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Bryan Roth, Natural Products, and the John Daly Legacy

BY SEPPIDEH SAMI, CC

On a tropically warm afternoon on September 6, Bryan Roth, the Michael Hooker Distinguished Professor of Protein Therapeutics and Translational Biometrics at the University of North Carolina (UNC) School of Medicine in Chapel Hill, North Carolina, delivered the 2023 John Daly Lecture, titled "Natural Products Reveal Receptors for Perception" at the Lipsett Auditorium.

The humid weather was fitting—a gift from **John Daly**, said the lecture host, **Kenneth Jacobson** of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)—as Daly was at times an "Indiana Jones" kind of scientist who periodically traveled deep into the Amazon to discover and characterize structurally and biologically new natural products (NPs), such as batrachotoxin, the toxic substance in frog skin used for poison arrows there.

Equally fitting was the selection of Roth to deliver the lecture. Roth is someone who "typif[ies] John Daly's scientific ideals…and is at the forefront of both pharmacological and structural research on GPCRs," or G-protein-coupled receptors, a major area of research for Daly, said Jacobson, the NIDDK John W. Daly Distinguished Scientist, in his introduction.

Daly's legacy

The John Daly Lecture Series resumed this year after a hiatus due to the COVID-19 pandemic. NIDDK initiated the series in

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Bringing Science to Tribal Community

Tribal Leaders Discuss Research Priorities, Glimpse Into Intramural Life

BY MICHAEL TABASKO, OD

CREDIT: CHIA-CHI "CHARLIE" CHANG

Tribal Advisory Committee (TAC) delegates toured NHLBI intramural labs at this year's annual TAC meeting August 16–17, 2023. Shown: Staff Scientist Yvonne Baumer at the Social Determinants of Obesity and Cardiovascular Risk Laboratory, led by Tiffany Powell-Wiley. Powell-Wiley explained the lab's community-centered research approach which has been gaining traction among health disparities researchers and those working with American Indian and Alaska Native populations.

Alicia Mousseau, Vice President of the Oglala Sioux Tribe, set the day's tone with an opening invocation, "that the research and efforts we do here are taken back to our communities and help them and continue to help us prosper and grow."

This was day two of NIH's annual Tribal Advisory Committee (TAC) meeting where Mousseau and other elected Tribal officials exchanged views, gathered information, and advised how NIH programs could best address the health challenges facing their respective nations. The TAC agenda typically includes panel presentations by American Indian and Alaska Native (AI/AN) researchers, a Tribal caucus, and discussions with NIH leadership.

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Welcoming Colleagues: The Honor is Ours

BY NINA F. SCHOR, DDIR

This is a challenging piece to write. Not because the words are hard to find. (While I cannot dance or sew to save my life, words and music have always come effortlessly to me.) No, this is difficult because I must write of hurt inflicted on many of us in our NIH community.

The hurt I speak of comes from condescending and belittling remarks, however unintentional they may be. I myself have been affected by these with some regularity since coming to the NIH. If *I* feel hurt sometimes—I, someone who trained and developed most of my career in an unforgiving era in which making women and people of color feel inadequate and unwelcome was a cottage industry and who now has the courage and career of her convictions—I can only imagine how those at early stages of their careers are made to feel.

Each year, we are honored and fortunate to have truly outstanding, creative, and passionate researchers join our community. Some come from within the NIH, while others join us from training, clinical, or investigative positions in other institutions around the world. Too often in the past six years, I have heard someone say to a newcomer to the NIH, "You are so lucky to be here. There is no place else in the world where you could do the kind and quality of science we do here."

Well, proud as we may be of the NIH, there are many premier research facilities across the globe. Brilliant minds do great research there, and the NIH Intramural Research Program can learn from them. Times have changed. The NIH now is blessed by our success in both training and funding leaders who built remarkable research programs around the U.S. and world. True, medical schools in the 1960s and '70s were apprenticeship enterprises, training clinicians in the art and science of diagnosis and treatment; but now academic medical centers are veritable hotbeds of outstanding research and biomedical product development.

In the decades while many at the NIH were steelily focused on the exceptional work they and others were doing within our campuses and were not watching beyond our borders, these academic medical centers were accruing endowments, creating partnerships with industry, garnering extramural funding from NIH, and recruiting the wonderful people we and they themselves train. They have grown truly remarkable research communities that honestly do things that the IRP is not equipped or meant to do. They represent an opportunity for partnership and a synergistic international community with which for us to engage.

So, imagine how it might feel to have spent more than a decade or two building skills, developing a career of substance, only to come to the NIH to have people make you feel like you were just born on the day you got your PIV card. I have commented to some that I must have been hired without anyone reading my CV! We must make an effort to say, "We are so lucky to have gotten you to come here" instead of ascribing to the luck of our recruits what was born of hard work and magnificent opportunity afforded them in non-governmental sectors.

My own experience has made me certain that many at the NIH think this wonderful institution is so unique, that nothing I experienced or did or earned in my 32 years in academia, just shy of 30 of them engaged in bench research funded by the NIH, provided me with skills and knowledge applicable to leadership here. (To be more candid than perhaps I should, if one more person starts a sentence with, "You don't know this yet, but…" or "You're too new to have developed trusting relationships with people here…," I think I shall totally lose my usually calm demeanor!)

I am seasoned; I am experienced; I am very tough and tend to view everything through the lens of humor. And even I have found the NIH hard to like, despite its being easy to love. We must attract the best and the brightest and the most collegial and collaborative whoever and from wherever they may be. We must make them understand that we are so excited to welcome them to NIH because of who they are and where they have been before they got here.

As we approach the close of another impactful year at NIH, let us applaud the richness of the scientific community all around the world and leverage this diversity of strengths for the advancement of science and health! ●

Sidransky and Singleton Win the Prestigious Breakthrough Prize

BY *NIH CATALYST STAFF*

NIHers Ellen Sidransky and **Andrew Singleton** have won the 2024 Breakthrough Prize in Life Sciences for their impactful scientific discoveries of the most common genetic causes of Parkinson's disease. They share this prestigious recognition with Thomas Gasser of the Hertie Institute for Clinical Brain Research in Tuebingen, Germany.

The Breakthrough Prize Foundation made the announcement on September 14, 2023. The citation reads: "For identifying *GBA1* and *LRRK2* as risk genes for Parkinson's disease, implicating autophagy and lysosomal biology as critical contributors to the pathogenesis of the disease."

CREDIT: NHGRI

Ellen Sidransky is Chief and Senior Investigator in the Medical Genetics Branch at the National Human Genome Research Institute. She identified mutations in the gene *GBA1*, which encodes an enzyme that breaks down fatty substances in cells, as a genetic risk factor for Parkinson's.

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Sidransky's discoveries in Parkinson's disease began through her long-term investigations into another disorder, Gaucher disease, a rare genetic condition that can present in childhood or adulthood and is caused by a disruption in cells' ability to break down fatty molecules. In symptoms and development, Parkinson's disease is vastly different from Gaucher disease, but her discovery of genetic links between these conditions could help develop future treatments for both diseases.

A patient of Sidransky's with Gaucher disease developed early-onset Parkinson's disease, leading her to wonder whether there was any connection between these two conditions. Sidransky then identified other patients with Gaucher disease who had Parkinson's disease and also found that many of her patients with Gaucher disease had family members with Parkinson's disease.

Sidransky's research story is relayed, in part, in her 2020 Wednesday Afternoon Lecture Series (WALS) Astute Clinician Lecture, "Gaucher Disease: How a Rare Disease Provides a Window into Common Neurodegenerative Disorders," archived at https://videocast.nih.gov/watch=38966.

Singleton is an NIH Distinguished Investigator in the National Institute on Aging and Director of the NIH Intramural Center for Alzheimer's and Related Dementias (CARD). He leads a worldwide team of researchers who study the genetics behind Parkinson's disease and other neurodegenerative disorders.

He and Gasser independently demonstrated that mutations in the *LRRK2* gene result in increased activity of a protein believed to contribute to neuronal damage in the disease. These discoveries offer clues to the disease mechanism, pointing to the role of the lysosome, the cellular organelle that degrades and recycles cellular components.

CREDIT: NIA

Andrew Singleton is an NIH Distinguished Investigator in the National Institute on Aging and Director of the NIH Center for Alzheimer's Related Dementias. He leads a worldwide team of researchers who study the genetics behind Parkinson's disease and other neurodegenerative disorders.

More specifically, Singleton's group discovered several genetic mutations that cause disease, including the alpha-synuclein multiplication mutation and mutations in *LRRK2*. His laboratory has identified most of the known genetic risk factors for Parkinson's disease. He was a founding member of the International Parkinson Disease Genomics Consortium and the Global Parkinson's Genetics Program.

Singleton's research story is relayed, in part, in his 2021 WALS G. Burroughs Mider Lecture, "Leveraging the Intramural Research Program to Effect Foundational Progress in Neurodegenerative Disease," archived at https://videocast.nih.gov/watch=44237.

Established in 2012, the Breakthrough Prize comprises a set of international awards bestowed in three categories: Mathematics, Fundamental Physics, and Life Sciences. Gasser, Sidransky, and Singleton will share a $3 million award. More information about the 2024 Breakthrough Prize is at https://breakthroughprize.org/News/83. ●

Building a Central Nexus of Computational Biologists Across NIH

NLM's New Scientific Director: Richard Scheuermann, Ph.D.

BY ANNELIESE NORRIS, NCI

CREDIT: NLM

Richard Scheuermann, a leader in informatics, data science, and computational methods, is NLM's new Scientific Director

The National Library of Medicine (NLM) welcomed **Richard Scheuermann** as its new Scientific Director in September. Scheuermann is a leader in informatics, data science, and computational methods with a breadth of experience in molecular immunology and infectious diseases. Prior to arriving at NIH, Scheuermann was Campus Director of the J. Craig Venter Institute (JCVI) in La Jolla, California, where he also served as Director of Informatics.

He held additional leadership positions as Adjunct Professor of pathology at the University of California at San Diego (San Diego), and at the La Jolla Institute for Immunology, Center for Vaccine Innovation (San Diego).

Best of both worlds

Scheuermann grew up with working-class roots in a small town in upstate New York. His father was a railman and his mother stayed home to raise the family before starting a travel agency. Surrounded by countryside dotted with dairy farms and apple orchards, he recalls having the best of both worlds. Only 60 miles from Manhattan, he could savor nature and also easily catch a Broadway show and enjoy the culture and myriad restaurants in the city.

While naturally drawn towards a career in science, Scheuermann was initially dissuaded by a doubtful high-school career counselor from applying to the Massachusetts Institute of Technology (Cambridge, Massachusetts). Intuitively, he didn't listen and would earn his bachelor's degree at MIT in life sciences, followed by a Ph.D. in molecular biology at the University of California at Berkeley (Berkeley, California). He would go on to lead laboratories and research programs at the University of Texas Southwestern Medical Center (Dallas) and Southern Methodist University (Dallas).

One of his biggest influences at MIT was David Baltimore, California Institute of Technology President Emeritus and Nobel laureate. To this day Scheuermann practices what Baltimore taught him: "Go straight to the methods and results [section on a paper] and then figure out yourself what the experiments really show," he tells his trainees.

Scheuermann speaks fondly of his second mentor, the late Annamaria Torriani-Gorini, Professor Emerita of Biology at MIT, who was Scheuermann's undergraduate thesis supervisor. "[Working on my thesis] was a great experience and convinced me that I really wanted to do research as my career," he said.

From molecular immunology to informatics

Scheuermann's interest shifted from molecular immunology to informatics when he was asked by the late Alfred Gilman, Nobel laureate and Dean of the University of Texas Southwestern Medical School (Dallas), to be part of a large-scale collaboration called the Alliance for Cellular Signaling, which categorized cellular signaling networks for use by the entire research community.

Scheuermann set up the wet lab part of the project. "It quickly became obvious that the limiting factor was how to manage and analyze the high-throughput data," he said. A sabbatical followed at the San Diego Supercomputer Center at the University of California at San Diego, where Scheuermann became serious about informatics. Following two successful NIH grant proposals, he was able to transition wholly to informatics research.

Scheuermann considers his contribution to the bioinformatics response to COVID-19 among his most important recent work. He was part of a team assembled by the National Institute of Allergy and Infectious Diseases to do real-time analysis of emerging SARS-CoV-2 variants. "It was exhausting…but very interesting and impactful," said Scheuermann of his tireless task to rapidly use informatics to predict the impact that mutations would have on viral fitness and subsequently on the efficiency of vaccines.

NLM: A professional nexus for computational biologists

Looking forward, Scheuermann has a vision for the NLM and hopes to establish collaborations with other intramural researchers in wet laboratories. "NLM provides the perfect ecosystem…to serve as a professional nexus for computational biologists across NIH," he said.

"It's been like drinking from a fire hose," said Scheuermann of his whirlwind inaugural months. "But it's been really nice to meet people and interact with the whole leadership team of the NLM."

When he's not working, you might find Scheuermann in the kitchen. "Cooking is like working in a laboratory, but you actually get to eat the results," he said; or on the pickleball court—a mixture of tennis and table tennis—"but it's a lot more sociable," he added with a smile. ●

Catherine Gordon Named New NICHD Clinical Director

Pediatric Endocrinologist Returns to NIH to Lead Clinical Research

BY MICHAEL TABASKO, OD

CREDIT: NICHD

Catherine Gordon is NICHD's new Clinical Director

"It was a transformative summer," said **Catherine Gordon** of her 1984 internship at NIH. "As a young student, there was this amazing buzz at the Clinical Center (CC)."

An aspiring medical student some 40 years ago, Gordon worked at the National Library of Medicine and volunteered on the CC's pediatric oncology ward that summer. She recalls the nurses, two of whom she lived with, teaching her about clinical protocols. Research emerged on her radar.

