THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

NATIONAL INSTITUTES OF HEALTH • OFFICE OF THE DIRECTOR | VOLUME 33 ISSUE 1 • JANUARY–FEBRUARY 2025

Breakthrough Research of 2024

A Showcase of Discoveries from NIH Intramural Labs and Clinics

BY *THE NIH CATALYST* STAFF

SCIENTIFIC BREAKTHROUGH RESEARCH presentations have become an end-of-year NIH Office of Intramural Research celebration.

On December 18, 2024, the scientific directors and clinical directors from each institute and center (IC) had three minutes and one slide to present a standout intramural research accomplishment from the past year.

We highlight some of our favorites.

CLINICAL CENTER: DEVELOPMENT, PRE-CLINICAL VALIDATION OF A PET TRACER

Fungal infections cause thousands of hospitalizations and deaths in the United States each year, and existing diagnostics can be invasive or not specific enough. A novel positron emission tomography (PET) tracer was safe and effective in assessing fungal activity in mice and could lead to human trials in 2025. (PMID: 39141701)

NCCIH: PIEZO2 AND SEXUAL FUNCTION

The PIEZO2 ion channel, found in peripheral neurons and known to mediate touch and proprioception, is also essential for interoception and reproductive health. Using in vivo functional imaging and genetic techniques, researchers found that a loss of PIEZO2 in mice and people can lead to bladder overfilling, stalled movements of the digestive system, and impaired sexual

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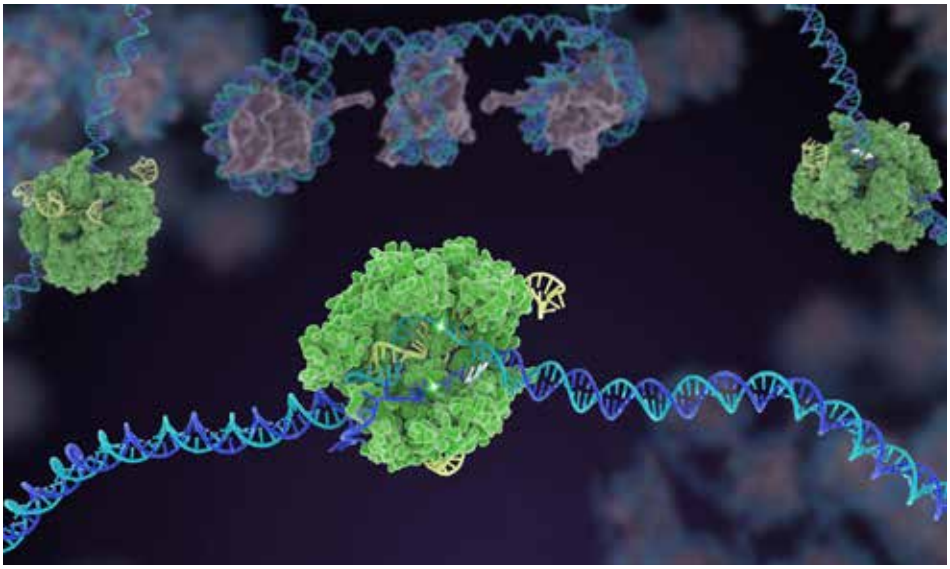
What's Cooking With CRISPR?

Simmering Advances in Genome Editing at NIH

BY MICHAEL TABASKO, *THE NIH CATALYST*



CREDIT: JANET IWASA

In the gene-editing tool CRISPR, a small strand of guide RNA identifies a specific sequence of DNA. Then, enzymes such as Cas9 (green) cuts the double-stranded DNA (blue and purple) in two places, removing the specific chunk. Scientists can then use different approaches to modify the gene and repair the DNA break.

IT'S BEEN OVER A DECADE SINCE CRISPR-BASED GENE EDITING TECHNOLOGY carried the ingredients of great promise into the biomedical kitchen. The technique is remarkably accurate and easy to use compared with prior gene-editing methods, and so the scientific community got to work refining it as a precision medicine tool. Myriad applications for CRISPR ensued, and the blue-sky goal seemed straightforward: One day, we would be able to simply snip disease from our genome.

That day hasn't arrived for all diseases and all people, but we are alluringly close. Consider Victoria Gray, a patient with sickle cell disease (SCD) who received the first FDA-approved gene therapy at Sarah Cannon Cancer Institute at TriStar Health (Nashville, Tennessee) using a version of CRISPR called Cas9 to eliminate her symptoms. So far, so good. But

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Science Will Light Our Way in 2025 and Beyond

BY NINA F. SCHOR, DDIR

Happy New Year, everyone! A new year often brings new ideas, new hope, and resolutions for turning over a new leaf. Newness augers change in so many dimensions, and change marks both opportunity and fear. How do we leverage the former and overcome the latter?

Over the course of my post-residency career, I have played many different roles at three different institutions. Each time I moved from one institution to another, although I did so in pursuit and on the promise of a new challenge and a new opportunity, I felt at least as much fear as excitement. I worried about what would happen if I failed, and because each successive institutional home gave me increasingly broad and impactful responsibility, I could not shake the belief that, if I failed, I failed bigger and more impactfully with each move. The key, though, was that I never let that fear become paralytic or grow bigger than my excitement. Opportunity always outweighed trepidation.

In the past several months, I have received many communications from colleagues at NIH and in the extramural world who play many different roles in our vast biomedical community. Some communications were related to seemingly abrupt or arbitrary staffing or policy changes. Others were related to the presidential election. Still others were related to the prospects of universal return-to-the-physical-workplace or Title 42(f) becoming Schedule F or restructuring of the NIH institutes, centers, and workforce. I have been asked why the Scientific Management Review Board has been reconstituted and whether that body will continue to function in the next administration. The truth is that I do not know for certain the answers to any of these questions. But there are several things I do know that make me excited, hopeful, and proud, and each allows me to manage the little bit of fear that comes from the unknown and the prospect of change.

First, I know that no person or people have cornered the market on the need for improved health. This is a human need and, whatever path is chosen to get from here to there, we are all headed for the same target.

> "I am excited to move forward with all of you into 2025 to forge a renewed and new path through science towards greater knowledge, better health, community engagement, and global understanding."

The road may be bumpy. Some paths may be longer or more twisty than others. We may take stock after walking a mile and have to go back many feet to reconsider and redirect. But no one can discern the path or get to the target without science. We are needed and skilled in a way that brings people together in pursuit of the same goal.

Second, the importance of science and the difference between science and fiction seem now to be more lost on a substantial fraction of our population than in the past. I say "seem" because I am not certain that it is really that different now than in the past. Loud and facile communication may be making it appear that way more than is reality. But in any case, much of science denial and science illiteracy is on us—the biomedical community. Being an educator, a writer, and a public speaker for close to my whole life, I am excited, energized, and passionate about meeting this challenge and I hope you plan to join me!

We must be loud about what we do and do not know and seek out what it will take to move the "do nots" to the "do" column. And, yes, I am more than a little scared of what will happen if I fail. But all of you will have my back. Of that, I am certain.

Finally, I know that change is hard for lots of reasons. But introspection and self-evaluation are critical and must happen with regular periodicity. In the universe in which we live, standing still is moving backward. It is healthy and important that we examine critically what we do, how we do it, and where we are going, and that we take action expediently and accordingly to ensure that our path remains on goal and in synch with our priorities and resources.

I am excited to move forward with all of you into 2025 to forge a renewed and new path through science towards greater knowledge, better health, community engagement, and global understanding. Happy New Year! ●

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function. Future research could explore whether PIEZO2 could be targeted to treat pain or digestive and urogenital disorders. (PMID: 37616369)

NICHD: BASE-EDITING FOR GLYCOGEN STORAGE DISEASE TYPE-IA

A humanized mouse model of a glycogen storage disease was used to show how base-editing technology can correct the metabolic abnormality. A base editor called BEAM-301 was delivered by lipid nanoparticles and corrected up to 60% of the genetic variant in liver cells.

The treatment restored blood glucose control in, improved metabolic abnormalities in, and conferred long-term survival on the mice. Clinical trials are planned for 2025. (PMID: 39523369)

NIDCD: EARLY-ONSET HEARING LOSS IN MOUSE MODELS OF ALZHEIMER'S DISEASE

Hearing loss is the largest modifiable risk factor in midlife for later developing dementia and interventions to slow hearing loss may slow cognitive decline.

NIDCD and NIA investigators developed a mouse model of Alzheimer's disease and found that the animals exhibited early-onset hearing loss before any cognitive or behavioral changes. The study provides a model system to explore the relationship and underlying mechanisms behind hearing loss and Alzheimer's disease. (PMID: 38500536)

NIDCR: STRUCTURE-GUIDED DISCOVERY OF ANTI-CRISPR, ANTIPHAGE DEFENSE PROTEINS

NIDCR scientists combined cutting-edge screening techniques to discover new proteins involved in the defense and counter-defense measures used by bacteria and phages, including anti-CRISPR proteins.

Understanding those defense systems could provide translational insights that inform CRISPR genome editing, help treat antibiotic-resistant bacteria, or could be used to develop phage therapies that modulate the microbiome. (PMID: 38245560)

NCATS: MMA GENE THERAPY

NCATS and NHGRI are leading the development of an adeno-associated virus gene-therapy candidate for methylmalonic acidemia, a rare inherited metabolic disorder. The gene-therapy product named MMA-101 was codeveloped by NHGRI's Charles Venditti, and a clinical trial is moving forward at the NIH CC in collaboration with NICHD, NHGRI, and NINDS. Read more: https://ncats.nih.gov/news-events/news/new-path-for-a-gene-therapy-trial-at-NIH-for-a-rare-metabolic-disease.

NCI-DCEG: MOSAIC X CHROMOSOME LOSS

In a large genome-wide association study of over 800 thousand women, 12% were found to have detectable mosaic loss of the X chromosome (mLOX). Researchers identified genetic variants associated with mLOX that may play a role in cancer predisposition and the development of autoimmune diseases. (PMID: 38867047)

NIA: INTERMITTENT FASTING

Both a healthy diet and intermittent fasting had positive effects on the brains of insulin-resistant older adults. Although intermittent fasting reduced weight more, both diets resulted in improved cognitive function and memory, as well as improved metabolism biomarkers. (PMID: 38901423)

NIAAA: SOCIALLY LEARNED THREATS

Advanced imaging techniques revealed neural networks involved in social learning and experiences of fear in mice. The findings could have important implications in treating disorders such as post-traumatic stress disorder. (PMID: 38326610)

NIAID: ANTIBODY TO PREVENT MALARIA

Nearly 600,000 people die each year from malaria, and children under age five make up most of those deaths. A monoclonal antibody blocked the ability of the malaria parasite to get from the bite site to the liver with one subcutaneous injection. The findings show that a single dose administered each malaria season was effective in preventing infection and reducing clinical symptoms. (PMID: 38669354)

NIBIB: SARS-COV-2 NUCLEOCAPSID PROTEIN

Biophysical techniques showed how the SARS-CoV-2 virus forms, revealing its molecular architecture and potentially offering an avenue for drug targets. (PMID: 38587193)

NIDDK: CONNECTOMICS, GLP-1, AND SATIETY

Optogenetics and chemical methods were used to identify critical neurons involved in suppressing appetite, demonstrating how the GLP-1 agonist weight loss drugs might work. (PMID: 39627618)

NIEHS: AIR POLLUTION EXPOSURE AND UTERINE CANCER INCIDENCE

Greater exposure to nitrogen dioxide, a marker of outdoor air pollution, was associated with a 20% higher incidence of uterine and ovarian cancers. (PMID: 38346713)

NINDS: A CEREBELLAR COMPUTATION TO TRACK TIME INTERVALS

Imaging the cerebellum in mice anticipating a reward showed how neural circuits can compute time scales relative to tasks. (PMID: 38870929)

NHLBI: R406 REDUCES LIPOPOLYSACCHARIDE-INDUCED NEUTROPHIL ACTIVATION

The immune modulator R406 (fostamatinib), sometimes used to treat severe COVID-19, shows promise in treating preclinical models of sepsis. (PMID: 39084187) ●

Keep an eye out throughout 2025 to learn more about these and many other scientific discoveries happening every day at NIH in the *NIH Catalyst*.

