

Annals of NIH History: From Yellow Berets to Nobel Laureates

BY ETHAN SMITH, NINR

IT MAY SEEM LIKE A COINCIDENCE THAT Nobel laureates **Michael Brown, Joseph Goldstein, Harold Varmus, and Robert Lefkowitz** all started their training at NIH in the summer of 1968. But it wasn't just happenstance, according to Raymond Greenberg, a professor at the University of Texas Health Center at Houston (Houston) and author of *Medal Winners: How the Vietnam War Launched Nobel Careers*. His book tells this overlooked story through the lives of those four men.

As the United States' involvement in Vietnam escalated in the late 1960s, a doctor draft ensured an adequate supply of freshly trained physicians for the armed forces. "If you were a male physician, you were subject to a special draft for physicians," said Greenberg during a virtual lecture he gave at NIH in November 2020. "Pretty much everyone was going to serve for some period of time."

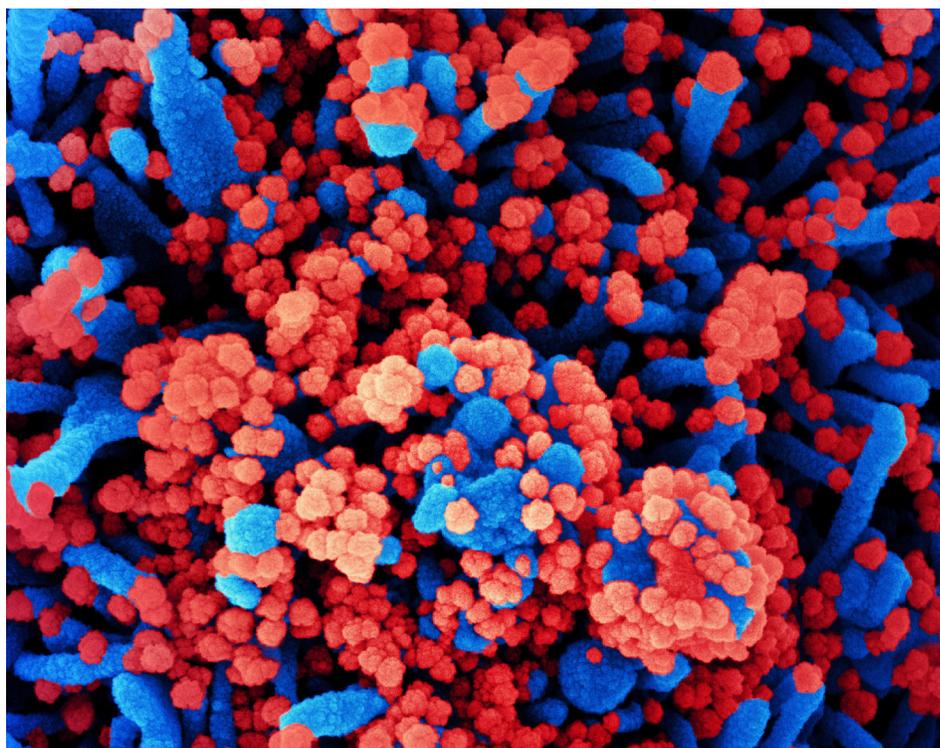
Not all of the drafted physicians served in the combat zone of Vietnam; some were posted to U.S. military hospitals around the world. But with public opinion of the war deteriorating, many physicians sought alternative types of public service to satisfy their draft obligation.

Yellow Berets. One such alternative was NIH's Associate Training Program (ATP), a two-year research program under the Commissioned Corps of the United

CONTINUED ON PAGE 6

The 1918 Flu and COVID-19: A Tale of Two Pandemics

BY EIMEAR HOLTON, NIAID



CREDIT: NIAID

Colorized scanning electron micrograph of a cell (blue) heavily infected with SARS-CoV-2 virus particles (red), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland.

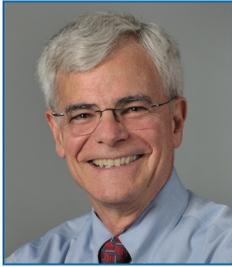
THE COVID-19 PANDEMIC IS NOT OUR FIRST RODEO WITH BATTLING A DEADLY virus, and it likely won't be our last. As we continue to process the past year, the juxtaposition of COVID-19 pandemic and the influenza pandemic of 1918 puts today's challenges into perspective. Two prominent NIH scientists shared their perspectives (virtually) at the January 12, 2021, launch of the Demystifying

CONTINUED ON PAGE 12

CONTENTS

FEATURES • **|1|** The 1918 Flu and COVID-19 **|5|** Fueling the Next Genomics Revolution **|10|** COVID-19 Timeline (January–February) **|14|** Introducing NIH's Newest Lasker Scholars **|18|** Stadtman Investigators Pursuing Their Passion for Science

DEPARTMENTS • **|1, 7|** NIH History: From Yellow Berets to Nobel Laureates; My Adventures as an NIH Yellow Beret **|2|** DDIR: How the IRP is Fighting COVID-19 **|3|** Abbreviations **|4|** Training: Becoming a Resilient Scientist **|8, 13, 17|** Research Briefs **|24|** Photographic Moment: A Visit From the New President



How the NIH Intramural Program Is Fighting the COVID-19 Pandemic

BY MICHAEL GOTTESMAN, DDIR

GIVEN THE CONSTANT PRESENCE OF NIH leaders such as NIH Director **Francis Collins** and National Institute of Allergy and Infectious Diseases (NIAID) Director **Anthony Fauci** in the popular press, on TV and radio and in print, and in commentaries in academic journals, it is clear that the NIH has played a major role in strategic planning, communication of public-health requirements, and development of strategies to prevent, detect, and treat infection caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2), the virus responsible for COVID-19. What may not be as clear to many intramural staff are the major contributions that have been made over the past year by intramural—and extramural—scientists, working in teams and as independent contributors, to the science underlying our current understanding of the diagnosis, prevention, therapy, and pathophysiology of COVID-19.

Early in the COVID-19 pandemic, we sought to document the contributions of our intramural scientists to the antipandemic effort by creating a dashboard in collaboration with **Christine Cutillo** (National Center for Advancing Translational Sciences, NCATS) listing all of the projects being carried out in the intramural research program (IRP).

Currently, there are 23 institutes and centers involved in COVID research with about 400 active projects—ranging from basic science to preclinical research to clinical trials—and 313 distinct PIs. The research areas are equally divided between immunology—host response and therapeutic (drugs and biologics) at 14%; 10% in pathogenesis; 8% in genetics and genomics; and 7% in structural biology. Bioinformatics, virology, computational and systems biology, diagnostics, epidemiology, and vaccines are all in

There have been so many important intramural contributions to the COVID-19 effort that it is difficult to choose just a few to highlight in this essay.

the 6% range. Natural history, clinical trial, and mental and behavioral health are in the 2–5% range. There are 63 reagents available in the registry.

Many of these research activities were highlighted in the October 29–30, 2021, workshop organized by the NIH COVID-19 Scientific Interest Group (chaired by **Pam Schwartzberg**, NIAID) and colleagues at the FDA. In addition, the Office of Intramural Research, with funding by NIAID, provided grant support for intramural scientists as part of the

Intramural Targeted Anti-COVID-19, a competition overseen by **Ted Pierson** in NIAID. Of 159 applications, 40 were funded.

There have been so many important intramural contributions to the COVID-19 effort that it is difficult to choose just a few to highlight in this essay, but I will do my best (and I hope that the architects of the equally important work that is not cited do not feel slighted).

The most obvious is the contribution of the dedicated team at NIAID's Vaccine Research Center (VRC) to the development of a structure-based vaccine. Since the SARS outbreak in 2002–2004, VRC Deputy Director **Barney Graham** and his many talented associates and colleagues, including **Kizzmekia Corbett**, (NIAID), have been working on the general principles for creating vaccines to counteract significant coronavirus epidemics. Targeting the coronavirus spike (S) protein, they discovered (with their collaborator **Jason McLellan**, an alumnus of the VRC and now at the University of Texas at Austin), that substitutions of two prolines between two key areas would stabilize the S protein in its native functional conformation. This engineered structure has become the basis for many of the vaccines under current development, all of which have proven to be exceptionally effective in



preventing SARS-CoV-2 symptomatic infections. Specifically, this variant is encoded by the messenger RNA present in the Pfizer and Moderna vaccines. It is also encoded by the adenovirus type 26 vaccine vector in the Johnson and Johnson–Janssen vaccine.

In the area of therapeutics, NCATS has done extensive work to screen existing drugs to be repurposed for treatment of SARS-CoV-2 infection. In addition, the team of **Emmie de Wit** and **Vincent Munster** at NIAID's Rocky Mountain Laboratories (Hamilton, Montana) was one of the first to demonstrate the efficacy of the antiviral agent remdesivir in rodents and nonhuman primates. Their work accelerated the development of this agent for treatment of hospitalized patients with moderate to severe COVID-19; remdesivir remains a standard of care.

There have been many contributions to understanding the structure of the virus and how it enters and leaves cells. In addition to the pioneering and elegant structural work from the Graham group, NIH structural biologists throughout the IRP have explored the structure of the S protein–angiotensin-converting enzyme 2 receptor complex, providing a much better understanding of the early steps in viral entry.

Also relevant to viral entry, the team led by **Kelly Ten Hagen** (National Institute of Dental and Craniofacial Research) showed that furin cleavage

in SARS-CoV-2 is modulated by mucin type O glycosylation, which possibly explains why the UK B.1.1.7 variant is more transmissible than the other variants, because some of the mutations in this variant are close to this site. At the other end of the viral replication cycle, **Nihal Altan-Bonnet** (National Heart, Lung, and Blood Institute) demonstrated that SARS-CoV-2 uses a lysosomal pathway to leave cells, an unexpected finding that could have important therapeutic implications.

Considerable progress has also been made in understanding what host factors predispose someone to severe disease. **Helen Su** and **Luigi Notarangelo**, NIAID, in collaboration with the laboratory of Jean-Laurent Casanova at Rockefeller University (New York), showed that in up to 15% of persons severely ill with COVID-19, defects in the pathways involved in the action of type 1 interferons (interferons alpha and omega), caused either by mutations or neutralizing autoantibodies, played a significant role. This work reinforces the role that even subtle defects in the immune system play in susceptibility to severe viral infection and may lead to potential therapies for severely ill patients who have such defects.

