works with diverse projects, a larger research team, and more resources.

One initial response from Dr. Bodelon was that "the dichotomy of academia versus industry has blurred" in the past ten years. When you choose a career path or a new job, ask yourself if you can see yourself doing *this* (whatever your potential job is) every day. When considering a career with the mindset of academia versus industry, Dr. Boehm stated: "Academia versus non-academia is a false choice." Instead, he recommended to reframe the question to: 'What do you want to achieve in your career?' Academic or not. Write down your expectations on a sheet of paper and hold that paper dear whenever you're going looking for your next position. And so, I did. I wrote down what I truly wanted out of my career, and doing as Dr. Boehm suggested, it provided clarity as to what my next career step should be.

Question: How was the transition from an academic setting into the pharmaceutical industry? And what advice would you give for someone doing this transition?

From my perspective (the author's), the environments between these two job settings can be drastic. After my undergraduate degree, I worked at Genentech in South San Francisco, California, for three years, and the initial learning curve was steep. In big pharma, there's a wide range of projects and specialties that can be overwhelming at first, but you become efficient at your specific role in driving the project pipeline forward. The resources within industry are phenomenal, and you have some flexibility within industry to do basic research, but at the end of

the day, your basic research must link to a potential clinical outcome. With this, I was interested in knowing if the panelists had similar experiences.

Dr. Galbrilovich advised that in the transition, you must change your mindset and realize that you're a part of a group with a common goal. However, he's noticed that this transition of individual projects in academic settings to discovery projects at AstraZeneca has been smooth for younger scientists. To prepare for this transition, Dr. La Frano noted that you really should take the time to ask all questions before you accept a role and during the transition. Doing such will give clarity on your daily responsibilities and how to perform well in your new role.

In addition to active communication and asking questions during career changes, Dr. Boehm added more general advice that I now implement into my training. To figure out what path is right for you, you can form a circle of mentors with various career paths for yourself. Engage with these mentors twice a year or more. Diversifying your points-of-contacts to individuals with different career paths allows for a more unbiased approach to the advice you receive. His advice reminded me to reach out to my previous mentors in industry and Research Experiences in Undergraduate (REU) institutions because my current mentorship circle only consists of scientific role models in government and academia. Dr. Boehm confessed that he regretted not seeking out other mentors aside from his direct advisor; once he received mentorship from a different perspective, he realized that there's a career path out there that was a better fit for him.

Question: How can you be marketable to a position where you don't 100% fit? As a researcher, we have all these transferable skills – how can we showcase that?

There are several ways to make yourself marketable, and the panelists emphasized networking at conferences and establishing an online presence by LinkedIn or X (formerly Twitter) as key. If you're looking for a job, Dr. Boehm mentioned that you don't have to wait for specific job listings. You can reach out to scientists within your group-of-interest. Dr. Bodelon suggested to practice concisely and broadly speaking about the work you do to showcase your strengths. This practice will allow your work to have wider reach and appeal to multiple audiences. Lastly, Dr. Galbrilovich stated that personal contact in industry is incredibly beneficial. When looking for a position, contact the hiring manager even if you only match 50% of the position qualifications. If you don't fit 100% of the qualifications, they'll teach you on the job.

Throughout the panel, they highlighted the importance of networking and asking questions to figure out what's right for you and your goals. At the end, the panelists were asked to say a few more words before parting with us, and I'd like to share these inspirational words with you:

Don't get discouraged; you will find the right fit.

You may not realize it, but as an NCI fellow, you are a brilliant scientist, and hiring managers will want YOU.

Maximize your experience here and learn as much as you can so that we're prepared.

When making a career choice, imagine looking at the end of your career and feeling that you've made the right choices.

Workshop: Communicating with Confidence and Clarity

By: Gabrielle Stearns

Tracy Costello, Ph. D., began her workshop with her arms crossed and eyes cast to the floor. She quietly told the room she would teach them how to communicate their science effectively. As intended, this, did not inspire confidence in the audience.

Then, Dr. Costello requested for a do-over. She straightened her posture, looked towards the audience, and began again. After adjusting her tone and demeanor, the audience found her captivating.

Dr. Costello is a career coach for scientists. She helps her clients set goals, prepare application materials, and cultivate the communication skills necessary for a successful research career. After finishing her Ph.D. in 2004, she spent the last 14 years with the National Postdoc Association, actively advocating for postdocs' rights and identifying areas where they need attention or support in addressing their additional support needs.

Efficient communication skills are pivotal in science, as we all need to communicate complex concepts to an audience with diverse backgrounds and knowledge. In more formal settings, these may include presenting posters or giving talks at seminars. However, Dr. Costello also highlighted how these skills are equally valuable when discussing research with mentors and mentees, articulating research interests in job interviews, or advocating for funding. This expansive view of communication allowed Dr. Costello to demonstrate multiple ways communication skills can aid scientists throughout their careers.

The workshop was highly interactive. Dr. Costello passed around the microphone and asked participants to share their own experiences speaking about science: their successes, challenges, fears, and goals. She acknowledged the vulnerability of sharing these personal stories and shared a few of her own. No one is immune to anxiety while giving presentations or job interviews, not even professional public speakers. Dr. Costello used her perspective and the concerns of the trainees in the room to offer advice and actionable steps to improve their communication skills. Here are the takeaways:

Know your audience

You likely discuss your research differently with your family than with your co-workers. However, even an audience consisting of Ph. Ds may not be familiar with every detail of your scientific field. While you could get your audience up to speed on all the terms in your paper, it takes up valuable time that could be spent on explaining more impactful findings. Aim to reduce jargon and instead use analogies to relate to your audience. They are much more likely to listen when they understand.

Streamline your content

Scientific talks are time limited, and poster presentations and elevator pitches are even shorter. Scientists must fit their research within the time constraints while conveying the importance of their work. Dr. Costello offered an exercise to practice this skill.

Start by writing down the most relevant aspect of your research on one sheet of paper. Then, re-write it on an index card, removing the information that isn't vital. If you are up for a bigger challenge, re-write the content one more time on a post-it note. You will get a streamlined version of your research with the most important details.

Start by answering "why" as it's the most interesting part

Scientific papers follow a strict order – introduction, methods, findings, and discussion. Although this is good for a manuscript, it isn't necessarily the best way to present content verbally. Dr. Costello recommends beginning science talks by answering "why." Why is this research important? Why should the audience care? These questions grab an audience's attention and serve as compelling entry points for a discussion of the context and applications of your research.

Confidence comes with practice

Preparation is important. Therefore, do not undervalue experience. Every opportunity to speak in front of an audience, whether it a colleague or a room full of peers, increases your comfort with science communication.

For more information about Dr. Costello, visit her website: www.coach4postdocs.com.