Gordon would go on to craft a decorated career in academic medicine, most recently as professor of pediatrics at Baylor College of Medicine (Houston). Her path has come full circle; she steps into the role of Clinical Director (CD) of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) this September.

Dual trained in pediatric endocrinology and adolescent medicine, she sees her new position as an opportunity to blend those professional passions.

"It always felt like a partnership," said Gordon of her NIH connection. She has received numerous extramural research grants for her pioneering work on childhood bone health and served on NICHD Director **Diana Bianchi's** Advisory Council from 2016 to 2020. During the pandemic, she led a front-line primary-care team as Chief of Adolescent Medicine at Boston Children's Hospital (Boston).

"That experience and watching the partnership of the federal government and health care centers working collaboratively planted a seed regarding a future career in public service," she said.

She looks forward to a synergistic relationship with NICHD Scientific Director (SD) **Christopher McBain**. While McBain thinks largely about basic and translational research, Gordon will focus on trials and other clinical studies, including FDA-regulated protocols, to ensure that all studies align with regulations.

"Clinical scientists like me might want to think more mechanistically and understand the etiology of what they are seeing at the CC," she said, adding that basic scientists may want to roll out their discoveries in the clinic. "As CD as I will be brainstorming with them and helping them to develop protocols to enable that."

Several ICs already have reached out to collaborate with her group's research. She's joining long-time colleague **Veronica Gomez-Lobo** in launching a protocol studying premature ovarian insufficiency, menopause in an adolescent, often unexplained, that has implications for bone health.

"We want to make NIH a destination center for these adolescents," she said.

Gordon has been on a mission to raise awareness about bone health during those critical developmental years. She brings to the NIH her own lab that has focused on discovering modifiable factors in childhood and adolescence that optimize bone development.

She is well known for studying the mechanisms behind bone loss in diseases such as anorexia nervosa and for proposing new oral treatments. She's interested in identifying and modifying lifestyle factors such as not getting enough calcium or vitamin D, or not engaging in the right physical activity. She also does research on progeria, the exceedingly rare condition marked by accelerated aging, and she was part of a team that tested a chemotherapeutic agent that was recently FDA approved to prolong those patients' lives.

At the NIH, another focus for Gordon will be developing tools that can be used to noninvasively, safely, and quickly evaluate the skeletal health of children and adolescents. To that end, NICHD has purchased a high-resolution peripheral quantitative computed-tomography scanner that enables bone density and skeletal strength assessments of the peripheral skeleton.

Of NICHD's 69 clinical protocols that she'll oversee, Gordon is excited by them all: "We're looking at childhood and adolescent obesity, thinking about its etiology and management, and delving into a number of rare diseases to investigate therapies and understand the natural histories, among many other areas."

She is thinking about social determinants of health and how even a ZIP Code might affect someone's access to protocols. Expanding the reach of satellite community-centered research clinics within certain neighborhoods will be a way to sample people more broadly and ask questions with less bias.

Gordon credits her career trajectory to the guidance of a long line of mentors: a pediatrician she volunteered with while growing up in her hometown of Raleigh, North Carolina; a hematologist-oncologist whose molecular biology lab she worked in at the University of North Carolina at Chapel Hill, where she earned her medical degree; and a clinical research scientist while a fellow at the Harvard School of Public Health. She hopes to pay it forward.

"It's great to be back to think about new discoveries to advance patient care," she said, "but also to mentor the next generation of scientists." ●

Bringing Science to Tribal Community

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This year, the delegates were also invited to tour intramural labs at NIH's Clinical Center (CC).

"We want to make sure that AI/AN people understand the research that we do here and that they have the opportunity to participate," said Senior Investigator and Clinical Director **Richard Childs** of the National Heart, Lung, and Blood Institute (NHLBI) as he welcomed the TAC to the CC's medical board room on August 17.

Childs gave them a flavor of what the CC does best: translating the elements of basic science into important clinical discoveries that would be often impossible to conduct anywhere else, technologies such as advanced cardiac magnetic-resonance imaging to accurately diagnose cardiovascular disease, or drugs that have dropped the mortality rate of the rare disease aplastic anemia from 80 percent to less than 5 percent in recent years.

He pressed the importance of increasing diversity in research, citing repeated examples where some ethnic groups were shown to metabolize and respond to drugs quite differently. "We believe that with diversity comes excellence," said Childs. "It's very important that when we do these studies, we determine that we have the correct dose for all groups."

That's a sentiment shared by **Julie Erb-Alvarez,** Chief of NHLBI's Patient Engagement and Recruitment. Erb-Alvarez is a member of the Cherokee Nation and is passionate about connecting science to underrepresented communities.

"We may not understand the burden of diseases in certain populations because of the lack of diversity in research," she said before the group departed for the CC labs. "This is just one of the ways that we can educate about what we do so that more people feel comfortable and choose to come here and be involved in research."

The TAC delegates' first peek into intramural lab life was at Childs' Laboratory of Transplantation Immunotherapy. Here, scientists explained how they grow natural killer (NK) and T cells to large numbers and then genetically alter them to be more effective at killing cancer.

Gathering around a microscope's digital display, the group peered down at glowing green multiple myeloma cells in a dish. The cancer cells' numbers had been decimated over the course of eight hours by reprogrammed NK cells.

"We're really good at killing cancer in vitro," said Childs, before detailing the rigorous, years-long process of optimizing safe and effective therapies in humans. "If you do this work well in the lab, when you bring it to human trials the treatment will have a much higher likelihood of being effective," he said.

Childs' lab is currently finishing up a phase 1 trial treating patients with a type of kidney cancer using genetically reprogrammed T cells.

Next up on the tour was the lab of NHLBI's Stadtman Investigator **Tiffany Powell-Wiley**. Her Social Determinants of Obesity and Cardiovascular Risk Laboratory founded a clinic in Washington, D.C., called the Hope Center to make it easier for individuals in underserved areas of the city to be a part of research. "That allowed us to build trust and bring patients here for our studies," she said.

The community-centered approach, in which underrepresented groups participate in all aspects of a research project to help tailor culturally relevant interventions, has been gaining traction. It's often used among researchers working with AI/AN populations experiencing multifaceted health challenges including addictions, access to behavioral health suicide preventions, and effects of climate change.

Beyond family risk factors, the Powell-Wiley lab is studying how the social environment, such as neighborhood crime rate, may be associated with cardiovascular disease. One theory is that high-stress environments can trigger a release of catecholamines—fight-or-flight hormones—and increase disease risk.

Powell-Wiley hopes to find interventions to build resilience among patients living in those adverse conditions. "How do social factors get under the skin, and how can we find interventions that target some of those pathways that we identify here in the lab?" she asked.

CREDIT: CHIA-CHI "CHARLIE" CHANG

Clinical Center Chief Operating Officer Pius Aiyelawo welcomes Tribal Advisory Committee (TAC) delegates to the north atrium. At the annual TAC meeting, elected Tribal officials exchanged views, gathered information, and advised on how NIH programs could best address the health challenges facing their respective nations.

CREDIT: CHIA-CHI "CHARLIE" CHANG

NHLBI Clinical Director Richard Childs explains to Tribal delegates how his Laboratory of Transplantation Immunotherapy grows natural killer and T cells to large numbers and then genetically alter them to be more effective at killing cancer. "We want to make sure that AI/AN people understand the research that we do here and that they have the opportunity to participate," he said.

Her lab is working on a physical activity intervention study to see how it improves cardiovascular health or changes some of the adversity-related biomarkers that they've discovered. And they're collaborating with extramural labs studying epigenetic markers and biomarkers of stress in the brain.

A second project is looking at how neighborhood factors and stressors play a role in immune function and vascular health.

Connecting the dots between environmental stress and disease risk resonates with Tribal communities, too. "How do we find out about these projects?" asked one of the delegates.

NIH's Tribal Consultation Policy ensures that Tribal leaders have early input into NIH programs and priorities. And **Karina Walters**, Director of NIH's Tribal Health Research Office (THRO), hopes to increase NIH presence in Tribal communities to listen to their health priorities and provide information about NIH's research programs.

Internal NIH cultural awareness training for staff to better understand AI/AN cultural considerations for ethical and appropriate inclusion in research is another priority. THRO also plans to develop and grow more NIH programs and opportunities that will increase the number of AI/AN researchers conducting biomedical and behavioral research.

"The combination of Indigenous strengths and knowledge in partnership with NIH's broad research interests and capacity have the potential to address AI/AN health challenges in a collaborative approach," said Walters.

Powell-Wiley suggested that perhaps future studies could incorporate questionnaires that capture the effects of intergenerational trauma and begin to tease out precisely how shared traumatic experiences influence health. "We are very open to thinking about other populations," she said, "where we could look into some of these pathways that we've seen in other cohorts, and sharing some of these methods that we do." ●

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
DIPHR: Division of Intramural Population Health Research, NICHD
FAES: Foundation for Advanced Education in the Sciences
FARE: Fellows Award for Research Excellence
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
OITE: Office of Intramural Training and Education
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health
OTT: Office of Technology Transfer

Bright, Fresh Ideas

Snapshots from Early-career Investigators

BY STEPHEN ANDREWS, NCI

A new cohort of early-career investigators from across the NIH set an enlivening tone for this year's NIH Research Festival with a series of lectures on September 18 and 19 in the Lipsett Amphitheater in Building 10 describing their innovative and collaborative research.

The unstated theme for the 2023 NIH Research Festival was "the next generation," and if these lectures are an indication, the future of NIH looks bright. From community-centered engagement to cutting-edge medical technology, Independent Research Scholars (IRS) and Assistant Clinical Investigators (ACI) showcased their high-impact work and creative spirit for new ways to answer difficult questions.

The next generation

Session one featured six IRS presenters, whose research runs the gamut from the microbiome to medial septum glutamate neurons.

First to speak was **Andrew Kesner** from the National Institute on Alcohol Abuse and Alcoholism. A neuroscientist by training, Kesner has long been interested in the ways that the brain can affect the way we as humans interact with and interpret stimuli. He outlined the ways in which glutamate neurons, brain cells that recognize a specific neurotransmitter, influence addiction.

CREDIT: MARLEEN VAN DEN NESTE, NIH

Independent Research Scholar Andrew Kesner of NIAAA outlined the ways in which glutamate neurons, brain cells that recognize a specific neurotransmitter, influence addiction.

Carrie Mae Long, from the National Institute of Allergy and Infectious Diseases (NIAID) Rocky Mountain Labs, presented her work on Q fever, a dangerous bacterial disease, admittedly rare but nevertheless high-risk in certain animal husbandry and veterinary settings. She is leading the charge in developing a better vaccine to prevent transmission and advanced disease.

Keeping with the infectious disease thread, NIAID's **Emily Ricotta** highlighted her data-focused approach to monitoring public health and emerging disease outbreaks. And **Oyebola Oyesola** from NIAID's Laboratory of Parasitic Diseases then described how parasitic worms known as helminths may play a role in immunity to SARS-CoV-2 in mice through the adaptive immune system.

CREDIT: MARLEEN VAN DEN NESTE, NIH

Carrie Mae Long, an Independent Research Scholar from NIAID's Rocky Mountain Labs, presented her work on Q fever, a dangerous bacterial disease. She is leading the charge in developing a better vaccine to prevent transmission and advanced disease.

Shaun Abrams of the National Institute of Dental and Craniofacial Research (NIDCR) outlined how intricacies of cell biology can affect how the face develops in utero. And **Mary Diaz Santana** of the National Institute of Environmental Health Sciences (NIEHS) closed the first session with insights on the epidemiology of breast cancer in Hispanic women.

Throughout these morning talks, it was apparent that the IRS program—with its dual goals of improving workforce diversity and prepping gifted scientists for the rigors of a future, tenure-eligible position—additionally allows early-career scientists the opportunity to be creative and ask unique questions to investigate issues that are less mainstream or perhaps understudied by the greater scientific community.

CREDIT: MARLEEN VAN DEN NESTE, NIH

Independent Research Scholar Oyebola Oyesola from NIAID's Laboratory of Parasitic Diseases described how parasitic worms known as helminths may play a role in immunity to SARS-CoV-2 in mice through the adaptive immune system.

Watch the Session I archive at https://videocast.nih.gov/watch=49913.

From clinical collaboration to neurosurgical insights

For the afternoon session on September 18, ACI presenters took to the stage. First up was **Blake Warner**, from NIDCR, whose research targets the impact of Sjögren's disease on maxillofacial immunopathology. Through large sequencing datasets, primarily with RNA, Warner can use patient salivary gland tissue from his procedures to elucidate signaling pathway differences that play a role in this disease pathology. He discovered a pathway that may be implicated and plans to continue validating these findings with new experiments.

Sara Inati of the National Institute of Neurological Disorders and Stroke (NINDS) detailed her work monitoring patient outcomes during and after temporal lobe surgery for epilepsy. With a multimodal approach to brain imaging, Inati can paint a full picture of the brain pre- and postoperation with a series of controlled functional magnetic-resonance imaging scans and subdural electroencephalogram modeling. She credited her work to a productive working relationship with other investigators and clinicians at NIH. "We cannot do anything without collaboration," said Inati.

This thread of collaboration within the NIH remained strong throughout the lecture sessions and provided a view of how these investigators are changing the landscape of medical research and affecting the outside community. **Lisa J. Reynolds** from the Division of Cancer Epidemiology at NCI spoke next. By blending clinical cancer care and epidemiology, Reynolds described her prospective "genotype-first" research on Fanconi anemia, a genetic condition that is associated with an increased risk for cancer, specifically acute myeloid leukemia.

Desmond Brown of NINDS closed Session II, still in his scrubs, fresh from the clinic. For his lecture, he described the value of using insights from neurosurgery to research the biology of aggressive brain cancers, such as glioblastoma multiforme. And then back to the clinic he quickly went.