Although these examples don't begin to touch the tip of the coronavirus iceberg at NIH, I think they are pretty “cool” science. We can expect much more to come. ●

NIH ABBREVIATIONS

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

From the Fellows Committee

Becoming a Resilient Scientist During My Trip to the Zoo

BY ERICA WYNNE-JONES, NIAID

I FIRST HEARD ABOUT RESILIENCE when I was in primary school in rural Australia. It was part of a cognitive-behavioral program at the school called “You can do it!” I volunteered to be on our “You can do it!” committee, where we would organize events based on one of the five keys to success: confidence, persistence, organization, getting along, and resilience.

Organizing events for the other keys was relatively easy, but resilience was much more difficult. As an 8-year-old, I had only the rudimentary understanding that resilience was the ability to “bounce back,” which sounded easy enough to me because I played a lot of four square handball (a game in which four players—on a square court divided into quadrants—bounce a small rubber ball back and forth between quadrants; players are eliminated when they fail to touch the ball into another player’s quadrant.)

We ended up organizing a coloring competition to build resilience in our peers. I’m not sure what we thought it had to do with resilience, but the ability to use crayons for coloring a black-and-white template seemed like an extremely valuable skill at the time. Twenty years on, I rarely use my coloring talents, and I’m learning a lot more about resilience through the monthly Office of Intramural Training and Education’s (OITE’s) series on “Becoming a Resilient Scientist.”

One of the recurring themes in the “Becoming a Resilient Scientist” series is empathetic, nonviolent communication. American psychologist Marshall Rosenberg, who developed nonviolent communication as a way to resolve conflict, coined the terms “jackal language” and “giraffe language” to describe the ways in which we can

communicate. Jackal language is violent and focuses on blame. Conversely, giraffe language is empathetic and forgiving, named after the giraffe’s large heart and its tall stature, which gives it the ability to see the forest for the trees. These styles apply not only to communication with others but also within ourselves.

For me, this resilience training came sharply into focus late last year. I was going through a tough time at work and struggling in the aftermath of a difficult conversation with a colleague. So, I went to the zoo. For me, the zoo is the perfect place to decompress. You get to walk around outside, and, really, how can you be upset when you’re watching a sea lion fetch a Frisbee disk? I was halfway around the zoo when my phone died during a podcast I was listening to. I had a battery charger, but alas I had just witnessed my phone’s last digital breath. My worst nightmare. In the zoo, I was able to distract myself with cute animals, but when I boarded the Metro to go home, I was left with nothing but my own thoughts. They were raging and twisting in my head as I replayed my bad conversation over and over and thought about what had happened. “Is it all my fault? Am I a horrible person? Is the other person a horrible person?”

At that point, I was really grateful for the work and training I’d done with OITE to build my resilience. I took a step back and thought about how all sides in this situation were understandable and that communication and relationships have become more difficult for everyone during the COVID-19 pandemic. Even though those thoughts didn’t solve all of my problems, where there was once a pack of vicious jackals who would tell me horrible things about myself and others, there is now



ERICA WYNNE-JONES, NIAID

a tower of giraffes who stand tall and can help me see the whole situation with more empathy. Practicing resilience seems to be a lifelong journey, but in the moment, I was glad to be riding the Metro with giraffes and not jackals. ●

To register for or watch recordings of OITE’s “Becoming a Resilient Scientist” series, go to https://www.training.nih.gov/nih_becoming_a_resilient_scientist_series. To learn about OITE’s weekly resilience discussions that focus on specific topics, go to <https://www.training.nih.gov/events/upcoming>.

Erica Wynne-Jones is an Australian visiting postdoctoral fellow in the Lab of Clinical Immunology and Microbiology at the National Institute of Allergy and Infectious Diseases, where she works on CD8+ T cells in viral skin infections. She is the Outreach Liaison on the Fellows Committee and is writing for and coordinating fellows’ contributions to the NIH Catalyst Training Page. Outside of work she enjoys cycling around Bethesda, cartooning, writing science-themed satirical articles and sitcoms, and performing stand-up comedy.

Fueling the Next Genomics Revolution

WALS Panel Discussion Highlights Achievements in Genomics

BY NATALIE HAGEN, NCATS

NIH CELEBRATED THREE SPECIAL anniversaries at a Wednesday Afternoon Lecture Series (WALS) special event on January 13, 2021: the 25th-year anniversary of the first complete bacterial genome; the 20th anniversary of the publication of the human genome; and the 15th anniversary of the first human metagenome (of microbial communities). NIH Director **Francis Collins** led a lecture and panel discussion featuring **Claire Fraser**, NIH alum and director of the Institute for Genome Sciences at the University of Maryland (Baltimore); **Charles Rotimi**, chief of the Metabolic, Cardiovascular, and Inflammatory Disease Genomics Branch at the National Human Genome Research Institute (NHGRI); and Eric Lander, president and founding director of the Broad Institute (Cambridge, Massachusetts) of MIT and Harvard.

The WALS event also marked one year since scientists at NIH's Vaccine Research Center began working with Moderna to create a COVID-19 vaccine, which has since received FDA Emergency Use Authorization and is being used to immunize millions of people. The ability to achieve this feat so rapidly can be attributed to advancements made in genomics over the past two decades.

Collins himself is an important figure in the genome arena. He served as director of NHGRI (1993–2008), made landmark discoveries of disease genes, and led the international Human Genome Project, which mapped the human genome.

Putting the past in perspective. Fraser, who worked at NIH from 1985 to 1992, uncovered the first complete genome of a free-living organism, *Haemophilus influenzae*, in 1995, using whole-genome shotgun sequencing (a method for sequencing random

DNA fragments, then using a computer to assemble them into chromosomes). Her work paved the way for a myriad of other projects. From reverse vaccinology, which uses a genomic sequence to identify vaccine candidates, to a genomic catalog of the Earth's microbiomes, almost no field has been left untouched. The future applications seem boundless. "We're in the infancy of microbiome-based diagnostics and therapeutics," pronounced Fraser.

The ubiquity of genomic sequencing has led to a reexamination of the concept of a genome altogether, with the result being the development of the pan-genome concept (all the genes in all the strains of a species.). There was found to be such extensive diversity that the strain-specific genes may even outnumber the size of the core genome.

The history of humanity. Rotimi, who came to NIH in 2008 to establish the trans-NIH Center for Research on Genomics and Global Health, highlighted the necessity of sequencing the genomes of African ancestry populations. Their genomes have more variability and carry more diversity than other genomes. He pointed out that Africa is the ancestral home of all humanity and the place of 99% of human evolutionary history. This greater genetic variation provides more power to detect the relationship of genes to phenotypes.

Rotimi also emphasized the importance of studying African genomes as a social justice issue. "If we do not change course and include more African genomes, will tomorrow's medicine work for everybody?" By leaving out African genomes, health and economic inequities will only be exacerbated, he added.

Future of genetics. Lander, who is now serving as the White House Science Advisor to President Joseph Biden, explained that the first "phase" of human genetics research, spanning from 1980 to 2015, involved mapping disease genes. However, it takes too long to identify individual genes that play a role in a disease.

He also talked about a future in which integrating human genome data and microbiome data becomes commonplace. "I would love to see longitudinal microbiome data collected from all the participants in the 'All of Us' project," NIH's research program to collect genetic and health data from one million volunteers in an effort to accelerate medical breakthroughs. By integrating human genome and microbiome data, "we can fully understand the genetic basis of common disease and go easily from maps to mechanisms to medicine."

As we enter the new phase of human genetics research—fueled by the establishment of large-scale human cohorts, the falling cost of genetic sequencing, and the rise of cloud-based data platforms—scientists aim to more efficiently determine disease mechanisms from human samples. Furthermore, the publication of datasets online allows for analysis by scientists all over the world. ●

To watch a videocast of the panel discussion, which took place on January 13, 2021, go to <https://videocast.nih.gov/watch=40165>.

Natalie Hagen is a postbaccalaureate research fellow in the National Center for Advancing Translational Sciences, where she is performing pharmacokinetics studies of novel drug candidates. After her fellowship is over in 2021, she is planning to pursue a Ph.D.

From Yellow Berets to Nobel Laureates

CONTINUED FROM PAGE 1

States Public Health Service. The small percentage of applicants admitted were known as clinical associates (CAs). The ATP had the pick of the best and brightest medical school graduates. After completing residency training, the successful applicants came to NIH where they performed clinical duties and conducted bench research in the lab of a senior scientist. The number of CAs in the ATP peaked around 200 per year at the height of the war, then fell precipitously after a peace treaty was signed in 1973.

Some people referred to the CAs as Yellow Berets. In contrast to the Green Berets, the Yellow Beret label implied cowardice, possibly because supporters of the war effort viewed the CAs as trying to stay out of harm's way.

The ATP proved to be an incredibly successful program, ultimately producing many of the top-notch physician–scientists of that generation. Compared with physicians who weren't in the program during the Vietnam War, NIH CAs were more likely to go on to hold academic positions as professors, department chairs, and deans. Six other physicians who were CAs during the war went on to receive Nobel prizes, too—**J. Michael Bishop** (1989), **Alfred Gilman** (1994), **Stanley Prusiner** (1997), **Ferid Murad** (1998), **Richard Axel** (2004), and **Harvey Alter** (2020). With such a cadre of distinguished alumni that also included National Institute of Allergy and Infectious Diseases Director **Anthony Fauci**, it's not surprising that the designation of Yellow Beret eventually became a badge of honor.

Learning to Think Like Scientists. In the summer of 1968, Brown, Goldstein, Varmus, and Lefkowitz became CAs and joined NIH's tight-knit, collaborative community of innovative scientists. The four attributed much of their later success to learning from their mentors, who taught them how to think like scientists.

Goldstein was the only one who had basic-research experience before coming to NIH. "If we think about our mythology about who goes on to be a great scientist and win Nobel Prizes, I think one of our preconceptions is that these people know from very early in life that this is the pathway that they're on," said Greenberg. None of the four future Nobel laureates had prior research experience or aspired to become serious scientists. The ATP

CREDIT: OFFICE OF NIH HISTORY AND STETTIN MUSEUM



NIAMD - CLINICAL INVESTIGATIONS - DECEMBER, 1968

ROW 1: PERRIER, LASTER, DECKER, ROBBINS, RALL, GORDON, WHEDON, di SANT'AGNESE, SHULMAN, AURBACH, ROSEN, THOMPSON, EDELHOCH.
 ROW 2: GOETZL, SCHULMAN, GORDEN, PASTAN, KALTREIDER, TALAL, METZGER, STEINBERG, WOLFE, BILSTAD, BROWN, PERLMAN, ASHMAN.
 ROW 3: ASKENASE, GREENE, WEISSMAN, PALLAVICINI, CAHNMANN, PAGES, ROBERTSON, CHASE, MELSON, DIBBINS, LEFKOWITZ, SHERMAN, GARDNER.
 ROW 4: FUJIMOTO, ITSCOTTZ, MARCHESI, LAPEY, BOAT, LEVY, A. WEINTRAUB, HIRSCHMAN, MALAN, SCHNEIDER, WILLERSON, STAPLES, VARMUS, BOYLE, DESBUQUOIS.
 ABSENT: BERNSTEIN, KAPLAN, LEWALLEN, LOEB, MARCUS, ROTH, SEEGMILLER, VARRONE, B. WEINTRAUB, WOLFF.