Workshop: Empowering your Training Journey: Navigating NCI Resources

By: Sukriti Sharma

Are you a trainee looking to chart your career path and make the most of the resources available at NCI? This year, the CCR-FYI Colloquium featured a "Empowering your Training Journey" workshop led by Dr. Chanelle Case Borden, Associate Director of Training Programs at the Center for Cancer Training. Dr. Case Borden shared invaluable advice to help make the most of time at NCI. Here are the key takeaways from the session:

Start Inward: Self-Reflection:

The first step on the path to a rewarding career begins with introspection. Take time to assess your skills, interests, values, and priorities. What tasks or skills would you like to develop professionally or personally? Exploring tools like MyIDP Science Careers can help identify suitable career paths. Seek advice from OITE counselors, training directors, and attend programs like Explore On Site (EXPOSE) which provide immense career exploration opportunities. The EXPOSE program is for current NCI postdoctoral fellows who are interested in exploring careers beyond academic research and increase awareness of science-based careers outside of independent, academic research and to facilitate networking and information exchange. The goal is to provide the tools and resources to enable fellows to identify a career(s) that match their skills, interests, and values, while providing opportunities to visit local employers.

Reverse Engineer Your Journey:

Once you have identified suitable career options, leverage the abundance of resources available at NIH and NCI to bridge the gap between where you are and where you want to be. Attend seminars, workshops, and events like the CCR-FYI Colloquium to expand your knowledge and network. Refine your CV/Resume through dedicated workshops and resources such as the Office of Intramural Training's (OITE) Guide to Resume and Curriculum Vitae workshop and seek feedback from peers. Nowadays, building and updating your professional profile on platforms like LinkedIn are key in making connections in your field. Additionally, the mobile app NanCI, developed by NCI, can be very useful in your career journey. It allows you to track your progress you made in your professional journey, connect with your peers, explore upcoming events at NCI, and discover scientific papers relevant to your interests.

Fill in the Gaps:

Take advantage of resources like the NIH Library, OITE and the Foundation for Advanced Education in the Sciences (FAES) to acquire missing skills or knowledge required for your desired career path. FAES conducts advanced educational programs and supports activities to promote the productivity of your professional life at the NIH. FAES offers management and entrepreneurial programs for scientists who want to bridge the gap between bench/bedside and business or other fields. Your Individual Development Plan (IDP) is also a powerful tool to help, support, and track your career development and learning opportunities. It is a dynamic

document that enlists the short- and long-term career objectives and is periodically reviewed and updated throughout your training period which helps keep track of your professional activities and achievements. Your IDP is a great tool to help in the planning process and to facilitate communication between mentees and mentors. Use it to set your goals, track your commitments, and hold yourself accountable.

Seek out ways to develop/enhance communication, leadership, and project management skills. Participating in activities like journal clubs, lab meetings, and branch meetings are great opportunities to do so. Mentoring high school students or summer interns can also add value to your skill set and bolster school and job applications.

Consider Transitional Fellowships:

If you are interested in careers outside of benchwork, your trainee experience may not directly translate to non-research roles. Strongly consider transitional fellowships like the Intramural AIDS Research Fellowship (IARF), Interagency Oncology Taskforce Fellowship (IOTF), or the NCI Technology Transfer Ambassador Program (TTAP). The IARF program is designed to further cross disciplinary research into HIV and AIDS at the NIH by providing funding to the next generation of AIDS researchers. This is a great opportunity for all those graduate students/postdoctoral researchers who have a well thought out career plan in AIDS research. The IOTF program is a unique opportunity to gain both research and regulatory review training. This program is jointly run by NCI and FDA that provides physicians and postdoctoral fellows the opportunity to conduct oncology research and regulatory review for up to three years. The fellows who envision themselves having a career in regulatory affairs can consider applying for this fellowship. Finally, the TTAP is another valuable program that is designed for postdoctoral fellows and other scientific staff at the NCI (e.g. staff scientists, staff clinicians, lab technicians and research fellows) who are seeking to enhance their current research activities with hands-on training in biomedical invention development, commercialization, and entrepreneurship. It is a beneficial opportunity for those interested in fields like federal technology transfer management, patent law, drug review, and more.

Be Kind to Yourself:

Remember to be kind to yourself throughout your training journey. It is essential to not get discouraged by setbacks or challenges and celebrate your progress along the way. Remember, career development is an ongoing process, and it's essential to think wisely, give yourself time and stay patient. Consider career development as a marathon; slow and steady progress will get you where you want to be.

You can empower your training journey at the NIH by leveraging its wealth of resources. Stay proactive, embrace growth opportunities, make connections, seek guidance, and most importantly, believe in yourself.

Intramural Keynote: Development and Translation of Strategies to Target Tumor Metabolism for the Treatment of Pediatric Solid Tumors

By: Riley D. Metcalfe

The second Intramural Keynote speaker at this year's CCR-FYI colloquium was Dr. Christine Heske, a physician-scientist in the Pediatric Oncology Branch (POB). Dr. Heske leads the Translational Sarcoma Biology Section, studying multiple pediatric sarcomas, including Ewing's Sarcoma and rhabdomyosarcoma. She primarily focuses on developing novel therapeutic strategies to target solid pediatric tumors, taking an approach that she describes as "bench-to-bedside and back." This consists of translating insights from basic bench research to the clinic, and then taking those clinical insights back to the bench, to develop novel therapeutic strategies or improve the approach. Dr. Heske acknowledged the major strength of the NCI—namely, that being "close to the clinic" enabled close collaboration between clinicians and researchers and allows research insights to be quickly translated. She also acknowledged the role of her trainees early in her talk, stressing their role in driving research at the NCI.

The focus of Dr. Heske's lab is on studying novel treatments for pediatric sarcomas. These are a diverse type of cancer that arise from bone or connective tissue. In adults, they are very rare, accounting for less than 1% of diagnosed cancers, while in children and adolescents they are relatively more common, around 15% of diagnosed cancers. Sarcomas are challenging to treat as they often arise from oncogenic fusion proteins, have a high mutational burden, and respond poorly to new therapeutic strategies such as immunotherapies. They can be very aggressive, often metastasize, are resistant to treatment, and can often relapse even after apparently successful treatment.

The focus of the talk was on a rare pediatric sarcoma, rhabdomyosarcoma (RMS). RMS is classified into three subtypes: fusion-negative (embryonal), which are typified by mutations in RAS; fusion-positive (alveolar), which typically are caused by oncogenic fusion proteins involving translocations between PAX3/7-FOXO1; and spindle-cell sclerosing, an extremely rare subtype (~10/year), caused by mutations in MYOD1. A major focus of Dr. Heske's group is improving survival in high-risk patients, those with metastatic disease. To illustrate the challenges, she gave a case study of a nine-year-old girl with embryonal RMS in her pelvis. The child had intensive treatment, which included seven-drug chemotherapy, radiation therapy, and surgery. Unfortunately, she relapsed three times after treatment. Each time, she was treated

again with aggressive chemotherapy and surgery, and suffering severe side effects as a result. As a last resort, she was enrolled in a clinical trial, but was taken off-trial as she did not respond to the drug. Ultimately, the case study that Dr. Heske presented illustrated her point that there had been few advances in treatment for RMS in decades, emphasizing the need for novel treatments.