Watch the Session II archive at https://videocast.nih.gov/watch=49915.

CREDIT: NIH VIDEOCAST

Chairs of the Independent Research Scholar lecture sessions, Tokunbor Lawal, (NINR) and Parinaz Fathi (NIBIB), introduced speakers and entertained questions

Clinical expertise informing data-driven research

Four more ACIs took the stage the next day for Session III, focused on investigations of cancer biology and neuroscience via data science and community engagement. The first speaker, **Padma Sheila Rajagopal** from NCI, detailed germline and somatic interactions in cancer, a relationship that is often overlooked in oncologic research. By using large, relational databases that connect sequencing data to patient information and outcomes, her group can make more appropriate conclusions that have been fruitful for common cancers, such as breast and prostate. Rajagopal hopes to apply the method to rare cancers, too. "The Rare Tumor Initiative here at NIH moves us in the right direction toward getting the data that we require for these studies," she said.

Cancer research through a different lens was the focus of NCI's **Ramya Ramaswami's** talk. Her work on Kaposi sarcoma biology highlighted the effects of health disparities both domestically and globally in how they affect the incidence of this HIV-associated pathology. Her work aims to close the gap in care for these patients. **Samira Sadowski** from NCI, a surgical oncologist, provided her perspective on pancreatic neuroendocrine tumors and how uncovering the epigenetic regulation of drug targets may improve outcomes for patients with advanced disease.

To conclude the session, **An Dang Do** of NICHD, who had doubled as the session moderator, described her research efforts to uncover biomarkers associated with stress responses in neurological conditions, highlighting how these ACI investigators are able to leverage their unique clinical expertise to inform cutting-edge, data-driven research.

Watch the Session III archive at https://videocast.nih.gov/watch=49935.

Expanding community research and probing pathogenesis

To conclude this year's early-career investigator lecture series, six additional IRS presenters took to the podium for Session IV. First to speak was **Jessica Madrigal** from NCI. She described her community-oriented approach to investigating the effect of air pollutants on the etiology of cancer in a variety of sociodemographic groups across the United States.

Another health-disparities researcher, NIEHS's **Alex Montiel Ishino,** outlined transdisciplinary approaches to epidemiological research in pursuit of health equity, the most philosophical presentation of those first two days of the Research Festival, included how the goal is to "create pipelines for communities and researchers" to make lasting connections.

CREDIT: MARLEEN VAN DEN NESTE, NIH

Crystal Peterson of NHGRI's Health Communication and Behavior Unit, Social and Behavioral Research Branch, gave a presentation about the Stigma Scientific Interest Group at a research festival session held in the NIH Library on Monday, September 18.

Yukiko Yano from NCI next provided insights into how the oral microbiome can affect health throughout the body. Then, **Tasha A. Morrison** from the National Institute of Arthritis and Musculoskeletal and Skin Diseases detailed her investigations deep into the molecular biology of the immune system's natural killer (NK) cells, which neutralize and kill damaged cells. She described how the *UGCG* gene affects glycosphingolipid synthesis, which is vital for the cytotoxic functions of these NK cells.

NICHD's **Philip Patrick Adams** explained his investigations into *Borrelia burgdorfei*, one of the main pathogens associated with Lyme disease. He described how bacterial motility could be associated with the increase in the rates of the disease seen in regions in the United States where ticks are prominent. To conclude the final session of lectures, **Portia Gough** of NIAID presented on another pathogenic organism, *Roseomonas mucosa*.

Across the two days of lecture, many of these presenters revealed how truly connected they are to the communities and patient cohorts that they serve. Such relationships, they emphasized, provide insights that drive their research questions and increase the impact of their work.

Watch the Session IV archive at https://videocast.nih.gov/watch=49937. ●

Hunting Down Good Science

Discovery on Display at the NIH Research Festival Poster Sessions

BY CODY CONRAD (NIAID) AND DARWING PADILLA ROLON (NIAID)

CREDIT: MARLEEN VAN DEN NESTE, NIH

David Adzrago of NIMHD explained his poster which explored associations between mental health and physical activity.

The air was astir with the rum-bling of fresh findings emanating from the postpandemic return of the NIH Research Festival on Monday, September 18. Over the next two days, nearly 400 posters capturing the breadth of NIH intramural research lined the Clinical Center FAES terrace, with an additional 40 showcased in a Wednesday virtual-only session.

Beaming scientists, both novice and tenured, stood poised at their stations, eager to present. A curious multitude of students, fellows, staff scientists, principal investigators, and more grazed about to network and to contemplate this latest crop of discoveries and ideas on display.

Among the presenters was Postdoctoral Fellow **Verity Ford** from the Clinical Center's Critical Care Medicine Department, who studies the effects of sepsis on the heart and focuses her passion for research to answer critical care medicine's most burning questions.

Ford's work in Senior Investigator **Charles Natanson's** lab demonstrated that the end-diastolic volume of hearts in surviving animals that are experiencing septic shock is substantially higher than in nonsurvivors. The damaged heart muscle becomes unable to pump blood properly, and this problem can lead to heart failure, highlighting the detrimental effect that sepsis can have.

Unexpectedly, the dry mass of the heart decreased markedly during sepsis, leading Ford to posit that heart endothelial cells, its intracellular contents, or the extracellular matrix may be damaged and being removed or sloughing off during disease. Her poster showed how magnetic-resonance imaging can be used to calculate decreasing heart mass in living organisms with sepsis.

Ford said that Natanson is equally intrigued by the new findings, and the scientists are ready to delve deeper into the data to uncover more about sepsis' effect on the heart as a way to understand the multi-organ failure that is the leading cause of death from sepsis.

Further down the maze of posters, postdoctoral fellow **Yi Wei Lim** at the National Center for Advancing Translational Sciences (NCATS) was ecstatic about measuring the immunological success in her tissue samples. Her enthusiasm about the resources available at NIH and her work shone through as she discussed the finer points of manufacturing full-thickness, immunocompetent skin.

Lim and her supervisor **Marc Ferrer**, Director of NCATS' 3D Tissue Bioprinting Laboratory, delight in defying the limits of what is possible in a laboratory setting where they produce, validate, and use 3D biofabricated tissues for disease modeling and drug discovery. She described the creation of a high-throughput system to evaluate the disease-modeling capabilities and immunological features of their biofabricated skin.

Her team found that in the presence of bacterial and viral stimuli, immune markers and components were highly upregulated and shown to be macrophage-dependent, demonstrating that the model behaved immunologically like real skin. And according to Lim, some markers of healing progressed faster than expected. "I was expecting pro-inflammatory macrophages to become anti-inflammatory macrophages later in the skin culture [immune response] but was surprised that the switch was rapid—within 72 hours," she said.

The investigators hope that their model will allow for high-throughput pharmacological, wound healing, and infectious disease studies involving epithelial tissue.

Ryo Sato's Fellows Award for Research Excellence-winning poster showed how class III beta-tubulin may be a potential biomarker for idiopathic pulmonary fibrosis, a condition in which the lungs become scarred, affecting breathing. Sato is a Visiting Fellow at Senior Investigator **Yosuke Mukoyama's** lab at the National Heart, Lung, and Blood Institute. Through high-resolution imaging they have shown how pericytes, specialized cells lining the walls of capillaries, induce the tubulin expression in response to inflammatory signals and modulate the detrimental effects that fibrotic macrophages and fibroblasts have on pulmonary fibrosis. According to Mukoyama, Sato's unexpected results have proven to be a significant discovery.

The team seeks to understand the neurovascular mechanisms behind that pathway, which could revolutionize the way we diagnose and treat pulmonary fibrosis.

"Mentoring fellows is among the most rewarding part about my work," said Mukoyama. He is excited to see what the future may hold for early-career investigators like Sato, and he enthusiastically supports his fellows' drive to start their own labs to expand on the clinical implications of their discoveries.

Jennifer Zink, a Cancer Prevention Fellow in the Behavioral Research Program at the National Cancer Institute, presented her work that analyzed screen-time data of 10-year-old youth. She used data from NIMH databases to evaluate whether different kinds of screen time—gaming, streaming, or socializing—were related to Body-Mass Index while also accounting for other factors such as physical activity and sleep. She found that boys with more socializing time had higher BMI.

To further probe that association, Zink used the traditional isotemporal substitution method, which models theoretical behavioral replacement effects. For example, if 30 minutes of gaming was replaced with 30 minutes of socializing, it had a theoretical beneficial effect on BMI. "I do think that there is some sort of interpersonal or social component that is contributing to these different associations [that needs] to be further investigated," Zink said.

While in graduate school Zink worked on similar research in which she studied how screen time may have a detrimental effect on mental health. She hopes to continue this kind of multidisciplinary approach to better understand the relationships between sociobehavioral factors and health.

For the first time at the NIH Research Festivals, the organizers arranged a virtual-only session particularly for NIH colleagues not on the Bethesda campus, such as those in North Carolina at the National Institute of Environmental Health Sciences (NIEHS).

Among the dozens presenting in this new format was Independent Resarch Scholar **Mandy Goldberg**, who presented research done as a postdoctoral fellow in NIEHS' Epidemiology Branch, led by **Dale Sandler**. Her virtual booth was packed with visitors eager to hear about personal-care product use during puberty and the incident breast cancer later in life. The unpublished work may be the subject of a future *Catalyst* article.

Anisha Singh, a postdoc in the NIEHS Division of Translational Toxicology, Integrative Health Assessments Branch led by **Andrew Rooney**, presented her group's early work in developing a systematic evidence map of autism research. This interactive database will be called aWARE, short for a Web-based tool for Autism Research and the Environment. Their objective is to identify and characterize published literature relevant to environmental exposures associated with autism spectrum disorder and summarize or map the research gaps and knowledge clusters—yet another project to follow.

Ian Trees, a postdoc in the laboratory of **Edwina Yeung** in the Epidemiology Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), reported on a nugget from the Upstate KIDS Study, a collaboration among the New York State Department of Health, the University at Albany (State University of New York), and NICHD. His team found evidence that prenatal exposure to particulate matter may affect birthweight depending on other pollutants and specific windows of exposure.

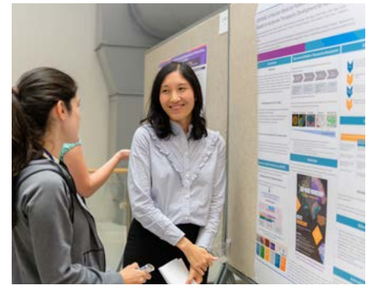
Collectively, the posters revealed a fantastic diversity of research thriving in the NIH IRP, with the science community not afraid to push the limits, think outside the box, and share ideas. To see poster abstracts, refer to https://researchfestival.nih.gov/2023/poster-sessions-presentations. ●

Cody Conrad is a postbaccalaureate trainee at the Laboratory of Viral Diseases (NIAID) where he studies the mechanisms of papillomavirus infection. In his spare time he keeps busy with music composition, chess, and pickleball.

Darwing Padilla Rolon is a post-baccalaureate Intramural NIAID Research Opportunities Fellow and is studying neuroimmune interactions in neuroimmunological diseases by developing cerebral organoids. Outside of the lab, he enjoys playing volleyball and traveling to see his family in Puerto Rico.

CREDIT: MARLEEN VAN DEN NESTE, NIH

A research team from NIAAA's Translational Biobehavioral and Health Disparities Branch presented their work on unravelling gut-brain communication mechanisms in patients with alcohol use disorder. Shown left to right: Nicole Farmer, Jennifer Barb, Rebecca Metellus, Stephanie Wildridge, Katherine Maki, Karleigh Fraser, Scott Reid, Ayaan Ahmed.



CREDIT: MARLEEN VAN DEN NESTE, NIH

Darawalee Zong (shown on right) from NCATS presented her work on a precision medicine platform to accelerate therapeutic development for rare diseases.

Dale Sandler on Risk Factors for Breast Cancer

"Sister Study" Cohort Reveals the Power of Population-Level Research

BY NAOMI GREENBERG, SPECIAL TO *THE NIH CATALYST*

CREDIT: NIEHS

Dale Sandler and colleagues developed a large-scale prospective study to identify environmental risk factors for breast cancer. As this year's chosen presenter of the G. Burroughs Mider Lecture, on September 20, she presented an overview of this famed "Sister Study," which she has led for 20 years.

Breast cancer is expected to affect one of every eight women during their lifetime, making it the most common cancer diagnosis in women after skin cancer. Although some genetic and environmental contributors to the alarming incidence have been identified, many of the risk factors are yet unknown.

Dale Sandler, a Senior Investigator at the National Institute of Environmental Health Science (NIEHS), and colleagues developed a large-scale prospective study to identify environmental risk factors for breast cancer. As this year's chosen presenter of the G. Burroughs Mider Lecture, on September 20, she presented an overview of this famed "Sister Study," which she has led for 20 years.

Launched in 2003, the Sister Study comprises 50,884 women who each had a sister diagnosed with breast cancer. Sandler and her research team have collected data about each woman's environmental exposures through questionnaires, blood tests, and linking residential histories to geospatial exposure databases.

In her talk, Sandler walked the audience through the risk factors this large dataset enabled researchers to identify—factors that included tobacco use, early life trauma, lack of physical activity, toxic chemicals in hair straighteners, and other environmental risks.

So far, the Sister Study dataset has been the underpinning of over 300 research papers, many funded extramural grants, and multiple dissertations.

But despite the study's broad success, Sandler said the journey has not been free of challenges. In particular, she said it has been difficult to convey the importance of population studies in a research environment that focuses more on clinical and bench science.

"An ongoing challenge for me has been how to convey the importance of observational epidemiology to those whose one true path to scientific discovery is a mechanistic one. That's not my true path," Sandler told *The NIH Catalyst*. "Fortunately, over time, there has been greater recognition that both observational studies and mechanistic ones are necessary and complementary."