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significant obstacles in bringing CRISPR to the masses remain. The high cost and tight regulations contribute to the slow development of gene-editing therapies, according to a Government Accountability Office report.

Nevertheless, CRISPR technology has proven curative in an exceptionally brief time frame. And the NIH has been in the midst of the CRISPR revolution. Here, we detail some history and current progress.

Invented in 2012, the elegant CRISPR-Cas9 tool is adapted from a bacterial immune system in which microbes incorporate a sequence of foreign DNA into their own genetic code to recognize and defend against viral invaders.

Eugene Koonin, an NIH distinguished investigator in NLM, was among the first to recognize, in 2005, that "spacer DNA" in the clustered regularly interspaced short palindromic repeats—that is, CRISPR—regions of bacteria and archaea matched sequences of bacteriophages and thus might be a part of an adaptive immune system (PMID: 16545108).

In 2020, Jennifer Doudna and Emmanuelle Charpentier, who realized CRISPR's potential for human disease therapy, were awarded the Nobel Prize in Chemistry for the discovery. The Cas9 part refers to one particularly efficient enzyme that is commonly used in the technology to make a double-stranded DNA break. A short sequence of guide RNA shepherds the cutting enzyme into a cell to dock at a programmed location in the genome. Researchers can then insert or delete genetic material and alter the function of a target gene using a variety of approaches.

At first, monogenic inherited disorders such as SCD were considered the most logical diseases to target with CRISPR techniques. But a steady rollout of research using the technology to treat diseases beyond SCD, from blindness (PMID: 38709228) to in vivo treatment of protein-folding disorders (PMID: 34215024), is expanding CRISPR's recipe book to benefit more people. Complementing that work are several CRISPR-based advances being pursued at NIH.

Editing infectious, inherited diseases

Attacking the hepatitis B virus (HBV) from different angles is illustrative of how gene editing might be used to combat infectious diseases. Although an HBV vaccine exists, there is no curative treatment for those already infected.

"Like many people, we are using CRISPR-Cas technology or a derivative of it as a tool to edit genes of interest," said **Jake Liang,** an NIH distinguished investigator at NIDDK's Liver Diseases Branch. His group edited a human stem cell line to express a known HBV-resistant gene in hepatocytes and showed that those cells indeed became resistant to HBV infection (PMID: 34853804). "This [result] is proof of concept that we can use CRISPR editing to confer immunity to certain infections," said Liang.

Another angle is to alter a virus's genome and render it harmless. For example, epigenetic mechanisms could be used to disrupt the genome of HBV as it hides within infected liver cells (PMID: 38015841). That strategy could represent one therapeutic approach, and Liang notes that CRISPR can make such epigenetic changes by turning genes on or off without permanently changing the genome, thus reducing the risk of unintended mutations. Others have harnessed in vivo delivery of CRISPR to show that cleaving the viral genome is feasible in a mouse model of chronic HBV (PMID: 33473359).

In vivo delivery is an area of substantial progress. One way to envelop and deliver CRISPR in the body is by packaging it in lipid nanoparticles, or LNPs. Compared with commonly used viral vectors for reprogramming cellular behavior, LNPs are easier to manufacture and have more cargo capacity to deliver bulkier molecular payloads.

What's more, the fat-derived molecules naturally gravitate to the liver when injected intravenously. In their quest for an elusive hepatitis C vaccine, the Liang lab is testing how LNPs might be used as a vehicle to deliver potential hepatitis C immunogens directly to the liver.

Infectious diseases such as herpes, HIV, and human papillomavirus could also land on CRISPR's chopping block by using epigenetic or gene-editing approaches, and possibly LNP delivery methods. "I see a real future for this technology for any number of these viruses that stay in the system for years and decades," said Liang.

According to Liang, gene therapy efforts to treat liver diseases have been ongoing for decades, and CRISPR technology has the potential to cure a whole slew of hereditary liver conditions with lethal complications such as hemochromatosis, alpha-1-antitrypsin deficiency, and other congenital pediatric liver diseases. "Like sickle cell disease, they are all well defined. We know the mutation and can target that," he said.

Also targetable are inborn errors of immunity (IEI), a group of inherited conditions that disrupt the immune system and can result in severe or life-threatening infections, excessive inflammation, or immune dysregulation. Although gene therapy has been used to the benefit of some of those patients, there is room for improvement.

Suk See De Ravin, senior research physician and chief of NIAID's Gene Therapy Development Unit, is developing new gene therapy and cell therapy approaches to treat IEI that are safer and more robust. In one approach, De Ravin's team used CRISPR to insert a functional gene to correct a form of IEI in a mouse model and in human cells. They used new techniques to enhance the DNA repair pathway and better manage the cellular response to DNA damage and were able

CREDIT: NORIKO SATO AND KEVIN QUIROZ CACEDA

Before (left) and after (right) PET scan images of an animal model showing marked increase in radiotracer uptake in the bone marrow after infusion with lipid nanoparticles (LNP). In the postinfusion image on the right, darker colors indicate successful LNP-mediated delivery of mRNA, providing the first evidence of LNP targeting the marrow in a large animal model. According to the Larochelle lab, the advancement is a pivotal step toward realizing in vivo gene-therapy applications for the treatment of inherited hematological disorders.

to achieve over 60% genetic correction, resulting in significantly improved immune cell function (PMID: 34086870). New work at De Ravin's lab used CRISPR-Cas9 base editors to precisely correct a single-base mutation without significantly disrupting other parts of the genomic sequence (PMID: 39413163). Base editing nicks a single strand of DNA, avoiding a double-strand break that could trigger unwanted mutations or cellular responses.

According to De Ravin, those findings provided robust efficacy and safety data to support a first-in-human stem cell base editing clinical trial to repair an IEI-causing mutation to treat patients with chronic granulomatous disease. A second clinical trial was FDA approved to repair a mutation to treat patients with X-linked severe combined immunodeficiency. "Our lab is excited to extend this highly precise approach for repair of gene mutations that cause other IEIs without involving use of [viral vectors]," she said.

Optimizing vehicles and cargo

LNPs may have an affinity for the liver, but they are showing promise to deliver CRISPR-based therapy in vivo to other organs, too.

Like SCD, Fanconi anemia is an inherited bone marrow disorder and searching for a gene therapy cure is a focus of **Andre Larochelle**, senior investigator at NHLBI's Laboratory of Regenerative Therapies for Inherited Blood Disorders.

Fanconi anemia leads to abnormal production of oxygen-carrying red blood cells and infection-fighting white cells, putting patients at risk for infection, anemia, bleeding disorders, and cancer. Those patients' fragile cells also have a DNA repair defect and poorly tolerate the stress of being modified outside the body in a lab.

In a pivotal step toward realizing in vivo gene editing for inherited bone marrow disorders in humans, preliminary findings in nonhuman primate biodistribution studies showed that LNPs infused intravenously can be taken up by the bone marrow.

"While the detection of LNPs in the bone marrow is encouraging," said Larochelle, "the majority of LNPs seem to be sequestered or degraded by the innate immune system."

To overcome those barriers, his team is conjugating LNPs with antibodies known to bind to stem cells in the bone marrow and testing methods to bypass the immune capture problem so that more LNPs successfully reach the marrow and deliver their CRISPR payload. Once optimized, these sorts of approaches could be made available to patients around the world and be adapted to other disorders.

"The same lipid nanoparticle could encapsulate a different RNA or DNA template to apply the same principle to a different disease," said Larochelle. "The goal is to apply this process to as many diseases as possible."

Extinguishing cancer

CRISPR is also being used as a de facto search engine to probe the inner workings of disease. Cas9 machinery can systematically knock out gene function in a mutant cell line and reveal weak spots that could then be exploited to develop therapies. This technology, known as CRISPR screens, can find genetic and epigenetic targets that explain why certain cancers are resistant to treatment, for example.

Javed Khan, a senior investigator at NCI's Genetics Branch, leverages cutting-edge CRISPR screens to engineer reporter cell lines that track protein expression, thus uncovering vulnerabilities in aggressive pediatric cancers such as rhabdomyosarcoma and neuroblastoma. His team tests over 2,000 compounds contained in a screening platform developed by NCATS and the Molecular Targets Program, which includes FDA-approved and experimental drugs, to identify therapies that suppress the expression or activity of *PAX3-FOXO1*, a central cancer-driver gene specific to rhabdomyosarcoma.

"Furthermore, using CRISPR gene knockout and activation technologies, we are identifying resistance or vulnerability mechanisms to develop powerful gene engineering methods to improve the efficacy of CAR T cells against these aggressive cancers," Khan told the *Catalyst*. CAR refers to chimeric antigen receptors that allow T cells to recognize and destroy cancer cells.

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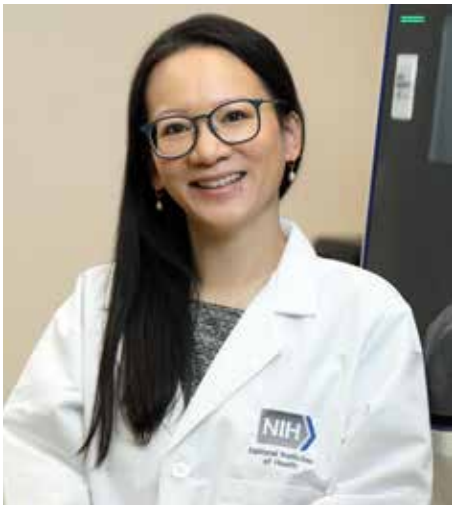
Similarly, **Rosa Nguyen**, a Lasker Clinical Research Scholar at NCI's Pediatric Oncology Branch, is working to understand why pediatric solid tumors such as neuroblastoma evade CAR T-cell therapy and uses CRISPR screens in her research. Often, the tumor environment can shut down an immune attack. Her lab found that modifying CAR T cells to express certain cytokines had potent antitumor activity in preclinical models (PMID: 36631162).

That therapy is moving towards clinical trials for children with neuroblastoma. Other efforts in her lab focus on combinatorial CAR T-cell therapy , for example, with low-dose radiopharmaceutical agents that remodel the tumor environment and enhance the function of CAR T cells.



CREDIT: NCI

Rosa Nguyen

Will it even work?

"A lot of my work is to figure out relevant animal models for human disease and use those models to test whether gene knock out or correction by CRISPR would work," said **Cynthia Dunbar**, an NIH distinguished investigator at NHLBI's Molecular Hematopoiesis lab. "They allow you to quickly design and carry out experiments to test if gene editing can pathophysiologically reverse the phenotype or not."

Sometimes, the answer is no. For example, the rare genetic *RUNX1* deficiency is another inherited bone marrow disease with an elevated risk of cancer and the RUNX1 Foundation was interested in seeing whether CRISPR gene editing could delete the mutation.

