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CARD Stacks the Deck Against Alzheimer's

NIH's Center for Alzheimer's and Related Dementias explores genetics, biomarkers, and more.

BY PAIGE JARREAU, NIA

Nearly ten million times a year—every three seconds worldwide—a new case of dementia is diagnosed. Often it is Alzheimer's disease (AD), the most common form of dementia. In AD, proteins build up abnormally or aggregate to form amyloid plaques and tau tangles, which seem to lead to the hallmark symptoms of impaired memory and thinking abilities.

Although dementia is synonymous with AD for many, this family of neurological degenerative diseases also includes Lewy body dementia (LBD), frontotemporal dementia (FTD) with or without associated amyotrophic lateral sclerosis (ALS), and vascular dementia. LBD is associated with abnormal deposits of alpha-synuclein that are also involved in Parkinson's disease (PD). FTD is strongly linked to ALS. Growing evidence suggests all of these diseases share some biological pathways and genetic risk factors. While the exact mechanisms of their onset and progression remain unknown, we are getting closer to a profound understanding.

Nested within the NIH's intramural research program is the NIA–NINDS Center for Alzheimer's and Related Dementias (CARD), where researchers are working to identify the underpinnings of these diseases and approaches to early intervention and treatment. CARD Director

CONTINUED ON PAGE 8

30 Years On, Undergraduate Scholarship Program Sows Scientific Excellence

Early Investment Nets Top Talent

BY MICHAEL TABASKO, *THE NIH CATALYST*

NIH has been investing in future scientists for 30 years through the Undergraduate Scholarship Program, which has yielded a multitude of biomedical breakthroughs at the NIH and beyond. Pictured, left to right, are former scholarship recipients Afua Asante-Otoo, Freddy Escorcia, Andrea Apolo, Sadhana Jackson, Yvette Pittman, and Luis Estrada.

Good financial advice says that investing early secures a fruitful financial future. The same could be said for bolstering the careers of aspiring young scientists.

The Undergraduate Scholarship Program (UGSP), authorized by Congress in 1994 to grant financial aid to undergraduate students from disadvantaged backgrounds committed to careers in biomedical, behavioral, and social science research, has yielded a multitude of biomedical breakthroughs at the NIH and beyond.

Consider technologies that improve brain tumor treatments, clinical trials that bring novel drugs to market, or tumor-seeking radioactive particles. These are but a few examples that have evolved from the work of UGSP "graduates." Each year, about 13 outstanding students are accepted to the program and receive up to $20,000 for undergraduate expenses.

CONTINUED ON PAGE 12

CONTENTS

Six Myths About Being a Mentor and a Mentee

BY NINA F. SCHOR, DDIR

Somehow, there are more myths about being a mentor or a mentee than about almost anything else in biomedical research. Perhaps this is because it is so hard to define either role in concrete terms. Some would say we all know a mentor when we see one. But it is likely the case that what we think we know as a mentor is different for each of us and may change over the course of each of our careers.

This issue of the *NIH Catalyst* features several articles that highlight our dedication to training the next generation of biomedical scientists and clinicians. Mastering mentoring and being mentored are among the most important developmental milestones in a trainee's NIH experience and career. In keeping with this theme, I will attempt to dispel some of the more commonly held myths about mentoring and being mentored.

Myth #1: The mentor–mentee relationship is unidirectional.

There is a commonly held belief that, while being a mentor is hard work, being a mentee is passive, like being a sponge and soaking up everything your mentor dishes out. Nothing could be further from the truth!

The mentee must take an active role in engaging the mentor, deciding on the periodicity, format, and agenda of formal meetings, and providing the mentor with updated information and feedback. As most mentees have several mentors for different aspects of their careers and academic activities, the mentee must collate and filter the collective advice and support obtained from his or her mentors. In addition, as careers and people evolve, the mentee must ask, over the long term, whether the current mentors are indeed the right mentors for the direction in which he or she is headed.

Literature on this subject lists characteristics that contribute to excellence in a mentee. They include being an active listener and learner; knowing how to mine the mentor's font of wisdom; mirroring the mentor and taking the path he or she models; demonstrating respect, focus, empathy, and attentiveness; being worthy of the mentor's trust; inspiring and motivating the mentor; cooperating with the mentor to solve problems; adapting ideas espoused by the mentor; and ensuring that the relationship with the mentor grows and evolves. This list is most interesting and informative in that it illustrates the notion that the mentee is sometimes following—mirroring, being attentive, listening, learning—and sometimes leading—inspiring, motivating, adapting, ensuring growth and evolution—the mentor in this relationship.

Myth #2: Only those with whom you have a formal, declared relationship are your mentors.

Just as Athena disguised herself as Mentor to best advise Telemachus, your mentors can take many forms and are people who accompany you on your journey.

They teach you about consequences of actions by advising you or modeling behaviors, and they guide you in the things that are best learned through experience and relational storytelling. As such, although the tendency is currently to set up formal mentoring committees and to schedule regular mentoring committee meetings, your need to run something by someone you trust, or your mentors' coming across something that provides a teachable substrate or moment, or a request or blow that comes out of left field from someone you barely know, won't often come on schedule. And, sometimes, the formal mentors with whom you already have relationships may not be the right people to engage around these unanticipated events.

Mentoring does happen under formal circumstances, and making time to build a long-term relationship and earning trust often requires a backdrop of formally scheduled and orchestrated interactions. But mentoring also happens in the context of unanticipated need, opportunity, and setbacks. The best mentors are always looking for something to share and someone with whom to share it. The best mentees are always alert to circumstances, people, and moments from which to learn.

Myth #3: Mentors are the kind of people who walk on water, always.

Have you ever learned from someone else's mistakes? Have you ever felt just a bit better when someone said to you, "I know you are frightened to begin this new endeavor, but you could not possibly make a mistake I have not made already." What about the people whose interactions with others you witness and then think, "I will never treat another human being like that."

In a way, all of those people are mentors. They relate or model behavior (some good and some not so good) that informs your behavior and understanding. Being a really good mentee means learning from whomever and wherever you can learn.

Myth #4: You should have one and only one mentor at a time.

It is likely that you are a multifaceted person who takes on issues and questions and tasks that are messy enough that they have many facets, too. If this is the case, you may well need several mentors, each of whom is the right person to help you through some, but not all, of those aspects. You will also need a variety of mentors for your professional life by itself, and in its interface with your personal life. As an NIH trainee, you also are likely to be tasked with mentoring others. Therefore, there is no reason to restrict mentorship to one individual upon whom you depend for all of the guidance and support you need. No mentor worth his or her salt would be insulted that he or she is not alone in being your mentor.

Myth #5: Mentors are forever. Choose wisely, because once you do, you are stuck with one another for your whole professional life.

For many reasons, it is healthy and good that your mentors may change over time. First, as your interests, talents, skills, and your professional activities change, so, too, will your needs for mentoring and the degree of concordance between your professional life and those of your mentors. Natural evolution during a career mandates that the complement of advocates, advisors, and supporters changes over that time. Second, try though you and your mentors might to match your needs to their abilities, the personalities may just not mesh. You each are human, after all. There is no reason to maintain a relationship that is simply not working. Third, the world of science, medicine, and scholarly pursuit changes at a fantastic rate. The skills you need to acquire, and the methods available to serve your objectives, may be very different tomorrow than today. You may need to add mentors to your team so that you can keep current with what skills and knowledge you need to advance.

The decision to phase out or change the nature of a mentor–mentee relationship should be arrived at mutually. Do not be afraid to approach a mentor to raise the question in the interest of sustaining productivity, collegiality, scholarship, and career development.

Myth #6: You will always be the student, and they will always be the mentor.

The very best mentor–mentee relationships evolve over time so that it becomes hard to tell who is the mentor and who is the mentee. If you both do your jobs right, eventually, your mentor will learn as much from you as you from him or her. What starts out as a mentor–mentee relationship optimally becomes a relationship between professional colleagues in which the identity of each as mentor or mentee switches back and forth from interaction to interaction. Nothing makes a mentor prouder than seeing a mentee progress to the point of being an equal!

At NIH, we are proud of the scientific network we continue to build and strengthen as each trainee takes our shared discoveries out into the world and continues to build upon their mentor–mentee relationships. ●

Clinical Center Hosts Its First Graduation for Clinical Fellows

Inaugural Event Marks New Spirit of Unity Across 30 Training Programs

BY CHRISTOPHER WANJEK, *THE NIH CATALYST*

CREDIT: NIH CLINICAL CENTER

The Graduate Medical Education Class of 2024 was the first class to be celebrated in a formal graduation ceremony on June 14, hosted by the NIH Clinical Center.

Within the NIH's extensive postdoctoral training program portfolio is graduate medical education, a lesser-known jewel in the NIH training crown coordinated by the NIH Clinical Center (CC) that provides residencies and unique clinical fellowships to approximately 300 physicians, some of them fresh out of medical school.

And on June 14, the CC held its first graduation ceremony, which recognized more than 70 fellows who completed their various training programs.

Although the CC has coordinated training for decades, this inaugural event celebrates a deepening sense of unity among the 30 fellowship and residency programs that participated in this year's ceremony.

The graduation idea was conceived by **Joyce Chung**, executive director for graduate medical education (GME) in the CC Office of Clinical Research Training and Medical Education (OCRTME), and **Nitin Seam**, associate chief and director of fellowship of the CC's Critical Care Medicine Department, who chaired the GME graduation committee.