According to Sandler, cohort studies such as the Sister Study often face criticisms based on their lack of generalizability to a broader population. However, given the sister study's size and its alignment with other studies, the researchers are confident in the broad applicability of their results and view prospective population-level research as essential to address human health questions that cannot be studied on a molecular or individual level.

"We can think about the problem on a larger scale: how we can take all this basic science knowledge and turn it into something that's meaningful to improve the health of the population at large," Sandler said.

Although Sandler also contributed to two other major cohort studies—one studying agricultural exposures and one studying exposure from the 2010 *Deepwater Horizon* oil spill in the Gulf of Mexico—she says the Sister Study is her proudest accomplishment. "This was something I never thought I'd have the opportunity to do," she said.

Sandler also said she is proud of her mentorship, for which she has received the NIEHS Mentor of the Year in 2013, the NIH Honor Award in 2018, and most recently the NIH Graduate Partnerships Program Outstanding Mentorship Award in 2019.

Alexandra White, who worked with Sandler throughout her career as a Ph.D. student, postdoctoral fellow, and now a co-investigator on the Sister Study as a Stadtman Investigator, said Sandler's mentorship is valuable to her trainees.

"She is such a force of nature, and she's so inspiring," White said. "I could not be more thankful that I had the luck of having her as my mentor."

CREDIT: NIEHS

Alexandra White worked with Sandler throughout her career as a Ph.D. student, postdoctoral fellow, and now a co-investigator on the Sister Study as a Stadtman Investigator. Sandler expects the next generation of researchers, including White, to take over leadership.

White emphasizes that the Sister Study would not be the same if it weren't for Sandler. "It's just really impressive, the level of research she's conducted throughout her career."

Although many findings from the existing data have been published, the applications of the Sister Study are far from over. Sandler expects the next generation of researchers, including White, to take over leadership. The near future of the study might include the totality of environmental exposures, while the long-term goals might include looking at the subsequent generation of sisters to assess intergenerational risks.

According to Sandler, her legacy in the field of breast-cancer research is already emerging as she sees younger scientists take on the mission of the Sister Study and use the data to better understand risk factors in human health.

"I am already seeing it in the former trainees who are now independent researchers elsewhere," Sandler said. "That will be a terrific legacy, to see them become successful in their careers building on the cohort that I built."

The Mider Lecture, part of the Wednesday Afternoon Lecture Series, is the highest-profile lecture at the NIH delivered exclusively by an intramural scientist. Dale Sandler's nomination came from the Women Scientists Advisors, who are a group of elected representatives from each institute or center whose function is to represent the interests of women scientists at NIH. You can watch Dale Sandler's lecture at https://videocast.nih.gov/watch=49939. ●

Naomi Greenberg was a 2023 summer Research Intern in the lab of Takashi Akera at NHLBI, where she studied meiotic drive in mice. She is pursuing a major in biology with a minor in journalism at Georgetown University (Washington, D.C.) and plans to apply to graduate school to pursue a Ph.D. in evolutionary genetics.

NEWS FROM AND ABOUT THE SCIENTIFIC INTEREST GROUPS

New SIG: iPSC-Neuroscience Scientific Interest Group

Diseases involving the brain that adversely affect cognition, intellectual ability, behavior, mood, memory, perception of reality, and social functioning are exceedingly complex and have no known uniformly effective preventive and therapeutic strategies.

Together, such diseases represent a substantial component of the global burden of disease and thus exert a hefty liability on health care. This broad and diverse group of human ailments include neurodevelopmental disorders such as autism spectrum disorder, neurodegenerative diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, and neuropsychiatric disorders such as schizophrenia, bipolar disorder, and major depression.

Advances in genomics have led to a better understanding of the genetics of these diseases, but the critical neurobiological mechanisms involved in pathogenesis remain to be fully defined. Because access to living human brain cells for studies is not feasible, researchers have used model systems that can recapitulate some aspects of the disorder. One such model is represented by induced pluripotent stem cells (iPSCs) and derivatives, which are renewable cells that carry the full genetic complement of the donor (patient or nonpatient).

Cells grown in a 2D format, as 3D brain organoids, or more recently, as assembloids, are extensively used to dissect the biology underlying genetics, potentially generating new targets for drug discovery and developing methods for cell therapy.

More than a decade ago laboratories in NIH's Intramural Research Program (IRP) started to pursue iPSC-based research, several of which were focused on diseases involving abnormalities of brain function. The number of labs engaged in iPSC-based neuroscience research, which encompasses multiple and diverse diseases in the NIH IRP, has since grown steadily over the years.

The iPSC-Neuroscience Scientific Interest Group was formed in 2022 with the following goals:

- To discuss the many existing and continuing challenges involved in iPSC research and propose approaches and solutions to these challenges
- To invite NIH IRP researchers to present their iPSC-neuroscience related work
- To invite investigators who pursue iPSC-based neuroscience research from various universities and institutions here in the United States and abroad to present their work and recent findings
- To mentor graduate students and postdoctoral fellows in the NIH IRP in the iPSC-Neuroscience field
- To hold in-person meetings at least once a year, as permitted

Since monthly meetings began in May 2022, the SIG has hosted a diverse list of speakers who have shared their work on iPSC-related topics in multiple neuroscience-related fields.

Meetings usually occur virtually every first Thursday of the month at 12 noon from September to June. Several speakers have already committed to present and explain their iPSC-based work at meetings through June 2024.

For more information, go to https://oir.nih.gov/sigs/ipsc-neuroscience-scientific-interest-group or contact **Sevilla Detera-Wadleigh** (deteras@mail.nih.gov) or **Francis McMahon** (mcmahonf@mail.nih.gov). ●

Bryan Roth, Natural Products, and the John Daly Legacy

CONTINUED FROM PAGE 1

2009, a year after Daly's death, to honor his memory and maintain his goals in science.

Daly's almost 50-year illustrious research career at NIH began in **Bernhard Witkop's** lab. Witkop commissioned him to go in search of frog alkaloids in the rainforests of South America. Little did Daly know that this would be the start of a lifelong quest with monumental impact.

Daly took on the trappings of an "Indiana Jones" character in trading his comfortable lab for the harsh and at times dangerous environment of the rain forest—although unlike Indy, he loved snakes. Throughout his career he personally collected NP treasures from exotic places, providing abundant samples for research in chemistry, pharmacology, and natural sciences for generations to come.

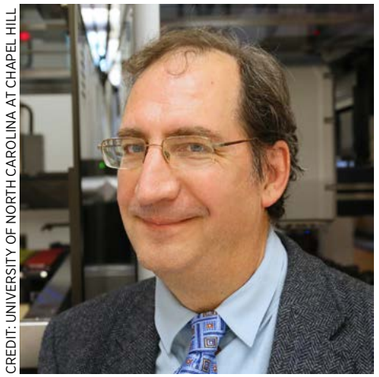
A premier and irreplaceable NP chemist and pharmacologist, Daly focused his research on the discovery, structure elucidation, synthesis, and pharmacology of alkaloids and other biologically active NPs. He used the molecules to understand receptor and ion channel biology.

Furthermore, Daly was influential in supporting trainees and their careers at NIH. He formed exceptionally deep connections, especially with his mentees.

CREDIT: CHARLES W. MYERS, HERPETOLOGICAL REVIEW, 2009

John Daly (NIDDK) was a pioneering chemist, pharmacologist, and field herpetologist whose work at NIH spanned five decades. Shown: Daly and a pack horse in the western Andes, on a 1970 Colombian expedition. The trip of 43 days was intended to close out a five-year survey of dendrobatid skin alkaloids. Instead, it stimulated further work by Daly that continued until his death in 2008.

"Perhaps without knowing it, John gave each of us a small piece of 'Daly-ness,'" said Fabian Gusovsky, one of Daly's former fellows, at the 2008 Tribute to John William Daly memorial shortly after Daly's death. "We took it and molded it and made it a part of our professional lives. We attempted to look at science in Daly's way," said Gusovsky, now in a leadership position at Eisai Inc., a Japan-based pharmaceutical company.



CREDIT: UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

Natural products have been used throughout human history to treat a wide spectrum of diseases, including psychological ones. Bryan Roth is unlocking the chemistry behind natural products such as hallucinogens, and revealing how they might be used to treat mental illnesses.

Roth's work

The Roth lab investigates the opioid and serotonin 5-hydroxytryptamine (5-HT) receptor families and their accessory proteins. During the lecture, Roth presented his work on salvinorum A (the active molecule of *Salvia divinorum)* and the multilayered process through which he and his collaborators identified its chemical structure and its high, and sole, affinity for the kappa-opioid receptor, a GPCR.

Because people who use salvinorin A have a specific and altered perception of their reality (dissociation), Roth and his collaborators concluded that the kappa-receptor is a receptor for perception that is internally generated.

"Dr. Roth's work has beautifully shown that NPs can be extremely powerful tools to unravel neural pathways," said **Carole Bewley**, NIDDK Laboratory of Bioorganic Chemistry Chief and Natural Products Chemistry Section Chief.

In recent years there has been renewed and serious interest in researching NPs such as hallucinogens, psychedelics in particular, as potential treatments for certain mental illnesses and drug development. Hallucinogens, a category of psychoactive compounds and classified by their mechanisms of action, produce altered states of consciousness experienced as major changes in perception, thought, and mood.

Roth explained that there is a science behind the classification.

"Not every compound that alters your perception is a psychedelic…and the phenomenology of the experience among different classes of hallucinogens is different," he said.

Roth is a scientific expert in, and one of few approved to study, psychedelics, and he is funded solely by the NIH and DARPA. He has explored the medical side of hallucinogens as a psychiatrist with patients and now focuses on GPCRs in the lab. He developed and runs the Psychoactive Drug Screening Program (PDSP) at UNC School of Medicine. PDSP allows for parallel physical screening to elucidate chemical biology of the "GPCR-ome" and other targets.

Roth said that with the renewed interest in psychedelics as therapeutics and claims that they can be used to treat neuropsychiatric disorders such as depression, cluster headaches, migraines, anxiety, and obsessive-compulsive disorder, it is important to understand the biology and pharmacology behind their therapeutic mechanisms, as well as potential risks in their widespread use as treatments.

Roth defines psychedelics as 5-HT_{2A} agonists, which induce LSD-like actions in humans. He believes that the 5-HT_{2A} receptor exists as a signaling complex at the synapse. So, the next frontier is to understand what the components are and solve the structures, he said. He would like to develop drugs that achieve the treatment benefits of these hallucinogens without the "trips."

Roth told *The NIH Catalyst* he was concerned that these natural compounds will be approved for use before we have enough information on how they work, and therefore how medical treatment should be safely and effectively implemented in a real-life setting. He hopes that once treatment drugs are approved, regulators will provide guidance on how medical professionals should screen potential patients and implement treatment plans, mindful of risk-management criteria.

"The next frontier here, the other thing my lab is really getting into, are complexes," Roth said. "We think that [the 5-HT_{2A}] receptor exists as a super-molecular signaling complex at the synapse, and we're trying to understand what all the components of this are and to solve the structures."

Roth's John Daly Lecture is archived at https://videocast.nih.gov/watch=51089. ●

Natural Products at NIH

Daly's legacy continues in many research laboratories across the globe, including at NIH.

"Natural product chemistry is highly important for biomedical research, as leads for more novel compounds that can interrogate biological systems and, in some cases, putting those new molecules on a translational path to possibly create new medicines," **Kenneth Jacobson** told *The NIH Catalyst*.

Carole Bewley is one of the scientists continuing Daly's legacy, both in the lab and in the field. Bewley scuba dives under the sea to personally collect specimens for her research. Daly was involved in recruiting Bewley for the NIDDK Bioorganic Chemistry lab, which he founded.

Inspired by nature, Bewley aims to find new molecules and use them to understand biological processes—in her case, anti-infective agents. Natural products are "nature's gifts to humanity because they are made by living organisms and enzymes and optimized for biological activities over millions of years," she said.

Other NPs players at the NIH include:

- **John Beutler**, Associate Scientist at the National Cancer Institute's Center for Cancer Research (NCI CCR) Molecular Targets Program, who has identified several natural products with potential for development as cancer drugs.
- **Barry O'Keefe**, Director of the Molecular Targets Program, who has pioneered the discovery of biotherapeutics from natural products, especially in the area of antiviral proteins.
- **Euna Yoo**, a Stadtman tenure-track Investigator in the NCI CCR Chemical Biology Lab, who uses NPs as chemical probes in the immune system.
- **Craig Hopp**, Deputy Director of the Division of Extramural Research at the National Center for Complementary and Integrative Health, who supports grants to researchers performing very large data mining and validation of NPs that exist in plants or dietary supplements.

Interested in natural products research? Join the Natural Products Scientific Interest Group at https://oir.nih.gov/sigs/natural-products-scientific-interest-group.

CREDIT: CAROLE BEWLEY, NIDDK

Carole Bewley underwater, collecting a rare yellow alga that produces a novel class of antibiotic known as chrysophaentins. Bewley's group just published a genome and analysis of the alga which can become a nuisance algal bloom when water temperatures rise, leading to huge biomass release from reefs and rocky substrates that eventually floats to the water due to the gases that are trapped inside the algal mucilage.

CREDIT: KENNETH JACOBSON

John Daily, Kenneth Jacobson and Kenneth Kirk at a 2004 Hillebrand Lecture

Chemists of the NIH, Unite!

BY CHRISTOPHER WANJEK, OD

The NIH Catalyst is commemorating 30 years of publishing with a series of updates to past coverage. In this issue, we highlight the exceptional contributions of NIH chemists in their pursuit of identifying molecular structures, synthesizing, isolating or formulating molecules of interest, or otherwise providing the backbone on which so much of NIH biomedical research is based.