Dunbar's team used CRISPR to knock out the function of the *RUNX1* gene and to reproduce the phenotype in a nonhuman primate model. Doing so allowed them to get critical insights into the different steps of marrow failure and platelet development before and after transplanting corrected cells back into the animals. Such models most closely resemble disease and therapeutic processes in humans.

But unlike SCD or cystic fibrosis, on which the gene mutation is limited to specific base pairs, *RUNX1* mutations can occur all over the gene and each family is unique.

"When we gave the animals the corrected cells, we found that they were outcompeted by the mutant cells," said Dunbar (PMID: 36322931). "It was an important experiment because it showed that you're never going to correct enough cells, and CRISPR gene editing at this point doesn't make sense."

Similar experiments went the other way, as with Diamond-Blackfan anemia, yet another inherited bone marrow disorder. In that case, healthy stem cells were shown to outcompete stem cells carrying the Diamond-Blackfan mutation, suggesting that if one could correct the mutation, then those edited cells might quickly dominate and result in a successful transplant.

The Dunbar lab is also using their models to test the long-term effect of edited stem cells in the body. One CRISPR approach uses a DNA repair pathway called homology-directed repair, which is known to be remarkably precise with a low chance of introducing genetic errors. But it might not work with all cell types,

CREDIT: NHLBI

Cynthia Dunbar

and Dunbar's animal models showed that hematopoietic stem cells edited with homology-directed repair did not engraft well compared with those edited with a lentiviral approach (PMID: 38508195).

"So, it shows that we have a ways to go with [homology-directed repair]," said Dunbar, noting a wave of interest in emerging CRISPR techniques such as base editing. She stresses the importance of a rigorous process beginning with in vitro assays and moving through relevant animal models before bringing forward therapies for clinical trials. "You have to go stepwise for these totally novel approaches [in which] you don't really know what's going to happen."

Gene editing tech may be trending toward maturity but needs more time to cook. A "CRISPR-for-all" future will depend upon support for ongoing research, lowering costs and improving accessibility, and addressing ethical concerns.

According to that same Government Accountability Office report, "Policy decisions made in the near future may affect the way in which human gene editing to treat or prevent disease is regulated, covered by health insurance providers, and accepted by society." ●

AstroKate Inspires Young Scientists During STEM Panel, NCATS Tour

Women in Leadership Discuss Challenges, Successes in Work and Life

BY TERRY RUDD, NCATS

NCATS landed NASA Astronaut Kathleen "Kate" Rubins for an inspiring day of scientific career discussions and a firsthand look at NCATS' earthbound and space-tested biotechnologies.

Popularly known online as "AstroKate," Rubins has flown two space-flight missions, logged 300 days in space, and conducted four spacewalks. Her tour of NIH included visits to NCATS and NHGRI labs.

At NCATS, she joined the NCATS Women in Science Leadership Panel discussion (available to view on VideoCast) with an all-women panel of NIH institute directors and Women in Science Diplomacy Association members.

NCATS Director **Joni Rutter** sat down with Rubins for a fireside chat to talk about her experiences in space and beyond. The panel members then shared their own career journeys in science, technology, engineering, and medicine. They also offered valuable insights to inspire the next generation of women shaping scientific research and innovation.

CREDIT: NCATS

Pictured from left to right are Claire Chen, NCURA Global Initiative senior executive; Joni Rutter, NCATS director; Mirielle Guyader, Embassy of France counselor for science and technology; Giusi Condorelli, Embassy of Italy science attaché for health; Kate Rubins, NASA astronaut; Carleen Klumpp-Thomas, NCATS Research Services Core team leader; Savannah Wood, NCATS Research Services Core member; Evelina Sante-Kahle, Embassy of Germany science counselor; and Kerstin Hildebrandt, Children's National Hospital vice president of research administration.

CREDIT: NCATS

ABOVE: Claire Chen and Kate Rubins examine a 1,536-well assay plate used in the NCATS Automation Laboratory.

BELOW: Kate Rubins holds a 3D tissue bioprinting plate while Cristina Antich Acedo of the NCATS 3D Tissue Bioprinting team explains her work.

CREDIT: NCATS

Rubins and her scientific colleagues then traveled to NCATS' Rockville, Maryland, state-of-the-art laboratories, where they talked tech and shared insights with intramural scientists doing 3D tissue bioprinting, high-throughput drug screening, compound management, and more.

Rubins is no stranger to NCATS-supported translational science technology—on earth or in orbit. While aboard the International Space Station, she worked with tissue-chip experiments as part of the NCATS-led Tissue Chips in Space initiative.

"We were truly over the moon to have Dr. Kate Rubins with us," said NCATS chief punsmith Rutter. "She is a true star." ●

NIH–Rwandan Partnership 'Graduates' Eighth Fellow

Global Collaboration Grows Expertise in Rwanda, Expands Research for Diabetes, Health Disparities, and More

BY CHRISTOPHER WANJEK, *THE NIH CATALYST*

CREDIT: NIMHD

Claudine Kabeza (center) poses after her "graduation speech" with members from NIH leadership. From left to right, Kelvin Choi (NIMHD), Marc Reitman (NIDDK), Eliseo Pérez-Stable (NIMHD), Anne Sumner (NIDDK), Michael Krause (NIDDK), and Roland Owens (OD-OIR). Anne Sumner, who leads the NIMHD–NIDDK–Rwandan Health Program, is also a member of the NIMHD adjunct faculty.

Year by year, program by program, fellow by fellow, Rwanda is building its public health infrastructure. And the NIH intramural research program is helping.

Since 2016, the NIMHD–NIDDK–Rwandan Health Program has offered a yearlong opportunity for an early-career clinician scientist from Rwanda to train at the NIH, learn from our global community, and return to the country with first-hand experience in clinical research.

On the Rwanda side, the program was initially coordinated by the Rwandan Ministry of Health. Currently, the University of Global Health Equity (UGHE) and nonprofit Partners In Health provide full support for travel to and from Rwanda and a guaranteed three-year university position at UGHE when the fellow returns to Rwanda.

On the NIH side, NIMHD provides a stipend and benefits for the fellow through its intramural research program, and NIDDK, through the Section on Ethnicity and Health, provides space, equipment, and funding for the fellow's research projects and travel.

The program has been led from its conception by **Anne Sumner**, a clinician scientist and chief of the Section on Ethnicity and Health in the NIDDK Diabetes, Endocrinology, and Obesity Branch, who has enthusiastically served as the fellows' primary mentor. Sumner noted that the Rwandan fellows have full access to all NIH resources—lectures, FAES courses and training, Fogarty International Center (FIC) programs, and the rich NIH-based "Africans in America" epidemiological cohort (NCT: 00001853).

In short, the entire NIH scientific community provides guidance, advice, and mentoring. As the saying goes, it takes a village.

How it all started

Rwanda is a country increasingly recognized for its progressive public health policies and resilience in rebuilding its health care system since the 1994 genocide against the Tutsi. In 2015, the Rwandan Minister of Health, Agnes Binagwaho, described her country's recovery at the annual David E. Barmes Global Health Lecture, sponsored by FIC and NIDCR. She spoke of dramatic improvements in child mortality, life expectancy, and reconciliation.

Sumner was in attendance and was riveted by the Binagwaho presentation. Also in the audience was Margaret Udahogora, a Rwandan-born nutritionist and researcher who teaches at the University of Maryland. Udahogora knew of Sumner's work, which focuses on preventing diabetes and heart disease in African immigrants, and recognized Sumner in the audience. As Sumner was leaving the Masur Auditorium at the end of the lecture, Udahogora introduced herself and asked if she could introduce Sumner to Health Minister Binagwaho.

Sumner was thrilled and in awe at the invitation. Udahogora inched up to Health Minister Binagwaho and her entourage and said a few words in Kinyarwanda, the language of Rwanda. Binagwaho turned and graciously spoke to Sumner at length, a bit to the latter's surprise. And so, the seeds of an NIH–Rwandan partnership were planted.

Subsequently, **Francis Collins** and **Roger Glass**, then the directors of the NIH and FIC, respectively, gave Sumner permission to formally interact with Health Minister Binagwaho (to interact with foreign government officials, NIH investigators must have permission from NIH leadership). Within a year of that first fruitful meeting, the NIMHD–NIDDK–Rwandan Health Program began.

The program grows

Eight fellows have since sequentially completed one-year fellowships within the Section on Ethnicity and Health. The eighth was Claudine Kabeza, who holds a doctorate in public health with specialization in diabetes education and management from the Faculty of Medicine of Carl Gustav Carus at the Technical University of Dresden in Germany and a nursing degree from the University of Rwanda (Kigali, Rwanda).

Kabeza gave her "graduation speech" on November 12 in the form of a lecture titled "Diabetes Screening and Physiology in Africans: Insight from the Africans in America Study," sponsored by NIMHD and broadcast via Zoom to Rwanda.

"Diabetes education and care have been my lifelong passion," said Kabeza, adding that conducting research in diabetes under the guidance of her mentor Sumner has been invaluable. "I was in the right place, at the right time, and working with the right people, and this [situation] has been a blessing and a success for me. I am excited to continue this impactful work as I return to Rwanda, where I look forward to making meaningful contributions to the field."

Fellows in this program have so far published more than 20 papers on diabetes in African immigrants during their tenure with the Section on Ethnicity and Health. Since their graduation and return to Rwanda, each fellow has continued to publish and contribute to improved public health in Africa.

To enhance their growth and contribution to Rwandan health on the completion of the program, the fellows remain in close contact with each other, with Sumner, and with Dominic Reeds, a professor of medicine at Washington University School of Medicine in St. Louis, who provides African fellows with clinical training in the fields of nutrition and diabetes.

Akanyoni katagurutse ntikamenya iyo bweze.

A bird that doesn't fly will not know where the harvest is.

—Rwandan Proverb

In September 2024, the African Diabetes Alliance was established, to be based in Rwanda and run by the graduating fellows in Rwanda, UGHE, Partners in Health, the University of Rwanda, and other collaborators for the purpose of developing diabetes screening and care and remission protocols designed and implemented by Rwandans in Rwanda.

The advising faculty include Sumner, Reeds, Udahogora, and most recently Todd Cade from Duke University (Durham, North Carolina), an expert on the impact of physical activity on diabetes risk and treatment.

NIMHD Director **Eliseo Pérez-Stable**'s support helped to make the NIH–Rwandan Program possible. He said that when Sumner brought the idea to him in 2015, he could immediately see how the proposed program was aligned with the NIMHD mission to improve the health of minority populations experiencing health disparities, build research capacity, and expand workforce diversity.

For example, Kabeza's research on diabetes management among Africans in the United States can provide keen insights into the high rate of diabetes among African immigrants and African Americans.

"While the NIMHD–NIDDK–Rwandan Health Program has helped to build research capacity and the public health knowledge infrastructure in Rwanda, the benefits of this program have been bidirectional in many ways," Pérez-Stable said. "By diversifying the NIH biomedical workforce with scientists and trainees from heterogenous backgrounds, we gain unique perspectives, creativity, and innovation in addressing health disparities among minority populations in the United States and globally, among other benefits."

NIMHD Scientific Director **Kelvin Choi** noted that NIMHD support will continue through at least fiscal year 2029. A new fellow starts in the new year, and the fellow to start for 2026 already has been selected.