"One of my goals has been to forge more cross-program communication and larger-scale events…and break down silos across ICs," said Chung, who joined the OCRTME in 2022 after serving as NIMH deputy clinical director and program director for clinical fellowships since 2010.

Chung noted that **James Gilman**, chief executive officer of the CC, agreed that a graduation would further help build community among NIH medical fellows, particularly post pandemic.

The simple ceremony included opening remarks from Gilman, prerecorded remarks from NIH Director **Monica Bertagnolli**, and clinical fellows' graduation speeches by **Mian Khalid** and **Hanna Blaney**, both gastroenterology fellows at NIDDK. Cheers rang out, some more raucous than others, as each graduate walked across the stage of Masur Auditorium to receive their certificate.

The festivities continued with a lively reception on the FAES Terrace, at which more than 100 current and graduating fellows met together, mostly for the first time, along with their family and friends.

In the United States, before a medical school graduate enters medical practice, they are expected to participate in residency training to learn a specialty, such as pediatrics or internal medicine. Some medical school graduates may opt for an additional fellowship in a subspeciality such as cardiology or oncology.

As the world's largest hospital dedicated to clinical research protocols, the CC is a sponsoring institution to support this system. Through the OCRTME, the CC coordinates three residency programs and 20 fellowship programs, all accredited through the Accreditation Council for Graduate Medical Education. The CC also supports 30 nonaccredited training opportunities in niche fields, such as cancer immunotherapy or movement disorders.

> "You have chosen the most noble profession, one that brings tremendous good to the world."
>
> — Director Bertagnolli

The novelty of an NIH clinical fellowship, Chung said, is the proximity to NIH intramural labs. Most NIH clinical fellows train here with an eye on translational research or a career in academic medicine.

The three NIH clinical residency programs are pathology and psychiatry, which are four-year programs, and neurosurgery, a seven-year program. The clinical fellowship offerings run the gamut from pediatric and adolescent gynecology to critical care medicine to hospice and palliative medicine. ●

The graduation ceremony is available on VideoCast at https://videocast.nih.gov/watch=54897.

Building the Bridge

My Journey from NIH Postbaccalaureate Fellowship to Medical School

BY STEPHEN ANDREWS, NCI

Working full time in a lab each week while living on my own in a new city was a stark shift from the college-town environment with a comfortable routine of classes and social events that previously filled my days. I felt lost on the very first day of my NIH postbaccalaureate fellowship as I roamed Building 10 searching for the Clinical Center. Fortunately, I was met with plentiful friendly faces who helped me find my way.

The first stages of my research fellowship consisted of many repeated, and sometimes failed, experiments. I initially did not experience much of the "discovery" I was hoping for, and I felt somewhat disconnected from the scientific process, which was disheartening. We quickly learn that research entails troubleshooting and negative data, in addition to discovery.

I had to learn how to pivot and treat every set of data as a piece of the larger puzzle. Now, I liken this stage of my scientific training to training wheels on a bike. Slowly, after mistakes that cause you to fall, you eventually learn to balance on your own.

Mentorship and support were vital for me at this stage. I felt supported by colleagues in the lab, by other postbacs who became my friends, and by informal mentors both within and beyond the walls of the NIH. I learned to ask questions, get curious, and advocate for myself.

Many of the techniques that we learn in science require specific skills that we must develop over time. Lucky for me, both the staff scientist and postdoc in my lab had many tips for success, including how best to run a sodium dodecyl-sulfate polyacrylamide gel electrophoresis and transfect fragile cancer cells. I learned that making a mistake or ending up with negative results does not define me as a scientist, and that sometimes negative results or an unsupported hypothesis are just as important in science as other outcomes. This mindset is how I started building resilience.

Once I found my balance in the lab, I was ready to take on an independent project. This came with its own challenges, of course, as I established my research question and hypothesis, which included reading a lot of literature and engaging in many constructive discussions with my aforementioned staff scientist, **James Madigan**, and principal investigator, **Samira Sadowski**, who is a physician-scientist in the surgical oncology program and head of the Neuro-Endocrine Cancer Therapy Section at NCI. I attended research talks and shadowed physicians, which was particularly helpful as I was intrigued by the transcriptomic and epigenetic mechanisms associated with cancer metastasis. I eventually figured out that single-cell sequencing technology would be the best-suited method to answer my research question.

I worked hard to establish trust with my PI to embark on a project that required funding and time. We have the privilege here at NCI, and the NIH more broadly, to think outside the box, to explore new ideas with new technology, and I believe I would not have had the opportunity to do what I do at my training level anyplace else. Getting that first impactful, positive result from your own research is exciting and fulfilling. I am most proud that I was able to use an innovative method to start blazing a path toward improved therapies for patients with a neuroendocrine tumor with liver metastasis.

Another key aspect of my postbac fellowship, what I call my bridge-building years, is how much it improved my candidacy for the next step in my career.

CREDIT: STEPHEN ANDREWS

Samira Sadowski's research team, from left to right, Steven Forsythe, James Madigan, Srujana Yellapragada, Stephen Andrews, and Sadowski.

The beauty of these bridge-building years was the time it allowed me to explore and reflect on my personal mission within science and medicine. I was able to walk from my desk to an operating room observation to watch my mentor resect a rare tumor from a patient. Then, I witnessed the data that sprang from our organoid modeling of that same tumor in the following months. I was amazed to see the seamless blend of science and medicine. So, I chose to focus on this in my medical school applications and my personal statement.

I addressed my research experiences in every medical school interview I sat through, and I was able to give each interviewer a glimpse into some of our intriguing findings. I believe that my experience at the NIH contributed significantly to my medical school acceptance.

I want to emphasize that none of us are alone on this journey. As we bridge from undergraduate studies to the next stage of our professional careers, it is important we take some time to learn from and grow alongside those around us.

Like a bridge, we need a solid foundation, strong support, and a bit of flexibility to succeed. Know that the time you spend at NIH will help get you from where you are now to where you want to be. ●

Collaboration, Prevention, and Service

New DTT Scientific Director Heather Patisaul is Focused on the Public Good

BY SEPPIDEH SAMI, CC

CREDIT: STEVE MCCAW, NIEHS

Heather Patisaul is the new scientific director of the Division of Translational Toxicology at NIEHS.

Heather Patisaul took the helm as scientific director of the NIEHS Division of Translational Toxicology (DTT). A respected neuroendocrine biologist, she was recruited in March from North Carolina State University (NCSU), where she was an associate dean for research. Patisaul sees the DTT as an ideal platform to do what inspires her the most: cross-disciplinary collaborative work and service to the community.

The DTT is a small, independent arm of the intramural research program at NIEHS that supports the National Toxicology Program. DTT's mission is to investigate how environmental factors influence the development and progression of disease. As such, the DTT is inherently collaborative with federal and state agencies, academia, and industry, and that thrills Patisaul about her new position.

"You can't really thrive and address the grand challenges without a diverse group of people at the table," Patisaul said. "How are we going to get the plastic out of the ocean? How are we going to create safe alternative chemistries for things like plastic bottles? A single discipline like neuroscience is not going to figure that out."

Wedded to the Earth

A daughter of a NASA engineer, Patisaul grew up in central Florida frequenting the John F. Kennedy Space Center and the nearby Merritt Island National Wildlife Refuge. She saw countless rocket launches, a fury of fire and sound, rise from the delicate tranquility of the refuge, and the contrast left a significant impression in her young mind about technology and the natural world.

"That is deep in my epigenome," she said. "Ensuring the chemicals that we develop and use are truly nontoxic is certainly achievable, and [this] is essential for the long-term health and wellbeing of ourselves, our future generations, and our planet."

Patisaul's academic experience and work in advancing science and innovation, as well as her collaborations with national and international expert groups related to environmental health and chemical policy, were key factors in being selected to lead DTT at a time when NIEHS is looking to forge ahead with novel ideas and precise technologies to find effective solutions.

"Dr. Patisaul's scientific expertise and leadership skills will steer DTT toward exciting horizons, helping to address critical health challenges and research gaps," wrote NIEHS Director **Rick Woychik** in the NIEHS *Environmental Factor* newsletter.

A career built on collaboration

At NCSU, Patisaul directed research programs investigating sex-specific mechanisms by which environmental factors affect brain development and behavior (PMID: 28674520). Much of her research focused on the endocrine-disrupting chemical bisphenol A (BPA). "I have learned from amazing mentors and phenomenal trainees who were exceptional to work with over the years," said Patisaul about her time at NCSU.

While at NCSU, she also worked in an interdisciplinary environment with experts such as chemists, engineers, and textile experts. The work was intellectually stimulating and rewarding because she experienced firsthand the importance of collaborative work with diverse groups while trying to solve multifaceted problems. One project established the key characteristics of endocrine-disrupting chemicals, or EDCs (PMID: 31719706).

At the DTT, Patisaul said she is excited to lead her team as they continue the important work of developing alternative animal and nonanimal assays for assessing developmental neurotoxicity in collaboration with other experts and scientists through the Organization for Economic Co-Operation and Development (PMID: 30496580).

A mountain to climb

With renewed commitment to addressing the many environmental factors affecting human health such as pollution, obesogenic chemicals, micro- and nano-plastics, and hazardous waste that affect human health, Patisaul is ready to explore preventative measures, too.

When she is not engaging in environmental science, she is still always engaging with the environment. She is an avid runner and kayaker. "I'm an outside kid," said Patisaul enthusiastically. "If it's outside, I'm going to do it." ●

Read a longer version of this article, as well as news about the NIEHS–NCCIH joint conference on EDCs, in our online version available at https://irp.nih.gov/catalyst/32/4.