Broadly speaking, cancer cells have altered metabolic requirements, have a greater requirement for bioenergetics and synthesis, and have trouble maintaining redox balance. This abnormal metabolic phenotype results in reprogramming of metabolic pathways, which can be due to genetic alterations or the tumor microenvironment. This reprogramming of metabolic pathways opens a therapeutic window—there is a lot of biochemical "space" between normal cells and cancer cells to target cancer cells specifically. This alteration is often disease specific, so specific cancers can be targeted as well. It is a validated therapeutic strategy, as metabolic targeting agents are under heavy investigation, and several are already in the clinic. The overall strategy that Dr. Heske presented for targeting RMS was to identify druggable metabolic pathways, identify resistance mechanisms, and then initiate clinical translation of the most promising candidates.

The initial strategy to identify druggable metabolic pathways was a high-throughput screen at the National Center for Advancing Translational Sciences (NCATS), which looked at over 200 cell lines using 1900 compounds, which included but was not limited to known metabolism-targeting drugs. The drug screen was conducted using four RMS cell lines—two fusion-positive, two fusion-negative. The screen identified three inhibitors of the enzyme nicotinamide phosphoribosyltransferase (NAMPT), which is involved in the salvage pathway for production of the critical coenzyme nicotinamide adenine dinucleotide (NAD). The salvage pathway is one of three redundant pathways for NAD production in cells. Inhibiting NAMPT will likely reduce the production of NAD, a critical enzyme co-factor, which should be lethal to the cancer. NAMPT inhibitors had been previously studied in humans, however clinical trials for first-generation inhibitors were discontinued due to concerns over renal and cardiac toxicity. Second generation inhibitors are currently under investigation and show reduced toxicity and improved safety. Due to the promising lead from the NCATS drug screen and the fact that NAMPT inhibitors had already undergone human clinical trials, Dr. Heske's group undertook an extensive study of the inhibitors.

At this point, Dr. Heske wanted to assess the overall translational potential of NAMPT inhibitors. To assess this, she needed to first find out the mechanisms driving NAMPT inhibitor sensitivity in RMS cells, and second, the downstream mechanistic effects of NAMPT inhibition in RMS cell models and in animal models of the cancer. Her group found that NAMPT inhibitors are exceptionally potent in these cancers, with an IC_{50} often in the picomolar range. Genetic NAMPT depletion using siRNA also resulted in cell death, and rescuing the pathway by adding the product of NAMPT, NMD, rescued the cells, showing that the target of the inhibitors is NAMPT and additionally that the cause for cell death is the depletion of NMD. Dr. Heske acknowledged that *in vitro* cell models of cancer, particularly cancer metabolism, are inherently flawed and do not capture the full complexity of the process. She thus quickly moved to *in vivo* mouse models of RMS. In mouse xenograft models of the cancer, it was found that treatment

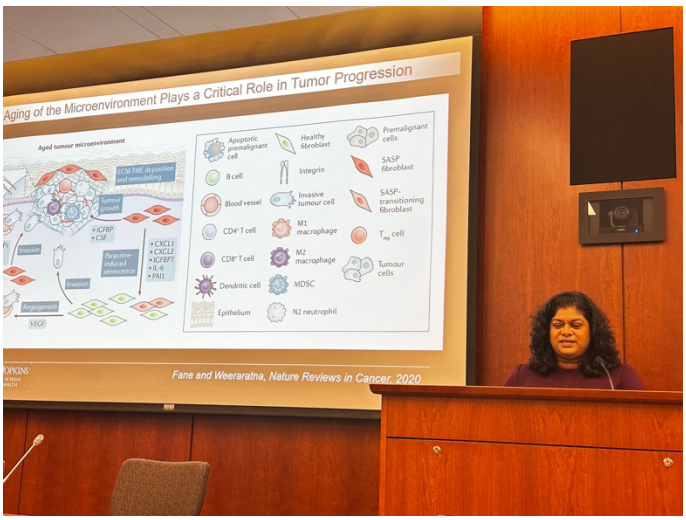
with a NAMPT inhibitor regresses the tumors without recurrence following the treatment. All these results support the core finding that NAMPT inhibition in RMS is a potential therapeutic avenue.

Dr. Heske was then interested in understanding the downstream metabolic consequences of NAMPT inhibition. She noted that NAMPT inhibition resulted in severe disruption of ATP production, which is unsurprising, as NAD is a critical co-factor in ATP production. Her team also noted using extracellular flux analysis, 'Seahorse', which measures the level of glycolysis/oxidative phosphorylation, that NAMPT inhibitor treatment results in a disruption of glucose metabolism, a finding which was recapitulated *in vivo* using 13-C magnetic resonance imaging experiments. This was also supported *in vitro* by measuring a decrease in lactate from NAD loss in treated cells, which reflects a decrease in glycolysis. Following from these results, Dr. Heske wanted to understand the mechanism of cell death in NAMPT inhibitor treated RMS cancer cells. Her initial suspicion was that the cells died through an apoptotic pathway, as this is the mechanism that occurs in a different cancer, Ewing's Sarcoma. To her surprise, in RMS, the cells die through necrosis, a very surprising result that Dr. Heske admitted that she asked be repeated several times before she would believe it. However, several RMS cell lines died through apoptosis, not necrosis, another surprising result. Dr. Heske noted that the cell lines that die through apoptosis do differ as they can relapse after NAMPT inhibitor treatment. Efforts are currently ongoing in her lab to understand the differences between these cell lines using RNA-Seq. Importantly, she is currently planning a phase 1 study on a combined NAMPT/PAK4 inhibitor, to translate her promising and interesting results at the bench into the clinic, to better treat a persistent and aggressive childhood cancer.

The research that Dr. Heske presented has been published in *Clinical Cancer Research*. Dr. Heske's presentation exemplified first stages of the "bench-to-bedside and back" approach that her lab aims to use. Her research shows how fundamental insights into molecular and cell biology at the bench can be used to better understand the mechanism of action of cancer drugs, and ultimately be translated into the clinic. She also showed the research that is possible at the NCI, as we can use our proximity to the clinic to collaborate closely with clinicians which ultimately leads to novel treatments for cancer patients.

Extramural Keynote: The Ravages of TiME: How the aging tumor immune microenvironment drives cancer progression

By: Ramesh Chingle



Dr. Ashani Weeraratna delivered the fourth keynote address of the CCR-FYI Colloquium 2024 on April 19th, 2024. Dr. Weeraratna is the Bloomberg Distinguished Professor of Cancer Biology, E.V. McCollum Chair of Biochemistry and Molecular Biology at the Johns Hopkins Bloomberg School of Public Health, as well as the Associate Director for Laboratory Research at the Sidney Kimmel Cancer Center, Johns Hopkins School of Medicine. She was previously President of the Society for Melanoma Research, and recently appointed by President Biden as a member of the National Cancer Advisory Board. Prior to joining Johns Hopkins, she was the Ira Brind Professor and Co-Program Leader, and a Immunology, Microenvironment & Metastasis Program Member at the Wistar Institute. Born in Sri Lanka, and raised in Lesotho in Southern Africa, Dr. Weeraratna first came to the United States in 1988 to study biology at St. Mary's College of Maryland. There she earned her undergraduate degree. She earned a Ph.D. in Molecular and Cellular Oncology at the Department of Pharmacology of George Washington University Medical Center. From 1998 to 2000, she was a post-doctoral fellow at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Oncology Center, before joining the National Human Genome Research Institute as a staff scientist. In 2003, she moved to the National Institute on Aging, where she started her own research program, before joining the Wistar Institute from 2011-2019.