Clinical Investigators class photograph, National Institute of Arthritis and Metabolic Diseases: Michael Brown (row 2, third from right), Robert Lefkowitz (row 3, third from right), Harold Varmus (row 4, third from right), and Ira Pastan (row 2, fourth from left) are among the investigators present.

proved to be a transformative experience, introducing them to bench science and launching their trailblazing research careers.

Brown worked in **Earl Stadtman's** lab, where he studied the activation of glutamine synthetase, an enzyme involved in bacterial nitrogen metabolism. Goldstein worked in the lab of **Marshall Nirenberg** (who shared the Nobel Prize in 1968 for the “interpretation of the genetic code and its function in protein synthesis”) and studied how translation, the process of building protein chains, is terminated. Luckily, NIH had access to patients with rare diseases that most physicians outside of NIH had never seen before.

In an event that sparked his curiosity and foreshadowed his lifelong partnership with Brown, Goldstein treated a girl with familial hypercholesterolemia, a condition that causes elevated concentrations of cholesterol and can lead to heart attacks in childhood. Already close friends, Brown and Goldstein both went to the University of Texas Southwestern (Dallas) after leaving NIH and discovered that people with familial hypercholesterolemia have a defect in the receptor for low-density lipoprotein. They won the Nobel prize in 1985 “for their discoveries concerning the regulation of cholesterol metabolism.” Their findings led to the subsequent development of cholesterol-lowering statin drugs.

Varmus joined **Ira Pastan's** lab and studied how lactose metabolites and cyclic adenosine monophosphate triggers the transcription of genes involved in lactose metabolism. Varmus left NIH for the University of California at San Francisco (San Francisco), later receiving the Nobel prize with fellow former CA J. Michael Bishop in 1989 “for their discovery of the cellular origin of retroviral oncogenes” that demonstrated how retroviruses can trigger proto-oncogenes to push a cell into

a cancerous state. Varmus later returned to NIH, serving as director (1993–1999), then president and CEO of Memorial Sloan-Kettering Cancer Center in New York (2000–2010), and later rejoining NIH again as director of the National Cancer Institute (2010–2015).

Lefkowitz also worked with Pastan as well as with **Jesse Roth**. At first, Lefkowitz experienced repeated failures in the lab and, in frustration, planned to leave research altogether. But in the process of labeling the adrenocorticotrophic hormone with radioactive isotope of iodine, and later demonstrating that the hormone attached to the membrane of adrenal-gland cells, he found his passion for science. He later joined Duke University (Durham, North Carolina), ultimately receiving the Nobel Prize in Chemistry with his former trainee Brian Kobilka, in 2012, for their work characterizing adrenaline receptors and the structure of G-protein coupled receptors. (See excerpt from his book on the right.)

The four Nobel laureates are still active in the scientific community: Brown and Goldstein hold endowed professorships at the University of Texas Southwestern Medical Center; Varmus holds a named professorship at Weill Cornell Medical College (New York); and Lefkowitz is a distinguished professor at Duke University and an investigator with the Howard Hughes Medical Institute. ●

To watch a videocast of Greenberg's virtual lecture go to <https://videocast.nih.gov/watch=38976>.

Ethan Smith is a postbaccalaureate fellow in the National Institute of Nursing Research. He is working on clinical studies involving biomarkers for traumatic brain injury.

My Adventures as an NIH Yellow Beret

BY ROBERT LEFKOWITZ WITH RANDY HALL

Excerpted from *A Funny Thing Happened on the Way to Stockholm: The Adrenaline-Fueled Adventures of an Accidental Scientist*, by Robert Lefkowitz with Randy Hall (Pegasus Books, New York, 2021).

The project that Jesse [Roth] and Ira [Pastan] had given me was to identify the receptor for a hormone known as ACTH, which is a key regulator of the stress response. For this project, the first thing I had to do was label ACTH with a radioactive tag, then separate the labeled hormone from the unlabeled. In theory, this sounds easy, but in practice, it was a titanic struggle....

I continued having technical troubles, but then suddenly, a year into my fellowship, a miracle happened: my experiments started working. The essential insight that led to my success was that I needed to ask others for help instead of just struggling by myself.... I sought out several expert chemists on the NIH campus to ask their counsel. With advice from these sages ... I finally got traction in achieving chemical separation of the labeled ACTH from the unlabeled.

Once I finally had some pure labeled ACTH, everything else moved with breathtaking speed. In short order, I showed that the labeled ACTH was biologically active, and then rapidly developed one of the very first assays for studying the binding of a hormone to its receptor. Later in my career, I realized that this is often how research works: You experience nothing but failure for weeks or months, and then suddenly you overcome a technical hurdle, like in this case finding the right chromatographic system to separate the two forms of ACTH, and suddenly everything starts moving like wildfire. These were heady months, as I felt intoxicated by the knowledge that I was exploring new realms of research where none had previously trodden. ●



Intramural Research Briefs



CREDIT: ERINA HE, NIH MEDICAL ARTS

NHLBI: A new blood test measures donor DNA fragments and detects acute heart-transplant rejection earlier than current methods. The illustration shows DNA fragments (yellow) derived from a transplanted heart alongside the patient's own DNA (blue).

NHLBI, NCI: NEW BLOOD TEST TO DETECT HEART-TRANSPLANT REJECTION

Researchers at NHLBI have developed a blood test for the early detection of acute heart-transplant rejection, a potentially fatal condition that can occur within a few months after receiving a heart transplant. In an article published in *Circulation*, the authors including **Sean Agbor-Enoh**, chief of NHLBI's Laboratory of Applied Precision Omics, estimated that by using this new test, doctors can safely avoid 81% of invasive heart-tissue biopsies, the current method used to detect rejection.

The new blood test involves a quick blood draw and measures donor-derived cell-free DNA (ddcfDNA), short fragments of DNA released by donor heart tissue into the bloodstream if a recipient's immune system attacks the heart. The researchers analyzed the blood concentrations of ddcfDNA in 165 heart-transplant recipients finding higher concentrations of ddcfDNA in patients with acute rejection. The ddcfDNA is highly sensitive in detecting acute rejection and its performance was better than that of heart biopsies. The new blood test may be able to detect rejection as early as 28 days (versus weeks or months) after a heart transplant. (NIH authors: S. Agbor-Enoh, C. Mutebi, K. Yu, P. Shag, I. Tunc, S. Hsu, H. Kong, A. Bikineyeva, A. Marishtam, K. Bhatti, Y. Yang, M.K. Jang, and H.A. Valantine, *Circulation* 2021)

[BY ETHAN SMITH, NINR]

NIEHS: FOXL2 LINKED TO ENDOMETRIOSIS, FEMALE INFERTILITY, AND CANCER

Two teams of NIEHS authors published companion articles that underscored the importance of the transcription factor forkhead box L2 (FOXL) in women's ovarian physiology and fertility and clarified the role of excess FOXL2 in endometriosis. FOXL2 regulates sex differentiation and reproductive function.

In humans, *FOXL2* genes that mutate or lose function are associated with premature infertility and ovarian cancer. Expression of *FOXL2* is increased in the uterine tissue of women with endometriosis, which can be influenced by endocrine disruptors in the environment. In the first study, the research team generated mice with overexpression of *FOXL2* and reported that too much altered differentiation and function of uterine epithelial cells. In addition, endometrial stromal cells showed increased fibrosis, interfering with development of the endometrial glands. The study identified mouse uterine pathways regulated by *FOXL2* that are similar to pathways elevated in women with endometriosis, suggesting the potential for better diagnostic and therapeutic tools to treat endometriosis.

In the second study, also based on a mouse model, the researchers evaluated the effects of irregular FOXL2 activity on female reproductive physiology and disorders. In ovarian development and function from the fetal stage through adulthood, excessive FOXL2 production made it harder for certain cells to differentiate, and the follicles did not form correctly. The female mice could not ovulate and were infertile. This study reveals that fine-tuned production of FOXL2 is absolutely essential for proper ovarian physiology and fertility. This potential cause of ovarian disorders in women may point to treatment targets. (Study 1: NIH authors: R. Li, S.-P. Wu, L. Zhou, B. Nicol, H.H.-C. Yao, and F.J. DeMayo, *Biol Reprod* 103:951-965, 2020; Study 2: NIH authors: B. Nicol, K. Rodriguez, and H.H.-C. Yao, *Biol Reprod* 103:966-977, 2020)

[BY KELLEY CHRISTENSEN, NIEHS]

NIDA: NATIONWIDE INCREASE IN METHAMPHETAMINE OVERDOSE DEATHS

In a study published in *JAMA Psychiatry*, researchers at NIDA found a more than five-fold increase in methamphetamine-involved age-adjusted overdose death rates over an eight-year period from 2011 to 2018, especially among American Indians and Alaska Natives. The analysis, based on data from the CDC's National Vital Statistics System examined overdose death rates of individuals aged 25-54 by gender and race/ethnicity. The researchers found that overdose death rates rose across all racial and ethnic groups and among both men and women, although men had significantly higher rates than women within each racial/ethnic group. American Indians and Alaska Natives had by far the highest death rates, which more than quadrupled over the study period. "Identifying populations that have a higher rate of methamphetamine overdose is a crucial step toward curbing the underlying methamphetamine crisis," said **Beth Han**, lead author on the study. "By focusing on the unique and culturally specific needs of individuals, we can begin to move away from one-size-fits-all approaches and toward more effective, tailored interventions." (NIH authors: B. Han, J. Cotto, K. Etz, E.B. Einstein, W.M. Compton, and N.D. Volkow, *JAMA Psychiatry*, 2021)

[BY HENRY DIECKHAUS, NINDS]

NIAID (RML): SALMONELLA SWIMMING BEHAVIOR MAY PROVIDE CLUES TO INFECTION

Scientists know a lot about *Salmonella enterica* serovar Typhimurium (*S. Typhimurium*), one of the most common causes of foodborne infection, and how these flagella-propelled bacteria swim in short, random spurts. Yet, until now, they didn't understand how the type of swimming can contribute to infection of the epithelial cells lining the inside of the intestine. Researchers at NIAID's Rocky Mountain Laboratories (Hamilton, Montana)



recently discovered that a certain protein can turn *S. Typhimurium* bacteria in the gut into tiny missiles that swim straight.