It all started with a perhaps not-so-innocent "call for catalytic reactions," a back-page question in the May–June 1996 issue that read, "We are working on an article about chemists at NIH. What role do you see for chemists in today's biomedical research environment? How do you think NIH in general has treated the chemistry profession?"

The editor sure got an earful about the perceived "low profile of chemistry at NIH." A few months later, for the September–October issue, the *Catalyst* dedicated nearly seven of its 16 pages to the concerns expressed by NIH chemists, including a full-page defense of sorts from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Scientific Director **Allen Spiegel**, who would become NIDDK Director in 1999.

Paul Kovac, NIDDK: "No matter whether some like it or not, everything around us is chemistry, including us, functioning or malfunctioning. Understanding any chemical phenomenon better can potentially help us understand complex phenomena in the life sciences. Therefore, any attempt to cut support of chemistry at NIH would be, putting it mildly, short-sighted."

"No matter whether some like it or not, everything around us is chemistry, including us, functioning or malfunctioning," said **Paul Kovak** in the 1996 September-October *Catalyst*

What the Chemists Say

Louis Cohen, NIDDK: "As a science, chemistry can never die. It is the *practice* of chemistry that is dying, but only because the NIH administration and directors of the individual institutes have chosen to kill it. This choice is terribly misguided and short-sighted. The currently popular arts—molecular biology, genetic manipulation, immunology, virology—are all built on the basis of chemistry and will sooner or later hit a stone wall without the input and collaboration of chemistry and chemists."

NIDDK's **Louis Cohen** comments on the practice of chemistry at the NIH in the 1996 September-October *Catalyst*.

Chemistry and Biology, Finding the Equilibrium at NIH

by Celia Hooper and Rebecca Kolberg

Maybe it's just part of the age-old scramble for scientific resources and respect. Maybe it's much ado about nothing. But then again, maybe it's a Kuhnian paradigm shift in which NIH scientists are increasingly turning to molecular biology, rather than pure organic chemistry, as the favored source of new raw materials, molecules, and ideas for their biomedical research.

Whatever is going on, one thing *is* certain: it's not easy being an organic or medicinal chemist at NIH these days. Some senior chemists report being squeezed out of lab space or finding themselves afraid to ask for funds to buy essential equipment. Younger chemists are fighting to convince their molecular biology colleagues—as well as tenure-review committees—that they are much more than simple crafts-people. And newly minted organic chemistry in the intramural program "... and have been assured by some chemists at NIH that the situation is as bad as I had feared."

Amy Hauck Newman.

For more on chemists and their work, see pages 9-14.

In the same vein, a former ACS president, Ned Heindel, wrote to NIH in late 1994 to warn about the "weakening" of NIH's biological and medici-

continued on page 9.

Front page of the 1996 September-October *Catalyst* showing **Amy Newman** at the bench. Newman is a highly cited medicinal chemist and now serves as NIDA Scientific Director and Chief of the Molecular Targets and Medications Discovery Branch.

The expertise among NIH chemists then and now goes without question. **Kenner Rice**, Chief of the Drug Design and Synthesis Section in the National Institute on Drug Abuse (NIDA), has made monumental contributions to understanding opioid receptor pharmacology through directed organic chemistry. **Amy Newman**, NIDA Scientific Director and Chief of the Molecular Targets and Medications Discovery Branch, is a highly cited medicinal chemist who designs and synthesizes novel ligands to study the structure and function of G-protein-coupled receptors and monoamine transporters associated with addiction.

NIDDK's **Kenneth Jacobson** has received numerous high-profile awards for his discoveries of medicinally active substances, including the 2023 E.B. Hershberg Award from the American Chemical Society. NIDDK's **Robert Tycko** and **Ad Bax**, albeit on the physics side of chemistry, are internationally recogized for using nuclear magnetic resonance methods to elucidate the structure and dynamics of myriad large molecules.

Although never stated, that 1996 *Catalyst* feature touched on the decades-long movement unfolding across the biomedical research enterprise, a transition from classical chemistry to molecular biology. Many prominent NIH chemists from the 1950s and '60s, such as immensely respected **Bernhard Witkop**, were beginning to retire, and they weren't being immediately replaced.

A Scientific Director's Views

NIDDK's strong support of chemistry is the legacy of Bernhard Witkop and other key chemists from a previous generation, including John Daly and Kenner Rice (present lab chiefs) and their academic "progeny," including Don Jerina, Phil Skolnick, and Ken Jacobson. Notwithstanding the complaints that chemists are making now, this tradition of support continues. In addition to having two major chemistry labs (Daly's and Rice's) with substantial space, positions, and budgets, there is a service facility (Lab of Analytic Chemistry) with three staff scientists and expensive mass spectrometry and nuclear magnetic resonance imaging equipment devoted to the analysis of compounds made by our chemists as well as by those of other institutes, such as NCI. NIDDK Director Phil Gorden has only half-jokingly referred to NIDDK's intramural research program as "the Intramural Research Program of NIGMS," reflecting our strength in many of the basic sciences traditionally supported extramurally by that institute. NIDDK's intramural research program obviously supports "mission-oriented" research in diabetes and digestive and kidney diseases, but it also heavily supports fundamental research in areas such as structural biology (both X-ray crystallography and NMR spectroscopy) and molecular biology. In this context, NIDDK's support of chemistry research is not an anomaly. It is in keeping with our general commitment to outstanding basic science.

Bill Branson

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In the 1996 September–October issue, the *Catalyst* dedicated nearly seven of its 16 pages to the concerns expressed by NIH chemists, including a full-page defense of sorts from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Scientific Director **Allen Spiegel**, who would become NIDDK Director in 1999.

A Senior Chemist's Perspective

by John Daly, Ph.D., NIDDK

I came to NIH in 1958 as a postdoctoral chemist with Bernhard Witkop of NIAMD's Laboratory of Chemistry after receiving my Ph.D. in natural products chemistry at Stanford University in Palo Alto, Calif. Thirty-eight years later, I find myself chief of NIDDK's Laboratory of Bioorganic Chemistry, which, with nearly 50 scientists, is one of the largest—if not *the* largest—chemistry labs in the intramural program.

One could write a book on how important chemistry is to all other research conducted at NIH, including the currently emphasized molecular biology research aimed at gene therapy. Our discipline has designed and synthesized or isolated and elucidated structures of virtually all drugs used to treat human disease. Despite this overwhelming evidence of the value of chemical research in achieving biomedical goals, NIH today is suffering from an acute lack of appreciation for chemistry, a serious diminution of resources for chemistry, and a disturbing decline in the morale of its chemists.

John Daly

In this era of fiscal restraint, NIH chemists often do not compete well for resources with the very costly field of molecular biology. At one time, my fellow chemists and I believed that our science was appreciated and fairly judged by the Board of Scientific Counselors, who used to have one chemist member rather than the current token, ad hoc chemist. Now, the counselors' reports usually state that our chemistry is good, but so what? If the biological aspects are not being pursued with brilliant success either by biologically oriented staff within the group or by strong collaborations outside the group, the program is judged a failure. If chemistry is a dying art at NIH, it is not dying because of the lack of excellent chemistry, but because of lack of money, positions, space, adequate review processes, and opportunities for collaboration.

Another difficulty facing chemists at NIH is the new two-pronged career path, which relatively early on classifies a promising postdoc as an independent "tenure-track scientist" or a more collaborative "staff scientist." During postdoc training, chemists develop insights into how chemical approaches can be applied to achieve biomedical objectives, for example, in pharmacology, drug design, and molecular biology. It is often easy to recognize an outstanding practitioner of the "art" of chemistry, but in most cases, only years will tell whether he or she will develop the all-important interface with biologically relevant programs. The tenure-track system does not serve chemistry well because most senior chemists at NIH have inadequate numbers of postdocs to pursue their own goals and hence are loathe to bring on a promising young chemist and provide him or her with two postdocs and complete independence for six years. If I were to do that, I would have no postdocs to pursue my own projects.

Unfortunately, chemistry now appears to be considered a science that NIH should, at best, keep at token levels. Consequently, the mindset of many intramural chemists has markedly changed for the worse over the years. Many biological scientists now seem to think that any chemistry needed at NIH could merely be contracted out. Somehow, strong, true collaborative links between biologists and chemists are now relatively rare at NIH, and chemists are often treated like "service providers." The development of such collaborations receives no apparent encouragement from the NIH leadership. I feel that NIH should increase or at least maintain support for chemistry, even if the good basic research does not have an obvious biomedical impact. No one can truly predict the direction and impact of basic research in chemistry—or in any other scientific discipline. At NIH, if there is not immediate biomedical gratification, chemistry receives poor marks.

Many other NIDDK chemists and I perceive, perhaps incorrectly, that the treatment of chemistry in our institute is designed to encourage us to leave, as well as to keep us from bringing on any young chemists to replace us. In fact, I have been told that my program will be abolished when I retire. I see in this decision a bittersweet recognition of my personal importance, and simultaneously, a failure to recognize the importance of natural products research to our institute and of chemistry to biomedical research as a whole. The programs of several other senior chemists also seem destined to be abolished when they retire. If no steps are taken to change the attitude toward chemistry at NIH, I fear that at some point, there will be no one left to continue NIH's once-proud tradition of chemistry. ■

Renowned NIDDK chemist **John Daly** gives his perspective on the state of chemistry at the NIH in the 1996 September-October *Catalyst*.

The latest issue of the *NIH Catalyst* is a déjà vu for us oldsters. Nobody formulated the need for chemistry in medicine better than Frank Westheimer in his introduction to the report that bears his name. The ACS publication "*Chemistry in Medicine*," on which I collaborated with leaders of academe and industry many years ago, and DeWitt Stetten's "*NIH: An Account of Research in Its Laboratories and Clinics*" provide additional convincing demonstrations of the absolute leading role of the properly understood organic chemistry in its wider sense, which certainly has no need for the superfluous epithet "molecular."

If tradition were to play a more important role in the pursuit of science, we would not have to re-invent the wheel so often. The late Dr. Phil Handler, past president of the National Academy of Sciences, used to say, "If ever we came closer to understanding the mystery of life, it can be described and expressed in only one language, that of organic chemistry."

—Bernhard Witkop
NIH Scholar Emeritus, NIDDK

Prominent NIH chemist **Bernhard Witkop's** letter to the editor in the 1996 November–December issue.

It took the IRP a few years to reposition itself. The National Cancer Institute, with its long tradition of chemists on staff, recommitted itself to the art and science of chemistry and hired many chemists, particularly at its Frederick campus. As the National Center for Advancing Translational Sciences (NCATS) was ramping up, the National Heart, Lung, and Blood Institute started the Ligand Probe Development Center, and the National Human Genome Research Institute launched the NIH Chemical Genomics Center. NCATS would soon rely on medicinal chemistry to identify and improve specific target affinities and selectivities. Concurrently, NIH PIs in several institutes by the end of the 1990s were embracing glycobiology, a relatively new field blending carbohydrate chemistry and biochemistry to understand glycans at the cellular and molecular level.

Newman, in her role as NIDA Scientific Director, and with support of NIDA Director **Nora Volkow**, has grown the number of medicinal and computational chemists recruited to that institute. NIDDK has traditionally been a home for chemists, and the legacy lives on there, too, particularly within the Laboratory of Bioorganic Chemistry under the leadership of **Carole Bewley**.

Today, nearly 70 of the NIH's approximately 1,100 PIs "self-identify" in the scientific focus area of Chemical Biology (see https://irp.nih.gov/our-research/principal-investigators/focus/chemical-biology), a prime list for future collaborations. ●

A Bedside-to-Bench-to-Bedside NIH Success Story

NIAID Research Leads to FDA-Approved Drug for Rare Disease

BY PETER MANZA, NIAAA

CREDIT: NIAID

Michael Lenardo leads NIAID's Molecular Development of the Immune System Section. His lab identified the first patient with CHAPLE disease, a severely debilitating and life-threatening genetic condition.

When Micael arrived at the NIH Clinical Center three years ago from rural Bolivia, the 15-year-old was suffering from debilitating symptoms that included severe gastrointestinal pain, nausea, vomiting, and lung infections. He was severely underweight and malnourished and feared that eating would trigger his stomach troubles.

He suffered from this condition from infancy and although doctors tried many treatments, none worked. He was one of fewer than 100 people worldwide looking for answers for CHAPLE disease, which stands for "complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy." Fortunately, researchers at the National Institute of Allergy and Infectious Diseases (NIAID) had already been investigating how to help.

NIAID scientists had determined that patients with CHAPLE disease possess two defective copies of the *CD55* gene, so their bodies cannot inhibit the complement, a part of the innate immune system. In a healthy body, complement proteins can be recruited to form a deadly attack complex on the cell membranes of bacteria and other infectious agents. But in CHAPLE disease, without CD55 inhibition, those proteins run amok and damage cells of healthy tissues, especially in the intestinal lymphatic system, and spill protein-rich blood into the gastrointestinal cavity, causing the abdominal problems and metabolic imbalance. Because they also lose antibodies contained in the blood, they are immunodeficient and get infections. By losing blood anticoagulant proteins, they also develop blood clots that can be life-threatening.

"People with this disease are in starvation mode their entire lives," said **Michael Lenardo**, Chief of the Molecular Development of the Immune System Section of the NIAID Laboratory of Immune System Biology. Lenardo described how the high rate of blood clots in people with CHAPLE disease almost universally leads to early death. "At one point, the oldest patient we knew of had died at 32. Untreated, this is a horrific disease."

Lenardo has devoted his career to investigating the molecular basis for genetic disorders such as CHAPLE. In 2006, Lenardo and **Helen Su**, Chief of NIAID's Human Immunological Diseases Section, organized the NIAID Clinical Genomics Program at the Clinical Center to pool resources from more than 20 different intramural research program groups and pharmaceutical companies, including Merck and Regeneron. This effort paid dividends in 2017 when Lenardo's team, co-led by then-Postdoctoral Fellow **Ahmet Ozen**, first discovered that CD55 mutations were a hallmark of CHAPLE disease (*N Engl J Med* **377**:52-61, 2017).