Dr. Weeraratna is an expert in melanoma metastasis, Wnt signaling, and aging. Her research focuses heavily on the effects of the tumor microenvironment on metastasis and therapy resistance. She is one of the first people to study how the aging microenvironment guides metastasis and therapy resistance in melanoma. For this innovative work, she was selected by *Nature* to be a part of their "Milestones in Cancer Research" video series, and in 2021 the NCI selected her as one of their "Top 5 Cancer Researchers Accelerating Cancer Research into the Future". Moreover, the quality and impact of Dr. Weeraratna's research is further recognized by the award of numerous peer-reviewed grants and awards.

Dr. Weeraratna has been a champion of increasing diversity for many years, and this is evident in her writings which highlight the importance of gender and racial equity in cancer research. She mentors junior faculty all over the world, and spearheads efforts to increase the diversity among the Hopkins faculty. In her own department she has successfully implemented strategies

to increase diversity both through faculty recruitment, and in the general student body. She has also written a book for the lay public called *Is Cancer Inevitable* meant to highlight the progress made in, and the importance of diversity in cancer research. She is also heavily invested in Public Health, and advocates for sun protection and cancer awareness through her social media presence, and community outreach.

Dr. Weeraratna's presentation at the CCR-FYI Colloquium shed light on the intricate dynamics of age-related changes in tumors, with a specific focus on myeloma. She highlighted that cancer mortality significantly increases in individuals over the age of 50, primarily due to the chronic accumulation of genetic damage. Her research underscores the complexity of tumor environments, and she famously stated, "no tumor is an island," emphasizing the intricate interactions between various cell types.

Dr. Weeraratna's analysis of the aging microenvironment revealed differences in fibroblast cells from individuals under 35 versus those over 50. Her study found that tumor metastasis is more efficient in aged mice, particularly noting that lung fibroblasts in older environments have faster proliferation of myeloma cells. Proteomics demonstrated that the secretomes of aged lung fibroblasts activate canonical Wnt signaling, enhancing cell proliferation. Additionally, sFRP2 was identified as a factor that causes high invasiveness but slow growth in tumors. Aged fibroblasts also secrete cytokines that adversely impact immune function.

In the next part of her talk, Dr. Weeraratna explored the role of exosomes in the aging myeloma microenvironment. Although there was no difference in the number and size of exosomes between young and aged fibroblast myeloma cells, a decrease in CD9 expression was observed in aged fibroblasts and their exosomes. A significant discovery was that during aging, sFRP2 levels increase while VEGF levels decrease. Interestingly, sFRP2 promotes angiogenesis during aging and inhibits the efficacy of anti-VEGF antibodies in vivo. This finding supports a mechanism to explain why younger patients respond better to Avastin compared to older patients. Moreover, extracellular matrix changes during aging may increase blood vessel permeability.

Dr. Weeraratna also discussed pancreatic cancer, noting that pancreatic ductal adenocarcinoma (PDAC) grows faster and metastasizes more extensively in aged mice. She highlighted that fibroblasts drive PDAC progression, identifying the molecule, GDF-15, as being significantly increased in aged fibroblasts.

Concluding her talk, Dr. Weeraratna summarized the following key points about pancreatic cancer and the aging microenvironment: i) Non-cancer associated pancreatic fibroblasts from aged pancreases in humans and animal models secrete factors that enhance cancer cell growth, migration, and invasion compared to those from younger individuals. ii) One identified aging-induced factor, GDF-15, is highly secreted by aged pancreatic fibroblasts but not by younger ones. iii) GDF-15 from the aged environment increases the tumorigenic properties of PDAC cells. iv) Targeting GDF-15 specifically inhibits tumor growth in aged mice, indicating its potential as a therapeutic target. Dr. Weeraratna’s leadership and groundbreaking work in understanding age-related changes in tumors are highly commendable and impactful to progressing cancer research.

Survivorship speaker: A Magazine Article Inspires a Dedication to Asking, "What About Kids?"

By: Kenneth Canubas

On any normal day, like any average person, Naomi Bartley can be found working at her job, attending to her daughter and family, or investing time in her various passions. She currently works as the Clinical Information Science Director at AstraZeneca in the Cardiovascular, Renal, and Metabolism (CVRM) therapy area. In this role, she has used her expertise to establish a pediatric center of excellence – a cross-functional group whose sole focus is optimizing the pediatric drug development process. Unlike most people, however, Naomi pours a considerable amount of time into projects she is passionate about, not conventional hobbies like art, painting, or a side job, but advocating for children with cancer and assisting cancer patients as they navigate through life with the disease. She attributes her life mission and impact to her personal experience with cancer and to the small acts of kindness she received from others. She compares it to a "simple ripple of water that has had far-reaching effects."

As a young girl, Naomi enjoyed many things. She loved going on bike rides and playing soccer and the violin. She was deeply devoted to her family and made it a priority to appreciate life's simple joys. At around six years of age, Naomi started experiencing joint and bone pain, fatigue, and a loss of appetite. At the time, physicians attributed her symptoms to influenza, a bad cold, growing pains, or some type of treatable bone infection. Like most children, she ignored the symptoms. Still, she continued to gradually develop additional symptoms, such as difficulty breathing, early satiety, pain with running, and significant weight loss. It wasn't until one day when she collapsed in gym class that her doctors and family knew something was wrong. She was transported to a hospital in London, Ontario (Canada) and was diagnosed with bone cancer. Initially, hospital physicians could not make a definitive diagnosis as her bone marrow was too fibrous and infiltrated with cancer. After sending a sample of her bone marrow to St. Jude's hospital in Memphis, Tennessee, she was diagnosed with acute myeloid leukemia (AML), a rare and very aggressive cancer with poor prognosis. At the time, this diagnosis seemed like a death sentence as bone marrow transplantation was highly experimental. Even following treatment, the chance of survival was approximately 5%. Unfortunately, due to these factors, palliative care seemed like the only realistic option for her.

Shortly after this dreadful diagnosis, her family experienced a miracle. A good Samaritan, perhaps even a stranger, left a *Reader's Digest* magazine on the porch of their home. Within the pages was a story of a young Canadian woman who had undergone successful bone marrow transplantation to treat AML. The patient's brother was the donor and, coincidentally, the patient's name was Naomi. Naomi's mother likens that experience to a pebble dropped into water which had a vast, wide-ranging effect, propagating hope and determination for her family. Inspired by the magazine article, her family decided to pursue bone marrow transplantation, despite the suboptimal odds. To their surprise, after further testing, her older brother Nathan was a perfect match and became her donor.

Prior to her transplant, Naomi was started on high-dose cyclophosphamide and anthracycline, two chemotherapeutic agents, alongside three days of total body radiation. She was placed in isolation in a room with limited and protected visitation. Word of the procedure reverberated through Canada and gained interest from newspapers and the Canadian Broadcasting Corporation. There were articles and documentaries about this act of faith, marveling at the prospects for new treatments and therapeutic approaches to bone cancer. For the procedure, pieces of Nathan's hip were excised and prepared for implantation. During the preparation process, a meat grinder and garlic press were used to grind and maximize the amount of marrow extracted from Nathan's bone, a testament to medical ingenuity. Shortly after collecting her brother's bone marrow, physicians transfused the harvested cells into Naomi, hoping this intervention would work. Amidst all the medical and media excitement, young Naomi lay in her hospital bed, alone, severely immunocompromised and defenseless against any infection. After several weeks of being closely monitored, Naomi began to improve; her biomarkers recovered, and blood counts began to normalize. The transplantation was deemed a success and a step in the right direction, not only for Naomi but also for many other children diagnosed with a similar disease with low prospects for survival.