The authors identified the protein McpC, short for methyl-accepting chemotaxis protein C, that causes the bacteria to swim straight when they are ready to infect cells. “In the presence of McpC, the bacteria swim in longer, straighter runs than McpC-defective mutants,” said **Olivia Steele-Mortimer**, senior author on the study. “This [longer, straighter run] is tightly coupled to invasion in the gut.”

McpC could be a potential target for developing new antibacterial treatments to hinder the ability of *S. Typhimurium* to infect and colonize the gut, according to the authors. The researchers hypothesize that controlled smooth swimming could be a widespread bacterial infection strategy and that their findings could result in the development of novel antibiotics. (NIH authors: K.G. Cooper, A. Chong, L. Kari, B. Jeffrey, T. Starr, C. Martens, and O. Steele-Mortimer, *Nat Commun* 12:article number 348, 2021)

[BY JUNE GUHA, NIAID]

NIDDK, CC, NINR, NIAAAA: COMPARING LOW-FAT AND LOW-CARB DIETS

NIDDK scientists led a small, highly controlled, inpatient study to compare the effects of a low-fat, high-carbohydrate, plant-based diet with a high-fat, low-carbohydrate, animal-based diet. They compared calorie (or energy) intake, hormone concentrations, body weight, and satiety levels. Twenty adults (11 men and nine women), housed in the NIH Clinical Center’s Metabolic Research Unit, were given one diet for two weeks, and then the other diet for two weeks. All were provided with three meals a day plus snacks and allowed to eat as much as they desired.

High-carbohydrate foods were expected to increase hunger and result in excess calorie intake because they can cause large swings in blood glucose and insulin.

But the results were surprising: When people were on the plant-based diet, they ate 550–700 fewer calories daily, but had higher insulin and blood glucose concentrations than when they ate the animal-based diet. Despite differences in calorie intake, there were no significant differences in terms of participant rating of hunger, enjoyment of meals, or feeling full. Both diets also resulted in weight loss, although this loss was only significant for the plant-based diet during the first week.

The findings suggest that the factors resulting in overeating and weight gain are more complex than the amount of carbs or fat in one’s diet. In fact, there could be benefits to both diets if only in the short term.

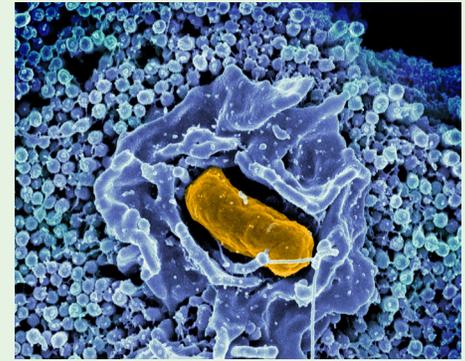
“While the low-fat, plant-based diet helps curb appetite, the animal-based, low-carb diet resulted in lower and more steady insulin and glucose levels,” said NIDDK Senior Investigator **Kevin Hall**, the study’s lead author, in a news release. “We don’t yet know if these differences would be sustained over the long term.” (NIH authors: K.D. Hall, J. Guo, A.B. Courville, J. Boring, R. Brychta, K.Y. Chen, V. Darcey, A.M. Gharib, I. Gallagher, R. Howard, P.V. Joseph, L. Milley, R. Ouwerkerk, K. Raising, I. Rozga, A. Schick, M. Stagliano, S. Torres, M. Walter, P. Walter, S. Yang, and S.T. Chung, *Nat Med* 2021)

[BY LEANNE LOW, NIAID]

NIAID: HOW THE GUT MICROBIOTA IS TRAINED TO PREVENT INFECTIONS

In an NIAID-led study, NIH scientists have made a quantum leap in our understanding of ways the gut microbiota wards off bacterial infections. They identified a nutrient—taurine—that helps the gut recall prior infections and kill invading bacteria, such as *Klebsiella pneumoniae* (*Kpn*).

The gut microbiota can shield us from *Kpn* and other bacterial infections via a mysterious process known as colonization resistance. The NIH researchers used two groups of pathogen-free mice—one harboring the gut



E.R. FISCHERR, A. ATHMAN, RML, NIAID

NIAID: A scanning electron micrograph of *Salmonella enterica* serovar Typhimurium (yellow), a common cause of food-borne infection, invading a human epithelial cell (blue).

microbiota of mice from the wild and the other experiencing a transient infection with an attenuated strain of the food-borne pathogen *Yersinia pseudotuberculosis*. They found that both groups showed enhanced resistance to *Kpn* infections, demonstrating that the microbiota that has already experienced an infection helps resist a subsequent infection.

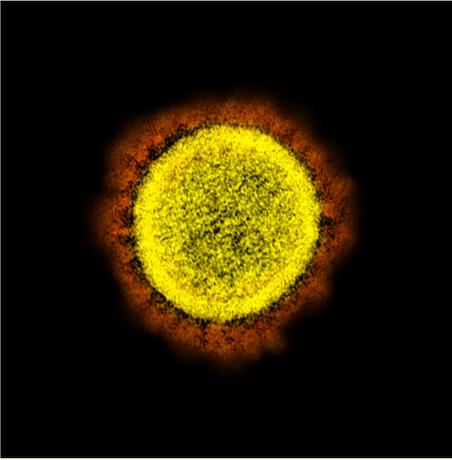
The researchers discovered that the prior infection resulted in the proliferation of a class of taurine-utilizing bacteria called Deltaproteobacteria in the gut. Taurine, an amino acid, helps the body digest fats and oils and is naturally found in bile acids in the gut. Remarkably, taurine given to mice as a supplement in drinking water was sufficient to train the microbiota to fight off *Kpn* infections. Further experiments revealed that poisonous hydrogen sulfide gas released as a byproduct of taurine promoted enhanced resistance, possibly by inhibiting pathogen respiration. This study may aid in identifying microbiota-based alternatives to antibiotics for fighting off life-threatening bacterial infections. (NIH authors: A. Stacy, V. Andrade-Oliveira, J.A. McCulloch, B. Hild, J.H. Oh, P.J. Perez-Chaparro, C.K. Sim, A.I. Lim, V.M. Link, M. Enamorado, G. Trinchieri, J.A. Segre, B. Rehmann, and Y. Belkaid, *Cell* 184:615–627.e17, 2021)

[BY SUBHASH VERMA, NCI]

Read more at: <https://irp.nih.gov/catalyst/v29i2/research-briefs>.



COVID-19 Timeline at NIH (January–February 2021)



CREDIT: NIAID

Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland.

January 5: NIH announces that a large clinical trial, sponsored by NIAID, will test combination monoclonal antibody therapy for people with mild to moderate COVID-19.

January 8: NIH launches a website outlining the COVID-19 Vaccination Plan for NIH Staff: <https://employees.nih.gov/pages/coronavirus/vaccination-plan-nih-staff.aspx>.

January 12: NIH Director's blog post is about the journal *Science's* announcements of breakthroughs of the year for 2020: <https://directorsblog.nih.gov/2021/01/12/what-a-year-it-was-for-science-advances/>. The biggest breakthrough for 2020 was the development of COVID-19 vaccines. *Science* also selected nine runner-up breakthroughs, three of which “involved efforts supported by NIH: therapeutic applications of gene editing; basic research understanding HIV, and scientists speaking up for diversity,” according to the blog post.

January 15: Seventh Virtual Town Hall is held to discuss the NIH COVID-19 Vaccination Plan. Videocast link (NIH only): <https://videocast.nih.gov/watch=41396>.

January 15: President-elect Joseph Biden announces key members of his White House Science Team and asks Francis Collins to remain as NIH director.

January 19: NIAID Director Anthony Fauci and others receive their second COVID-19 vaccine.

January 19: HHS Secretary Alex Azar gives the HHS State of the Department address in which he highlights NIH's accomplishments in fighting COVID-19 and developing the vaccine to fight it. This is his final address before leaving office on January 20 when President-elect Joseph Biden and Vice-President-elect Kamala Harris will be inaugurated.

January 20: Inauguration of President Joseph Biden and Vice-President Kamala Harris.

January 21: NIAID Director Anthony Fauci is immediately integrated into the White House COVID team. In December 2020, Biden had asked Fauci to serve as his chief medical advisor and on his COVID team.

January 21: Eli Lilly announces that the phase 3 BLAZE-2 COVID-19 trial (conducted in partnership with NIAID) showed that prophylactic use of its monoclonal antibody bamlanivimab (LY-CoV555) reduced the risk of contracting symptomatic COVID-19 among residents and staff of long-term care facilities by as much as 80%.

January 22: In his email message to staff, NIH Director Francis Collins shares all kinds of COVID-related news and updates on the COVID-19 Vaccination Plan for NIH Staff. “Until we receive additional vaccine from state health departments in the states where we have facilities, staff may see a slowdown in vaccination scheduling for first doses. We ask for your patience as we await additional supplies,” he writes. He also advises that people who are 65 years of age check with their county health departments to see if they are to receive a vaccine there. The goal is to have staff vaccinated as soon as possible.

January 22: NIH announces the results of an arm of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)–4 inpatient trial, part of an international study, showing that administration of full-dose heparin provided significant benefit to moderately ill hospitalized patients with COVID-19 compared

with the more traditional use of low-dose heparin. This trial was mounted by NHLBI through the ACTIV partnership, motivated by observations that COVID-19 induces a state of overactive blood clotting that can contribute to bad outcomes.

January 26: Vice President Kamala Harris and Second Gentleman Douglas Emhoff receive their second doses of the Moderna COVID-29 vaccine, at the NIH Clinical Center. Later NIAID Director Anthony Fauci joins them in filming a public service announcement to build confidence in COVID-19 vaccines.

January 26: NIH launches a database to track neurological symptoms associated with COVID-19. The new NINDS-supported database—COVID-19 Neuro Databank/Biobank (NeuroCOVID), which was created and will be maintained by NYU Langone Health (New York)—will collect information from clinicians about COVID-19-related neurological symptoms, complications, and outcomes as well as COVID-19 effects on pre-existing neurological conditions. The database will be a resource of clinical information as well as biospecimens from people of all ages who have experienced neurological problems associated with SARS-CoV-2 infection.

February 8: An international phase 3 clinical trial, part of the NIAID-supported Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-3 inpatient master protocol), will evaluate the safety and efficacy of ADZ7442, a combination of two investigational long-acting monoclonal antibodies developed by AstraZeneca. Initial participants will be hospitalized patients with mild-to-moderate COVID-19 and fewer than 13 days of symptoms.