The implication of this research was clear: If researchers could use a drug to support or mimic the function of CD55, it might slow the runaway complement activity and help the patients' symptoms improve.

A monoclonal antibody that blocked complement, eculizumab, was already FDA-approved as a treatment for another genetic disease, paroxysmal nocturnal hemoglobinuria. Yet according to Lenardo, they could not come to terms with the drug's manufacturer to test it in their research.

At about this time, Ozen had returned to his faculty position at Marmara University in Istanbul, Turkey, and was determined to find another path forward. He was able to convince the Turkish health ministry to purchase eculizumab for compassionate use therapy of CHAPLE patients. The ensuing study by Ozen and Lenardo culminated in a January 2021 publication in which the team first reported a tremendous improvement in the symptoms of 16 patients in Turkey with CHAPLE (*Nat Immunol* **22**:128–139, 2021).

"The low protein that had been observed in these kids their entire lives had jumped back into the normal range within a week or two," Lenardo said. The clinical team was astounded, as Lenardo describes: "When you give that first shot [of eculizumab], literally within hours, the children stop having stomach problems. Within a day or two, they go back to eating and normal activities."

In 2019, when positive results were becoming clear, Lenardo and Ozen sought to build upon this success and develop a drug that could be approved specifically for CHAPLE disease and widely available throughout the world. In partnership with Regeneron, they initiated an international 110-week trial using Veopoz (pozelimab-bbfg), a unique complement inhibitory antibody, in 10 people with CHAPLE. Lenardo credits the unique resources and people at NIH and the Clinical Center for a crucial role.

"They have so many ways that help investigators do clinical research," Lenardo said. "The Clinical Center and Children's Inn were instrumental in bringing Micael from Bolivia to participate in the trial, and [he'd] spend almost the entire pandemic living on campus with his sister, who served as his legal guardian."

For Micael, efforts have paid off spectacularly. He is now symptom-free, enjoying a life of normal eating and activities for the first time, and he has experienced substantial growth in height and weight. The treatment has given him a new life. He says his favorite thing is that he can eat whatever he wants! In August 2023, the FDA registered Veopoz as the first approved treatment for CHAPLE disease.

Lenardo sees these successes as only the beginning. "The complement system has been implicated in all sorts of diseases, including heart disease and neurodegeneration. Having a medication that potently inhibits this pathway is likely to be very useful in other diseases in the future," he said.

Leveraging the strong research infrastructure at NIH, Lenardo has been participating in an effort led by **Daniel Reich**, a Senior Investigator in the National Institute of Neurological Disorders and Stroke, and Christina Farias of the Foundation for Advanced Education in the Sciences to establish a center for biomedical innovation to accelerate treatment for disorders of the future. "They have championed the idea that we need an ecosystem to accelerate medical innovation with industry partners," Lenardo said.

Lenardo emphasized that bringing clinical teams, scientists, and pharmaceutical experts together requires an infrastructure that supports taking discovery research from bench to bedside. "When you do that, the reward is enormous." ●

Peter Manza, a research fellow at the National Institute on Alcohol Abuse and Alcoholism, is studying how chronic drug use changes brain function and how the brain recovers after people enter treatment for substance-use disorders. In his spare time, he enjoys cooking, hiking, strumming the guitar, and playing beach volleyball.

Constructing Clinical Research

New Display in the NIH Library Celebrates John Gallin's Career

BY DEVON VALERA, OD

This August saw the opening of *Constructing Clinical Research: Dr. John Gallin*, a new display by the Office of NIH History and Stetten Museum (ONHM) located in the NIH Library in Building 10.

CREDIT: THE OFFICE OF NIH HISTORY AND STETTEN MUSEUM

Candice Townsend (left) and John Gallin cut the ribbon to the new ONHM display on August 28, 2023. To Gallin's right is his wife, Elaine Klimerman Gallin, and Colleen McGowan.

John Gallin was NIH Clinical Center Director from 1994 to 2017 and Chief Scientific Officer and Scientific Director from 2016 to 2023, leading a period of extraordinary growth in the number and diversity of clinical trials conducted at the Clinical Center.

The display celebrates Gallin's long and distinguished career at NIH. As Clinical Center Director, Gallin advocated for and coordinated the creation of the Mark O. Hatfield Clinical Research Center, the Safra Family Lodge, and the Department of Bioethics, among other programs. "The Clinical Center and the practice of clinical research around the world have immeasurably benefitted from Dr. Gallin's vision and leadership," said ONHM curator and assistant director **Michele Lyons**, who conceived the display.

The display includes objects that highlight Gallin's contributions to information systems and medical publications, two focuses of the NIH Library. One set of objects is from the Medical Information System, established in 1975 to collect, transmit, and store patient information. This early technology, created before Gallin joined the Clinical Center, included hard drives with seven discs that held 5,000 patient records. In the early 2000s, Gallin brought the NIH Clinical Center into the new millennium with the Clinical Research Information System, the electronic medical record used for NIH patients today.

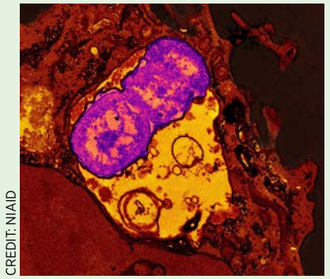
The display also highlights *Introduction to the Principles and Practice of Clinical Research*, a textbook developed and edited by Gallin. Now in its fourth edition, the book addresses ethical considerations, study designs, biostatistics, technology transfer, funding, infrastructure, and much more. As of 2023, more than 103,000 researchers around the world have enrolled in this textbook's correspondence course, directed by Gallin himself.

Present for the ribbon cutting were **Colleen McGowan**, Director of the Office of Research Services; **James Gilman**, Chief Executive Officer of the NIH Clinical Center; and Gallin's long-time friend and collaborator **Harvey Alter**, Scientist Emeritus in the Department of Transfusion Medicine and the NIH Clinical Center's first Nobel Prize laureate.

"We plan to continue our partnership with the Office of NIH History and Stetten Museum to highlight various collections, including photographs, clinical instruments, documents, and important literature throughout the year," said **Candice Townsend**, Chief of Information Resources and Services Branch at the NIH Library.

Lyons said the ONHM looks forward to the many stories the office can tell with generous support from the NIH Library. ●

Intramural Research Briefs



CREDIT: NIAID

NIAID: A human neutrophil (red) containing ingested Klebsiella pneumoniae (purple).

NIAID: INVESTIGATING MULTIDRUG-RESISTANT AND HYPERVIRULENT BACTERIUM

NIAID researchers at Rocky Mountain Laboratories investigated hypervirulent *Klebsiella pneumoniae* in a study to evaluate how its strains evade human host immune defense.

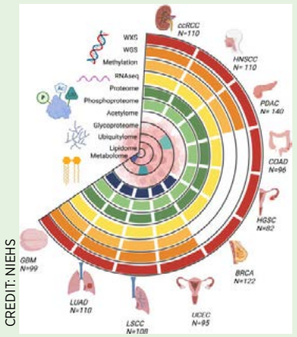
Two kinds of hypervirulent strains were investigated, hypervirulent *K. pneumoniae* (hvKp), which emerges in healthy populations, and multidrug-resistant hypervirulent *K.* (MDR hvKp). The research group evaluated the genomic characteristics of hvKp and MDR hvKp in 19 clinical isolates for the presence of virulence genes and loss-of-function mutations. They found several enzymes and/or mutations that could influence susceptibility to the human immune system.

The team also tested the survivability of hvKp and MDR hvKp in normal human blood and serum and found that MDR hvKp isolates had significantly lower survivability over time in blood and serum than hvKp isolates.

The findings demonstrated variability among *K. pneumoniae* clinical isolates and pointed to their persistence. For example, the researchers determined that human neutrophils (white blood cells) ingested less than 5% of the hvKp strain but were able to digest more than 67% of the MDR hvKp strain. Neutrophil ability to digest hvKp increased with addition of host defense antiserum, presenting a potential clinical solution to treating infection.

In future studies, the authors plan to explore other factors that might make MDR hvKp strains more susceptible to human host immune defenses than hvKp strains, which could inform treatment strategies to prevent or decrease disease severity. (NIH authors: F. DeLeo, A. Porter, S. Kobayashi, and B. Freedman, *mBio* 2023; DOI:10.1128/mbio.01949-23e0194923)

[BY ARTHI RAMKUMAR, NIAID]



CREDIT: NIEHS

NCI: Illustration showing an overview of the available molecular data types for the CPTAC pan-cancer cohort. Whole exome, whole genome, transcriptome, proteome, and phosphoproteome data are available for all ten cancer types

NCI: COMPREHENSIVE PROTEOGENOMIC DATASET TO AID IN CANCER RESEARCH

NCI's Clinical Proteomic Tumor Analysis Consortium (CPTAC) has created a comprehensive proteogenomic dataset to serve as an open-access resource for the global cancer research community. Proteogenomics is the study of how information about the DNA in a cell or organism relates to the proteins made by that cell or organism. The resource will help scientists, organizations, and institutions dedicated to studying and finding solutions for cancer link genomic mutations to their broader impact on function and further understand the cellular and molecular mechanisms of tumor formation.

Generated from individual studies of more than 1,000 tumors across 10 tumor types, the dataset standardizes and integrates genomic, proteomic, imaging, and clinical data. Access to such data could reveal how cancers develop, progress, and evade treatments.

The CPTAC dataset will help scientists further understand the pathophysiology behind tumor formation by addressing the need for a true proteogenomic approach that links tumor genotype to phenotype.

The launch of the CPTAC dataset is part of the goal of the Biden–Harris Administration's Cancer Moonshot initiative to accelerate progress in cancer research. This dataset is made publicly available through the NCI Cancer Research Data Commons repositories, including the Genomic Data Commons, the Proteomic Data Commons and the Cancer Data Service. (NIH authors: M. Thiagarajan, A.I. Robles, E. An, J. Bavarva, T. Hiltke, M. Mesri, H. Rodriguez, X. Zhang, and the Clinical Proteomic Tumor Analysis Consortium *Cancer Cell* 41:1397–1406, 2023; DOI:10.1016/j.ccell.2023.06.009)

[BY JOHN CARLO JADORMEO COMBISTA, NIMH]

NIEHS, NCI: PARTICULATE AIR POLLUTION ASSOCIATED WITH BREAST CANCER

Inhaling fine particulate matter less than 2.5 micrometers in diameter (PM2.5) may increase the risk for breast cancer, according to new research by NIH scientists. PM2.5 contains solid particles and liquid droplets that can be inhaled deep into the lungs. Sources of PM2.5 include motor vehicle exhaust, industrial emissions, and burning vegetation.

In one of the largest studies conducted to date that considered the effects of geographic variability on the incidence of breast cancer, and of tumor subtype, NIEHS and NCI researchers combined historical air-quality data with breast-cancer data using a cohort of women from the NIH-AARP Diet and Health Study. The women averaged 62 years old, and most self-identified as non-Hispanic white and lived in various geographical areas across the United States.

Researchers estimated annual PM2.5 concentrations for each participant's residence and exposures during a period of 10–15 years before study enrollment. Over approximately 20 years, 15,870 breast-cancer cases were identified, with an 8% increase in incidence among those with higher levels of PM2.5 exposures.

The investigators also found that PM2.5 was associated with a higher incidence of estrogen receptor-positive tumors, versus estrogen receptor-negative tumors, the former being the most common among U.S. women.

The results indicate that PM2.5 may affect breast cancer through an underlying biologic pathway of endocrine disruption.

The authors suggested future research should explore how geographical differences in air pollution, including the various types of PM2.5 that women are exposed to, could influence the risk of developing breast cancer. (NIH authors: A.J. White, J.A. Fisher, N.D. Freedman, D.T. Silverman, and R.R. Jones, *JNCI* 2023; DOI:10.1093/jnci/djad170)

[BY SEPPIDEH SAMI, CC]

CREDIT: SAMUNELLA/ADOBESTOCK

NINDS: Cerebral angiography showing cerebral vasculature, a common site for strokes to occur.

NINDS: HIGHLY COLLABORATIVE STUDY EVALUATES TREATMENT CANDIDATES FOR STROKE

Uric acid is a potential therapy for acute ischemic stroke and worthy of further investigation, according to a preclinical study by NINDS scientists and their collaborators.

Orchestrated by NINDS, the study assessed the efficacy of a preclinical study network to make results reproducible in other laboratories. Scientists from six independent research institutions used a common protocol to perform a four-stage preclinical project using mice and rats to evaluate the effectiveness of six potential neuroprotective interventions selected through rigorous NIH peer-review.

To evaluate each treatment, mice were provided one of six treatments and filmed during two behavioral tests 7 and 30 days after sustaining a simulated stroke. Videos of the tests were then interpreted by assessors who were unaware of the given intervention. Results indicated that only one treatment, uric acid, exceeded the efficacy boundary established by investigators.

The authors identified no significant differences in the execution of the protocol or results of the study among the six research teams. Brain scans of lesion size were also performed; however, the researchers prioritized the behavioral test as the primary outcome because the success of stroke interventions in humans is often measured by the patients' survival and improved wellbeing. (NIH authors: F. Bosetti and J. Koenig, *Sci Transl Med* 2023; DOI:10.1126/scitranslmed.adg8656)

[BY CODY R.K. CONRAD, NIAID]

NHLBI, NIDDK: NEW GENE-THERAPY PROCEDURE PRESERVES FERTILITY

Researchers at NHLBI, NIDDK, and their colleagues successfully tested in animals a new antibody-drug conjugate, or conditioning agent, that could preserve fertility in people undergoing gene therapy for sickle cell disease (SCD) and other genetic blood conditions.