After these extraordinary efforts by Naomi and her medical team, Naomi returned home and quickly grew despite her sickness. In many ways, she was a changed person. Where once she had long, straight, blonde hair she quickly grew curly black hair. She explored new hobbies and regained her appetite. On the other hand, she was burdened with physical and emotional turmoil and experienced new and debilitating side effects. These side effects were not unique to her, but a shared struggle by other children living with cancer. Several years later, Naomi's symptoms improved, and she went to university. She became increasingly frustrated by the lack of consistent follow-up care after "graduating" from her childhood hospital oncology program. As a result, she took the initiative and contacted the same media personnel who documented her bone marrow transplantation. Together they collaborated on a follow-up piece that illuminated the hidden costs and difficulties of surviving childhood cancer. Survivors are often "on their own to deal with the effects of [cancer] treatments." Shortly after, she finally coped with her experiences and grasped what would become her life's work – she became an advocate for those dealing with the obvious and veiled consequences of cancer.

Unfortunately, Naomi's troubles did not stop there. While studying at university, during her first physical exam in a cancer follow-up clinic, she was told that she had a small lump in her neck. After testing, she was diagnosed with papillary thyroid carcinoma, a secondary cancer caused by the total body radiation she had received in her childhood. To combat her condition, she was given high-dose radioactive iodine treatment, a necessary intervention, but not without costs or side effects.

After her thyroid cancer treatments, Naomi immigrated to the United States for work. She was still receiving low-dose full-body radioactive iodine annually and was required to have a series of tests completed before each scan. In 2008, Naomi surprisingly learned that she was 12 weeks pregnant. She experienced many complex emotions, especially given her medical history. Nonetheless, various obstetrics and gynecology medical teams worked tirelessly to prevent further complications. Sadly, treatment for Naomi's cancers circled back to haunt her as her

daughter, Hope, was born prematurely after only 24 weeks of gestation. Hope struggled in the neonatal intensive care unit for 111 days, which Naomi believes was a tragic side effect of her past cancer treatments. Fortunately, though, both Naomi and Hope were discharged and able to return home.

During her seemingly never-ending follow ups, Naomi regularly found herself dragging along a huge binder of her past medical history, composed of all the tests, treatments, diagnoses, and results. Over time, she became frustrated with the limited abilities and current state of electronic medical technology. Although there were patient portals and electronic records, their function was incomprehensive and non-transferable between hospitals and institutions. Calling upon her innovative spirit, she decided to apply her work experience in research and life experience as a cancer survivor to create an application for smart phones called iCANcer for cancer patients and their families. To this day, it is a “one-stop shop” for tracking medical history, cancer treatments, lab results, appointments, questions for providers, and other vital medical information.

Based on her technological innovations, Naomi was recently appointed Patient Advocate for the Childhood Cancer Data Initiative. This initiative is a collaborative effort focused on advancing research and improving outcomes for children and adults diagnosed with cancer. It also seeks to enhance the availability of resources by linking information from multiple sources, adding another ripple of optimism for those affected by cancer.

The beginning of Naomi Bartley’s life was fraught with hardship and uncertainty. As a child she fell victim to cancer, one of the most unfortunate and taxing circumstances anyone can face. However, due to a few unrelated inspirational moments, events that she refers to as “pebbles dropped in the water,” she was able to combat both of her cancer diagnoses and fuel beneficial systemic changes. She urges others to remember the power of synergy, advising all to never lose sight of the impact patient input can have. She reminds others that even small actions may have a dramatic impact, a ripple effect, that may extend far beyond our initial intentions. Naomi Bartley finds solace in passionately supporting cancer patients and continually asking, “What about kids?”

We thank Naomi Bartley for sharing her amazing story and for doing her part to inject real solutions and hope into the medical field. We wish Naomi the best of luck as she continues acting on her passions and mission to advocate for cancer patients.

Panel: Navigating Career Transitions into Science Writing, Policy, and More

By: Giana Vitale

Many fellows are familiar with "traditional" science careers working as research scientists either in academia or industry. However, there are many other fascinating "nontraditional" career paths, such as those in science writing, policy, law, and management. This year, the CCR-FYI Colloquium hosted a career panel titled, "Navigating Career Transitions into Science Writing, Policy, and More," to educate fellows about these options.

The panelists included Dr. Luz Cumba, an AAAS Science and Technology Fellow and Advisor to the Office of Mexican Affairs within the Department of State; Dr. Paz Vellanki, a medical oncologist specializing in thoracic, head, and neck cancer at the FDA; Dr. Vijay Walia, the senior director of the Companion Diagnostics program at Quest Diagnostics; and Dr. Claudia Frehe, a senior patent agent at Cooley LLP and a law student at UNH Franklin Pierce School of Law.

Panelist Profiles:

Dr. Paz Vellanki: As a medical oncologist, Dr. Vellanki's primary responsibility is to work with a team of multidisciplinary scientists to examine data from clinical trials of candidate cancer drugs and determine which drugs are safe for FDA approval for use in patients. She and her team also engage with pharmaceutical companies before and during the clinical trial to ensure their trial designs fulfill legal criteria and deliver significant results. She also travels to conferences and presents her team's findings on trends in the drug development field. Finally, she works hands-on with a cohort of clinical trial patients once a week to maintain her bedside practice. Before becoming a medical oncologist, Dr. Vellanki wanted to be a principal investigator and work in academia. During her residency, she was exposed to other opportunities, like the FDA. To her, the most interesting part of the job is identifying and understanding the drug development landscape before anyone else in the pharmaceutical industry.

Dr. Luz Cumba: Dr. Cumba's work as a policy advisor is centered around communication. Her days are filled with meetings with politicians, scientists, diplomats, and health officials to coordinate regulatory standards between the US and Mexico. She also works as a science activist and communicator, a role in which she focuses on making relevant scientific knowledge accessible to the Latin American public by teaching scientists and law makers how to better communicate with each other. Dr. Cumba has always been passionate about presenting and sharing science with the world and focused on preparing to enter the diplomacy world

throughout her PhD. One of the most exciting projects she has worked on was coordinating a meeting between nine Latin American regulatory bodies to discuss and harmonize their policies for the benefit of patients.