Common Data Elements

A Critical Charge to Standardize Data

BY ANNELIESE NORRIS, NCI, AND ARTHI RAMKUMAR, NIAID

"To better understand relationships between the genes we inherit and the environmental and societal factors that surround us, and to deliver more evidence-driven health care, research must be integrated into clinical care and community settings, reaching patients from all walks of life."

So wrote **Monica Bertagnolli** in June in her first *Science* editorial (PMID: 38843323) as NIH director, announcing NIH's $30 million investment into a pilot research network that integrates clinical research with community-based primary care.

Key to achieving this goal will be a keen focus on common data elements (CDEs). These are standardized, precisely defined questions, paired with a set of specific allowable responses, used in clinical and other research studies to facilitate data sharing, comparison, and interoperability across research domains. For example, to capture age, instead of asking how old a participant is, one might ask a bundle of questions that includes both age in years and date of birth.

Bertagnolli has long championed efforts to adopt data standards that allow information from the clinical care environment to clinical trials to be combined, shared, and reused across disciplines. Collecting data in a common language can enhance existing artificial intelligence tools, expose health disparities, and augment the ability of researchers from around the globe to collaborate and build on each other's work.

"Standardization is the key for unambiguity in data analysis, making it possible for investigators to share and compare datasets," said **Belinda Seto**, deputy director of the Office of Data Science Strategy (ODSS), who points out that CDEs are community-driven and consensus-building, meaning that everyone needs to follow the same definition (e.g., of a particular clinical observation), and in the clinical setting, the same collection process.

Seto and colleagues have been tasked by the NIH Scientific Data Council, with guidance from Congress, to collect feedback from the NIH community to develop a set of minimal core CDEs that will be required for all NIH-funded clinical research, and to define new CDEs in disease areas such as immune-driven conditions.

The core CDEs currently under discussion and that have received public input include demographic and identity elements such as age, gender identity, sex assigned at birth, and race/ethnicity.

"When you don't have community consensus, you are not going to get broad adoption and utility," Seto said, citing diabetes as an example in which the lack of consensus has resulted in over 100 data elements describing the disease.

Another ODSS priority is to determine a set of core CDEs that reflect social determinates of health (SDoH), which are nonmedical conditions that affect a person's health. Asking about SDoH could capture whether a person has experienced traumatic events, food insecurity, poverty, or lack of access to affordable quality health care—just to name a few—and offer critical insight into the social, economic, and environmental factors influencing health outcomes.

"SDoH screening assessments should be included in all human research, even if the interest to delve deeper into the social drivers is not part of the study," said **Deborah Duran**, a senior advisor to the NIMHD Director. Duran has worked tirelessly across the federal fold to help develop the first set of NIH-endorsed SDoH, which include questions to assess employment status, postal zip code, educational attainment, and where a person usually seeks health care.

While the ODSS team is building NIH-wide consensus, looking at how individual institutes, centers, and offices across NIH are applying CDEs offers a glimpse into what a data-unified future across the agency might look like.

NCI's **Chuen-Yen Lau**, associate research physician at the HIV Dynamics and Replication Program (HIV DRP), uses CDEs in a current protocol (NCT: 05419024) and collects clinical data from participants with HIV, including CDEs on age, gender, and ethnicity.

According to **Frank Maldarelli**, an HIV DRP principal investigator, "CDEs will be critical for future analyses to [compare] data across cohorts and as new language processing models are developed." The NIMH Division of AIDS Research, expects grantees to collect a set of CDEs that include age, sex at birth, gender identity, HIV status, and assessments for anxiety or depression.

Across NIH, CDEs shared among different initiatives illustrate the utility of harmonized data. CDEs developed by NICHD reflecting maternal health are used at the RECOVER Initiative. In addition to using COVID-specific CDEs, RECOVER integrates SDoH that capture housing and employment status that were created by RADx Underserved Populations.

Furthermore, several institutes such as NINDS, NIDA, NIA, and NIMH have catalogs of CDEs specific to each institute's research portfolio. ●

Check out our online version of this article for links to more information on CDE repositories available around the NIH https://irp.nih.gov/catalyst/32/4.

Andrew Singleton, a distinguished investigator at NIA, leads the center with a mission to initiate, stimulate, accelerate, and support research in AD and AD-related dementias (AD/ADRD).

Dedicated in 2022 in honor of former Senator Roy Blunt (R-MO), CARD is housed in a dedicated 24,000 net square foot building (T44) on the NIH Bethesda campus, CARD comprises diverse scientists and collaborators from across and beyond several NIH institutes, centers, and offices. CARD staff work at the forefront of many areas including genome sequencing, functional genomics, lab automation, data science and data sharing, and open-source tool development. CARD's early projects involved creating stem cell models of disease, such as the iPSC Neurodegenerative Disease Initiative (iNDI) project, using long-read DNA sequencing to identify novel disease-causing genetic variants, and developing strategies to clear protein aggregates from the brain. Since its launch, CARD also has used advanced data science and open science approaches to accelerate discoveries.

Today, CARD continues to advance these projects. The center has new projects, too, that involve searching for missing causal genetic variants in non-European populations, developing complex multicellular models of neurodegeneration, and identifying biomarkers, to name a few.

Searching for ancestrally diverse genetic causes, risk factors

Researchers have identified hundreds of regions of the genome associated with AD/ADRD. These regions, known as loci, often are identified in genome-wide association studies (GWAS). Yet mysteries remain about which specific variants in most of these loci are causal, or responsible for disease-related changes. With a specific variant identified, researchers must still determine its effect on gene regulation and cell biology in different populations.

One barrier to solving these mysteries is that most genomic studies of neurodegenerative disorders lack genetic diversity and thus leave out potential ancestry-specific genetic factors of disease (PMID: 37198259). This makes it more difficult to determine which genetic variants across all populations may be causal. CARD's Expert Groups are working to address this issue.

"Much of the information we have on regions of the genome linked to AD/ADRD risk, age at onset, and progression comes from European populations. This fact limits our understanding of dementia," said **Sara Bandrés-Ciga**, a staff scientist and leader of the Genetics Expert Group as well as Training and Outreach at CARD. "Including data from dementia cases and controls from different ancestral populations gives us more statistical power and resolution. We can narrow down causal genes and mechanisms by overlaying diverse haplotype structures. It also allows us to identify population-specific genetic factors linked to disease etiology."

CARD has demonstrated the value of more diverse genetics research. In a study published in *Nature Genetics*, CARD scientists and collaborators curated ancestrally diverse PD data (PMID: 38155330). With these data, they identified 12 potentially novel loci associated with PD. They then chose the potential causal genetic variants within six of the loci using a process called fine-mapping. Fine-mapping identifies the specific mutation likely responsible for a locus association with disease.

In the largest multiancestry meta-analysis of previously published GWAS to date, CARD researchers identified two novel AD/ADRD loci and fine-mapped nine previously identified loci (PMID: 37198259). This study also provided further evidence that known risk factors for AD, including *APOE4*, have different effects across different ancestral populations.

CARD is working with the Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat) to sequence data from people with and without AD and other dementias in Chile, Argentina, Brazil, Perú, Colombia, Mexico, and other countries.

"Collaborators send DNA samples that we help produce genetic sequencing data for," Bandrés-Ciga said. "We then train our collaborators on how to analyze these data so that they can address their own scientific questions."

Developing cellular models for dementia research

In addition to cultivating more diverse genetic data, CARD researchers are creating cellular models of neurodegeneration to study how specific genetic variants affect downstream processes. These models include genetically engineered stem cell lines and organoids.

CARD's iNDI is a large genetic engineering project devoted to creating induced pluripotent stem cell (iPSC) lines for dementia research (PMID: 33831364). Each cell line carries a single genetic variant associated with AD/ADRD. Scientists can use any of these lines to investigate how a specific variant affects gene expression, biological pathways, and cell behavior. So far, the project has generated nearly 200 different iPSC lines used by more than 450 laboratories across 26 countries (PMID: 36459969).

Elise Marsan leads the new Molecular Pathology Unit at CARD. She and her group are excited to pursue a new step in the development of cell-based models for studying dementia. They plan to grow brain organoids, which are 3D models of iPSC-derived brain cells. These organoids closely mimic the multicellular complexity of the brain. "We can look at the interplay and communication between different types of brain cells and how this is affected by dementia-related mutations,"

Marsan said. She aims to leverage brain organoids to explore how changes to the TDP-43 protein contribute to dementia pathology in AD, FTD, and a recently discovered type of dementia called LATE, or limbic-predominant age-related TDP-43 encephalopathy.

"Traditional methods of studying dementia in the lab typically involve looking at postmortem brain tissue or cerebrospinal fluid," said **Phil Gross**, a postdoctoral fellow in Marsan's lab. "These samples come from people who are already pretty far into disease or already deceased. We want to use organoids to model the development of these diseases at earlier stages. Organoids have a lot of advantages. You get a lot of the complexity, different cell types, and cortical organization that you don't get with other in vitro models."

Additionally, CARD is working on ways to isolate and analyze other aspects of neurodegeneration in the lab, such as a project with NIDDK that aims to model the aging process in neurons.