Week of February 8: Other trials for therapeutics for COVID-19 are underway. This week, NIAID announces the start of five substudies under two master protocols of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership. This brings the total ACTIV and ACTIV-associated trials to 27 studies testing

20 therapeutic agents, with several already showing promising results. NIAID also announces the addition of four substudies under the ACTIV-2 outpatient protocol to test interventions for safety and efficacy in participants who have tested positive for SARS-CoV-2 but do not require hospitalization. Participants also must have a risk factor that puts them at higher probability of progressing to severe COVID-19. The investigational agents being tested are SNG001, an inhalable beta interferon developed by Synairgen that is delivered by nebulizer; AZD7442, a long-acting monoclonal antibody combination developed by AstraZeneca that will be studied as both an infusion and an intramuscular injection; and camostat mesilate, an orally administered serine protease inhibitor developed by Sagent Pharmaceuticals that may block SARS-CoV-2 from entering cells.

February 9: Walter Reed Medical Center (Bethesda, Maryland) provides doses of both the Pfizer and the Moderna vaccines to NIH to help with the shortfall of vaccines.

February 10: In a *Journal of the American Medical Association* “Viewpoint” essay by NICHD Director **Diana W. Bianchi** and colleagues, NIH calls for greater inclusion of pregnant and lactating women in COVID-19 vaccine research. (*JAMA* 2021)

February 11: President Joseph Biden visits NIH’s Vaccine Research Center (NIAID) and later gives a virtual presentation (<https://videocast.nih.gov/watch=41581>) to NIH employees thanking everyone for their important work on COVID-19: “On behalf of a grateful nation, I want to thank you and your families for your work and sacrifice.” He also talks about his plans to expand the distribution of the COVID-19 vaccine.

February 11: NIH receives 2,400 doses of the Pfizer vaccine through the federal supply chain.

February 12: In his email to NIH staff, NIH Director **Francis Collins** announces that “We expect that the federal supply chain will be our primary source of vaccines moving forward.”

February 12: NIH Director **Francis Collins** also announces, in his all-staff email, that the genetic sequencing of SARS-CoV-2—in NIHers who have tested positive for COVID-19 and have given consent—initiative, led by NIAID Senior Investigator **Elodie Ghedin**, identified one case of B.1.351 (the South African variant) and one case of B.1.1.7 (the U.K. variant) out of 108 samples tested. Collins also recommends that nonclinical staff in high-exposure situations follow new guidance from the CDC on how to improve mask fit and the use of a cloth mask over a medical-grade mask to improve protection from these fast-spreading variants.

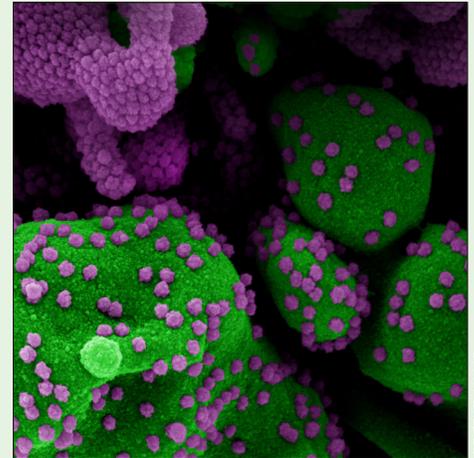
February 12: NIDDK researchers report that facemasks substantially increase the humidity in the air that the mask-wearer breathes in and may lessen the severity of COVID-19. (*Biophys J* 2021; DOI:10.1016/j.bpj.2021.02.002)

February 12: Enrollment has begun to test additional investigational drugs in the NIAID-sponsored Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program.

February 12: In an editorial published today in *JAMA*, NIAID Director **Anthony Fauci**, **John R. Mascola**, director of NIAID’s Vaccine Research Center (VRC) and **Barney S. Graham**, deputy director of the VRC, outline how new COVID-19 variants have arisen, concerns about whether current vaccines will continue to protect against new variants, and the need for a global approach to fighting SARS-CoV-2 as it spreads and acquires additional mutations. (*JAMA* 2021; DOI:10.1001/jama.2021.2088)

February 12: A new study, supported by NIMH, has identified early risk factors that predict heightened anxiety in young adults during the COVID-19 pandemic. (*J Am Acad Child Psy* 2021; DOI:10.1016/j.jaac.2021.01.021)

February 17: NICHD announces the launch of a new study to evaluate the effects of remdesivir in pregnant women who have been prescribed the drug to treat COVID-19. The study will be conducted at 17 sites in the United States and Puerto Rico.



CREDIT: NIAID

Colorized scanning electron micrograph of an apoptotic cell (green) heavily infected with SARS-CoV-2 virus particles (purple), isolated from a patient sample. Image at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland.

February 24: NCI study finds that people with SARS-CoV-2 antibodies may have a low risk of future infection. (*JAMA Intern Med* 2021; DOI:10.1001/jamainternmed.2021.0366)

February 26: In his all-staff email, NIH Director **Francis Collins** announces that this week NIH received 4,400 doses of the Moderna vaccine—3,400 doses from the federal supply chain plus 1,000 doses from the Maryland Health Department.

February 27: The FDA issues an Emergency Use Authorization (EUA) to the Janssen Pharmaceuticals Companies of Johnson & Johnson for its single-shot COVID-19 vaccine, called Ad.26.COV2S or JNJ-78436725. NIAID and the Biomedical Advanced Research and Development Authority, part of HHS, supported late-stage clinical testing of the vaccine. The Johnson & Johnson vaccine, which can be kept in regular refrigerators and does not require the ultracold storage that the Moderna and Pfizer vaccines do, is a recombinant vector vaccine that uses a human adenovirus to express the spike protein found on the surface of the SARS-CoV-2 virus that causes COVID-19. It is the third COVID-19 vaccine in the United States to be granted an EUA by the FDA. ●

1918 Flu and COVID-19

CONTINUED FROM PAGE 1



At the Demystifying Medicine lecture on January 12, 2021, NIAID Director Anthony Fauci gave a state-of-affairs address on what we know about the COVID-19 pandemic and what the future might hold.

Medicine lecture series for its 2021 season: National Institute of Allergy and Infectious Diseases (NIAID) Director **Anthony Fauci** and **Jeffery Taubenberger**, chief of NIAID's Viral Pathogenesis and Evolution Section. Fauci gave a state-of-affairs address on what we know about the COVID-19 pandemic and what the future might hold. Taubenberger highlighted the similarities of the COVID-19 pandemic to the influenza pandemic of 1918—the pandemic that “never really went away.”

The State of Coronavirus Affairs

“We have been working with coronaviruses for decades and decades,” said Fauci. He pointed out that many are zoonotic diseases in which animals serve as intermediate hosts and viral reservoirs—such as severe acute respiratory syndrome (SARS), which went from bats to civet cats to humans in 2002, and Middle East respiratory syndrome (MERS), which went from bats to camels to humans in 2012. SARS and MERS, however, didn't evolve into the pandemic that COVID-19, also a zoonotic disease, has.

“We in the United States have been hit harder than any other country in the world,” said Fauci. At the end of February 2021, the United States had more than 28 million cases and over 500,000 deaths, compared with 112 million cases and about 2.5 million deaths worldwide. He painted a sobering picture of the reality of the pandemic: about 40–50% of transmissions were attributable to asymptomatic cases; older people and those with underlying medical conditions (representing 40% of Americans) are most at risk of severe disease; and racial and ethnic disparities in health-care access led to an increased incidence of infection and severity of disease among underrepresented minorities. In addition, “we are learning more and more about a very interesting phenomenon of post-acute COVID-19 syndrome,” Fauci continued. Some “individuals, after they clear the virus, have persistence for up to six months and maybe longer of lingering problems dominated by fatigue that's profound, muscle aches, temperature dysregulation, [and] brain fog, or the inability to focus

or concentrate.”

He briefly described the virology of coronaviruses, highlighting the importance of the spike proteins that sit crownlike (or corona-like) around the surface. He moved on to describing how COVID-19 is transmitted from person to person. “It's respiratory, mainly through exposure to respiratory droplets that tend to drop within six feet,” Fauci said.

Fauci cited therapeutics such as remdesivir as well as the many COVID-19 vaccines as reasons for hope. In less than one year, we've gone from the availability of the genomic sequence of SARS-CoV-2, the virus that causes COVID, to the development and administration of efficacious and safe vaccines—it really was warp speed!

A Tale of Two Epidemics

Taubenberger, whose laboratory was the first to sequence the genome of the influenza virus that caused the 1918 pandemic, took us through the not-so-distant history of that cataclysmic global event.

“Pandemics have happened, are happening, and will happen again,” but we've been caught flat-footed and found ourselves chasing this pandemic as a new coronavirus emerged in 2019, he said. In fact, our response to the 1918 pandemic was surprisingly similar, and it seems that we're still rather “mystified” by how pandemics form, with Taubenberger pointing to a book written by a German doctor in 1820 that asked essentially the same questions we are asking today: “What is influenza? Where does it come from? How did it behave in the past? How can we predict future occurrence and halt spread?”

He also likened the world's embrace and resistance of today's public-health measures to those introduced in

1918—from mask wearing to school closures, as well as a moratorium on handshakes—and spitting! Despite triumphs in technology and science, this past century’s deemphasis of public-health systems have left us in an even more delicate situation than in 1918.

With 80,000 fatalities caused by influenza in 2018, are we now in a twin pandemic? As the media is consumed by the latest global coronavirus outbreak, we have heard comparatively little about this year’s flu season. One explanation for this relative lull in attention could be due to variations in influenza strains from year to year and subsequently when it might peak—we might have a later peak in 2021—and obviously our infrastructure is overburdened right now, resulting in a lack of resources for the surveillance of influenza. Taubenberger poignantly reminded us that all influenza A virus strains trace their origin to the 1918 flu—“the founder virus”—and its zoonotic jump to humans was similar to that of COVID-19. He emphasized our need to be ahead of viruses through surveillance of animal spillover events,

to understand better why some viruses are more deadly than others, and to ultimately feel the urgency to develop “universal” vaccines against all viruses, not just influenza and coronaviruses.

Looking to the past for insight for our future, both scientists pointed to important lessons from past eras. Merely 100 years ago the world was devastated by the 1918 influenza, killing 675,000 people in the United States alone, equivalent to 2.5 million in today’s terms. We’ve had outbreaks before, and we’ll have them again. A universal vaccine is the way forward. ●

To view the videocast of the January 12, 2021, Demystifying Medicine lecture, “COVID-19 and Influenza,” go to <https://videocast.nih.gov/watch=41281>. For Demystifying Medicine’s full schedule and links to past lectures, go to <https://demystifying-medicine.od.nih.gov>.

Eimear Holton is a social media, web, and outreach program specialist in NIAID.