Back in Rwanda, the program is producing significant dividends. Utumatwishima Jean Nepo Abdallah, the first fellow, recruited in 2016, is now the Rwanda Health Minister of Youth, having served as director general of two Rwandan hospitals since his return. Several others are pursuing doctorates to complement their medical degrees, as the M.D.–Ph.D. dual degree is highly valued for Rwandan leadership positions.

"Fogarty applauds the tremendous success of the NIH-Rwandan partnership and its emphasis on robust science, innovation, and capacity strengthening," said **Kathleen Neuzil**, who was appointed the 13th FIC director in March 2024. "Diabetes adversely affects the quality of life of far too many people in the U.S., Rwanda, and around the globe. We look forward to following the contributions of these talented fellows as they bring fresh ideas to the study of diabetes prevention and control and move forward in their promising careers." ●

Read profiles of past NIH–Rwandan Health Program fellows at https://www.nimhd.nih.gov/programs/collab/rwandan-health.

Intramural Research Briefs

Read about Scientific Advances and Discoveries by NIH Intramural Scientists

NCI: CAR-T-CELL THERAPY SHOWS GREAT PROMISE IN GASTRIC AND COLORECTAL CANCERS

Advanced gastric and colorectal cancers are difficult to treat. The primary reason is that the cancer has spread to other organs, rendering traditional cancer treatments such as surgery and chemotherapy nearly futile. Thus, there is an urgent need to develop more effective therapies for these patients.

Chimeric antigen receptor (CAR) T-cell therapy is a relatively new weapon in the anticancer arsenal, but it has mostly been successful against blood cancers. However, investigators at NCI led by **Raffit Hassan** and postdoctoral fellow **Sameer Mir** in the Thoracic and GI Malignancies Branch have taken a novel approach to extend CAR-T-cell therapy to the realm of solid tumors.

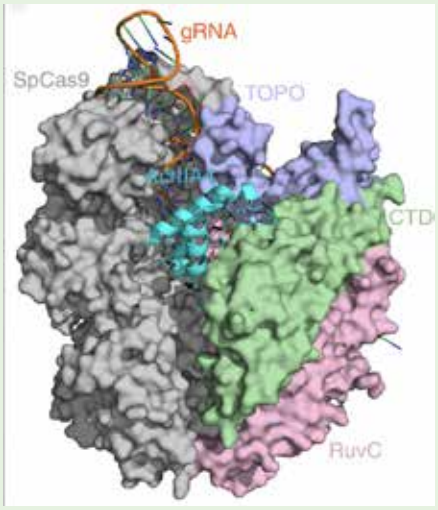
As detailed in a November 2024 *Clinical and Translational Medicine* article, Hassan's team effectively targeted human gastric and colorectal cancers grafted into the bodies of specially-bred mice. Building on research by other groups, the team used a CAR T cell called hYP218, which is designed to recognize mesothelin, a cell-surface protein that is overexpressed in these types of cancers.

T cells are a natural part of the immune system, and CAR T cells are essentially trained to kill cancer cells rather than viruses, bacteria, or other harmful agents in the body. The idea behind using hYP218 CAR T cells is that, because mesothelin is far more abundant on the surface of cancer cells, targeting it with these bioengineered immunotherapeutic T cells will kill the cancer while minimizing damage to healthy cells that have little to no mesothelin protein. The research team noted that activated hYP218 CAR T cells persisted in the tumor microenvironment and retained their cytotoxic activity.

Hassan's team additionally found that these CAR T cells had an enhanced efficiency when combined with the drug pembrolizumab, particularly in mice with larger, more established tumors. Pembrolizumab is a checkpoint inhibitor that blocks the PD-1 pathway, a naturally occurring mechanism that suppresses T-cell activity.

"Based on the promising preclinical activity against different solid tumors, a phase 1 clinical trial of hYP218 CAR T cells will open at the NIH Clinical Center in 2025 for the treatment of patients with advanced mesothelin-expressing solid tumors who have failed standard therapies," said Hassan, who will serve as the principal investigator of this clinical trial. (NIH authors: S. Mir, A. Venugopalan, J. Zhang, N.U. Nair, M. Sengupta, M. Khanal, C. Stathopoulou, Q. Jiang, and R. Hassan, PMID: 39548594)

NHGRI: CRISPR SCANNING METHOD REVEALS PROTEIN FUNCTION



CREDIT: NHGRI

NHGRI: Shown in cyan is the structure of the AcrIIA4 protein binding to the Cas9 enzyme (specific domains in green, lavender, and pink, with the remainder in gray). NHGRI scientists tested a new method that revealed just how AcrIIA4 functions to foil bacteria's CRISPR-Cas9 gene-editing machinery.

CRISPR technology, often associated with gene therapy, could be deployed to accurately and efficiently understand protein function, according to a new study by NHGRI scientists.

The researchers tested an approach known as deletion scanning on AcrIIA4, a protein that bacteriophages (phages) encode to foil bacteria's CRISPR-Cas9 immune defense. Phages and bacteria have been battling it out for eons, and many phages have evolved the ability to resist CRISPR-Cas9, a mechanism whereby bacteria incorporate a sequence of viral DNA into their own genome.

To uncover the workings of phage's anti-CRISPR adaptation, the investigators, somewhat ironically, used CRISPR to comprehensively generate thousands of genetic deletions affecting specific regions of AcrIIA4. They were then able to test the effect of each modification on blocking the activity of Cas9, an enzyme that cuts DNA.

The high-throughput data showed that AcrIIA4 acts upon Cas9's ability to bind to a short sequence of DNA used by the enzyme to recognize target sites just before cutting the DNA strand.

Beyond working out the function of AcrIIA4, the authors note that such comprehensive deletion scanning could have many applications. Those include engineering new or improved proteins, revealing evolutionary adaptations, and understanding how deletion variants contribute to genetic diseases. (NIH authors: A.B. Iturralde [now at University of Virginia, Charlottesville], C.A. Weller, S.M. Giovanetti, and M.J. Sadhu, PMID: 39570312)

NIEHS: BRAIN RESPONSE TO SOCIAL STRESS INFLUENCES LATER BEHAVIOR

Stressful experiences can alter how an individual responds to future social interactions. A study led by NIEHS researchers suggests that the effects of stress on social behaviors depends on how resilient the brain is during those experiences.

By exposing mice to a stressful social experience—being socially defeated by a more aggressive, dominant mouse—the investigators examined the neurobiological processes that differ between those who are more and less susceptible to stress-driven behavioral changes.

Avoidant behaviors and reduced social exploration were evident in mice that experienced social defeat and persisted for weeks after the event. Moreover, mice that exhibited defensive behavior during the defeat were more resilient and were more likely to socialize later than the mice who fled the stressful encounter. This effect was found to be driven by activity in the cornu ammonis 2 (CA2), a subregion of the hippocampus that is critical for social learning and aggression in mice.

The scientists used viral targeting of molecules to selectively silence CA2 neurons during acute social stress and to trace the downstream projections of these neurons. Experiments revealed that decreasing CA2 activity enhanced avoidant behaviors after social stress, suggesting that activation of the CA2, and its downstream targets in the hippocampus and cortex, promotes resilience and reduces behavioral sensitivity to acute social stress. (NIH authors: D. Radzicki, K.E. McCann, G.M. Alexander, and S.M. Dudek, PMID: 39548322)

[BY ASHLEY PRATT, NICHD]

NIMH: OPTOGENETICS REVEALS HOW NEURONS FILTER INPUT IN VIVO

How information flows in living neurons may share similarities with how information is processed by artificial intelligence (AI) systems, according to a study by NIMH scientists. Using new techniques, they measured activation functions, that is, the firing rate produced for a given input level, of the neurons of active brains in awake mice for the first time.

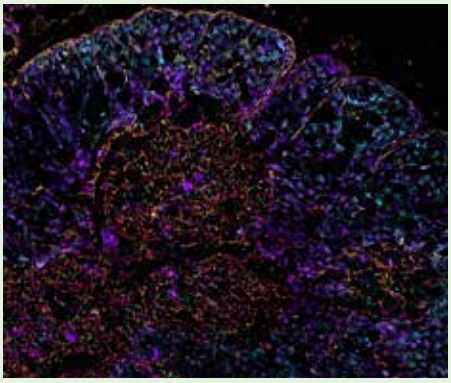
The researchers used an advanced method called two-photon holographic stimulation, which uses two high-powered lasers to image and stimulate cells at the same time. The technique relies on optogenetics technology, which modified the brain cells to activate in response to light. Neurons were stimulated in combination with visual input, allowing the team to collect data from hundreds of neurons in various states of activity.

They found nearly linear responses when neurons' activity level was elevated, and in contrast, significantly attenuated responses when neurons' activity was suppressed. This result shows that living neurons can, by changing activity level, filter out certain inputs while prioritizing others.

According to the authors, the findings suggest that both brains and AI systems face similar selection pressures—perhaps as the result of the need of both to learn—and this activation function shape is a common and shared solution. (NIH authors: P.K. LaFosse, Z. Zhou, J.F. O'Rawe, N.G. Friedman, V.M. Scott, Y. Deng, and M.H. Histed, PMID: 39485801)

NIAID: HIGH-RESOLUTION MAPPING OF HUMAN THYMUS ADDED TO THE HUMAN CELL ATLAS

CREDIT: ANDREA RADTKE, RONALD GERMAIN, LABORATORY OF IMMUNE SYSTEM BIOLOGY



NIAID: Iterative bleaching extends multiplexity (IBEX) image of the human thymus. Thymic epithelial cells are labeled with DEC205 (cyan), pan-cytokeratin (purple), keratin 5 (red), and keratin 14 (yellow).

Researchers at NIAID and their international colleagues developed a novel mathematical model that combines highly multiplex, high-resolution optical imaging, single-cell RNA sequencing, and spatial transcriptomic data.

Termed OrganAxis, the model can be applied to any tissue, and when applied to the human thymus, the scientists produced the most detailed description of the organ to date. The thymus is a vital immunological organ that supports the maturation of T cells. Disorders affecting the thymus can result in devastating autoimmune diseases, immunodeficiencies, and cancers.

By combining technologies, including NIAID-developed iterative bleaching extends multiplexity, known as IBEX (PMID: 33376221), the researchers established a framework called the corticomedullary axis. They applied that framework to map the cellular landscape of the human thymus in exquisite detail, including the trajectories of immune cells (thymocytes) as they pass through the organ during maturation and selection together with the signaling gradients that guide them.

"The common coordinate framework established here empowers integration of diverse datasets, providing a strategy for charting thymic changes using new single-cell and spatial technologies," said **Andrea Radtke**, a senior author on the study.

According to **Ronald Germain**, fellow author and NIH distinguished investigator, combining both high- and low-resolution technologies revealed how valuable such imaging can be in creating very precise maps of a tissue. "Our ongoing methods are now extending such imaging to 3D, which will produce true organ-level maps in the near future," he said.

The thymic atlas adds to a global collaborative attempt to map every cell in the human body, collectively termed the "Human Cell Atlas." (NIH authors: B.T. Wachter, R.T. Beuschel, M. Bosticardo, F. Pala, L. Notarangelo, R. Germain, and A.J. Radtke, PMID: 39567784)

[BY TAYLOR FARLEY, NIAID]

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https://irp.nih.gov/catalyst/33/1

Building Bridges: It's What Engineers Do

NIBIB-led Conference Leveraged Partnerships Across Engineering, Technology, and Biomedical Research

BY CHRISTOPHER WANJEK, *THE NIH CATALYST*

CREDIT: MARLEEN VAN DEN NESTE

NIBIB Director Bruce Tromberg and BETA Center Director Manu Platt discuss the day's agenda moments before being joined by NIH Director Monica Bertagnolli.