Improving diagnosis, treatment

CARD scientists are also conducting large-scale studies on proteins to determine how genetic changes affect gene expression and to help find potential biomarkers. **Andy Qi** leads the Proteomics Expert Group at CARD. In collaboration with the Advanced Analytics Expert Group, Qi's group has created a fully automated pipeline for quickly analyzing proteins from many different samples (PMID: 38181731). The pipeline enables robust and reliable comparisons between samples, which help accelerate the search for potential biomarker proteins present in disease but absent in control samples.

"Protein biomarkers have become the most common clinical markers in body fluids," Qi said. "We are working to identify clinically relevant protein biomarkers for AD/ADRD."

CREDIT: NIA, CARD

Qi's group combines genetic and protein data from human tissue, blood, cerebrospinal fluid, and cultured cell samples. This comprehensive "proteogenomic" strategy helps the group identify observable changes in proteins caused by genetic variants associated with AD/ADRD.

"Our strategy is powerful for biomarker discovery and investigation of the fundamental biology of Alzheimer's disease and related dementias," Qi said. His group works with collaborators, including ReDLat and NINDS, to investigate promising biomarkers (PMID: 37168844).

In a project with NINDS, Qi's group has found that abnormal proteins produced by RNA splicing errors can be detected in the cerebrospinal fluids of FTD and ALS patients (PMID: 38277467). An RNA splicing-regulator protein called TDP-43 causes these splicing errors.

"TDP-43 pathology is involved in both ALS and FTD," said Colleen Bereda, a postbaccalaureate fellow working in CARD's Proteomics Expert Group and at NINDS. The TDP-43 protein regulates RNA splicing. In disease it gets "mislocalized" within the cell. The protein then produces splicing errors that result in cryptic RNA transcripts, which result in other abnormal proteins.

"We're hoping that some of these cryptics could be useful as biomarkers," Bereda said. "The goal is to find RNA or proteins that are robustly present in disease and absent in healthy controls. Ideally, we can find these biomarkers via tests on blood or cerebrospinal fluid—even before people have symptoms."

CARD's Neurogenomics and Diagnostics Research Unit, led by senior scientist **Kendall Van Keuren-Jensen**, aims to further explore various RNAs and proteins as novel biomarkers. The unit will focus on improving AD/ADRD diagnosis and patient stratification. The latter is the process of placing patients into subgroups based on specific disease characteristics that might affect their prognosis and response to available treatments, for example.

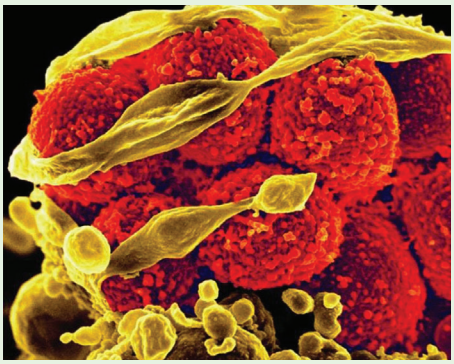
Shaping CARD's future

Researchers can access CARD's data and tools via the CARD website. CARD is always open to feedback and collaboration to best serve the dementia research community. Indeed, CARD's success relies on collaboration among its own scientists, the broader NIH, and increasingly, with others from around the world. To maintain momentum, CARD needs a diversity of scientific perspectives at the table. If you're interested in collaborating with CARD, they invite you to learn more about submitting a CARD Research Challenge, available at https://card.nih.gov/research-programs/alzheimers-dementias-research-challenge. ●

Intramural Research Briefs

Read about Scientific Advances and Discoveries by NIH Intramural Scientists

CC, NHLBI: RETROSPECTIVE STUDY REVEALS WIDESPREAD USE OF SUBOPTIMAL ANTIBIOTICS



CREDIT: NIAID

CC, **NHLBI**: Scanning electron micrograph of methicillin-resistant *Staphylococcus aureus* bacteria (red, round items) killing and escaping from a human white blood cell.

A research team led by CC and NHLBI investigators reviewed data from 619 hospitals across the United States to examine the use of a variety of antibiotics in the treatment of gram-negative infections with difficult-to-treat resistance (DTR). Among the 2,631 DTR hospitalization episodes over the study period, 41.5% were treated with generic antibiotics, such as aminoglycosides, polymyxins, and tigecycline, that are known to have suboptimal safety-efficacy profiles.

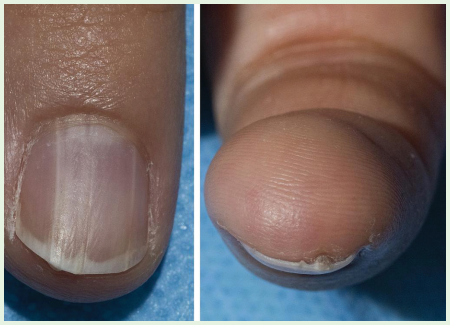
Of the seven newly approved next-generation antibiotics, ceftolozane-tazobactam and ceftazidime-avibactam were used more extensively than the other five. Even after controlling for patient- and hospital-level covariates, the treatment rates for DTR infections with next-generation versus traditional antibiotics differed substantially with more than one-third of the hospitals experiencing DTR episodes not treating patients with any next-generation antibiotics.

Several factors with significant positive preferential use of new over old antibiotics were identified, such as admission during November versus April, culturing from blood versus nonblood, and the hospital's practice to test pathogens' susceptibility to novel antibiotics. Factors associated with hospital staff preferring to use old versus new antibiotics included do-not-resuscitate status, acute hepatic failure, and smaller facilities located in rural areas, according to a press release.

The researchers recommended better use of the available antibacterial armamentarium and pioneering newer drugs with innovative mechanisms that have higher-quality evidence on their effectiveness. (NIH authors: J.R. Strich, A. Mishuk, A. Lawandi, W. Li, C.Y. Demirkale, A. Mancera, B.J. Swihart, M. Walker, C. Yek, M. Neupane, N. De Jonge, S. Warner, S.S. Kadri, and the NIH Antimicrobial Resistance Outcomes Research Initiative Team, PMID: 38639548)

[BY CODY R.K. CONRAD, NIAID]

NIAMS, NCI: NAIL HEALTH SCREENING MAY HELP DIAGNOSE CANCER RISK



CREDIT: NIAMS

NIAMS, **NCI**: A fingernail with onychopapilloma.

During a baseline assessment at the CC, an observant patient being screened for a rare genetic condition noticed slight changes in his nails. Clinicians later determined it to be a benign abnormality called onychopapilloma. It turns out that this condition is linked with a rare disorder known as BAP1 tumor predisposition syndrome.

The syndrome is caused by mutations in the *BAP 1* gene and can result in developing tumors in the tissues of the chest and abdomen, as well as the skin, eyes, and kidneys. In a study led by NIH investigators, of 47 people with *BAP 1* pathogenic variants, 88% of those over the age of 30 had onychopapilloma. The authors suggested that the discovery highlights how multidisciplinary teams can uncover insights behind rare diseases, and that nail screening could help clinicians identify individuals at risk of developing BAP1 tumor predisposition syndrome. (NIH authors: A. Lebensohn, A. Ghafoor, L. Castelo-Soccio, K. Karacki, O. Hathaway, T. Maglo, C. Wagner, M.G. Agra, A.M. Blakely, D.S. Schrump, R. Hassan, and E.W. Cowen, PMID: 38759225)

NCI, NCATS: NOVEL MACHINE LEARNING PIPELINE PREDICTS PATIENT RESPONSE TO CANCER TREATMENT

NIH researchers and their colleagues developed a novel machine learning pipeline named PERCEPTION (Personalized Single-Cell Expression-Based Planning for Treatments In Oncology) that was trained on publicly available datasets to predict patient response to cancer treatments. The machine learning pipeline was trained in three steps.

First, the model was built using a bulk RNA sequencing and drug-response dataset, allowing the pipeline to learn how cancer treatments affect cell lines that might share similarities with patient-derived tumors.

In the second step, the model was trained on single-cell RNA sequencing data from cell lines, allowing the bulk-expression models to be applied to single-cell sequencing data. Each human is molecularly distinct, and so are each individual's tumors, which consist of a constellation of different tumor cell types with unique mutations and gene-expression patterns, which may lead to potential resistance to cancer treatments. Therefore, for the most accurate prediction of a patient's response to treatment, single-cell sequencing of an individual's tumor can help identify resistant or susceptible clones before beginning a treatment regimen, to better predict patient response to treatment and help physicians

choose the best treatment options.

Finally, to evaluate its predictive performance on independent patient datasets, PERCEPTION was applied to single-cell RNA sequencing datasets from multiple myeloma, breast, and lung cancer tumor samples to predict the clinical response of the patients. Encouragingly, its performance outperformed previous methods of response-prediction modeling based on bulk-expression sequencing data.

The authors note that there is still a paucity of single-cell RNA sequencing data on patient tumors, partly driven by the high cost of sequencing, but by knowing the intricacies of the disease, methods such as PERCEPTION could be applied to tailor therapies for the highest chance of success. More information about PERCEPTION is available at https://github.com/ruppinlab/PERCEPTION. (NIH authors: S. Sinha, R. Vegesna, S. Mukherjee, A.V. Kammula, S.R. Dhruba, N.U. Nair, I. Grishagin, K.D. Aldape, P. Jiang, C.J. Thomas, A.A. Schäffer, and E. Ruppin, PMID: 38637658)

[BY TAYLOR FARLEY, NIAID]

NIDDK, NIA: DATA ON WHOLE-BODY RESPONSE OF AN ANIMAL ENDURANCE-EXERCISE STUDY MADE AVAILABLE FOR FURTHER RESEARCH

CREDIT: MOTRPAC

NIDDK, NIA: Data from the MoTrPAC study paves the way for further exploration and potential development of personalized exercise regimens to combat metabolic diseases and improve overall health.