New Insights into What Fuels an Aggressive Form of Kidney Disease

ADAPTED FROM AN NCI-CCR NEWS ARTICLE

SCIENTISTS IN THE NATIONAL CANCER Institute have uncovered an important mechanism that fuels an aggressive form of kidney disease: Hereditary leiomyomatosis and renal cell carcinoma (HLRCC). The results, published recently in *Science Signaling*, show how deficiency of an enzyme called fumarate hydratase (FH) severely impairs cells’ ability to repair and maintain healthy mitochondrial DNA. The resulting mitochondrial DNA mutations causes the cells to become more aggressive.

W. Marston Linehan, chief of NCI’s Urologic Oncology Branch, has studied HLRCC in the past and found that a FH deficiency is associated with a shift in how HLRCC cells process energy. Whereas healthy cells typically use mitochondria to convert oxygen into energy, cancerous HLRCC cells tend to rely on a different mechanism—called aerobic glycolysis—for energy production that doesn’t require oxygen. Linehan and his colleagues sought to better understand the mechanism behind this shift. They collected and analyzed 25 tumor samples from patients with HLRCC and found that, without sufficient FH, a harmful amount of fumarate, which is an oncometabolite, accumulates in the cells and can trigger cancer.

Genetic analysis revealed that the accumulation caused damage to important mitochondrially encoded genes, including *POLG*, that are responsible for replicating and maintaining healthy DNA. “These findings provide the foundation for the development of targeted therapies for patients with [these] cancers,” said Linehan. ●

Read more at <https://irp.nih.gov/catalyst/v29i2/research-briefs-kidney-disease>.

Demystifying Medicine
January 12, 2021

From 1918 Influenza to COVID-19:
The Continual Threat of Pandemic Emergence

Jeffery K. Taubenberger, M.D., Ph.D.

NIH National Institutes of Health

CREDIT: NIH

Jeffery Taubenberger highlighted the similarities of the COVID-19 pandemic to the influenza pandemic of 1918—the pandemic that “never really went away.”

Introducing NIH's Newest Lasker Scholars

Program Gives Boost to Early-stage Investigators

BY BRANDON LEVY, OD

If TV shows such as *The Voice* and *America's Got Talent* are any indication, there are many extremely talented people out there who could become huge successes if presented with the right opportunity. A similar circumstance occurs in science, with thousands of extremely bright individuals quietly toiling away in their mentors' labs as they await the chance to establish research programs of their own.

Fortunately, initiatives like the NIH's Lasker Clinical Research Scholars Program exist to boost promising young researchers onto the next stage of their careers. Every year, the Lasker program allows a small group of early-stage physician-scientists to establish their own labs at the NIH and carry out independent clinical research there for at least five years.

The six talented investigators selected as 2020 Lasker Scholars are pursuing a wide range of research questions, from how the immune system influences blood clotting to the mechanisms driving a rare skeletal disorder. Read on to learn more about the latest crop of researchers ramping up labs of their very own.

Yogen Kanthi, M.D.: "Inhibiting Immune Assault on Blood Vessels"

Yogen Kanthi is used to long journeys, having bused and backpacked his way through more countries than there are candles on his birthday cake, including a camping trip to the polar icecap in Greenland. More recently, his selection as a Lasker scholar in the National Heart, Lung, and Blood Institute triggered a 500-mile move from the University of Michigan (Ann Arbor, Michigan) to NIH's campus in Bethesda, Maryland, where he is continuing his investigation of the immune system's



Yogen Kanthi

role in diseases that damage blood vessels and lead to potentially deadly blood clots.

Over the course of his career, he has also migrated from the clinic into the lab. A chance encounter with a physician-scientist during his medical residency "changed my view of research," Kanthi said.

"I spent a couple of months in his lab and realized that a research career would be creative and fulfilling," he continued. "In the research lab, I was able to ask and answer questions that would often come up during patient encounters."

Kanthi's research focuses specifically on the relationship between blood clots and inflammation in blood vessels. While at the University of Michigan, his team discovered that a common inflammation-inducing chemical in the body can cause blood clots to form in veins; the team found a way to prevent the clotting using an FDA-approved drug. More recently, in work done at the NIH and in Michigan, his lab has made important contributions to our understanding of how overactive immune cells and other components of the immune system contribute to breathing failure and

the formation blood clots in some patients with COVID-19. He subsequently launched an ongoing clinical trial through which his lab, along with colleagues at the University of Michigan, are testing a safe and inexpensive FDA-approved medication as a treatment for excessive inflammation and blood clotting in COVID-19 patients.

"The NIH has a unique environment that fosters curiosity-driven science to make big impacts on health and disease," Kanthi said. "There is incredible depth of expertise here across a breadth of disciplines. The institutional and infrastructure support is unparalleled, and the NIH is able to launch projects that couldn't be done anywhere else."

Jacqueline Mays, D.D.S., M.H.Sc., Ph.D.: "Enabling Safer Transplants of Blood-producing Cells"

Jacqueline Mays loves to bring smiles to people's faces. As a teenager, she spent a year in Germany entertaining audiences as the sole American member of a traditional folk choir. Now, as a trained dentist, she works hard to preserve the health of her patients' mouths and teeth.



Jacqueline Mays

“I grew up in a very rural community without fluoridated water and saw my family dentist frequently while growing up,” she said. “Their gadgets and their ability to quickly help patients made a deep impression, and my initial career plan was to become a dentist. Fortunately, as I learned more about both dentistry and science, I discovered there was a clear path to combine them.”

Mays has been able to apply her skills in those domains at the National Institute of Dental and Craniofacial Research for more than a decade, most of which she has spent trying to combat the side effects of hematopoietic stem-cell transplants, a procedure used to treat certain blood-borne diseases such as leukemia. The procedure attempts to reboot patients’ immune systems by wiping out the defective stem cells in their bone marrow that produce blood cells and replacing them with properly functioning stem cells from a healthy donor. However, many patients who undergo this procedure develop chronic graft-versus-host disease, in which their new immune systems attack tissues throughout the body including in the mouth.

So far, Mays’s efforts have produced important insights into how graft-versus-host disease affects the mouth, as well as how those effects might be more effectively assessed and alleviated. As the first dentist-scientist to be selected as a Lasker Scholar, she hopes to leverage the opportunity not only to bolster that important research but also to pave the way for more dentists to participate in the program.

“As a strong advocate of building an excellent and diverse pipeline of oral-health scientists, I hope that this selection serves as a sign of the rigor of the oral-health sciences and that more outstanding dental scholars will follow,” she said.



Ian Myles

Ian Myles, M.D., M.P.H.: “Managing Our Microbial Menagerie to Improve Skin Health”

People often claim to know things “like the backs of their hands,” but in recent years it has become increasingly clear that what we see when we look at our hands and other parts of our bodies is not a complete picture. Teeming multitudes of organisms too tiny for the human eye to detect live on every inch of our skin, and scientists like Ian Myles are determined to learn as much as they can about how these organisms—collectively called the skin microbiome—influence our health. In particular, Myles investigates how their interactions with the environment affect their ability to guide the immune system’s response to skin disease and damage.

“I went to medical school thinking I would go into research in spinal-cord regeneration, but became fascinated by the way the immune system is able to tell the difference between the outside world and ourselves,” Myles said. “The narrow margin for error afforded the immune system and the need to balance inflammation with repair grabbed my interest.”

Myles began his NIH career working in the Bacterial Pathogenesis Unit at the NIH’s National Institute of Allergy and Infectious

Diseases, which focused on skin infections caused by the bacterium *Staphylococcus aureus*. Now that he leads his own NIH lab, he is investigating how the bacteria that live on our skin are involved in eczema, a common skin ailment associated with an increased risk of staph infections. His research team is currently running a clinical trial to see whether applying a different species of bacteria, *Roseomonas mucosa*, to the skin of eczema patients relieves their symptoms. The study so far has shown promising results, with the patients who received the topical bacterial treatment seeing “significant improvement in their disease,” according to Myles.

“I wanted the opportunity to work on a new approach to a common disease,” he said. “The Lasker program affords me the ability to take on challenges that I could not tackle as a postdoc. I enjoy the ability to take an idea directly from the bench and put it into an intervention that might improve the lives of patients and their families.”

Stephanie Chung, M.B.B.S.: “Improving Care for Youth with Type 2 Diabetes”

Most weekends during her childhood, Stephanie Chung and her sister accompanied their cardiologist father on his rounds and then played on the hospital grounds while he saw to his patients. When she followed her father into the medical field, she chose to specialize in both internal medicine and pediatrics, with a focus on helping young people with obesity and type 2 diabetes.

“Maybe it was the cartoons on the walls, or the fact that we had to learn how to play with the kids and examine, cure, and treat them all at the same time,” Chung said, “or maybe it was their innocence and vulnerability to the social,

CONTINUED ON PAGE 16

Laskers

CONTINUED FROM PAGE 15



Stephanie Chung

genetic, and environmental factors that mediate health disparities and childhood diseases.”

Although she has been working with this population at the NIH since 2013, Chung’s selection as a Lasker Scholar in the National Institute of Diabetes and Digestive and Kidney Diseases will allow her to take her work to the next level. Her new lab aims to understand how genetic, environmental, and lifestyle factors contribute to the increased susceptibility of young people from minority groups to diseases such as diabetes, obesity, and heart disease. She is also attempting to figure out why the drug metformin, a commonly prescribed treatment for type 2 diabetes, successfully lowers blood sugar in adults but fails to help roughly half of young people with diabetes. Already, her work has identified important differences in the way blood sugar behaves in young people and adults with type 2 diabetes and uncovered clues as to why metformin is less effective in children and teens.

In addition to furthering her research, Chung hopes the boost provided by the Lasker Scholars program will enhance her ability to assist and influence future scientists. As a Chinese Jamaican who grew

up and attended medical school in Jamaica before continuing her medical studies in the United States, she is particularly dedicated to bringing people from diverse backgrounds into her field.

“I believe that success is born out of hard work that comes from people from all different backgrounds, experiences, abilities, and world views,” she said. “I love teaching and mentoring and I am committed to diversifying the scientific workforce and inspiring the next generation of leaders.”

Derek Narendra, M.D., Ph.D.: “Pushing Forward Our Understanding of Movement Disorders”

As an avid hiker, runner, and downhill skier, movement is an essential part of life for Derek Narendra. It is not surprising, then, that his research at the National Institute of Neurological Disorders and Stroke focuses on Parkinson disease, a neurological condition that robs patients of their ability to move.

Parkinson disease occurs when a specific set of neurons in the brain that control movement begin to die off. When it comes to figuring out why that

happens, it helps to home in on cases of Parkinson disease that can be traced to an identifiable trigger, which is why Narendra specifically works with patients who have genetic mutations that cause early-onset Parkinson disease.