Fantastic advances are happening in the field of biomedical engineering. Bio-integrated prosthetics now allow people with lost limbs to regain mobility and independence; precision imaging and artificial intelligence-guided analysis can identify the onset of cancer and heart disease; nanoparticles deliver targeted therapy directly to diseased tissue, minimizing side effects; and rapid progress in tissue regeneration is reversing damage to bone, cartilage, and muscle. And in this issue of the *NIH Catalyst*, we report on the first FDA-approved gene therapy, an advancement developed at the NIH for sickle cell disease.

Scientists see this all as the beginning of a new medical revolution. On October 22, 2024, the NIBIB hosted a daylong conference on the NIH campus, "Building Bridges Across NIH and the Broader Engineering Community," to tap into this excitement and enrich the NIH intramural research program with expertise from medically minded engineers within and beyond the NIH.

Hundreds of scientists and engineers attended—many visiting the NIH for the first time. The NIH conference was timed to coincide with the Biomedical Engineering Society (BMES) annual meeting in Baltimore.

"To me, this is what biomedical engineering is all about and what drew me to the field in the first place," said **Manu Platt**, an NIBIB senior investigator who directs the Center for Biomedical Engineering Technology Acceleration (BETA Center) and who organized the meeting. "People from all walks of life and [who have] many different types of technical training in medicine, biology, chemistry, and the multiple engineering specialties, bringing their interests and expertise together to solve biomedical problems across the human condition. This is the power of bringing community together."

The seeds of this conference date back more than four years when **Bruce Tromberg** arrived from University of California at Irvine in 2019 to serve as NIBIB director. Tromberg began planning what he called an NIH Bioengineering Festival for March 20, 2020.

The emergence of COVID-19 thwarted that conference, but two rather significant and related developments happened in its place that would nevertheless put NIBIB in the national spotlight.

The first was the creation of the RADx® program, with a name so good that we had to register it as a trademark. RADx® stands for Rapid Acceleration of Diagnostics, an NIH-led and NIBIB co-coordinated program to develop, validate, manufacture, and deploy at-home and point-of-care COVID tests. RADx® Tech, an NIBIB subprogram to find solutions to health care problems beyond COVID-19, demonstrates the very core of the NIBIB mission: "To transform, through technology development, our understanding of disease and its prevention, detection, diagnosis, and treatment."

The second development was the creation of the NIBIB-led BETA Center. Launched in 2023, the BETA Center is a biotechnology resource and catalyst for NIH intramural researchers akin to the successful "bench-to-bedside" concept—but here, NIBIB brings together scientists and engineers across NIH to collaborate in an iterative process to perfect a tool or

or technique. The BETA Center has since enlisted more than 100 intramural researchers from 16 ICs to join as BETA Center affiliates.

The Building Bridges conference was a natural extension of RADx® Tech and the BETA Center, "a bit of a coming-out party to the broader community," Platt said.

"I attended the BMES conference afterwards and heard continuous positive feedback from those who attended the day, and even more from people who wish they had attended because of the connections and science they heard [about] from others that did participate."

NIH Director **Monica Bertagnolli**, who has an undergraduate degree in engineering from Princeton University spoke with clear passion for the field in a fireside chat with Tromberg and Platt at the outset of the day.

CREDIT: MARLEEN VAN DEN NESTE

More than 100 researchers presented their work...and had a little fun...during the two poster sessions on the FAES Terrace.

"As NIH director, my lodestar is this principle: Our work is not finished when we deliver scientific discoveries. Our work is only finished when people are living long and healthy lives. And that's what engineering helps us do," she told the audience.

Areas ripe for bioengineering expertise include diagnostic tools, particularly for those in rural communities and women who live in "maternal health deserts," and methods to detect lingering viruses, such as those thought to cause long COVID symptoms, Bertagnolli said, to bridge the gap between discovery and care.

CREDIT: MARLEEN VAN DEN NESTE

John Tisdale, an NHLBI senior investigator, presented his innovative work on bone marrow transplants and gene therapy for sickle cell disease.

By Tromberg's estimate, between 14% and 15% of the NIH budget supports bioengineering research. That's approximately $7 billion, far more than NIBIB's $440.6 million budget, and testament to the importance of NIBIB serving as a bridge—a bridge between scientists and engineers, between doctors and patients, and between experts and junior biomedical engineers.

John Tisdale, an NHLBI senior investigator who directs the Cellular and Molecular Therapeutics Laboratory, delivered the day's first plenary talk on the aforementioned sickle cell gene therapy.

Other conference talks and breakout sessions reflected the diversity of the field: bioimaging, probe development, drug delivery, 3D bioprinting, orthopedics, gene therapy, artificial intelligence, and more.

Want to connect? The BETA Center hosts monthly idea-swapping meetings. Join their LISTSERV newsletter by e-mailing BETACenter@mail.nih.gov or linking to BETACENTER-ANNOUNCEMENTS.

Hot off this successful conference, Platt said the BETA Center will continue to grow in 2025 with several collaborative opportunities:

• A BETA Center Makerspace is opening in January. NIH researchers can directly access rapid fabrication equipment including 3D printers and a laser cutter. Space, equipment, and supportive staff will be in Buildings 10 and 13.

• The BETA Center additionally now offers expertise in soft biomaterials with a team member who can assist labs interested in using biomaterial strategies but who had felt the bar was too high to try on their own.

• Similarly, the BETA Center now has expertise in computational and systems biology modeling to lower the barrier of entry for labs looking to use more mathematical approaches to analyze complicated biological systems.

• Workshops to educate investigators on specific techniques will be coming soon.

• Also on the horizon, the BETA Center intends to host sabbaticals for external collaborators to share their expertise and learn from NIH staff. ●

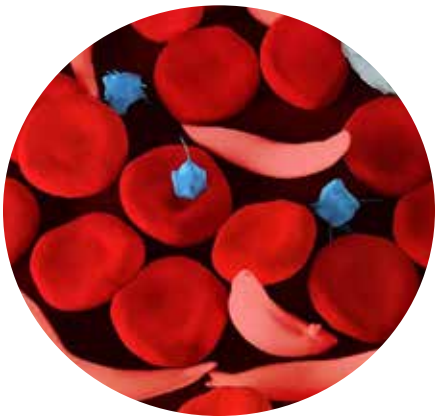
CREDIT: MARLEEN VAN DEN NESTE

Pictured from left to right at the afternoon panel discussion on innovation and working with industry are Rashid Bashir (University of Illinois at Urbana-Champaign), a panelist and later "extramural" keynote speaker; Cherie Butt (Biogen), Vincent Ho (Uniformed Services University of the Health Sciences), Brad Wood (CC), and Peter Pinto (CC).

Slaying Sickle Cell

Foundational Work at NIH and Today's Transformative Treatments

BY MICHAEL TABASKO, *THE NIH CATALYST*



CREDIT: NHLBI

Illustration of sickle red blood cells and normal red blood cells. The misshapen cells occlude circulation and can result in disease manifestations including sudden pain crises, chronic pain, organ damage, and anemia.

In 1958, biochemist Makio Murayama was recruited to the NIH to study sickle cell disease (SCD), then known as sickle cell anemia. Famously, he constructed a meticulous three-foot-tall 3D model of a hemoglobin protein in his home basement laboratory to work out the molecular mechanisms behind why red blood cells sickle. The misshaped cells are a hallmark of the disease that can occlude circulation, leading to organ damage, stroke, anemia, and sudden episodes of pain.

In his NIH oral history, Murayama expressed his penchant for working alone, his solitary endeavors perhaps analogous to the paucity of research devoted to understanding SCD at that time. Down the road, the work would ultimately pay dividends, and his conclusions about hemoglobin dynamics would inform the first drugs used to treat the disease (PMID: 4952917).

CREDIT: JERRY HECHT, OFFICE OF NIH HISTORY AND STETTEN MUSEUM

NIH scientist Makio Murayama with the molecular model of hemoglobin that he built to study SCD and explain why red blood cells take on a sickle shape.

Science has since steamed ahead, and for the 100,000 people in the United States and 8 million people worldwide with SCD, there are now two big reasons to be optimistic.

Two FDA-approved gene therapies for SCD have been added to the armament of potentially curative therapies, which until recently was solely the realm of stem cell transplants requiring a genetically matched donor's healthy tissue. While tantalizing, these transformative new genetic approaches cost in the millions of dollars, are risky and cumbersome to administer, and don't work for everyone. But they do represent a future in which a cure is available to more people.

Formative years

The discovery in several laboratories that sickle hemoglobin formed long fibers inside red blood cells, which impaired circulation and drove disease manifestations, renewed interest among a handful of NIH investigators in biophysical studies that would eventually lead to treatments. "When I came to NIH in 1965, SCD was presented as an example of the accomplishments of modern biochemistry in determining that the abnormality in hemoglobin was due to a single mutated gene," said Christian B. Anfinsen Distinguished Scientist **Alan Schechter,** a senior investigator at NIDDK's Molecular Biology and Genetics Section, Molecular Medicine Branch.

Approved drugs were still decades away. Schechter and colleagues focused on using new methods at that time, such as nuclear magnetic resonance, to understand the thermodynamics of how sickle hemoglobin molecules aggregate or polymerize inside deoxygenated red blood cells.

Other foundational scientists, including **William Eaton**, an NIH distinguished scholar and chief of NIDDK's Biophysical Chemistry Section, Laboratory of Chemical Physics, elucidated both the thermodynamics and kinetics of sickle hemoglobin fiber formation (PMID: 4531026) and showed how diluting the concentration of sickle hemoglobin could prevent sickling (PMID: 3603036). After more than 50 years of research on SCD, Eaton is still at it today and focused on drug development. In collaboration with several NHLBI teams, he developed a quantitative screening assay and identified more than 100 antisickling compounds, 20 of which could be drug candidates (PMID: 36161945).

Also, genomic work at NIH in the 1970s aimed at one day developing a gene therapy. Scientists including Phillip Leder, Gary Felsenfeld, and others explored the structure of the hemoglobin genes and how they were transcribed into sickled hemoglobin, normal hemoglobin, and fetal hemoglobin.

Fetal hemoglobin, which typically declines after birth, became the prime therapeutic target because it slows the kinetics of the polymerization of sickle hemoglobin and had been associated with less severe forms of SCD. "Back then there were discussions of genetic ways to increase fetal hemoglobin, and we were doing biophysical studies to determine how much was necessary to get effective therapy for SCD," said Schechter (PMID: 2447498) .

Ensuing laboratory and clinical work at the NIH and elsewhere led to extensive interest in hydroxyurea (HU) as an agent of choice for increasing fetal hemoglobin with minimal side effects. More support for the potential use of HU came from a detailed study of 10 patients at the CC (PMID: 1690857) under the direction of

Griffin Rodgers, now NIDDK director.

That study's success led to a multicenter study of HU in almost three hundred sickle cell patients, supported by NHLBI, which provided definitive evidence that the drug reduced painful crises and blood transfusions (PMID: 7715639). In 1998, HU became the first FDA-approved drug for treating adults with SCD, and in 2017 the FDA approval was extended to pediatric patients over two years of age. According to Rodgers, while not curative, it gave people the opportunity to pursue and enjoy their lives more fully than before.