Current successful gene therapies use toxic compounds, such as busulfan, as a conditioning agent to remove diseased stem cells and allow healthy stem cells to form. This process sometimes results in infertility in subjects undergoing clinical trials and is a common reason why some people of reproductive age choose not to pursue treatment.

In this study, the investigators used a single dose of a new conditioning agent called CD117-ADC in nonhuman primate gene-therapy models. They found that a single dose of CD117-ADC promoted successful engraftment of gene-modified hematopoietic stem cells while maintaining fertility, indicated by the pregnancy of the treated females and the females paired with the treated males. Additionally, the modified cells were shown to increase the oxygen-carrying protein fetal hemoglobin, which can reduce complications associated with SCD.

The authors note that the proposed intervention's single-dose design gives it practical use but that additional research and clinical trials are needed to validate and improve this promising fertility-preserving therapy. (NIH authors: N. Uchida, U. Stasula, S. Demirci, P. Germino-Watnick, M. Hinds, A. Le, R. Chu, A. Berg, X. Liu, A.E. Krouse, N. Seth Linde, A. Bonifacino, S. Gun Hong, C.E. Dunbar, R.E. Donahue, and J.F. Tisdale, *Nat Commun* 14:6291, 2023; DOI:10.1038/s41467-023-41153-5)

[BY DARWING PADILLA ROLON, NIAID]

NIEHS, ORS: AI AND MACHINE LEARNING CAN SUCCESSFULLY DIAGNOSE POLYCYSTIC OVARY SYNDROME

Artificial intelligence (AI) and machine learning (ML) proved to be useful tools in detecting polycystic ovary syndrome (PCOS), according to a study published by NIEHS scientists and their colleagues. The study was a systematic review of the literature published from 1990 through January 1, 2022, during which time a range of AI/ML software was identified and used to successfully detect and diagnose PCOS, the most prevalent yet underdiagnosed hormone disorder among women.

With the help of NIH library Biomedical Librarian **Nancy Terry**, the researchers found 31 eligible studies to include in the review. The type of AI/ML used varied among the studies, but all performed a similar task of sifting through patients' clinical, radiological, or biochemical data to find indicators of PCOS. The software was then able to identify which patients were likely to have the condition.

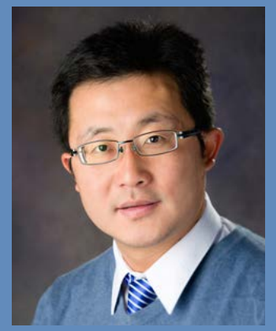
According to the senior author of the paper, NIEHS Assistant Research Physician and endocrinologist **Skand Shekhar**, the AI/ML programs used in the review performed extremely well, accurately identifying 80% to 90% of patients.

These findings could prompt physicians to add AI/ML to the diagnostic process, potentially leading to an earlier diagnosis for millions of women with PCOS, which often goes undetected due to its diversity in clinical presentation and overlap of symptoms with other conditions. The authors note that early and more efficient diagnoses could reduce the burden of PCOS on both patients and the healthcare system. (NIH authors: E.D.L. Brown, J.E. Hall, N. Terry, and S. Shekhar, *Front Endocrinol* 14:1106625, 2023; DOI:10.3389/fendo.2023.1106625)

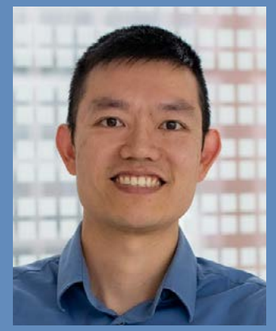
[BY MEAGAN MARKS, NIAAA]

Recently Tenured

RAMAPRASAD SRINIVASAN, NCI



SHUO GU, NCI



JOHNNY TAM, NEI

ANDREA MARZI, NIAID

EMMIE DE WIT, NIAID

KELLY FERGUSON, NIEHS

CHANDRA JACKSON, NIEHS

RAMAPRASAD SRINIVASAN, M.D., PH.D., NCI

Senior Investigator, Head, Molecular Cancer Section, Urologic Oncology Branch, National Cancer Institute (NCI)

Education: Bangalore Medical College, Bangalore, India (MBBS); University of Texas MD Anderson Cancer Center and Graduate School of Biomedical Sciences, Houston (Ph.D.)

Training: Oncology and Hematology Fellow, National Institutes of Health, NCI and National Heart, Lung, and Blood Institute (1999–2003); Resident, University of Texas Health Science Center, Houston, Department of Internal Medicine (1997–1999); Resident, State University of New York at Stony Brook, New York, Department of Internal Medicine (1996–1997)

Came to NIH: In 1999 as a Research Fellow, NCI

Outside interests: Travel; reading; running; tennis; cooking

Research interests: My lab leads efforts to develop novel treatment strategies for patients with kidney cancer within the Urologic Oncology Branch and the Center for Cancer Research. My work is focused on developing and evaluating individualized, mechanism-based proof-of-concept studies based on the recognition that there are inherent genetic and molecular differences between various subtypes of kidney cancer. I pioneered the evaluation of systemic treatment strategies in patients with von Hippel-Lindau disease (VHL) and co-led an international study that ushered in the FDA approval of the HIF2-alpha inhibitor belzutifan, heralding a paradigm shift in the management of VHL (*N Engl J Med* **385**:2036-2046, 2021).

Our work has also led to the development of a new standard of care in patients with metastatic kidney cancer associated with hereditary leiomyomatosis and renal-cell cancer. I am currently investigating a variety of newer targeted agents as well as novel immunotherapy approaches in clear cell and papillary kidney cancer, as well as in hereditary kidney cancer syndromes.

SHUO GU, PH.D., NCI

Senior Investigator, RNA Mediated Gene Regulation Section, RNA Biology Laboratory, Center for Cancer Research (CCR), National Cancer Institute (NCI)

Education: Tsinghua University, Beijing (B.S. in biology); City of Hope Medical Center, Duarte, California (Ph.D. in molecular biology)

Training: Postdoctoral training in molecular biology, Departments of Pediatrics and Genetics, Stanford University at Palo Alto, California (2011–2013)

Before coming to NIH: Research Fellow, Stanford School of Medicine

Came to NIH: In 2014 as a Stadtman Investigator, NCI-CCR

Outside interests: Reading; running; swimming

Research interests: My laboratory studies how microRNAs (miRNAs), a class of small noncoding RNAs, are regulated. We aim to understand how sequence alterations at miRNA 5' and 3' ends diversify miRNA function. We became interested in this problem through the study of miRNA isoforms (isomiRs), which are abundantly detected in cells.

My laboratory has made significant contributions to elucidating the mechanisms of isomiR biogenesis and function. We developed a novel algorithm that allows us to detect and annotate isomiRs from next-generation sequencing data with high confidence (*Bioinformatics* **35**:1576-1578, 2019). Using this method, we demonstrated that isomiR profiles are cell-, tissue-, and disease-specific.

By combining genetic studies with biochemical and structural approaches, our work established the tertiary structure of pre-miRNAs as well as their specific interactions with DROSHA as major determinants for 5' isomiR production (*Cell Rep* **26**:447-459, 2019). Our studies also yielded insights into how 5' isomiR biogenesis is regulated in cancer. For 3' isomiRs, our discovery that uridylation can alter the way miRNAs recognize their targets revealed that 3' isomiRs possess unique functions (*Mol Cell* **75**:511-522, 2019).

We also uncovered a mechanism by which a subset of miRNAs is degraded via 3' uridylation (*Nat Commun* **11**:2765, 2020). By investigating the selective actions of the major uridylation enzymes, our recent studies support a model in which TUT4 mediates mono-uridylation while TUT7 carries out oligo-uridylation on mature miRNAs, resulting in altered target-site selection and changes in miRNA stability, respectively (*Nat Commun* **13**:5260, 2022).

JOHNNY TAM, PH.D., NEI

Senior Investigator, Clinical and Translational Imaging Section, Ophthalmic Genetics and Visual Function Branch, National Eye Institute (NEI)

Education: University of California at San Diego (B.S. in bioengineering and B.A. in mathematics); University of California at San Francisco and University of California at Berkeley, California (joint Ph.D. program in bioengineering)

Training: Postdoctoral training in superresolution microscopy and biophysics, Institute of Photonic Sciences (ICFO), Castelldefels, Spain (2012-2014)

Before coming to NIH: Whitaker International Postdoctoral Fellow, ICFO

Came to NIH: In 2014 as a Research Fellow, NEI

Outside interests: Spending time with family, especially with my young children

Research interests: I am an engineer with a passion for developing new imaging technologies for clinical applications in ophthalmology and vision science. My lab brings together experts from diverse fields spanning biology, microscopy, optics, computer science, engineering, genetics, and ophthalmology to invent, design, build, and implement fully custom optical instruments capable of resolving individual neurons, capillaries, and epithelial cells in the living human eye. Our imaging approach is based on adaptive optics, a technology that is widely used in modern ground-based large astronomical telescopes for correcting distortions to light traveling through earth's atmosphere.

Highlights of our lab's multidisciplinary accomplishments to date, successfully translated to the living human eye, include: 1) establishing that retinal epithelial cell mosaicism can be used to longitudinally track cells in health and disease (*JCI Insight* **4**:e124904, 2019); 2) surpassing the optical diffraction limit of light in the living human eye to reveal the smallest cellular structures in the eye (*Optica* **8**:333-343, 2021); 3) developing novel methods for visualizing transient red blood cell stasis patterns in the choriocapillaris (*iScience* **26**:105755, 2023); 4) leveraging generative artificial intelligence approaches to improve image annotation and analysis (*IEEE Trans Med* **40**:2820-2831, 2021); and 5) revealing that photoreceptors and retinal pigment epithelial cells are differentially affected in genetic eye diseases such as choroideremia (*Commun Biol* **5**:898, 2022) and vitelliform macular dystrophy (*Invest Ophthalmol Vis Sci* **63**:27, 2022).

ANDREA MARZI, PH.D., NIAID

Senior Investigator, Immunobiology and Molecular Virology Unit, National Institute of Allergy and Infectious Diseases (NIAID)

Education: Friedrich Alexander University Erlangen, Nürnberg, Germany (B.Sc. and M.Sc. in biology, Ph.D. in virology)

Training: National Microbiology Laboratory, Public Health Canada, Winnipeg, Canada (2007–2008); Laboratory of Virology, Rocky Mountain Labs (RML), NIAID (2008–2012)

Came to NIH: In 2008 as a Postdoctoral Fellow, RML, NIAID

Outside interests: Baking; reading; going on walks and hikes with my dog and husband; jigsaw puzzles; golfing

Research interests: My research focuses on filoviruses (Ebola and Marburg viruses), particularly on host–pathogen interactions and medical countermeasure development.

Although Ebola virus (EBOV) has been extensively studied over the past few decades, there still are gaps in our understanding of the mechanism of pathogenesis. Using our established capacity for in vitro and in vivo experiments in the BSL-4 laboratory at the RML, we are leveraging molecular approaches including virus reverse-genetics systems combined with animal models to gain insight into potential mechanisms of pathogenesis.

In 2019, the first EBOV vaccine was approved for human use: a live-attenuated vesicular stomatitis virus (VSV)-based vector expressing the EBOV glycoprotein (VSV-EBOV; Ervebo by Merck) as viral antigen. This vaccine was extensively characterized in preclinical studies at RML (*Science* **349**:739-42, 2015; *PNAS* **110**:1893-8, 2013) and deployed in phase 3 clinical trials during the West African EBOV epidemic in Guinea in 2015.

Following the successful strategy of the VSV-EBOV, we are developing and characterizing VSV-based vaccines for other human pathogenic filoviruses including Marburg virus and Sudan virus (*eBioMed* **89**:104463, 2023; *Lancet Microbe* **4**:e171-e178, 2023). Accompanying these efforts is the development of animal models for novel filoviruses such as Lloviu virus (*J Infect Dis* 2023; DOI:10.1093/infdis/jiad226) in order to conduct countermeasure efficacy studies and also to evaluate the pathogenic potential of these new viruses. My long-term goal is to develop approaches that can be applied to any highly pathogenic and emerging virus threatening global public health.

EMMIE DE WIT, PHD, NIAID

Senior Investigator, Laboratory of Virology, Rocky Mountain Laboratories (RML), National Institute of Allergy and Infectious Diseases (NIAID)

Education: Utrecht University, Utrecht, the Netherlands (M.S. in biology); Erasmus University Rotterdam, Rotterdam, the Netherlands (Ph.D. in virology)
Training: Postdoctoral training in virology, Erasmus Medical Center, Rotterdam (2007-2009); and Laboratory of Virology, RML, NIAID (2009-2016)
Before coming to NIH: Postdoctoral Researcher, Erasmus Medical Center, Rotterdam
Came to NIH: In 2009 as a Postdoctoral Fellow, RML, NIAID
Outside interests: Cycling; hiking; camping; baking

Research interests: In my lab, we study the pathogenesis of emerging respiratory viruses that cause severe lower respiratory tract disease. The COVID-19 pandemic highlighted the devastating effect of emerging respiratory viruses on global public health and economies. It also showed the difficulty of treating viral lower respiratory tract infections, underscoring that our current understanding of their pathogenesis is insufficient to drive the development of effective treatments. Our main goal is therefore to increase our understanding of the pathogenesis of emerging respiratory viruses to such an extent that we can devise new treatment strategies.