Care to give your ol' serous membrane a workout? Or how about an epithelial tissue warmup? Sure, evidence shows numerous benefits of regular exercise for improved muscle strength, heart health, mood, sleep quality, weight management, disease prevention, and longevity. But according to an NIH-supported study published in *Nature*, benefits of exercise also extend to molecular changes in the tissues and organs not typically linked with exercise.

Scientists in the Molecular Transducers of Physical Activity Consortium (MoTrPAC) found that all bodily tissues in male and female rats responded to exercise. They identified over 35,000 biological molecules that adapted to eight weeks of endurance training. MoTrPAC, launched in 2016 and supported by the NIH Common Fund, is a network of researchers devoted to understanding how exercise aids the body's systems by creating a comprehensive catalog of exercise-affected molecules in humans, mapping molecular changes, and linking them to the benefits of physical activity. The rat was selected as the model organism to aid in the study of the whole-body response to exercise.

Widespread differences were observed in the rats between sexes, most notably in the adrenal gland, where 4,000 genes were found to be differentially regulated, leading to a decrease in gene expression associated with steroid synthesis pathways and mitochondrial function in female rats. In males, however, expression in those genes increased. NIH policy on the inclusivity of sex as a biological variable was supported by findings on the sex differences in response to exercise, according to **Ashley Xia**, a NIH program director at NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases.

By analyzing thousands of tissue samples, researchers uncovered crucial changes in genes, proteins, and other small molecules vital for the body's metabolism, offering hope for more effective nondrug treatments. For example, the liver was shown to be highly metabolically regulated in the mitochondrial, amino acid, and lipid metabolism.

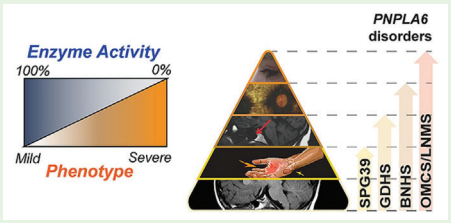
As a companion for human study, the rat analysis identified exercise-responsive molecules in tissues and organs that are unable to be studied by human studies, such as liver, heart, intestine, brain, and adrenal gland, that were linked to diseases such as liver disease, type 2 diabetes, heart disease, and obesity.

"MoTrPAC's goal is to make all [these] data accessible for the world," said Xia. "The resource provides a valuable platform for translating these findings to human health research. If a scientist is interested in specific genes or a particular metabolic pathway, our data are available to support generating new hypotheses in further research." (NIH authors: A. Xia and J. Williams, PMID: 38693412)

Access the MoTrPAC data repository at https://motrpac-data.org.

[BY HÉCTOR CANCEL–ASENCIO, NINDS]

NEI, NHLBI, NINDS: CLASS OF NEURO-DEGENERATIVE DISORDERS DEFINED BY ENZYME BIOMARKER



CREDIT: NEI

NEI, NHLBI, NINDS: NTE helps regulate lipid metabolism and membrane stability within neurons. Mutations in the *PNPLA6* gene inhibit NTE activity, leading to a spectrum of neurological disorders.

A constellation of neurodegenerative conditions affecting gait, vision, and hormonal regulation can be explained by a reduction in enzyme activity caused by mutations in the *PNPLA6* gene, which encodes the enzyme neuropathy target esterase (NTE), according to a study led by scientists from NEI, NHLBI, and NINDS.

Reduced NTE activity destabilizes the membrane within neurons and is linked to several neurodegenerative disorders. The investigators conducted a review of data from more than 100 patients with PNPLA6 mutations and found that symptom severity was inversely related to the activity of NTE.

Next, the researchers created a mouse model with the same *PNPLA6* variations found in humans and observed similar findings. "This knowledge will enable us to learn more about the spectrum of PNPLA6-related diseases in humans and positions us for future clinical trials, potentially using NTE as a biomarker," said **James Liu**, an NEI postdoctoral research fellow and study co-author, in a press release. (NIH authors: J. Liu, Y. He, C. Lwin, M. Han, B. Guan, A. Naik, C. Bender, N. Moore, L.A. Huryn, Y.V. Sergeev, H. Qian, Y. Zeng, L. Dong, P. Liu, J. Lei, C.J. Haugen, C. Blackstone, and R.B. Hufnagel, PMID: 38735647) ●

CONTINUED FROM PAGE 1

They can apply for up to four years of assistance, and for each year they receive the scholarship, they owe NIH two paid service obligations of 10 weeks in the summer and one full year of work either before or after their graduate studies. Many UGSP scholars had been community college students transferring to a four-year university, and several had to work other jobs to support themselves and sometimes their families.

"We see that many don't have to have that second job and can focus more on their academics," said **Darryl Murray**, UGSP director since 2007. He added that many scholars arrive with tremendous potential, such as Kizzmekia Corbett-Helaire, a UGSP participant from 2005 to 2008 who returned to NIH in 2014 and was an instrumental part of the team that rapidly developed Moderna's COVID-19 vaccine.

"It's a cross section of the nation. There are individuals from rural communities to urban environments, and you get a chance to watch that cohort grow as a group and watch each individual grow in their own respective way."

Some of those UGSP scientists decide to stay; others accept research leadership positions at universities or companies. Read on for a sample of their achievements and commitment to mentoring, diversity, and effecting positive change in the scientific community.

Early star bolsters cancer portfolio

In 2010, the NCI's first bladder cancer research program was built from the ground up by **Andrea Apolo**, senior investigator in the Genitourinary Malignancies Branch and among the UGSP's first cohort in 1996. As an undergraduate student, she worked full time at restaurants while trying to keep up her grades and get into medical school.

"I don't think I could have continued doing that," said Apolo, who went on to earn an M.D. at Albert Einstein College of Medicine (New York), completed an internal medicine residency at the Joan and Sanford I. Weill Medical College of Cornell University (New York) and a medical oncology fellowship at Memorial Sloan Kettering Cancer Center (New York), and returned to the NIH as a fully trained medical oncologist.

Apolo now leads a large team that runs more than a dozen active protocols. They were the first to do in-human studies demonstrating the efficacy of avelumab, now an FDA-approved drug for bladder cancer (PMID: 28375787). Another trial tested a kinase inhibitor combined with an immunotherapy to treat bladder cancer (PMID: 32915679), which led to further trials for multiple tumor types including kidney cancer (PMID: 33657295). This year, she presented promising results from the Ambassador study, a large clinical trial that tested an immunotherapy to reduce the risk of disease recurrence in patients with muscle-invasive urothelial carcinoma, a difficult to treat bladder cancer.

Apolo, recipient of the 2020 Arthur S. Flemming Award for her avelumab work, is paying it forward like many UGSP alumni by mentoring two UGSP scholars in her lab: **Ian Stukes**, a postbac research fellow doing basic research and developing drug resistant models to study mechanisms of resistance to antibody-drug conjugates.
Andre Kydd, a medical oncology fellow doing his UGSP payback in both basic research and clinical, working on helping develop clinical trials for rare bladder cancers.

Breaking barriers

The delicate process of delivering drugs to brain tumors requires bypassing the blood-brain barrier (BBB), a highly selective membrane that tightly controls our central nervous system's environment.

"Our lab looks at those challenges and restrictions so we can be strategic about what therapies we select for these patients," said **Sadhana Jackson**, a pediatric neuro-oncologist at NINDS' Developmental Therapeutics and Pharmacology Unit with a joint appointment at NCI's Pediatric Oncology Branch.

Jackson is conducting a clinical trial testing a technique called intratumoral microdialysis in patients with midline glioma, a particularly aggressive brain tumor affecting children and young adults (NCT: 05413304). The procedure monitors how much of an anticancer drug is getting to the tumor and is one way that Jackson's team is intelligently selecting treatments that can cross the BBB and optimally impair tumor growth.

Her team also is studying ways to make the BBB temporarily permeable to improve drug delivery. Involved in that work was Melissa Cesaire, postbac fellow and UGSP scholar who joined Jackson's NINDS lab and stayed an extra year before heading off to medical school this year. She left NIH a published author on a paper describing how an agent transiently opens and then closes the BBB in a mouse model of glioma (PMID: 38589905).

Recalling her own journey, Jackson hopes her mentees' time at NIH is formative. "I tell them that the most important thing to deciding what and where you'll be in the future is having a variety of exposures to many different experiences."

Jackson, who was first exposed to NIH as a high school senior doing research through Howard Hughes Medical Institute's program at NCI in 1998, also has a strong commitment to diversity and equity. She served as co-chair of the NIH UNITE Initiative's T committee aimed at ending structural racism in biomedical research, and was recognized with NIH Director's Awards for her work supporting that project. Perhaps most prestigious, she and her team received the 2023 HHS Mary Brodie-Henderson Call to Service Award for their dedication and leadership supporting NIH's 8 Changes for Racial Equity (8CRE), where Jackson serves as communications lead.

Keeping good company

At NCI, cutting-edge bioengineering underway at **Freddy Escorcia**'s Laboratory of Molecular Radiotherapy involves developing molecules that are specific to hepatocellular carcinoma, a common liver cancer sensitive to radiation. They attach a radioisotope to those molecules that release emissions that can be picked up by positron emission tomography for tumor diagnosis, or they can switch isotopes to emit ionizing particles that cause DNA damage to specific cancer cells while sparing healthy ones (PMID: 36997331).