"I am proud to say that so much of our understanding of SCD, from how it is inherited to the amino acid change responsible for the creation of sickle-shaped blood cells, has been uncovered through research funded by or conducted at the NIH," Rodgers told the *Catalyst*, adding that, while promising, current treatments from new drugs to genetic cures do not work for every patient with SCD, and access to life-changing therapies can be limited due to where they live and other social and economic factors. "Addressing health disparities will be necessary for the development of treatments that are effective for even more people living with SCD and that are accessible to all who need them."

From new drugs to genetic cures

Boosting fetal hemoglobin is also behind how one (exagamglogene autotemcel) of the new gene therapies works, but unlike HU, it does so permanently. When NHLBI's **Swee Lay Thein** was at Kings College (London), she conducted a genome-wide association study (GWAS) and discovered that the *BCL11A* gene suppressed fetal hemoglobin at birth, a finding for which she was awarded the prestigious 2024 Shaw Prize in Life Science and Medicine.

The discovery made possible the current CRISPR-based gene editing approach that disrupts the *BCL11A* gene's function and turns back on fetal hemoglobin. According to the FDA, the treatment was effective in a remarkable 93.5% of patients with SCD and was soon after approved for treatment of beta-thalassemia, a related disorder.

Other scientists, such as Ambroise Wonkam at Johns Hopkins University (Baltimore), aren't stopping at the *BCL11A* gene. Wonkam is running GWASs on people of African ancestry to discover even more gene therapy targets that affect fetal hemoglobin (PMID: 36815490).

Thein, now chief of the Laboratory of Sickle Cell Genetics and Pathophysiology, is running a clinical trial of the drug mitapivat as another way to mitigate the sickling process, the root cause of the disease. "My focus and research interests are to develop more small-molecule drugs that can reach far more patients," she told the *Catalyst*.

CREDIT: NHLBI

Recent Shaw Awardee Swee Lay Thein's discovery that the *BCL11A* gene was involved in turning fetal hemoglobin off at birth led to using a CRISPR-based gene-editing approach to disrupt that gene's function and resulted in one of the newly approved gene therapies for SCD and beta-thalassemia.

The second approved gene therapy (lovotibeglogene autotemcel) also has an NIH story. "When I got here in the 1990s, I was interested in developing gene therapy using a patient's own bone marrow cells modified by a viral vector to modify the disease," said **John Tisdale**, senior investigator and chief of NHLBI's Cellular and Molecular Therapeutics, who was instrumental in starting the NIH stem cell transplant program for SCD.

"We knew bone marrow transplant worked because it worked for a patient with leukemia who also had SCD and she was cured of both."

Tisdale's team, including **Matthew Hsieh**, senior staff clinician at the CC who has worked with scores of patients with SCD, began optimizing allogenic, or donor, stem cell transplants. They found that because healthy red cells live 3-4 months, compared with 3-4 weeks for sickle red cells, complete replacement of the patients' bone marrow is not necessary.

As low as one-in-five of the blood cells in the bone marrow factory coming from healthy donor stem cells may be enough to fix the disease, and this result suggested that reaching a 20% threshold with gene therapy methods might be successful. However, aiming for higher levels of replacement by donor stem cells or genetically modified cells would ensure longevity of these healthier blood stem cells.

So in 2014, Tisdale joined forces with a biotech company, and their collaboration culminated in a gene addition strategy that uses a lentiviral vector to deliver a working copy of the gene encoding for normal hemoglobin into the patient's bone marrow cells (PMID: 35773052). In a clinical trial leading to its approval, 88% of patients saw their disease manifestations completely resolve.

However, as with the CRISPR approach, the delicate process can have serious side effects. Toxic conditioning protocols such as chemotherapy are necessary to ensure the bone marrow does not reject the modified cells. Then there are the hospital stays to prepare and collect a patient's stem cells, modify them in a lab, and reinfuse the corrected cells. Those are followed by a lengthy period of medical monitoring to ensure enough healthy hemoglobin continues to be produced.

According to Tisdale, in vivo gene editing might be one way to bring down costs, improve treatment accessibility, and

CONTINUED ON PAGE 16

simplify the whole process. Work is underway to encode viral vectors or lipid nanoparticles with antibodies expressed in the bone marrow, which would act as a ZIP Code for their intended destination. The vector could then be administered intravenously, travel directly to the bone marrow, and precisely deliver its gene-correcting payload. It's not all science fiction: In vivo gene therapy using lipid nanoparticles is currently being used to treat some liver conditions.

"We got COVID vaccines around the globe, basically lipid nanoparticles with RNA inside. This is what we're trying to make—a lipid nanoparticle with RNA inside to treat sickle cell disease," said Tisdale, who notes his collababorators receive funding from the Bill and Melinda Gates Foundation that supports the development of in vivo gene delivery applications.

Another hurdle to overcome is the high expense of producing viral vectors. Tisdale's group developed a vector that is 10-fold as high in its titer to bring down costs.

CREDIT: BJORG GUDMUNDSDOTTIR

The 2024 Cellular and Molecular Therapeutics Laboratory staff, led by John Tisdale. Front row (from left to right): Matthew Hsieh, Selami Demirci, John Tisdale, Josiah Ballantine. Middle row: Shruti Sathish, Anh Le, Avery Bradley, Melody Engle. Back row: Oswald Phang, Julia Ball, Bjorg Gudmundsdottir, Henna Butt, Naoya Uchida.

Optimizing stem cell transplants

Stem cell treatments have traditionally been reserved for children with SCD who had a sibling donor who was a complete tissue match, a luxury only available to about 15% of patients. Because they have less organ damage than adults with the condition, children are better able to tolerate the rigorous myeloablative conditioning regimen required to make space in the bone marrow and to ensure the donor cells aren't rejected.

By offering stem cell treatments to people who have donors who are a partial genetic match (haploidentical), **Courtney Fitzhugh**, a Lasker Clinical Research Scholar at NHLBI's Laboratory of Early Sickle Mortality Prevention, has expanded the possibility of stem cell treatments to 90% of patients with SCD. Furthermore, her group is optimizing lower-intensity conditioning protocols to make the procedure safe for more adults, even those with severe organ damage.

"Curative therapies need to be myriad to meet all the different populations of patients with SCD," added **Emily Limerick**, a staff clinician in Fitzhugh's lab who manages all aspects of patient clinical care at the CC before and after treatment. "Everyone comes with this wondrously optimistic hope of what these curative therapies represent, and the idea of a new beginning is an exciting and pretty universal sentiment among our patients."

The NIH is one of the originators of low-intensity conditioning protocols, and the Fitzhugh team is exploring using antibodies as a replacement for radiation during the conditioning process. "We think radiation may contribute to some of the complications we see including leukemia, solid tumors, and other short-term complications," she said. "We're not just trying to reverse SCD; we want to impact quality of life, prolong survival, and see how different conditioning regimens impact organ function."

Fitzhugh's team has shown improved heart function (PMID: 37282828) with stable or even improved lung function (PMID: 39189784). The team is about to submit a paper showing preservation of kidney function after lower-intensity conditioning transplants. Work is also underway to identify genetic markers for future leukemia development after transplant. "If patients have those biomarkers at baseline, we wouldn't recommend gene therapy because it depends on their own cells versus donor cells," said Fitzhugh, who is involved in a multicenter study with hundreds of patients to better understand the multifaceted impact of transplants (NCT: 05153967).

CREDIT: MOHAMED ALI, NHLBI

Emily Limerick manages the comprehensive clinical care of patients being treated for SCD at the NIH Clinical Center. Her patients seeking a cure come from as far away as France or Honduras, and as nearby as Maryland.

"We'll be comparing children versus adults, transplanted versus not transplanted, high- versus low-intensity conditioning protocols, and gene-therapy strategies versus more traditional types of transplants."

Back on the floor of the CC, Limerick is optimistic for what the expanding range of curative treatments represent for SCD patients, and she emphasizes the importance of making gene therapies scalable and available to people across the globe who need them most. She's betting that over time technology will continue its rapid march, and capacity to deliver transformative cures will improve. "These early gene therapies are just the beginning," Limerick said. "They're just the tip of the iceberg and there's a lot more to come." ●

A World of Clinical Regulatory Information at Your Fingertips

A Decade of ClinRegs

BY THE CLINREGS TEAM, NIAID

NIAID's ClinRegs website is a free, online database designed to save intramural and other clinical research professionals time by providing a central resource for country-specific clinical research regulatory information. Starting with 12 countries in 2014, ClinRegs has expanded to now include 23 countries.

Each country profile includes 36 topic areas that are updated at least once a year and provide a summary of the applicable requirements and links to official regulatory and ethics guidance documents, forms, and other resources. Additionally, English translations are provided, when available.

Recent updates to ClinRegs include a tabular dashboard on every country page, which provides easy access to new requirements as they are issued, quick facts, current research and sites, details on profile updates, and other helpful links.

Users can now filter which topic areas they want to view, compare up to four countries side by side, hide the left-hand menu, and filter search results by country and by topic.

CREDIT: NIAID

The ClinRegs website launched in 2014. Today, 10 years on, the resource offers 23 country profiles that include 36 topic areas. Visit NIAID's ClinRegs website at https://clinregs.niaid.nih.gov.

In the past year, 68,000 users in 166 countries have visited the ClinRegs website.

To learn more about what the site has to offer and how ClinRegs can help you, watch the recorded webinar "Utilizing NIAID's ClinRegs Website to Support International Clinical Research Regulatory Compliance," available at https://youtu.be/SSHJtqnDCNM?si=bqsJB9CTP7LfM11L.

To receive the latest ClinRegs information, subscribe to country- or topic-specific email updates on the website. ●

NIAID strives to make ClinRegs a useful resource for intramural researchers. Email the ClinRegs team with any comments, insights, or suggestions to NIAIDClinRegsSupport@mail.nih.gov

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The NIH Catalyst is seeking volunteer photographers and writers to join our team.

If you are interested in science writing or photography, and would like to learn more about working with the *NIH Catalyst*, please email us at catalyst@nih.gov.

Colleagues: Recently Tenured

Meet your recently tenured colleagues: **Andre Ballesteros-Tato** (NIAID), **Yarimar Carrasquillo** (NCCIH, NIDA), **Beatriz León** (NIAID), and **Chuan Wu** (NCI).

ANDRE BALLESTEROS-TATO, PH.D., NIAID

YARIMAR CARRASQUILLO, PH.D. NCCIH, NIDA

BEATRIZ LEÓN, PH.D. NIAID

CHUAN WU, M.D., PH.D., NCI

ANDRE BALLESTEROS-TATO, NIAID

Senior Investigator, Chief, Adaptive Immunity and Immunoregulation Section

Education: University of Vigo, Vigo, Spain (B.S. in biology); Autónoma University, Madrid (Ph.D. in molecular biology)

Training: Postdoctoral research fellow, Trudeau Institute, Saranac Lake, New York (2008); University of Rochester, Rochester, New York (2008–2012); University of Alabama at Birmingham, Birmingham, Alabama (2012)

Before coming to NIH: Professor, Department of Medicine, University of Alabama

Came to NIH: In 2024 as senior investigator

Outside interests: Reading; cooking; exercise; spending time with family

Website: https://www.niaid.nih.gov/research/andre-ballesteros-tato-phd

Research interests: My primary research interest is to define the cellular and molecular mechanisms that balance protective and pathogenic adaptive immune responses to allergens. The ultimate aim of my work is to develop innovative immunotherapies for treating and preventing food and respiratory allergies without causing significant immunosuppression. Leveraging advanced cellular and molecular techniques, my group has deep expertise in studying adaptive immune responses to respiratory pathogens and allergens (PMID: 37699392; PMID: 34516781; PMID: 31519812; PMID: 28892471). My research focuses on three main areas: 1) Characterizing the mechanisms that regulate adaptive immune responses—particularly memory T and B cells, and T follicular helper cells—in the context of food and respiratory allergies. 2) Investigating the interplay between infections and allergies to understand how infections may contribute to allergy development and how existing allergies influence immune responses to pathogens and vaccines. 3) Developing novel immunotherapies that achieve a balance between protection and controlled immunosuppression for food and respiratory allergens.