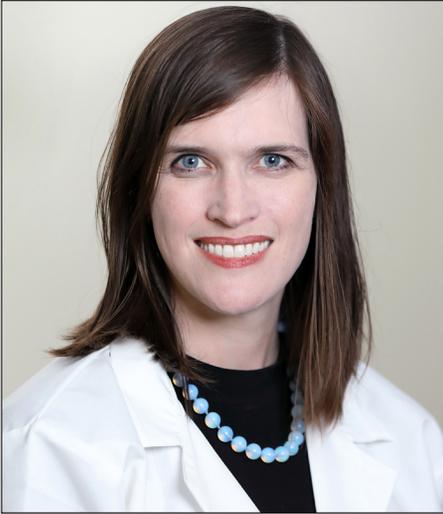
“In medical school, I was always fascinated by Parkinson disease,” Narendra explained. “I wondered why it is that this little subset of cells could be selectively vulnerable and could lead to such a profound difference in the movement of someone who has lost them.”

Narendra began studying Parkinson disease as a Ph.D. student in the lab of Senior Investigator **Richard Youle**, where he made important discoveries about why mutations in two genes called *PARKIN* and *PINK1* cause the disorder. Nowadays, his interests have shifted to other genes involved in the illness. For example, he has studied a patient with a unique variety of Parkinson disease caused by previously unreported mutations in both copies of the *DJ1* gene, and he has also investigated the cellular effects of mutations in two other genes linked to the illness, *CHCHD2* and *CHCHD10*. As a newly minted Lasker Scholar, Narendra looks forward to collaborating with his NIH colleagues on more studies that will shed light on the functions of these and other genes linked to Parkinson disease.

“I’m very excited about it,” he said. “The Lasker program puts you in a community of like-minded people within the NIH, and also kind of connects you to a larger network of physician-scientists to help inspire you and guide your work.”



Derek Narendra



Alison Boyce

Alison Boyce, M.D.: “Making Breakthroughs for a Rare Bone Disorder”

Alison Boyce has been a science enthusiast all her life, fondly recalling the many hours she spent watching the science-themed television program *Mr. Wizard's World* as a small child. Later, the collaborative nature of medicine and the opportunity to witness firsthand how science affects people's lives drew her to apply to medical school, after which she chose to specialize in the treatment of bone disorders.

“Bone is a really fascinating field because it requires you to think about biological systems on multiple levels,” Boyce explained. “Part of my research focuses on cell signaling and how different types of bone cells differentiate, but I also need to consider bone on a structural level—how it forms the scaffolding that moves our bodies through space and helps us interact with the world. Even small changes in bone biology can lead to huge impacts on health and well-being.”

At the National Institute of Dental and Craniofacial Research, Boyce's research is focused on a rare bone disorder called fibrous dysplasia/

McCune-Albright syndrome, in which bone progressively transforms into fibrous tissue, leading to fractures, physical deformities, and problems with movement, vision, and hearing. The condition also affects the delicate balance of hormones flowing through the body, potentially causing early puberty, thyroid issues, and other problems. In addition to examining numerous patients with the disease to learn more about their symptoms, Boyce's team has identified promising therapeutic targets for the disease, leading to an ongoing clinical trial investigating whether inhibiting a protein called RANKL improves some of the disorder's symptoms.

Along with the opportunity to work in the NIH Clinical Center and collaborate with other NIH experts in bone biology, Boyce believes her research benefits from all of the time she spends outside of work with her face buried in a book.

“I'm a big reader and usually finish one or two books a week,” she said. “I especially like literary and speculative fiction. I think engaging your brain with stories helps people think more creatively, which is especially important in science.” ●

To learn more about the Lasker Clinical Research Scholars Program and read about other scholars, go to <https://www.nih.gov/research-training/lasker-clinical-research-scholars>.

Brandon Levy is a Health Communications Specialist for the NIH Intramural Research Program and particularly enjoys writing about the cutting-edge research performed at NIH. He also produces videos, podcasts, and content for social media.

SPECIAL ISSUE: JOURNAL OF WOMEN'S HEALTH

A SPECIAL ISSUE OF THE *JOURNAL OF Women's Health (JWH)* characterizes the increasing problem of maternal morbidity and mortality (MMM) in the United States. Articles in the issue suggest solutions and propose a research agenda for understanding, treating, and preventing maternal health complications. U.S. women—particularly those from underrepresented racial and ethnic populations and those who reside in rural areas—are more likely to die from complications related to pregnancy or childbirth than women in peer nations. Office of Research on Women's Health Associate Director **Samia Noursi** served as the guest editor for the *JWH* special issue and, along with NIH leadership colleagues, wrote the introduction. The authors state that the articles describe “epidemiological patterns and trends, biological and physiological risk factors, external risk factors, social determinants of health, and proven and potential interventions that are poised to be delivered to a broader audience.” Many NIH scientists contributed articles to the issue: <https://home.liebertpub.com/spcoll/preview-maternal-morbidity-and-mortality/1121/>.

Articles focus on how underrepresented racial and ethnic groups, transgender individuals, and women of advanced maternal age have higher rates of MMM as a result of socioeconomic disadvantages, comorbidities, and implicit bias; the risk of MMM increases as the result of co-occurring conditions; other factors including homicide, suicide, drug overdose, and intimate partner violence; environmental factors; dietary supplements during pregnancy; and current and proposed efforts to mitigate the problem of MMM. ●

Read more at <https://irp.nih.gov/catalyst/v29i2/research-briefs-maternal-morbidity-and-mortality>.

Stadtman Investigators Pursuing Their Passion for Science

Trans-NIH Recruitment Attracts a Diversity of Researchers

BY LAURA STEPHENSON CARTER

“BEING A SCIENTIST AT NIH IS ONE of the greatest jobs you can dream of,” said **Eric Calvo**, a Stadtman Investigator in the National Institute of Allergy and Infectious Diseases, and one of 18 investigators in the 2017-2018 class of Stadtman recruits.

That sentiment is shared by the more than 100 Stadtman Investigators who have been recruited since 2009 when the Earl Stadtman Tenure Track Investigators program, named for the legendary biochemist who worked at NIH for 50 years, began. Since then about 25% of them have become tenured investigators.

“The program identifies the best institute that fits my research goals, not the other way around,” said fellow Stadtman **Payel Sen**, in the National Institute on Aging.

Traditionally, institutes and centers (ICs) conducted their own individual, programmatic searches to recruit new investigators. But the Stadtman program, which began in 2009, complements this process by conducting broad searches that cross all areas of biomedical research. It’s designed to attract a diverse group of talented early-career scientists who might not apply to a more narrowly defined position description at the NIH. Applicants are asked to describe their research, and, for those qualifying, NIH tries to create a tenure-track position in one of the ICs to match that talent. Once the Stadtmans are selected, they are offered competitive salaries, research space, resources, supported positions, and an operating budget.

“The Intramural Research Program has unparalleled resources and outstanding scientists,” said Class of 2017-2018 Stadtman Investigator **Alexandra White**, who came to the National Institute of

Environmental Health Sciences as a postdoc in 2015. “It provides the ideal opportunity to conduct cutting-edge science.”

The 18 Stadtman investigators featured in this article have research interests ranging from cancer, kidney disease, and vector-borne diseases (including malaria) to minority health, aging, and gene regulation. Several of them have also been named NIH Distinguished Scholars (DSP), a program launched in 2018 to facilitate the hiring and career progression of tenure-track investigators who have demonstrated a commitment to promoting diversity and inclusion in the biomedical-research workforce. For more on the DSP, go to <https://diversity.nih.gov/programs-partnerships/dsp>.

“I applied to the Earl Stadtman program because it provides a way for young investigators to develop research programs that cannot be developed elsewhere,” said **Jennifer Jones**, a Stadtman Investigator in the National Cancer Institute.

Read on to learn more about this group of Stadtman investigators. For more on the Stadtman program, how to apply, and links to stories about other Stadtmans, go to <https://irp.nih.gov/careers/trans-nih-scientific-recruitments/stadtman-tenure-track-investigators>.

BEHDAD (BEN) AFZALI, M.D., PH.D., NIDDK

Chief, Immunoregulation Section, Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases

Joined NIH: In 2014 as a clinical research fellow in NIAMS; in 2018, became a Stadtman Investigator in NIDDK.

Research focus: Kidney diseases are often the result of autoimmune or inflammatory insults to the kidneys. My team is investigating how immunoregulation is

perturbed in these diseases and why the resolution of inflammation can be followed either by tissue healing or irreversible scarring that can lead to loss of kidney function over time. We are looking at how transcriptional signals are integrated into immune cells to determine inflammatory versus regulatory immune responses; and how mediators produced by immune cells determine whether inflammation results in tissue healing or scarring. We hope to develop strategies that manipulate the balance between inflammatory and regulatory immune responses to minimize or prevent kidney scarring.

What attracted you to the program?

It encourages high-risk, high-reward, imaginative research programs that cross traditional scientific disciplines. I found the resource support and the time provided to pursue key questions in my field, together with the extraordinarily rich and diverse scientific environment of the NIH, especially appealing.

ERIC CALVO, PH.D., NIAID

Chief, Molecular Entomology Unit, National Institute of Allergy and Infectious Diseases

Joined NIH: In 2004 as a postdoctoral fellow in NIAID; became a Stadtman Investigator and NIH Distinguished Scholar in 2018.

Research focus: Vector-borne diseases (West Nile virus, Lyme disease, malaria, and others) are infections transmitted by blood-feeding arthropods such as mosquitoes, ticks, and fleas. My group is deciphering the mechanisms of the vector-host and vector-pathogen interactions at the biochemical and molecular level; extending the functional characterization of salivary proteins from blood-feeding arthropods



BEN AFZALI, NIDDK



ERIC CALVO, NIAID



CHONGYI CHEN, NCI-CCR



SHERINE EL-TOUKHY, NIMHD



JENNIFER JONES, NCI-CCR

and their role in pathogen transmission; and furthering the understanding of disease transmission and the host's response to vector-borne diseases. We aim to develop new transmission-blocking strategies for such diseases.

What attracted you to the program?

Being a scientist at NIH is one of the greatest jobs you can dream of (nerds in heaven?). The Stadtman program gives you the opportunity and freedom to pursue your own scientific questions to understand the mysteries of nature.

CHONGYI CHEN, PH.D., NCI-CCR

Laboratory of Biochemistry and Molecular Biology, Center for Cancer Research, National Cancer Institute

Joined NIH: In 2018.