But as an undergrad, Escorcia admits his path wasn't so well defined. During his first UGSP summer at NIH in 2002, he worked in **Susan Gottesman**'s lab and distinctly recalls the difference that networking with new colleagues made. He remembers being surrounded by peers who had been accepted to the ranks of high-profile medical schools such as Harvard Medical School (Boston) or the Columbia University Roy and Diana Vagelos College of Physicians and Surgeons (New York).

"They were telling me I was competitive. It gave me a bit of a confidence boost, and I would have not applied otherwise, to be honest." Escorcia left Gottesman's lab that summer with their work immortalized in a high-impact paper (PMID: 12975324) and would go on to earn his M.D.-Ph.D. at the Joan and Sanford I. Weill Medical College of Cornell University, Memorial Sloan Kettering Cancer Center, and Rockefeller University (New York).

He would return to NIH in 2017 as an assistant clinical investigator and became a Lasker Clinical Research Scholar in 2021. Escorcia is equally committed to making scientific careers accessible to the next generation. He received NCI's Outstanding Mentor award and serves on the American Society for Radiation Oncology's Health Equity, Diversity, and Inclusion Council.

Escorcia is currently hosting an NIH Oxford-Cambridge Scholar who is the first author on an upcoming study that improves upon their innovative imaging technique. "The images we're producing now are much better, and we've patented that method and hope to move it into clinical trials," he said.

A clinical calling

Other UGSP grads find their passion in multidisciplinary pursuits away from the bench. At the CC, inpatients receiving treatment or enrolling in a protocol often rely on the team of **Afua Asante-Otoo**, staff physiatrist at the Rehabilitation Medicine Department, to maintain physical function and ease the transition back home. "The most rewarding part is helping patients who have limited access to medical care outside of here," she said, recalling a pediatric patient from the Middle East.

"Physical therapy, occupational therapy, and I collaborated to educate the parents and provide recommendations for a walker and other equipment for the patient to walk safely."

> "Now 24 years later, I have my dream job seeing patients, conducting cancer research, and teaching the youth."
>
> —Sadhana Jackson

During her first two UGSP summers, Asante-Otoo delved into basic bench research at NCI. After her first year at Wayne State University School of Medicine (Detroit), she returned for another summer investigating neurorehabilitation at NINDS.

"Having NIH on my resume boosted my applications. It came up as a talking point in almost every interview," she said, adding that the motivation to apply to the UGSP came from an email sent by her uncle, a biochemistry professor. "The application was so long, but I didn't want to disappoint him! It ended up changing my whole life and trajectory of my career."

Asante-Otoo's work is now 85% clinical, and along with being involved in research on neurologic disorders affecting gait and function, she looks forward to seeing an expansion of protocols helping pediatric patients. "I am excited and hoping to get enough pediatric equipment so we can help keep these kids moving during their long hospital stay. If we can treat them earlier, we'll see [fewer sequelae] later."

A collective story

As each generation of UGSP scholars builds upon the last, they contribute to a collective story. "We're not only enriching the scientific community, we're building the citizenry," said Murray of the program's alumni, who include intellectual property attorneys, university professors, biotech industry researchers, and DEIA leaders.

One more UGSP scholar is **Luis Estrada**, who began their journey in NIH's High School Scientific Training and Enrichment Program in 2017. They have just fulfilled their NIH obligations and are off this fall to the Icahn School of Medicine at Mount Sinai (New York) to pursue a Ph.D. in microbiology.

Estrada spent the past two years in **Daniel Douek**'s Human Immunology Section in the Vaccine Research Center studying the humoral response to viruses from Zika to SARS-CoV-2. Douek's team pioneered a technique called rapid assembly transfection and production of immunoglobulins that speeds up the process of sequencing and identifying the antibody and B-cell response to infections (PMID: 36517467), and hope to unravel immune system dynamics and find potential targets for therapeutics and vaccines.

Estrada intends to pursue their passion for immunology, perhaps in academia. "I'm very grateful for all of my experiences at the NIH, which gave me not only a scientific foundation but a great perspective of who I want to become as a professional and a leader."

And so, the circle remains unbroken. ●

Read more UGSP profiles online at https://irp.nih.gov/catalyst/32/4.

From the Fellows Committee: Navigating Housing Challenges

Insights from NIH Trainees and an Exploration of Supportive Resources

BY STACY LIANG, NIAID

CREDIT: FAES

FAES housing offers single-occupancy bedrooms with flexible agreement terms and affordable monthly fees that include utilities. Each unit features its own full bathroom and offers each occupant a separate pantry and refrigerator. Additional units will be available after summer 2025.

Housing, where we spend the majority of our daily lives, significantly affects both personal wellbeing and professional performance. Given that each person has unique needs and preferences, finding suitable accommodations can be a challenging and stressful task.

In June, I conducted an informal survey about the housing situation for NIH trainees. The survey received 54 responses from mostly postdocs (87%), but also research fellows (5.6%) and other trainees (7.4%). The results suggest that most trainees struggle to find affordable housing that meets their needs. Specifically, 74% disagree or strongly disagree that housing is affordable in their area, and 62% disagree or strongly disagree that it is easy to find housing that meets their needs.

Fellows who come to the NIH from other countries face significant challenges in securing housing when moving to the United States, often due to lack of a Social Security number or an American bank account. Survey respondents shared that apartments to which they applied wanted supervisors to cosign leases or required security deposits with checks only from U.S. banks. One anecdote noted a leasing office requiring proof of at least $2,000 in a savings account at a U.S. bank to rent an apartment.

To help combat the need for affordable housing for NIH trainees, the Foundation for Advanced Education in the Sciences, Inc. (FAES) has built numerous dwellings near the Bethesda campus and is renting them at a more modest rate than similarly sized and located apartments.

Located close to the NIH main campus in Bethesda, FAES Housing offers large private single-occupancy bedrooms that offer advantages over traditional rentals, including flexible agreement terms and affordable monthly fees, which include utilities, maintenance, monthly cleaning services, and basic household supplies. Each unit features individual amenities such as a separate pantry and refrigerator for each occupant and several washers and dryers in the laundry room; each unit also has its own full bathroom.

FAES housing currently has limited availability. It accommodates 30 trainees and plans to expand with the construction of seven additional buildings by summer 2025, each offering five single-occupancy bedrooms. This expansion will create 35 more housing opportunities for NIH fellows.

Although FAES housing has proven to be a valuable resource for NIH fellows in Bethesda, only 35.2% of my survey respondents would consider renting from FAES housing because of varying life circumstances, such as having children, being caregivers of other dependents, or having pets.

To assist NIH fellows nationwide with their housing needs, the Office of Intramural Training and Education (OITE) provides online guidelines for each NIH U.S. location. NIEHS, in North Carolina, has an online resource for trainees moving to Research Triangle Park, for example. These guidelines are a compilation of information that fellows can use during their housing search.

As one smart survey respondent noted, "The cost of rental housing is not something that NIH can fix." They are correct, but by leveraging these and other resources that NIH develops, and exploring options such as FAES housing, NIH fellows can better navigate the complexities of the challenging housing market. ●

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Reflections on a 'Research Year' in Urology

BY JESSICA HSUEH, NCI

CREDIT: JESSICA HSUEH

A cohort of MRSP and CRTA fellows have completed their medical school research year at the NIH. Pictured are (top row from left to right): Schuppe, Gelikman, Azar, and Hsueh; (bottom row) Parikh, Hyman, and Rathi. Standing on the first step is Jay Siva, a summer intern.

Across the country, medical students have found themselves asking the same question: "Should I take a research year?" While such an experience may not be for everyone, I can say that I and my NIH cohort benefited immensely from a yearlong immersion at the NIH.

Coming into medical school, I pondered the possibility of taking a year to explore my passions within medicine. As I juggled classes and rotations with research, I knew that I wanted to dedicate significantly more time to investigating my personal clinical research interests. When I discovered my love for urology and how interwoven innovation and creativity are in this field, I was energized with a desire to take an extra year in medical school to focus on growing as a researcher.

As I embarked on the daunting process of finding a home for my research year, I never imagined it would eventually take me to the NIH, a place I didn't realize had such a diversity of research opportunities. But it was here where I met dozens of similarly minded medical students, including six I would bond with who, like me, came to pursue a research year at NCI. Five of us entered through the Medical Research Scholars Program (MRSP), a year-long program dedicated to training the next generation of physician-scientists. Two others were conducting their research year through the NCI Urologic Oncology Branch as Cancer Research Training Award (CRTA) fellows.

Although we are all united in our shared passion for research, we also had our own individual reasons for wanting to work at the NIH. "Coming from a fairly new community-based program, I was impressed that the NIH could provide me the opportunity to directly pursue answers to questions I had from prior research but was unable to engage in at home," Kyle Schuppe said. Schuppe, an MRSP scholar, has been able to participate in both clinical and bench research, focusing on new therapies and novel metabolic imaging techniques for the treatment and monitoring of castrate-resistant prostate cancer.

Jason Hyman, a CRTA fellow, participated in multiple projects assessing the relationship between genetic events and clinical courses of von Hippel-Lindau syndrome and exploring the benefits of a novel HIF-2-alpha inhibitor. One of the more compelling aspects about working at the NIH was the opportunity to develop tangible research skills by taking classes at the Foundation for Advanced Education in the Sciences (FAES).