Dr. Claudia Frehe: As a senior patent agent, Dr. Frehe is responsible for securing patents for her clients. This includes regularly discussing their needs and the details of their inventions. Much of her work involves writing patent applications. She also interfaces with the US patent office, receiving feedback on her patent applications and submitting revisions until they are approved. She began her pursuit of patent law after attending a career panel like the one that she was now presenting at while a postdoctoral fellow. She originally joined a law firm as a technical advisor, the most entry-level position in patent law. After gaining experience and studying for a year or two, she passed the "patent bar," a difficult exam designed to test one's knowledge of patent law and its application. Passing the patent bar elevated Dr. Frehe to the position of patent agent, thus allowing her to file patents, prosecute them before the patent office, and act as a client's agent. Because she is not yet a patent attorney, Dr. Frehe cannot give legal advice independently. However, she is currently attending law school, sponsored by her firm, to remedy this. She thinks the most interesting part of working in patent law is the privileged knowledge she has of new and exciting inventions, and the diversity of scientific fields she is exposed to through her work.

Dr. Vijay Walia: At Quest Diagnostics, Dr. Walia serves as the senior manager of a collection of teams that collectively work to develop diagnostic tools for specific drugs intended for use in clinical trials. As a manager, Dr. Walia's days revolve around meetings and presentations. He coordinates R&D, manufacturing, quality, project management and regulatory teams, interacts with the FDA during device submissions, and communicates with clients. He also reviews the results of each team and decides what their next steps should be. As a postdoctoral fellow, Dr. Walia was uncertain about what kind of career he wanted to pursue. He originally planned to enter academia, but after his grant applications were not funded, he pivoted to industry. He was not initially successful, but after some effort joined the FDA commissioner program. After leaving the commissioner's program, Dr. Walia briefly worked in industry as a product manager before returning to the FDA as a scientific reviewer. His final transition involved attending Harvard's MBA program before joining Quest Diagnostics. Although circuitous, Dr. Walia is grateful for each phase of his career. One of the most exciting projects he has worked on was with the FDA, where he was a part of the Emergency Use Authorization team during the peak of the COVID crisis. Although hours were long, he reveled in seeing scientific boundaries pushed so quickly for the benefit of patients.

How Fellows Can Prepare for These Jobs:

Fellows interested in pursuing any of these professions are strongly encouraged to gain practical experiences in their field of choice. Networking is also key to securing jobs in these areas. Additionally, fellows should conduct informational interviews with people working in their field of interest.

Those who are specifically interested in the FDA should consider the ORISE fellowship, a program like a postdoctoral fellowship within an FDA lab; the ASCO program, a one-day

workshop that introduces trainees to the FDA regulatory process; and the AACR fellowship, a program that provides research training for postdocs and clinical fellows in collaboration with companies in industry.

Fellows aspiring to join scientific diplomacy should explore fellowships provided by the National Science Policy Network, attend science policy conferences, take courses in science policy (such as those offered by FAES), and participate in leadership training workshops.

To gain experience in patent law, fellows should apply to work in a technology transfer office, such as the one at NIH, to learn more about intellectual property and its licensing processes. They can also consider applying to become technical advisor at a law firm, an entry level position with significant mentorship.

Finally, those interested in industry and managerial jobs should pursue internships and co-ops with companies they are interested in.

There are many interesting and fulfilling career opportunities outside the traditional research scientist roles that most fellows are familiar with. By learning more about the paths taken by our panelists, fellows can better understand how they, too, can pursue these careers.

Workshop: Grant Writing Decoded

By: Monika Chandravanshi

The 24th annual CCR-FYI Colloquium featured exciting and informative seminars that provided attendees with valuable information for their training and career planning at NCI. One of the most notable presentations, titled, "Grant Writing Decoded,", was delivered by Dr. David Armstrong, founder and president of Grant Writing Mentors, LLC.

Dr. Armstrong is also co-director of a graduate course in Grant Writing and adjunct professor at the Uniformed Services University of the Health Sciences. Previously, he was the principal investigator on multiple grants from both the National Institutes of Health (NIH) and private foundations to study neuronal vulnerability in Alzheimer's disease and stroke. Within the research space, he has also published more than 100 peer-reviewed articles, served on numerous NIH review panels, and maintained positions on the editorial boards of many journals.

In 2001, Dr. Armstrong joined the Center for Scientific Review as Chief of Brain Disorders and Clinical Neurosciences. In 2005, he accepted the position of Chief of the Scientific Review Branch, National Institutes of Mental Health (NIMH). As a result of his dedication to the NIH and public service, Dr. Armstrong received various NIMH and NIH Director's Awards.

In his talk, Dr. Armstrong outlined the essential steps for successful Grant Writing. Specifically, his secrets to securing funding are:

1) **Understanding the NIH:** The NIH is comprised of 24 divisions, institutes and centers (IC). Ensure to choose the NIH IC that aligns with your research interests and specific focus. For information, visit the IC's web page to understand its overall scientific mission and research areas. Investigate research areas with collaborations across ICs to allow for options.

2) **Researching Your Ideas**: Ensure your research aligns with funding priorities, addresses novel problems, is supported by prior research, and is contextualized through platforms like PubMed, BioRxiv, Scopus, and Web of Science.

    a) Prior to grant writing and application submission, prepare research questions and strategies, and analyze your career gaps.

    b) Understand Peer Review: Collaboration is key in research; work with others to convey your ideas effectively.

3) **Utilizing NIH Resources:** Use NIH RePORTer (https://reporter.nih.gov/) and Matchmaker (https://reporter.nih.gov/matchmaker) to identify similar projects, potential competitors, collaborators, program officers, and other NIH contacts.

4) **Understanding NOFOs:** Familiarize yourself with Notice of Funding Opportunities (NOFOs), as they will provide an overview of the areas in which a funder seeks to know what funders are looking for. Get to know the major NIH grant programs: R (Research), P (Program Project), K (Career Development), F (Individual Fellowship), and T (Institutional Training).

5) **Pre-Application Planning**: Read the NIH Guide for Grants and Contracts, as well as the SF424 (Application Guide**)**. Both provide thorough instructions for all parts of the process. A common reason for grant rejection is not following these instructions meticulously. Note that requirements may vary between ICs; ensure to adhere to specific guidelines accordingly.

6) **Understand Peer Review**: Know the peer review process to tailor your application effectively. Note that this differs between different ICs and different grant programs.

Overall, Dr. Armstrong provided attendees with a more comprehensive understanding of the grant writing process. Study aims, methodology, and potential impact should be clear and concise, tailored to the funding organization's priorities.

Panel: Cultivating Inclusion: A Roadmap for Scientists in Training

By: Katie E. Hebron

This interactive panel session featured Dr. Giovanna Guerrero-Medina, Director of Diversity, Inclusion, and Equity (DEI) at the Yale School of Medicine and Executive Director of Ciencia Puerto Rico; Dr. Tiffany Wallace, a Program Director in the NCI Center to Reduce Cancer Health Disparities (CRCHD); and Dr. Danny Dickerson, a retired United States Air Force member and current Director of the Division of Inclusion and Diversity at the NIH. Dr. Ashley Bear, the Director of the National Academies of Science, Engineering, and Medicine Committee on Women in Science, and Dr. Robert Winn, the Massey Comprehensive Cancer Center Director at Virginia Commonwealth University (VCU) and President of the American Association of Cancer Institutes, joined virtually. The questions and responses are summarized below. Dr. Doug Lowy, principal deputy director of the NCI, kicked off the discussion with an insightful question:

Q1: Given that health disparities (HD) are even greater when considering low and middle-income countries (LMIC), how do we ensure that inclusion efforts within the United States also impact the global community?