YARIMAR CARRASQUILLO, NCCIH, NIDA

Senior Investigator, Pain Neurocircuitry and Cellular Plasticity Lab

Education: University of Puerto Rico, Rio Piedras, Puerto Rico (B.S. in biology); Baylor College of Medicine, Houston (Ph.D. in neuroscience)

Training: Postdoctoral research scholar, Washington University, St. Louis (2005–2011)

Before coming to NIH: Staff scientist, Washington University, St. Louis (2011–2013)

Came to NIH: In 2014 as a principal investigator, NCCIH

Outside interests: Cycling; hiking; anything outdoorsy

Website: https://www.nccih.nih.gov/research/intramural/intramural-labs/pain-neurocircuitry-and-cellular-plasticity-lab

Research interests: I am a neuroscientist specializing in studying pain. My lab is interested in identifying brain mechanisms underlying bidirectional modulation of pain and in determining whether these processes are sex dependent. We use multidisciplinary approaches that include cellular physiology, molecular genetics, neuroanatomy, and behavioral rodent assays to tackle questions at molecular, cellular, and circuit levels that we then causally link to pain-related behaviors.

We have focused on the central amygdala (CeA), a forebrain limbic structure well positioned to link noxious stimuli to defense and affective responses. Our studies uncovered a dual function of the CeA in pain processing, showing that this brain region bidirectionally modulates pain and that the directionality of pain modulation is encoded by cell-type-specific changes in neuronal activity (PMID: 31597095). At the cellular level, we have shown that genetically distinct CeA neurons are also morphologically and electrophysiologically distinct (PMID: 33188006; PMID: 34101729) and that neurons in the parabrachial nucleus (a brain region that relays nociceptive inputs to the CeA) undergo divergent changes in excitability after an injury (PMID: 38331576).

At the circuit level, we identified and functionally characterized CeA efferent and afferent projections that modulate pain-related behaviors (PMID: 36269044; PMID: 36473754; PMID: 37542159). Our studies have revealed important sex differences in brain mechanisms of pain modulation (PMID: 35559931). In a recent study, we further showed that neuroplastic processes in amygdala cells and circuits contributing to increased pain after an injury are time-dependent, demonstrating that chronic pain is mechanistically distinct from acute pain (PMID: 39178115).

Future directions: Our ongoing efforts are focused on studying the CeA neurons and inputs and outputs involved in situations presenting competing pressures in pain states. Our ultimate goal is to build a CeA circuit map with synaptic and cellular components describing cell-type and pathway-specific functions of distinct pain-related behaviors.

[COMPILED BY SEPPIDEH SAMI, CC]

BEATRIZ LEÓN, PH.D., NIAID

Senior Investigator, Laboratory of Allergic Diseases, Innate Cells and Th2 Immunity Section

Education: Complutense University, Madrid (B.S. in biology); Autónoma University, Madrid (Ph.D. in molecular biosciences)

Training: Postdoctoral fellow, Autónoma University (2007–2008); postdoctoral fellow, Trudeau Institute, Saranac Lake, New York (2008); postdoctoral fellow, University of Rochester, Rochester, New York (2008–2012); postdoctoral fellow, University of Alabama at Birmingham, Birmingham, Alabama (2012)

Before coming to NIH: Tenured associate professor, University of Alabama

Came to NIH: In 2024 as a senior investigator

Outside interests: Outdoor adventures; family movie nights; reading; indoor plant growing

Website: https://www.niaid.nih.gov/research/beatriz-leon-phd

Research interests: Our section integrates mouse models, immunological techniques, and next-generation molecular tools to investigate how common airborne allergens trigger and sustain allergic diseases. Additionally, we explore how genetic factors, environmental exposures, microbiota, diet, and other influences contribute to these processes.

One of our key interests is understanding why and how inhalant allergens are perceived as pathogenic by the immune system and how they initiate harmful immune responses—leading to allergy (PMID: 37810200)—and sustain chronic inflammation over the long term (PMID: 26825674).

Another focus is identifying genetic and environmental risk factors that predispose individuals to allergies or, conversely, provide protection (PMID: 37100645; PMID: 36704753). Our lab has identified genetic risk factors for airway allergies (PMID: 37046042; PMID: 34965421) and uncovered mechanisms driving susceptibility to allergic diseases during critical periods such as infancy (PMID: 30635238).

We will continue to explore environmental influences, including diet, gut microbiota, and metabolism, to understand how these factors affect allergy risk during vulnerable windows such as infancy, pregnancy, and the impact of genetic defects.

Future directions: In our future research, we hope to identify potential intervention targets for preventing or treating allergic diseases.

CHUAN WU, NCI

Senior Investigator, Experimental Immunology Branch, Center for Cancer Research

Education: Shanghai Jiao Tong University School of Medicine, Shanghai (M.D. in clinical medicine); Münster University, Münster, Germany (Ph.D. in immunology)

Training: Postdoctoral fellow, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston (2010–2015)

Before coming to NIH: Assistant professor, Brigham and Women's Hospital, Harvard Medical School

Came to NIH: In 2017 as an Earl Stadtman Investigator, NCI

Outside interests: Painting; running; music

Website: https://irp.nih.gov/pi/chuan-wu

Research interests: My lab is interested in understanding intercellular regulation on intestinal barrier integrity. We have contributed impactful discoveries concerning intercellular cross-talk in mediating gut homeostasis by regulating epithelial barrier integrity, host-commensal symbiosis, neuroendocrine homeostasis, and immune balance, which are correlated to inflammatory bowel disease and colon cancer.

My lab identified that intestinal epithelial cells play a critical role in establishing commensalism and maintain intestinal barrier integrity (PMID: 34287641). Further, our work suggests that goblet-cell-mediated protein sialyation is crucial for intestinal mucus integrity and host-microbial homeostasis (PMID: 35303419).

More recently, my lab established the role of the gut-liver axis in intestinal stem-cell fitness (PMID: 38280375). We also made discoveries in T-cell responses for mucosal tolerance and barrier integrity, which led to several impactful publications (PMID: 29346764; PMID: 37040761; PMID: 37436991; PMID: 37429951).

Additionally, we made significant contributions towards understanding immune-neuron cross-talk for intestinal neuroendocrinal homeostasis, particularly in controlling serotonin release for local and systemic physiology (PMID: 33220232; PMID: 34871362; PMID: 37354904).

Our studies of cellular and molecular machineries of cell-cell interactions for regulating intestinal barrier function will have broad implications across the fields of immunology, physiology, and neuroendocrinology. ●

Paying Tribute

Each year, the *NIH Catalyst* pays tribute to NIH employees past and present who are no longer with us. Our condolences are with their friends, family, and colleagues who knew and loved them.

BY *THE NIH CATALYST* STAFF

CREDIT: ERNIE BRANSON, NIH

Pictured are Steven Rosenberg (NCI) and President Jimmy Carter at the NIH. Carter visited in 1988, post-presidency, to see his brother Billy Carter, who received treatment at the Clinical Center for pancreatic cancer.

Jimmy Carter, 100 (died Dec. 29), was the 39th U.S. president, having served from 1977–1981. Jan. 9 has been declared a National Day of Mourning.

Akwasi Addae, 45 (died Jan. 10), joined NIH in 2015 and was an electrician in the Clinical Center Facilities Management Branch.

Robert (Bob) Adelstein, 90 (died May 6), came to NHLBI in 1966 and became chief of the Laboratory of Molecular Cardiology in 1981. His lab was internationally known in understanding the various mechanisms for regulating smooth muscle contraction.

James Selby Alexander, 88 (died Oct. 7), was appointed NIH's first equal employment opportunity officer at the Clinical Center in 1974 and founded the NIH Office of Intramural Training and Education. He served NIH for more than 30 years conducting targeted outreach to increase the applicant pool of diverse scientists.

Bruce Ames, 95 (died Oct. 5), worked at NIH from 1953 to 1967, first as a postdoc, then as a biochemist, and then as chief of the Microbial Genetics Section in the Laboratory of Molecular Biology in what is now NIDDK. He famously created the Ames test, a widely used tool to determine the mutagenic potential of chemical compounds.

Norman Anderson, 68 (died March 1), was a clinical psychologist who served as inaugural director of NIH's Office of Behavioral and Social Sciences Research from 1995 to 2000.

Bill Arnwine, 89 (died April 19), served in the United States Army before beginning a federal career working in a variety of capacities at NIH and the Department of Defense. He retired from NIH having served as mail manager and former chief of the Travel and Administrative Services Branch.

David Badman, 81 (died Oct. 12, 2023), was a hematology grants program director who advanced research on iron overload in children with sickle cell anemia, among his many other accomplishments. His career spanned three decades at NIDDK's Division of Kidney, Urologic, and Hematologic Diseases before retiring in 2005.

Ellen Berg, 69 (died Aug. 9), was a nurse who worked at NIH for several years in the 1980s caring for some of the earliest patients with AIDS.

Hydeia Broadbent, 39 (died Feb. 20), was one of the first patients to stay at the Children's Inn at NIH after it opened in 1990. Broadbent was 4 years old when she arrived at NIH as part of the first generation of HIV/AIDS research.

Edwarda Buda-Okreglak, 75 (died May 6), was a physician who specialized in hematology-oncology and was associated with Walter Reed Army Medical Center and the NIH during her career.

C. Norman Coleman, 79 (died March 1), came to NCI in 1999 as a senior investigator and served as associate director of the Radiation Research Program in the Division of Cancer Treatment and Diagnosis. Coleman wrote extensively in the fields of radiation modifiers and on preparedness and planning for radiological or nuclear emergencies and global health.

Norvell "Van" Coots, 65 (died June 12), forged a distinguished 36-year career as a United States Army officer before coming to NIH in 2021. Coots was chair of the Clinical Center Research Hospital Board, which oversees operations at the NIH Clinical Center focused on policy to strengthen clinical care quality, oversight, and compliance.

Igor Dawid, 88 (died Feb. 13), was a developmental biologist who came to NCI in 1978. In 1981, he was appointed chief of the Laboratory of Molecular Genetics at NICHD, where he continued to make discoveries about early development until his retirement in 2016. Among his honors, he was elected to the National Academy of Sciences in 1981.

Seema Desai (died April 2024) came to NIH in 2022 and was a program director in NIMHD's Division of Integrative Biological and Behavioral Sciences. She was an immunologist, microbiologist, and HIV research scientist with multidisciplinary minority health research experience and was widely recognized for her scientific contributions in those areas.

Robert Eiss, 69 (died Oct. 2023), came to the Fogarty International Center in 1993 and served as a program officer at the Division of International Relations and later as director of the Office of International Science Policy and Analysis.