MRSP scholar William Azar similarly benefited from a combination of NCI and FAES offerings, developing a profound understanding of the impact of technology in health care. "Because I am conducting research on medical-device development and the applications of artificial intelligence (AI) and large language models in medical data extraction and analysis, I chose to enhance my skills by taking courses in Python, R, and statistics programs," he said.

Our research year has undoubtedly left us with invaluable experiences, shaping our career trajectories as future surgeon-scientists. MRSP scholar Nityam Rathi dedicated his year to studying hereditary renal cancer syndromes after having previously investigated the medical and surgical management of localized and metastatic kidney cancer.

David Gelikman, also an MRSP scholar, studied applications of AI to improve diagnosis of prostate cancer using magnetic resonance imaging (MRI). "Working in a radiology lab that focuses on genitourinary imaging, I gained a unique perspective on diagnosis and continued surveillance of multiple urologic malignancies," Gelikman said.

After exploring the use of 3D quantitative transmission ultrasound tomography and MRI for prostate cancer detection, this research year solidified CRTA fellow Sahil Parikh's desire to become a physician-scientist and integrate research into his practice. "My year has stressed the importance of interdisciplinary collaboration, with a reinforced desire to combine academic pursuits with clinical practice," Parikh said. "This year has shown how important it is to have a support system and a mentor that believes in you and that all have a common goal."

Ultimately, what has made our research year so special is the strong sense of community and camaraderie at the NIH. "My favorite experience has been meeting and collaborating with trainees who share a similar passion for academic urology," Rathi said.

From sharing lunches and attending happy hours, to board game nights and trips to Washington, D.C., monuments, we have bonded inside and outside of the NIH. As our research year concludes, we are infinitely grateful for the opportunities we have been given at the NIH, and we cannot wait to pursue our urology careers—together, as colleagues and lifelong friends. ●

NIH's FY 2025 Budget Hearing Held on Capitol Hill

Directors Highlight Research Accomplishments

BY JENNIFER HARKER, *THE NIH CATALYST*

A CONGRESSIONAL HEARING FOR NIH'S fiscal year 2025 budget request was held May 23 on Capitol Hill. The Senate Appropriations Subcommittee on Labor, HHS, Education, and Related Agencies directed questions to NIH Director **Monica Bertagnolli**, and to NCI Director **Kimryn Rathmell**, NIAID Director **Jeanne Marrazzo**, NHLBI Director **Gary Gibbons**, NIA Director **Richard Hodes**, and NIDA Director **Nora Volkow**. The budget hearing was a first for Bertagnolli as NIH director, and for Rathmell and Marrazzo as IC directors. Topic highlights included the following health concerns and scientific advancements at NIH that are top-of-mind for Congress.

Addiction, Alzheimer's Disease: Senator Shelley Moore Capito (R-WV) discussed recent research led by NIDA grantee Ali Rezai, who is a West Virginia University neurosurgeon using a focused ultrasound technique to open the blood-brain barrier to aid in treatments for addiction (PMID: 37610405) and Alzheimer's disease (PMID: 38169490).

"This is the perfect example where science has transformed the way that we can tackle problems," answered Director Bertagnolli. "This is possible because of our understanding how the brain works, and through brain technologies developed by the BRAIN Initiative. Dr. Rezai is using our low-intensity focused ultrasound to basically restructure the way that the nucleus accumbens, which is the area of the brain involved with reward, actually gets disrupted by drugs."

The 10th annual BRAIN Initiative Conference occurred June 16–18. Program updates from the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative director, **John Ngai**, as well as sessions on building neural networks with music, a NeuroAI Research effort, and many other innovative topics can all be viewed on the virtual conference website.

Avian Flu and H5N1: At the time of the hearing, H5N1 had infected 51 dairy cattle herds across nine states. Since, those numbers have risen. "This is a pathogen that has been on our radar for a long time," said NIAID Director Marrazzo, adding that investigators across the country have been monitoring H5N1 for more than a decade through the Centers of Excellence for Influenza Research and Response, or CEIRR Network. "The good news is that we are really prepared to not only test the current vaccines that we have in the stockpile but also to develop specific vaccines. We are also working closely with other agencies and continuing to develop monoclonal antibodies, vaccines, and antiviral drugs," she said.

Long COVID: Congress appropriated $1.2 billion in 2021 for long COVID research. "I am very pleased to speak on this as the NIH Director," Bertagnolli said, adding that long COVID is an all-of-NIH activity. "What has been accomplished is to understand a new disease that dropped on us that we did not understand before. RECOVER Initiative researchers have been collecting biospecimens and electronic health record data that have allowed for five platform clinical trial structures: autonomic dysfunction, cognitive dysfunction, exercise intolerance and fatigue, sleep disturbances, and viral persistence."

Women's Health Research: Bertagnolli addressed questions about maternal health, maternal mortality, NIH's role in the White House Initiative on Women's Health Research, and menopause. Senator Patty Murray (D-WA) said to the directors present, "I think it was Senator [Lisa] Murkowski (R-AK) who said to us, 'If men went through menopause we'd have an institute at NIH.' We are not asking for that, we are just asking to make sure we really focus on it, so I appreciate your efforts."

Relatedly, on June 14, House Energy and Commerce Committee Chair Cathy McMorris Rodgers (R-WA) released a document detailing a proposed structural reform of the NIH that suggests reducing the number of ICs from 27 to 15. The full report is available for download in the online version of this article at irp.nih.gov/catalyst.

At the congressional budget hearing, members expressed their unwavering support for the NIH. "This is national security," said Senator Dick Durbin (D-IL) about funding the NIH. "I am not going to take one penny away from the Pentagon, but for God's sake, the NIH is doing things which is going to save as many lives as anybody that works in the Pentagon, maybe more."

Murray concurred, adding, "The fact of the matter is NIH is fighting some of our nation's most devastating adversaries: cancer, Alzheimer's, heart disease, opioid addiction, long COVID, to say nothing of rare diseases or pandemic threats. The life-saving work happening at NIH really shows, as I have been reminding my colleagues, that if we are serious about protecting our families here then we need robust defense and nondefense spending. I hope we can all come together to support this work along with many of our other crucial domestic priorities."

The budget hearing is available at https://www.appropriations.senate.gov/hearings/a-review-of-the-presidents-fiscal-year-2025-budget-request-for-the-national-institutes-of-health.

Garnett Retires

BY DANA TALESNIK, *THE NIH RECORD*

CREDIT: CARLA GARNETT

Carla Garnett retired in July after 41 years of federal service, including more than 30 years with the NIH Record (a sister publication of the *NIH Catalyst*), where she has served as a writer, associate editor, and for the past three years, editor. Garnett also served as editorial operations branch chief in NIH's Office of Communications and Public Liaison (OCPL).

"There's a reason she is so admired and respected by her staff, peers, and leadership alike," said **Scott Prince**, OCPL deputy director for public information. "And it's much more than her obvious skills and talents. It's her professionalism, kindness, and warmth that make her such a pleasure to work with."

Garnett came to NIH as a high school graduate in the National Junior Fellowship Program.

Collins Joins Past Directors on Halls of Building 1

The official portrait of **Francis Collins**, the 16th and longest serving NIH director, was unveiled on June 18. The portrait features Collins with "Rosalind," a guitar gifted to him by NHGRI colleagues at a farewell celebration in 2008 when he stepped down as NHGRI director. Rosalind was custom-made for Collins by a company near his hometown of Staunton, Virginia, and features a mother of pearl inlay of a double helix on the fret board. The portrait was created by artist and photographer Visko Hatfield, who is the son of former Senator Mark Hatfield (R-OR) after whom the Clinical Research Center is named. It will hang with the other NIH director portraits in Building 1 on the Bethesda campus.

CREDIT: CHIA-CHI CHARLIE CHANG

HHS-wide Brain Trust Tackles Rare Diseases, Gene Therapies

CREDIT: NCATS

In June, NIH leaders, including NIH Director **Monica Bertagnolli**, DDIR **Nina Schor**, and NCATS and NCI directors, met with colleagues from the Food and Drug Administration, Centers for Medicare and Medicaid Services, and other U.S. Department of Health and Human Services agencies to discuss how best to join forces in tackling each agency's priorities regarding rare diseases, including gene therapies and other innovations. The brain trust identified new avenues in which the agencies could collectively work together to explore and speed up the research to marketplace continuum.