Dr. Wallace agreed that this is a great concern in HD research and highlighted initiatives of the NCI, such as the Center for Global Health, that seek to bridge lessons learned about HD in the United States and international efforts. Dr. Guerrero-Medina also emphasized the value of international scientists who come to the US for training, stating that their influence aids the translation of US discoveries to the global community. As an AAAS Multidisciplinary Working Group member, she actively influences workforce development policies and guidelines to address issues that are specific to international scientists, such as visa issues and funding opportunities. Dr. Lowy had a follow-up question:

Q2: Is the rising anti-immigrant mentality further impeding diversifying the scientific workforce? Are there efforts specifically targeting this population?

With his direct role in workforce development, Dr. Dickerson observed that access clearance and credentialling at the NIH can be difficult for international scientists. He reassured the audience that despite the cumbersome process, the innovations brought by international scientists are immeasurable. Dr. Winn reiterated Dr. Guerro-Medina's statement that international HD and workforce development issues are closely linked. By exchanging ideas, we can provide valuable information to LMICs, *and* we can learn from them, especially regarding implementation and community connection. In his experience, many national and international communities feel disconnected from and unseen by science. He encouraged scientists to look to these communities when considering how we can bring diverse and international perspectives and experiences to tackle our biggest scientific questions.

Q3: As trainees, how can we support foreign-born colleagues who are struggling to continue in science due to discrimination or funding opportunities?

Dr. Guerrero-Medina emphasized that showing genuine interest in colleagues' unique backgrounds makes them feel welcome and safe. Trainees should model this behavior and encourage supervisors and mentors to participate. Dr. Dickerson acknowledged that making a difference as a trainee with limited decision-making power is challenging but encouraged trainees to embody the values of their Diversity Statement throughout their day and carry this commitment into their future careers. Dr. Wallace advised trainees to prioritize inclusion in all interactions and to speak out against hurtful language or discriminatory acts. Drs. Wallace and Dickerson agreed that practicing these habits takes courage. Dr. Bear suggested that trainees inquire with institutional leadership about implementing best practices for hiring, retention, and promotion, as well as collecting data to ensure the effectiveness of these policies outlined by institutions like the National Academies.

With a prompting comment from Dr. Lowy, the panel then discussed how novel, and costly, screening technologies may *increase* HD by limiting access. Dr. Winn highlighted the AACR Cancer Disparities Progress Report 2024, which discusses this issue. Saying, “High tech without high touch will reach some people but not everyone,” he emphasized that collaboration across communities and disciplines (basic scientists, technology developers, clinicians, behavioral scientists, and community members) will ensure that new discoveries reach the intended targets. Dr. Guerrero-Medina highlighted that, at its core, this is another DEI issue because the implementation of technology and advances can vary drastically by community and country. Considering the perspectives of scientists within each community and culture will enhance the international translatability of scientific and treatment advances.

Q4: How can basic scientists incorporate HD work into their science, accurately and as seen in real communities? beyond a superficial line in the introduction mentioning a disparately affected population?

Dr. Wallace began the discussion by saying that the NCI recognizes that HD research is not done in a silo, and basic studies should be designed through an “HD lens,” ensuring that diverse and representative samples are used, demographics are accounted for, and their conclusions are equitable, rather than considering HD as an afterthought. She indicated that all applications will soon be required to address these issues directly. Dr. Winn explained that the VCU Masey Cancer Center has implemented a “people to pipette” model that connects behavioral scientists with basic scientists to help framework effective data collection from the community, which is then used to refine the questions and approach of basic studies.

Q5: How do you build trust with communities that may have been done wrong by science/investigators in the past?

Dr. Wallace acknowledged this as a fundamental question because community engagement that is not thoughtful or well done is more damaging than not doing it at all. She noted that the CRCHD requires the engagement of scientists with community members for their funding applications, such as community advisor boards and through the recruitment of collaborators with experience in community engagement. She emphasized that such engagement is essential for building trust with the community. Dr. Guerrero-Medina stressed the importance of considering the community as a partner and recognizing the value of their knowledge. She cited

the established best practices in community engagement, such as fair compensation, sharing results with the community, and involving the community in decision-making. Dr. Dickerson emphasized that communities are diverse and that it is essential to understand these differences through ongoing engagement, rather than just seeking their participation. Dr. Winn concluded the discussion by highlighting the potential for researchers to enhance institutional trust by genuinely engaging with the community.

Q6: How can you encourage trainees who are hesitant to pursue HD research because they are not members of the community they are interested in studying?

According to Dr. Guerrero-Medina, being humble and recognizing your positionality within the topic or issue, how others perceive you, and how that may create challenges is important. She said it is essential for investigators to learn the nuances and context of the experience of the community you wish to study, even for investigators who are part of the community, as each experience is individual. Dr. Wallace noted that it is essential to avoid placing the burden of HD research on underrepresented investigators. As with any other research, the drive for HD should be your passion for the subject. All identities can do HD research as long it is done well and thoughtfully.

Q7: How do we combat social media and public pushback against DEI policy?

Dr. Dickerson shared that enthusiasm for DEI policy has ebbed and flowed throughout his career, yet progress continues. Although words and acronyms may be vilified, if the principles of DEI still guide workforce development, the name becomes irrelevant. Dr. Winn suggested that scientists and clinicians may be our own worst enemies in this regard. Using phrases such as “dumbing down the science” to describe communicating in an understandable manner is both harmful and inaccurate. Currently, the messages from scientists are competing against media and social media voices for the public’s attention. Investigators must convey their message, whether about science or DEI principles, in a way that is accessible and engaging.

Q8: What are initiatives for practicing connecting to and engaging the community to communicate your science?

Noting that the initiatives differ by the target population, Dr. Guerrero-Medina referenced the Letters to a Pre-Scientist program, which connects STEM professionals with students to broaden their understanding of STEM careers. She also suggested connecting with local news outlets for opportunities to contribute articles. Dr. Bear also emphasized the importance of connecting your work to broader issues.

Communication was a driving theme throughout the panel. Whether it’s engaging with the community to gain trust and establish a great working relationship, reaching across disciplines to find collaborators to move your work forward, or relaying the importance of DEI initiatives to the public, effective communication is critical. Therefore, for those interested in cultivating inclusion, practicing written and oral communication skills early and often is not just a suggestion, but a powerful tool on the journey to promoting equity in science.

Closing Address

By: Anna Newen

"*The way I think about the freedom of the intramural program is that it has enabled me to do research for which I was not qualified.*"

To bring us full circle, Dr. Douglas R. Lowy, Deputy Director of the National Cancer Institute (NCI) and former Acting NCI Director, closed out this year's Colloquium with his inspiring talk, "Embracing Challenges and Changes Through a Professional Career" and awarding our outstanding conference presenters with travel awards.

Research is his passion

"*It is the most exciting time for me, all the time, when I'm in the lab.*"

For Dr. Lowy, research is a team effort, allowing us to examine what others have observed and discover what no one else has seen. While research is continually challenging, the ability to pose questions, test hypotheses, find answers, and constantly learn makes it incredibly rewarding. Ultimately, benefiting our community is what makes it all worthwhile.