Claire Fagin, 97 (died Jan. 16), was a trailblazer in the field of nursing and nursing research. She came to NIH in the early 1950s to serve as the first director of children's programs at the NIH Clinical Center for NIMH.

Ned Feder, 95 (died March 26), began his 40-year career at NIH in 1967 and was known as a staunch advocate for integrity in science and medicine. His research ranged widely from studies on fungus and fungal infections, to developing methods of preparing tissues, some of which are still in use today.

Gary Felsenfeld, 94 (died May 1), came to NIDDK in 1961 and was known for his research on how chromatin structure and its role in gene expression and epigenetic regulation are associated with diseases such as cancer and diabetes. See the back page Photographic Moment in this issue for more about Felsenfeld.

Franklin Marshall Fountain, 89 (died Feb. 7), joined NIAID in 1978 as equal employment opportunity coordinator, where he served until his retirement.

John Gallin, 81 (died Oct. 1), was an eminent clinician-scientist who led the NIH Clinical Center from 1994 to 2017 as its longest serving director. Gallin began his decorated career at NIAID in 1971 and leaves his legacy in the next generation of clinical researchers through his passion for mentorship and training. He also served as editor of the *NIH Catalyst* from its first issue, in 1993, through the March–April 2023 issue, when he retired from the NIH.

Harry Handelsman (died Nov. 3) was an osteopathic physician who came to NIH in 1973 and joined NCI's Cancer Therapy Evaluation Program as a project officer. He worked at NIH for over a decade in several roles including positions at the Division of Cancer Control and Rehabilitation, and the Division of Resources, Centers, and Community Activities.

Caroline Hannaway, 81 (died March 14), was a historian and editor at the Office of NIH History and Stetten Museum from 1992 to 2008. Her work included contributing to the office's oral history collection and to the history of HIV-AIDS.

Dale Hereld, 64 (died April 26), joined NIAAA in 2008 to oversee the basic research portfolio on fetal alcohol spectrum disorders within the Division of Metabolism and Health Effects. Hereld's areas of expertise included signal transduction and chemotaxis, and he represented NIAAA on several NIH-wide committees and projects until his retirement in 2018.

Wanda Hill, 65 (died Oct. 17), dedicated over 40 years to federal service including 22 years as a program support specialist in the Office of Disease Prevention. Hill also supported the director of the Division of Cancer Prevention and Control at NCI.

Marian Kafka, 96 (died March 15), came to NIH as a research scientist in 1965. She joined NIMH in 1982 and became head of a neurobiology and psychopharmacology grant-review committee from 1986 to 1990. Kafka's work included research on cell membranes, nerve receptors, and circadian rhythms.

Edward Korn, 95 (died March 31), joined NHLBI in 1954, where he established his own Laboratory of Cell Biology in 1974 and pursued pioneering research in cytoskeletal biology and biochemistry for the next 65 years. He served as scientific director of NHLBI and was elected to the National Academy of Sciences in 1990.

Thomas Lehner, 64 (died Nov. 6), worked at NIMH for 15 years. He was a distinguished scientist and pioneer in neuropsychiatric disease genomics whose work significantly advanced our understanding of complex brain disorders.

Judith H. Levin, 89 (died Dec. 8, 2023), joined NHLBI in 1962 and then NICHD from 1973 until her retirement in 2014. She was known for her research on the molecular mechanisms involved in retrovirus replication.

William B. Marks, 90 (died June 9), was a biophysicist whose research at NINDS focused on the neurophysiology of locomotion and computer modeling of the growth of neurons in three dimensions.

Henry McFarland, 83 (died Jan. 11), joined NINDS in 1975 and was a distinguished figure in the field of multiple sclerosis research until his retirement in 2009.

Ralph Nossal, 86 (died Nov. 2), came to NIH in 1966 and was a senior investigator and lab chief at NICHD's Division of Basic and Translational Biophysics. Nossal developed the model for laser Doppler measurements of the blood flow in tissues and elucidated the physical mechanism of the negative resistance of biological membranes containing voltage-dependent ion channels.

Harish Pant, 85 (died Dec. 22, 2023), joined NIMH in 1974 and made many contributions to the understanding of neuronal cell biology and the pathophysiology of neurodegenerative disorders.

Paul D. Parkman, 91 (died May 7), came to NIH in 1963 and worked in the Laboratory of Viral Immunology at NIH's Division of Biologics Standards. He was the first person to isolate the rubella virus and partnered with Harry Meyer to develop the vaccine that would prevent infection and the resulting birth defects.

Dilys Parry, 80 (died Feb. 2), was a clinician and principal investigator at NCI for 30 years before retiring in 2007. Her medical genetics research focused primarily on genetic and clinical studies

CONTINUED ON PAGE 22

of neurofibromatosis 2, chordoma, and adult brain tumors.

Paul Plotz, 86 (died Jan. 13), came to NIAMS in 1964 and dedicated nearly four decades of service to science at NIH. He was a rheumatologist and principal investigator who was recognized as an expert on myositis. Plotz was also scientist emeritus editor of the *NIH Catalyst* from 2015 to 2019.

Richard "Rick" Race, 78 (died Nov. 13, 2023), was a research veterinarian who studied prion diseases, infectious neurodegenerative diseases that include Creutzfeldt-Jakob disease in humans and bovine spongiform encephalopathy, "mad cow disease," in cattle. He came to NIAID in 1970 and worked for 37 years at Rocky Mountain Laboratories in Hamilton, Montana.

J. Sri Ram, 95 (died March 2), joined NIH in 1965. He spent the last 28 years of his career at NHLBI and retired in 2005, where he served as group leader of the Training and Special Programs, Airway Biology and Disease Program in the Division of Lung Diseases.

Thomas Reese, 89 (died Oct. 11), was a world leader in structural neuroscience who developed cutting-edge applications that advanced understanding of synapses and cells in the brain. Reese, a member of the National Academy of Sciences, was a senior investigator and chief of the Section on Structural Cell Biology at NINDS, where he served the worldwide scientific community for six decades.

Paul J. Schmidt, 97 (died Sept. 23, 2023), came to NIH in 1965 and became director of the Clinical Center blood bank, where he served until 1974.

Richard Julius Sherins, 87 (died Nov. 2), worked at NIH for 20 years and served as clinical investigator and section chief of reproductive endocrinology at NICHD. His research focused on male reproductive physiology, clinical application of treatments, and the effects of cancer treatments on male fertility.

Maxine Singer, 93 (died July 9), came to NIH in 1956 as a postdoctoral fellow. She conducted studies in the emerging field of nucleic acid research at NIAMDD and moved to NCI's Laboratory of Biochemistry in 1975 to lead the Nucleic Acid Enzymology section, where she became chief in 1980. She was elected to the National Academy of Sciences in 1979.

Maria Spatz, 99 (died Jan. 26), was one of NIH's first leading women scientists and known for her research on the blood-brain barrier at NINDS. She served as section chief in the Laboratory of Neuropathology and Neuroanatomical Sciences from 1970 to 1990 and the Stroke Branch from 1991 to 2005.

Margaret Becker Zurkowski, 91 (died Oct. 23), worked as a biologist at NIH's Division of Biologics Standards and was known for her pioneering research with HeLa cells and significant contributions to the rubella vaccine. ●

NIH ABBREVIATIONS

CARD: Center for Alzheimer's and Related Dementias
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
FAES: Foundation for Advanced Education in the Sciences
FelCom: Fellows Committee
FNIH: Foundation for the NIH
FNLCR: Frederick National Laboratory for Cancer Research
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
NSTC: National Smell and Taste Center
OBSSR: Office of Behavioral and Social Sciences Research
OD: Office of the Director
ODP: Office of Disease Prevention
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health

On Display

Jacqueline Whang-Peng Visits Clinical Center Display Featuring Her Work

BY THE OFFICE OF NIH HISTORY AND STETTEN MUSEUM STAFF

CREDIT: EMILY CHIN-HSIEN TAI

Jacqueline Whang-Peng stands before the display honoring her work as chief of NCI's Cytogenetic Oncology Section from 1960 to 1994.

Jacqueline Jia-Kang Whang-Peng returned to the NIH this October to claim her slice of NIH history. Accompanied by family members, former colleagues, NIH scientists, and the curatorial staff of the Office of NIH History and Stetten Museum, Whang-Peng visited a new display in the Clinical Center featuring her work and life.

Whang-Peng was chief of NCI's Cytogenetic Oncology Section from 1960 to 1994, a position that few women, let alone Asian women, held at the time. An expert in cytogenetics, which is the study of chromosomes and their effect on cell behavior, she contributed to our knowledge of many cancers.

In 1960, the role of chromosome (gene) changes as a cause of cancer was not yet recognized because there was not an established technique for observing chromosome changes in the laboratory.

Whang-Peng and her mentor, Joe Hin Tjio, developed the technique to prepare mammalian cells for chromosomal research, observing and analyzing the chromosomes inside of the cell. Their 1962 paper described a "squash" method and an "air-dry" method.

One of her first results was the ability to study leukemia in tissue culture.

Whang-Peng quickly became the primary consultant on chromosomal abnormalities and cancer at NIH and collaborated with scientists from within NCI—helping to research a stunning number of cancers—as well as researchers from other NIH institutes and outside of NIH.

In 1972, Whang-Peng became one of the first two women to win the Arthur S. Flemming Award honoring outstanding young federal workers, being recognized for her chromosomal and leukemia research.

CREDIT: EMILY CHIN-HSIEN TAI

Whang-Peng, her daughter Sarah Freedman, and her son-in-law Scott Freedman at the display. Sarah Freedman described how her mother would bring home chromosome sheets for the children to help her cut up.

In 2008, Whang-Peng added the L'Oréal-UNESCO Award to her long list of honors. She was the first Taiwanese national to receive the award, which celebrates the accomplishments of women scientists.

Born in mainland China in 1932, Whang-Peng and her family fled to Taiwan in 1949 to escape the Chinese Civil War. She was the first woman trained in surgery at National Taiwan University's Medical College (Taipei), earning her M.D. in 1956, and the first female surgeon from Taiwan to do an internship in the United States. During her internship at Boston's New England Hospital, the plight of people with cancer inspired her to change her focus, leading to her career at NCI.

After retiring from a career at NIH spanning more than three decades, Whang-Peng returned to Taiwan.

A dynamo of energy, she has had a fruitful second career establishing research programs, training investigators, and conducting public education in cancer prevention and treatment. She is still working, even though she is in her early 90s.

The display about Whang-Peng is located on the first floor of the NIH Clinical Center, toward the Lipsett Amphitheater near the entrance to the Bioethics Office—next to our antique microscope display. ●

CREDIT: EMILY CHIN-HSIEN TAI

Susan Wong (NHLBI/ORS), Whang-Peng, and Emily Chin-Hsien Tai (NCI) at the display. Tai arranged the visit and escorted the family. Wong contacted the Office of NIH History and Stetten Museum, which set the wheels for the display in motion.

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National Institutes of Health
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https://irp.nih.gov/catalyst/33/1

PHOTOGRAPHIC MOMENT

CREDIT: DONA JONES, NINR

A Door to Discovery: Gary Felsenfeld (1929–2024), scientist emeritus, NIDDK's Laboratory of Molecular Biology, displayed correspondence he received throughout his 62-year NIH career on his office door. Each instance features some misspelling of his name. Felsenfeld classified the misspellings into point mutations, frameshift mutations, insertions, deletions, and translocations. ●

The NIH Catalyst is published bimonthly for and by the NIH Office of Intramural Research.

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