This became very urgent when SARS-CoV-2 emerged only months after I started my lab. We quickly pivoted to studying SARS-CoV-2 in January 2020 and were able to help inform public health decisions through our own work and collaborations with other labs. In February 2020, we developed a nonhuman primate model of SARS-CoV-2 infection (*Nature* **585**:268-272, 2020). This model was used by labs worldwide for preclinical testing of all COVID-19 vaccines that were approved for human use. In March 2020, we showed that remdesivir treatment was effective in preventing lower respiratory tract disease in rhesus macaques (*Macaca mulatta*), data that contributed to the licensing of remdesivir for use in COVID-19 patients (*Nature* **585**:273-276, 2020). We also used this model to investigate why older people are more likely to develop severe COVID-19 (*Life Sci Alliance* **5**:e202101314, 2022) and to assess the threat posed by emerging variants of concern (*Sci Adv* **7**:eabj3627, 2021).

Now that our pandemic response work is slowing down, we are developing human distal lung organoid models to help us bridge the gap between animal models and human clinical data, enabling us to study the pathogenesis of our viruses of interest on a molecular level in the human host.

Many emerging respiratory viruses also cause neurological complications, and we have also started to study these viruses. Especially during Nipah virus infection, neurological complications are a major cause of death in humans. The pathogenesis of Nipah virus neurological disease is rarely studied and poorly understood. We are trying to fill that gap by developing in vitro (for example, cerebral organoids) and in vivo models.

KELLY FERGUSON, PH.D., NIEHS

Senior Investigator, Epidemiology Branch, Perinatal and Early Life Epidemiology Group, with a secondary appointment in the Reproductive and Developmental Biology Laboratory, National Institute of Environmental Health Sciences (NIEHS)

Education: University of Michigan, Ann Arbor (B.S. in biopsychology and cognitive science); University of Michigan School of Public Health (M.P.H. in occupational and environmental epidemiology and Ph.D. in environmental health sciences).
Training: Postdoctoral Research Fellow and NIEHS P30 Center Scientist, Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor (2014-2015)
Before coming to NIH: Research Assistant Professor, Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor
Came to NIH: In 2016 as a Tenure Track Investigator, Epidemiology Branch, NIEHS Division of Intramural Research
Outside interests: Outdoor activities like biking, hiking, and swimming at home in North Carolina or back in Michigan; cooking up new recipes (current focus area: pies); University of Michigan football.

Research interests: Adverse pregnancy outcomes have extensive individual and societal repercussions, and the contribution of environmental factors is of increasing interest to researchers, policy makers, physicians, and parents. My research examines environmental chemical exposures in pregnancy and their associations with adverse pregnancy outcomes as well as long-term health effects in the mother and child. A major focus of my research is on exposure to phthalates, which are commonly used as plasticizers and in personal care products. Exposure to phthalates is widespread in the US and worldwide. Since coming to NIEHS, I have been investigating the relationship between exposure to phthalates in pregnancy and preterm birth. This work culminated in my work establishing a consortium of 16 U.S. cohorts and over 6,000 pregnant participants. In this study we found robust evidence of associations between prenatal urinary concentrations of several phthalate metabolites and preterm delivery (*JAMA Pediatr* **176**:895-905, 2022).

Another major emphasis of my research has been on understanding how multiple chemical exposures may work together to impact health. In a multi-ethnic cohort from the Netherlands, we found that exposure to a mixture of chemicals, including phthalates, bisphenols (like BPA), and pesticides, was associated with reduced growth of the fetus in utero (*Environ Health Perspect* **129**:117008, 2021). These findings are important since most studies examine chemicals one-at-a-time, ignoring their potentially cumulative impact.

Finally, my research highlights the importance of oxidative stress and inflammatory pathways as key mechanisms in the relationship between prenatal chemical exposures and adverse pregnancy outcomes. Using molecular markers of these processes, we have shown that exposure to chemicals in pregnancy is associated with inflammation, and that, at the same time, inflammation is central in the etiology of pregnancy outcomes like preterm birth and preeclampsia, as well as growth of the fetus during pregnancy (*Pharmacol Ther* **239**:108181, 2022).

CHANDRA JACKSON, PH.D., NIEHS

Senior Investigator in the NIEHS Social and Environmental Determinants of Health Equity Group.

Education: Bethune-Cookman University (B.S. biology); Harvard T.H. Chan School of Public Health (M.S. in cardiovascular epidemiology); Johns Hopkins University (Ph.D. in cardiovascular epidemiology)
Training: Alonzo Smythe Yerby Postdoctoral Fellowship, Nutrition/Epidemiology, Harvard T.H. Chan School of Public Health (2012-2014)
Before coming to NIH: Research Associate, Population Health Research Program, Harvard Catalyst Clinical and Translational Science Center at Harvard Medical School, Boston (2014-2016)
Came to NIH: In 2017 as an Earl Stadtman Investigator (tenure-track), NIEHS Epidemiology Branch, and as an Adjunct Investigator, Intramural Research Program, National Institute on Minority Health and Health Disparities.
Outside interests: I enjoy daily nature walks and bike riding; domestic and international travel; many art forms such as wood working, painting, and sculpting; and attending concerts as well as comedy shows with friends and family.

Research interests: Sleep, an essential human need for maintaining biological homeostasis, is a seemingly simple behavior and yet complex physiological state (*Lancet Public Health* **8**:e820-e826, 2023). It is not entirely endogenous and is, therefore, positively or negatively affected by modifiable physical (e.g. light; temperature; noise), as well as social (e.g. psychosocial stress) environmental factors. These factors vary by race, ethnicity, and socioeconomic status (*Sleep* **43**:zsaa037, 2020). Preventing or minimizing the impact of environmental disturbances on sleep duration, quality, and timing could help populations avoid or delay a host of chronic diseases, such as cardiovascular disease, while addressing health disparities (*J Hypertens* **39**:2210-2219, 2021).

My research group seeks to determine the social and biological pathways linking these upstream, modifiable physical and social environmental factors to sleep and cardiovascular health in the overall population and by race, ethnicity, and socioeconomic status. ●

NIDCR Summer Poster Day Highlights Students Working, Learning in Labs

BY MICHELLE MCGINN, NIDCR

Each summer, the NIH hosts hundreds of college students as summer research interns. NIDCR welcomed 22 such interns, who each conducted full-time research in the laboratory of an NIDCR intramural investigator. The students also attended networking events, a graduate and professional school fair, a scientific lecture series, and a research day held in collaboration with the University of Maryland School of Dentistry (Baltimore).

Below, you can read how a few of the presenters at NIDCR's Summer Poster Day described their NIH experience. A full version of this article featuring all sixteen students is available at nidcr.nih.gov.

CREDIT: BELINDA HAUSER, NIDCR

NIDCR welcomed 22 summer research interns, who each conducted full-time research in the laboratory of an NIDCR intramural investigator. The students also attended networking events, a graduate and professional school fair, a scientific lecture series, and a research day held in collaboration with the University of Maryland School of Dentistry (Baltimore).

Lovelace Adeniseun—Seeking New Therapies for Head and Neck Cancer

School: Howard University (Washington, D.C.)

Poster title: Testing mTORC3 Small Molecule Binders in Head and Neck Cancer Cells

Principal Investigator: Beverly Mock

Small-molecule binders—compounds that bind to unique protein targets and affect cellular activity—are novel therapies used to treat head and neck cancer. Lovelace Adeniseun spent her summer learning how these small molecules work mechanistically with the goal of helping to create more-targeted, less-harmful treatments. "We've found several that are very promising," she said.

When asked about her NIH experience, she said, "I was surprised at how long everything takes. There is a lot of repetition to confirm or validate your results to ensure you're getting the right information to the public."

Minelis Brito—Understanding Viruses to Improve Gene Therapy

School: Louisiana State University (Baton Rouge)

Poster title: Analyzing the Relationship Between Genome Length and Viral Protein Length in T1 Particles

Principal Investigator: John A. Chiorini

The type of cell a virus can infect is based largely on the structure of its capsid, the protein shell that encapsulates viral genetic material. The simplest arrangement of capsid proteins, known as T1, forms an icosahedron, like a 20-sided die. Many current gene therapies harness T1 viruses as gene-delivery vehicles (first, the viruses are stripped of their disease-causing ability). The T1 group of viruses have genomes that vary in length from 1 kilobase (kb) to more than 5 kb. To better understand how T1 virus particles form, Brito investigated whether there is a correlation between the length of the viral genome and the size of the capsid protein. Understanding this relationship could lead to the development of new capsids for use in gene therapy.

"I found that I really enjoyed computational biology," she said. "I'm still exploring everything going on in my lab, but I hope I keep going with computational biology."

Janaylin Carela—Understanding Periodontitis

School: American University (Washington, D.C.)

Poster title: Characterizing the Activity of the *Fusobacterium nucleatum* Glycosyltransferase PelF in Pel Exopolysaccharide Biosynthesis

Principal Investigator: Nadine Samara

Janaylin Carela spent her time at NIH studying bacteria associated with periodontitis, a serious gum infection that can lead to pain and tooth loss. The condition is typically caused by poor brushing and flossing habits that allow a sticky biofilm of several species of bacteria to build up on the teeth and harden. Carela focused on characterizing an enzyme called PelF in *Fusobacterium nucleatum*, a species of bacteria that plays a key role in the development of periodontitis. She hopes her work will help reduce dental disparities by bringing an affordable treatment to those most affected by periodontitis, including people living in rural and low-income areas of America.

Carela says she gained valuable life skills in the program: "You learn how to speak to others and gain confidence in yourself when conducting these experiments. You also learn to be a problem-solver and act more independently in your work. You grow a lot and can become really resilient."

Peyton Green—Neurons, Ion Channels, and Pain Perception

School: Howard University

Poster title: Subcategorizing the Response Profiles of TRPV1-Neurons

Principal Investigator: Mark Hoon

Have you ever heard of the capsaicin receptor? It's an ion channel found on certain sensory neurons, and it triggers the burning pain we feel when we eat spicy foods such as chili peppers. It also helps our bodies sense temperature changes. Over the summer, Peyton Green studied the nerve cells that express this ion channel, which is more formally called transient receptor potential vanilloid subtype 1 (TRPV1). She learned how TRPV1-nerves can detect painful stimuli—and possibly serve as a target to relieve it.

"I wish I could have more time to see where my research goes next," she said. "I came here not knowing too much of anything about this research topic. I'm in dental school, so I have a general science background. But I've never been able to dive into anything like this in depth before. I could definitely see myself doing research on the side after I become a dentist."

Eric Mao—Visualizing Neural Crest Cells

School: Columbia University (New York)

Poster title: Development of Neural Crest Reporter iPSC Lines for CRISPRi Screens

Principal Investigator: Achim Werner

Neural-crest cells play a vital role in early development and give rise to diverse cell types throughout the body. Eric Mao's research focused on developing a way to detect and visualize neural-crest cells using a fluorescent "reporter" protein. Malfunctions in neural-crest cells account for about a quarter of all birth defects. Mao worked to develop a stem-cell line designed to provide other researchers with a consistent tool to detect cells that successfully differentiate into neural-crest stem cells and bone-cell precursors (osteoblasts).

"The NIH is the size of a university," he observed. "There are so many people here, and everyone is so passionate about science, about biomedical research.... It's really neat to be surrounded by so many exciting and passionate people."

Sabahat Rahman—Engineering Bone Marrow Cells

School: Johns Hopkins University (Baltimore)

Poster title: Developing a Strategy to Knock Out Hypertrophy-Associated Genes in Bone Marrow Stromal Cells

Principal Investigator: Pamela Robey

Sabahat Rahman spent her summer figuring out how to knock out genes in bone-marrow stromal cells. These cells seem ideally suited for stem-cell therapies designed to repair cartilage in injured or diseased joints, but they have a major drawback. Although they initially make cartilage, the cells eventually balloon in size and remodel into bone, a process called hypertrophy. Rahman sought to solve this problem by knocking out genes associated with hypertrophy.

Rahman said her work had a slightly anticlimactic ending: the in vitro conditions often proved too toxic for the cells under study. She's not discouraged, however. "We can explore this further, and it opens up new possibilities for us," she says.

She has this advice for future summer research interns: "Background research is a key to success. In the first two weeks, I underestimated how much just reading papers would help me. Also, strive to form a good relationship with your mentor. I had a great workplace environment, and that made the summer really enjoyable."

Danielle Smith—Tumor Prognosis via T Cells

School: Howard University

Poster title: CD8 Regulatory T Cells and B16-F10 Mouse Melanoma Model

Principal Investigator: Wanjun Chen

Melanoma is the deadliest form of skin cancer and is most successfully treated when detected early. Using mice injected with melanoma cells, Danielle Smith investigated whether certain white blood cells could serve as a marker for melanoma. She demonstrated that a particular type of white blood cell—the CD8 regulatory T cell—increased in number in melanoma tumors as the tumors grew.

She said the NIH internship program revealed a variety of career options. "There's working in a hospital setting, there's research work—it's so broad." For future interns, she offers these thoughts: "If you're part of next year's cohort, take advantage of your time here. There's so much to see, everyone is friendly, and they don't mind helping." ●

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CATALYTIC REACTIONS?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation or confession that scientists might appreciate and that would be fit to print in the space to the right, why not send it via e-mail: catalyst@nih.gov; or mail: *The NIH Catalyst*, Building 1, Room 160.

Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

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PHOTOGRAPHIC MOMENT

Former NIAID Fellow Drew Weissman Earns a 2023 Nobel Prize

CREDIT: NIAID LABORATORY OF IMMUNOREGULATION

You may recognize a few faces in this 1992 photograph of the NIAID Laboratory of Immunoregulation, then led by Anthony Fauci. Drew Weissman, co-winner with Katalin Karikó of the 2023 Nobel Prize in Physiology or Medicine "for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19," is seated crosslegged in the first row, third from the right. Weissman was a NIAID fellow from 1991 to 1993. More than 20 NIH fellows have gone on to win a Nobel Prize.

NIH PIs: Take those lab photos! Save those lab photos! Send those lab photo to the Office of NIH History and Stetten Museum! They are filled with diamonds in the rough, waiting to shine.

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