Like many great careers, Dr. Lowy's journey has been anything but linear. He began as an art history major during his undergraduate studies before transitioning to clinical training, earning an M.D. in internal medicine and dermatology. He recounted an early, memorable experience from medical school: brimming with enthusiasm, he arrived at his first-choice lab with a project proposal in hand, only to be rejected by the head of the lab within ten minutes.

It was instead his microbiology teacher, Dr. Jan Vilcek, who took him into his lab. Although this first research experience "accomplished very little", Dr. Vilcek's encouragement and belief in Dr. Lowy's potential led him to try for a second and more successful experience at NIAID.

"*Having a mentor who believed in me was absolutely critical...*"

The Human Papillomavirus (HPV) Vaccine

"*Doug's five stages of scientific discovery (when it works!): Inspiration. Perspiration. Frustration. Elation. Repeat.*"

Dr. Lowy presented us with a stark reality: the significant racial and global disparities in cervical cancer incidence and mortality rates. Addressing this vast issue required a collaborative effort, which he embarked on through a long-term research partnership with Dr. John T. Schiller.

Starting out, neither had experience in translational research, vaccines, immunology, or HPV structural proteins and virus structure. What they did have was fifteen years of basic cancer research, experience in papillomavirus biology, and the freedom of the NCI intramural research program. Above all, they had the persistence to work through endless challenges and rejection, both of which are "inherent in what we do."

The HPV vaccine has made remarkable progress in preventing cervical cancer and achieving herd immunity. Yet, Drs. Schiller and Lowy persist in their efforts to enhance the vaccine and

expand its global reach. Dr. Lowy also offered his insights on health disparities research from the vantage point of a basic scientist. He underscored the value of community engagement with underrepresented populations but emphasized that basic scientists can make an equally significant impact in mitigating disparities through their laboratory work.

Where do your current ambitions lie?

"*Ars longa, vita brevis.*

Developing expertise takes time, life is short."

Dr. Lowy turned this question back to us. Do our ambitions seek to serve ourselves, our patients, our family? To retire early or have a work-life balance? To be as successful as possible? Something else? He took a moment to highlight the importance of family – that although he worked tirelessly at NCI, he was simultaneously focused on his kids as a single parent for several years. Ultimately, he advises to make some sort of commitment, do the thing that scares you, and know that it is fine if the path changes over time.

For him, taking on leadership was his fear. As an introvert working in a position designed for extroverts, Dr. Lowy has found that having a policy position enables him to have an impact beyond his own research and dynamically interact with many people.

As we came to an end, Dr. Lowy concluded with guiding principles that shape his life and leadership:

- Focus on today and the future, learning from the past.
- Be optimistic and proactive.
- Prioritize feasible solutions over dwelling on problems.
- Set a few ambitious goals.
- Lead by example, not intimidation.
- Value people over structures.
- Always listen to others.
- Dedicate time for thoughtful reflection.
- Don't hesitate to seek help.
- Ensure everyone feels respected and valued.

2024 CCR-FYI Colloquium Award Winners

- Outstanding Postdoctoral Fellow – Dan Li, PhD., Laboratory of Molecular Biology
- Outstanding Postgraduate Fellow – Maxine Rubin, Laboratory of Cell and Developmental Biology
- Outstanding Oral Presentation:
    - Domenico D'Atri, PhD., Laboratory of Molecular Biology
    - McKenna Crawford, Chemical Biology Laboratory
    - Helena Muley Vilamu, PhD., Neuro-Oncology Branch
    - Natalia Yakobian, Pediatric Oncology Branch
- Outstanding Poster Presentation:
    - Ian Bettencourt, PhD., Cancer Innovation Laboratory
    - Briana Branch, Laboratory of Cell and Molecular Biology
    - Theressa Ewa, Laboratory of Human Carcinogenesis
    - Manjari Kundu Sil, PhD., Women's Malignancies Branch

Activities of Interest for Fellows

Join the Fellows and Young Investigators Steering Committee!

FYI

Are you interested in networking with other fellows, exploring careers in science, gaining marketable skills, or giving back to the community?

Who can participate?
We welcome postdocs, postbacs, graduate students, research fellows, clinical fellows, technicians, and staff scientists.

Meetings
The last Thursday of every month at 4:00PM via MS Teams.

Check out our website!

Open leadership positions!

- Outreach Chair
- FYI-Seminar Series Chair (Frederick)
- Frederick Social Chair
- Seminar Series & Career Development Chair
- E-Communications Chair

Supported by the CCT Office of Training and Education and the CCR Office of the Director

NIH NATIONAL CANCER INSTITUTE

Sallie Rosen Kaplan Postdoctoral Fellowship for Women Scientists in Cancer Research (SRK Program)

What happens during the transition from trainee to Independence? How do we better retain and advance the careers of women in science? How can we better face the competitive nature of the job market?

SRK Program Provides

• Leadership skills • Confidence building• Additional mentorship • Networking Opportunities • Peer-to-peer connections

SRK Program Elements

• 30-week professional coaching with customized program • Monthly meeting with second mentor selected from senior women in government, academia, or industry • Additional workshops by NCI Office of Workforce and Professional Development • Additional coaching on presentation and communication skills • Career development panel discussion • Grantsmanship seminar

For more information:

https://www.cancer.gov/grants-training/training/at-nci/srk

NIH NATIONAL CANCER INSTITUTE Center for Cancer Training

Frederick Diversity Committee FDC

Frederick Diversity Committee

Promoting Diversity

FDC Mission and Goals:

Celebrate diversity and inclusion on the Frederick campus

Promote productivity, work-life balance and career satisfaction

Meetings:

every 3rd Friday of the month at 1pm

Benefits:

Personal and Professional Development

Career Exploration and Enrichment

Networking

Mentorship

More information can be found at https://ncifrederick.cancer.gov/Diversity

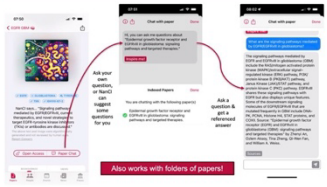
NanCI by NCI – Connecting Scientists

NanCI is an AI-powered app that connects you to interesting science and scientists to build your career.

Scientific literature in your pocket

- NanCI keeps an eye on the literature, finds new papers and alerts you to new related publications.
- NanCI presents papers with an image, keywords, a one-sentence summary and easy access to the full paper (if available).
- Find and follow authors, and if they are on NanCI, connect with them.

Chat with Papers



- Interact with open-source papers or a folder of papers via an AI-driven chat: ask questions and see referenced answers based on the content of the paper(s).
- Select text in a paper and ask NanCI to explain it at different expertise levels (from five-year-old, to college student to expert)

Watch a brief video to see NanCI in action!
https://vimeo.com/873470307/80a486ace1

On NanCI's Roadmap

- Social - users interact on the app and easily form groups around shared interests, including closed groups with a private folders
- Expanded view of the world of science with other data sources, like grants
- Jobs: connecting job opportunities to the literature – imagine that when you see a paper you would also see the authors' lab have a postdoc position open.

Download today!

Currently for iPhone/iOS. Android version will launch soon.
https://www.cancer.gov/grants-training/training/nanci-app

NanCI