NIH ABBREVIATIONS

CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
FAES: Foundation for Advanced Education in the Sciences
FelCom: Fellows Committee
FDA: Food and Drug Administration
FNIH: Foundation for the NIH
FNL: Frederick National Laboratory
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCATS: National Center for Advancing Translational Sciences
NCBI: National Center for Biotechnology Information
NCCIH: National Center for Complementary and Integrative Health
NCI: National Cancer Institute
NEI: National Eye Institute
NHGRI: National Human Genome Research Institute
NHLBI: National Heart, Lung, and Blood Institute
NIA: National Institute on Aging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAID: National Institute of Allergy and Infectious Diseases
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB: National Institute of Biomedical Imaging and Bioengineering
NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA: National Institute on Drug Abuse
NIDCD: National Institute on Deafness and Other Communication Disorders
NIDCR: National Institute of Dental and Craniofacial Research
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
OD: Office of the Director
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health

Colleagues: Recently Tenured

Meet your recently tenured colleagues: **Adrienne Campbell-Washburn** (NHLBI), **Leah Cook** (NCI), **Michael Michaelides** (NIDA), and **Alexander Sodt** (NICHD)

ADRIENNE CAMPBELL-WASHBURN, PH.D., NHLBI

LEAH M. COOK, PH.D., NCI

MICHAEL MICHAELIDES, PH.D., NIDA

ALEXANDER SODT, PH.D., NICHD

ADRIENNE CAMPBELL-WASHBURN, NHLBI

Senior Investigator, Laboratory of Imaging Technology, Cardiovascular Branch, NHLBI

Education: University of Western Ontario, London, Ontario, Canada (B.Sc. in honors physics); University College London, (Ph.D. in medical physics)

Training: Postdoctoral visiting fellow, Laboratory of Cardiovascular Interventions, NHLBI (2013–2016)

Came to NIH: In 2013 as a postdoc; became a staff scientist in 2016; became a Stadtman tenure-track investigator in 2020, NHLBI

Outside interests: Traveling; hiking; dance; family

Website: https://irp.nih.gov/pi/adrienne-campbell-washburn

Research interests: My lab aims to develop magnetic resonance imaging (MRI) methodology for cardiac imaging, pulmonary imaging, and MRI-guided cardiac catheterization procedures. We develop rapid image acquisition methods and advanced image computation methods that integrate into the clinical environment for new MRI applications that are efficient and patient-friendly (PMID: 38501940; 32291845; 38469944). Moreover, we strive to translate these techniques for clinical impact through patient assessment, open-source software development, and partnerships with industry. Recently, my lab pioneered a high-performance lower-field MRI system, which combines modern hardware and software with a lower magnetic field strength (PMID: 31573398). Conceptually, this system shifts the burden of MRI from the magnetic field hardware, which is expensive, to algorithms, software, and computing, which are inexpensive. This system has been commercialized as a more cost-effective and accessible imaging technology, and we have demonstrated its value for cardiac and pulmonary imaging applications (PMID: 34250492; 34652290; 34023254; 32423456).

Future directions: In the future, my goals are to expand on our work to develop smarter patient-tailored imaging methods, establish 0.55T as the standard for assessing cardiopulmonary interactions, improve functional lung MRI, translate methods outside of NIH, and improve the overall accessibility and useability of cardiac imaging.

LEAH M. COOK, NCI

Senior Investigator, Cancer Innovation Laboratory, NCI-CCR

Education: University of Alabama at Birmingham (B.S. and M.S. in biology; Ph.D. in molecular and cellular pathology)

Training: Postdoctoral fellowship at Moffitt Cancer Center, Tampa, Florida (2012–2017)

Before coming to NIH: Associate professor with tenure, University of Nebraska Medical Center, Omaha, Nebraska (2017–2024)

Came to NIH: In March 2024 as a senior investigator, NCI

Outside interests: Reading; any outdoor water activities like kayaking; zombie movies and shows

Website: https://ccr.cancer.gov/staff-directory/leah-m-cook

Research interests: Bone metastatic prostate cancer (BM-PCa) is the deadliest aspect of prostate cancer and is currently incurable. In bone, PCa cells induce excessive bone breakdown and abnormal bone formation resulting in the release of bone-derived growth factors, such as transforming growth factor beta (TGF-beta), which drive tumor growth. PCa cells rely heavily on interactions with bone-resident cells to survive and proliferate in bone. The most abundant immune cell in bone are neutrophils. Neutrophils are "first-responder" innate immune cells that mount a rapid response during inflammation and infections that is resolved by macrophages. My lab previously discovered a key phenomenon that bone marrow neutrophils are initially protective against BM-PCa that in bone metastasis of prostate cancer and transforming growth factor beta (TGF-beta) signaling in cancer-induced bone disease

has disseminated into the bone compartment (PMID: 32114681). However, we found that the tumor inevitably becomes resistant to neutrophil antitumor responses and suppresses neutrophil function, a finding that can be leveraged for the development of novel immunotherapeutic treatment options.

We have identified several mechanisms associated with tumor–neutrophil interactions that contribute to prostate tumor evasion of neutrophil antitumor immune response, including PCa STAT5 expression, reactive oxygen species (ROS), and androgen therapy (PMID: 32114681, 35604506, and 37940068, respectively). We are primarily focused on the intersection between bone metastatic prostate cancer, tumor-associated neutrophils, and prostate cancer-induced bone disease. Our main goal is to identify novel immunotherapeutic targets for treating and curing bone metastatic prostate cancer.

Future directions: Our next five projects, described in detail on my lab website, aim to understand 1) the role of STAT5 in PCa progression and response to neutrophils; 2) the role of Nox2, ROS, and redox metabolism in BM-PCa; 3) androgen-mediated regulation of neutrophils; 4) how neutrophils kill prostate cancer cells; and 5) IL-8 regulation of mesenchymal stem cells and PCa-induced osteogenesis.

MICHAEL MICHAELIDES, NIDA

Senior Investigator and Chief, Biobehavioral Imaging and Molecular Neuropsychopharmacology Section, NIDA

Education: Stony Brook University, Stony Brook, New York (B.A. in economics and Ph.D. in integrative neuroscience)

Training: Postdoctoral fellow, Icahn School of Medicine at Mount Sinai, New York (2010–2015)

Came to NIH: In 2015 as a tenure-track investigator, NIDA

Outside interests: Traveling with family; basketball; weight lifting; cooking; gardening

Website: https://irp.nih.gov/pi/mike-michaelides

Research interests: My laboratory combines techniques spanning behavioral neuroscience, in vitro and in vivo pharmacology, imaging, molecular and synthetic biology, and neuromodulation to study the mechanistic, molecular, and circuit basis of mood and motivational disorders. My laboratory has dissected the mechanism of action of popular medications with known abuse liability—for example, ketamine and methadone (PMID: 33859356; 35768639; 38291050; 38145984). We have also developed novel imaging agents for positron emission tomography (PMID: 35999424) and technologies for combined brain imaging and neuromodulation (PMID: 28774929; 30872534; 33895327; 31604917; 37494470). Our imaging work emphasizes state-of-the-art, noninvasive whole-brain molecular approaches in behaving subjects (PMID: 33549570).

Future directions: Ongoing and future work includes 1) assessing the mechanistic basis and promise for the use of ketamine as a treatment for addiction; 2) developing novel opioid-based pain medications with lower adverse effect profiles than existing opioid medications; 3) developing novel pharmacotherapies for addiction; and 4) developing novel translational imaging and neuromodulation technologies.

ALEXANDER SODT, NICHD

Senior Investigator, Unit on Membrane Chemical Physics, NICHD

Education: University of Washington, Seattle (B.S. in physics and chemistry); University of California at Berkeley (Ph.D. in chemistry)

Training: Postdoctoral fellow in biophysics, University of California at Berkeley (2007–2009), postdoctoral fellow in biophysics, NHLBI (2009–2015)

Came to NIH: In 2009 as a postdoctoral fellow, NHLBI; Stadtman tenure-track investigator in 2016

Outside interests: Spending time with my family; running; woodworking; tennis

Website: https://irp.nih.gov/pi/alexander-sodt

Research interests: My lab applies computational techniques to understand how lipid chemical structure determines the mechanics of biological membranes. Membrane mechanics refers to a model of the response of the membrane to an external force, such as from a protein. What I find particularly exciting about a biological lipid membrane is its dual role as a thin but very effective surface barrier, and its in-plane liquid nature that allows the hundreds of different lipids of the cell to get where they need to be. This dynamic liquid aspect makes membranes difficult to study experimentally, but, given their importance, makes them a prime target for molecular-scale simulation. Recently, my lab has developed methodology for interpreting how small differences in lipid chemical structure change membrane mechanics (PMID: 34005918). In particular, our modeling can resolve impactful differences between cholesterol precursors, including those related to developmental disease. Additionally, with our lab's publicly available software we have built intermediates in membrane reshaping (fusion or fission pores) that show, counterintuitively, how a sterol that stiffens membranes can drive a reshaping process through its dynamic lateral redistribution (PMID: 36588341).

Future directions: With the ability to quantify the effects of small changes in lipid chemical structure, we are now applying these tools to answer the question of "Why do we have the lipids we have?" from the standpoint of lipid mechanics. I am particularly interested in the roles of lipids in viral entry into the cytoplasm, and how immune system factors like IFITM3 may shift the energetics of membrane-mechanical barriers to viral fusion. ●

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PHOTOGRAPHIC MOMENT

CREDIT: CHIA-CHI CHARLIE CHANG

HOPE: Congressional staffers visited the NCI-CCR Pediatric Oncology Branch and the Children's Inn at NIH on May 29 to learn more about NIH's efforts in combating childhood cancer. Pictured left to right are Dana Richter, senior policy advisor to Senator Shelley Moore Capito (West Virginia); Meg Barnes, senior legislative assistant to Representative Bonnie Watson Coleman (New Jersey); Andrew Karasick, Brookings Institution LEGIS Congressional Fellow to Representative Kim Schrier (Washington); Jill Boland, senior health advisor to Senator Jack Reed (Rhode Island); Jennie Lucca, chief executive officer, the Children's Inn at NIH; Zilly, official therapy dog of the Children's Inn at NIH; Kenneth Downs, legislative correspondent to Senator Chris Van Hollen (Maryland); NCI Director Kimryn Rathmell; Harsh Patel, health policy advisor to Representative Ami Bera (California); Laura Bell, legislative director to Representative Susan Wild (Pennsylvania); Kathleen Bochow, legislative correspondent to Senator John Boozman (Arkansas); and Rhett Styles, legislative assistant to Representative Michael McCaul (Texas).

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