Research focus: My lab is combining single-cell assays and genomic technologies to examine chromatin structure and gene expression in human cells. We are also developing new assays and techniques in single-cell genomics, epigenomics, and transcriptomics. We hope to apply the new knowledge in chromosome biology and the new methodologies in single-cell -omics to cancer biology and medicine.

What attracted you to the program?

I was attracted to the NIH and the Stadtman Program by its stable funding and ample resources to support my research,

so that I can focus on my scientific interest without many distractions.

SHERINE EL-TOUKHY, PH.D., NIMHD

Digital Health and Health Disparities Research Unit, Population and Community Sciences, National Institute on Minority Health and Health Disparities

Joined NIH: In 2014 as a postdoctoral fellow in NHLBI and NIMHD; became a Stadtman Investigator and NIH Distinguished Scholar in 2018.

Research focus: My research group leverages digital technologies to improve minority health and reduce health disparities. We design, implement, and evaluate individual-level just-in-time adaptive behavioral interventions such as smoking-cessation interventions using mobile phones (mHealth); examine disparities in system-level adoption, integration, and impact of digital technologies within hospitals such as electronic health records; and identify connection points between individual- and system-level digital technologies to maximize the reach of behavioral interventions and improve clinical decision-making.

What attracted you to the program?

The Stadtman program shines a spotlight on a pool of diverse investigators pursuing pioneering research questions who might

not be recruited under a traditional search. The Stadtman position is a perfect avenue for investigators who are dedicated to the pursuit of lifelong passion for research that better people's health and lives.

JENNIFER JONES, M.D., PH.D., NCI-CCR

Head, Translational Nanobiology Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute

Came to NIH: In 2012 as an assistant clinical investigator in NCI's Vaccine Branch; became a Stadtman Investigator and NIH Distinguished Scholar in NCI's Laboratory of Pathology in 2018.

Research Focus: Decoding the biological lexicon of circulating extracellular vesicles and particles. My hypothesis is that this decoded lexicon has the potential to provide critical knowledge on the status of patients' tumors, the status of patients' responses to treatment, and the complex landscape of their other biological systems. We are developing new ways to "read" the functional status of each patient's many various interconnected systems, and we are seeking to use that information to improve patient care and quality of life.

What attracted you to the program?

It provides a way for young investigators to develop research programs that cannot be developed elsewhere. The NIH Clinical

CONTINUED ON PAGE 20

Stadtman

CONTINUED FROM PAGE 19

LAURA KEROSUO-PAHLBERG,
NIDCREROS LAZZERINI DENCHI, NCI-
CCR

ANDRES LEBENSOHN, NCI-CCR



MARCOS MORGAN, NIEHS



MEERA MURGAI, NCI-CCR

Center is the only hospital in the world that is entirely dedicated to translational research to advance patient care, and it is uniquely nested within a research community that has expertise across countless disciplines. Those qualities alone would have been sufficient motivation to apply for the NIH Stadtman program, but what has been even more valuable than those qualities is the wisdom and support of my mentors and colleagues within the NIH community who have generously provided input and recommendations for how to make our work more robust and more impactful.

LAURA KEROSUO-PAHLBERG, PH.D., NIDCR
Neural Crest Development and Disease Unit, National Institute of Dental and Craniofacial Research

Joined NIH: In 2018.

Research Focus: I am studying the neural crest, the stem cells that give rise to various cell types ranging from melanocytes and peripheral ganglia to cells contributing to the formation of the craniofacial skeleton and endocrine tissues. About 10% of birth defects are derived from the neural crest including cleft palate and other craniofacial malformations as well as cancers such as melanoma and neuroblastoma. My group aims to understand the molecular

mechanisms of neural-crest stemness, provide a comprehensive picture of early neural-crest development, and obtain a better understanding of how neural-crest-derived diseases arise.

What attracted you to the program?

It caught my attention due to its reputation for rigorous science and the generous infrastructure the NIH provides to its investigators. I saw the program as an opportunity to dive in and use all possible creativity my team can come up with to achieve exciting discoveries. With no teaching obligation and a generous budget, the program truly felt like an amazing chance to grasp even the riskiest of projects, which one would hesitate to invest in as an assistant professor outside the NIH.

EROS LAZZERINI DENCHI, PH.D., NCI-CCR
Laboratory of Genome Integrity, Center for Cancer Research, National Cancer Institute

Came to NIH: In 2018; tenured as a senior investigator in March 2021.

Research Focus: Chromosome endcaps, called telomeres, shorten as one ages. I am interested in the mechanisms by which telomeres protect chromosome ends, thus ensuring chromosome and genome stability. My lab is identifying telomere-associated proteins to define their role in preventing

the activation of the DNA damage-response pathway and suppression of end-to-end chromosomal fusions. We are also probing the role of telomere shortening in aging and tumor onset, using mouse models that recapitulate telomere dysfunction in stem cells and other cellular compartments.

What attracted you to the program?

The chromosome biology community at NIH is excellent, supportive, and scientifically diverse. I enjoy access to advanced technologies and colleagues from a wide range of disciplines. I can focus 100% on the science without the pressures of teaching commitments and securing funding.

ANDRES LEBENSOHN, PH.D., NCI-CCR
Laboratory of Cellular and Molecular Biology, Center for Cancer Research, National Cancer Institute

Came to NIH: In 2018.

Research focus: My lab studies how cell-signaling pathways are used, reused, and repurposed to drive the many cellular processes that give rise to tissues and organs during embryonic development, and maintain them in adult life. Through powerful genetic screens we discovered several new regulatory mechanisms in WNT signaling, a fundamental



PEDRO PEREIRA DA ROCHA,
NICHD



MERU SADHU, NHGRI

pathway that orchestrates patterning and morphogenesis during development, and promotes tissue renewal and regeneration in adults. Dysregulation of WNT signaling can lead to many diseases, most notably cancer. Based on our mechanistic insights, we aim to design more-effective and -selective therapies to target WNT-driven tumors.

What attracted you to the program?

I was looking for a position where I could dedicate myself entirely to doing cutting-edge research in a stimulating and collegial environment. I also wanted full intellectual freedom and access to all the necessary resources to pursue bold research ideas. The Stadtman program checked all the boxes.

MARCOS MORGAN, PH.D., NIEHS

Head, Male Reproduction and RNA Biology Group, National Institute of Environmental Health Sciences

Came to NIH: In 2019.

Research focus: Dysregulation of cellular RNA amounts leads to growth defects and cancer. My team's goal is to understand the role of RNA metabolism during development. We investigate animal models with deficiencies in RNA modification pathways. We hope to bridge the gap between the mechanistic knowledge of

gene regulation at the cellular level and the principles that define multicellular organization.

What attracted you to the program?

The generous support allows me to focus on my science.

MEERA MURGAI, PH.D., NCI-CCR

Laboratory of Cancer Biology and Genetics, Center for Cancer Research, National Cancer Institute

Came to NIH: In 2013 as a postdoctoral fellow; became a Stadtman Investigator and an NIH Distinguished Scholar in 2019.

Research focus: Metastasis causes most cancer deaths, and we need new therapies based on a deeper understanding of this process to improve patient survival. My research centers on perivascular cell plasticity and heterogeneity in the metastatic microenvironment. My group has been using single-cell sequencing, immunofluorescent imaging, and computational methods to elucidate the stromal-cell populations that play pro- and anti-tumor roles in premetastatic and metastatic microenvironments. We hope our findings will provide insight into future therapeutic interventions to limit metastasis.

What attracted you to the program?

NIH offers a strong and diverse community of highly engaged scientists, provides access to leading technologies, and grants the ability to tackle exciting high-risk long-term questions. The collaborative environment will enhance and accelerate our research.

PEDRO PEREIRA DA ROCHA, PH.D., NICHD

Unit on Genome Structure and Regulation, National Institute of Child Health and Human Development

Came to NIH: In 2018.

Research focus: DNA organization influences cell behavior and ultimately animal development and health. My group is investigating the mechanisms through

which DNA folding is established and regulated and which proteins are involved. We are exploring cell-lineage differentiation, gene regulation, and how noncoding DNA elements and the 3D architecture of chromosomes contribute to these processes during development and disease. We are also fascinated with early mammalian development as a system to decipher how cells make lineage decisions and how gene-regulatory networks are established.

What attracted you to the program?

The emphasis on innovative and high-risk science together with a strong mentorship program makes NIH an exceptional place to start an independent research program.

MERU SADHU, PH.D., NHGRI

Head, Systems Biology and Genome Engineering Section, Genetic Disease Research Branch, National Human Genome Research Institute

Came to NIH: In 2018; became an NIH Distinguished Scholar in 2019.

Research focus: I am striving to systematically identify the phenotypic consequences of genetic differences. My group is studying the functional effects of genetic diversity, such as natural variation between individuals or between species, or novel genetic changes that we create. We apply genome-engineering methods and use CRISPR gene-editing technologies, large-scale oligonucleotide synthesis, yeast models, and high-throughput phenotyping and genotyping to generate and study the effects of thousands of unique genetic variants. We also aim to develop new approaches to study genetic diversity.

What attracted you to the program?

I was very excited that researchers in the NIH's intramural program can focus so completely on their science. That, combined with the extraordinary breadth of research here, made the NIH my ideal destination.

CONTINUED ON PAGE 22

Stadmans

CONTINUED FROM PAGE 21

PAYEL SEN, PH.D., NIA

Head, Functional Epigenomics Unit, Laboratory of Genetics and Genomics, National Institute on Aging

Came to NIH: In 2019

Research focus: My lab is trying to figure out what drives aging. We are investigating chromatin changes that occur during senescence, aging, and age-related diseases. To delineate the mechanisms that regulate aging, we rely on experimental, computational, and high-throughput technologies to discover novel epigenetic targets of aging. With the help of a naturally aged mouse model, we hope to identify key enzymes and transcription factors. Our long-term goal is to modulate these factors using epigenetic drugs, CRISPR/Cas9 gene editing, and other cellular reprogramming strategies to improve health and, ultimately, extend life.

What attracted you to the program?

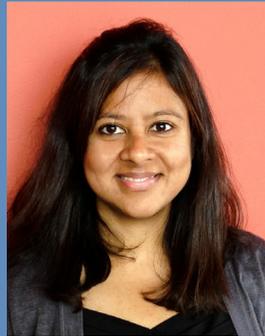
There are two primary reasons I chose to apply to the Stadtman Program: 1) The program identifies the best institute that fits my research goals, not the other way around; and 2) The program gives junior scientists the freedom to devote time at the bench and mentor the next generation of scientists through hands-on training.

HUGO TEJEDA, PH.D., NIMH

Chief, Unit on Neuromodulation and Synaptic Integration, National Institute of Mental Health

Came to NIH: In 2008 to complete graduate and postdoctoral fellowships at NIDA; in 2018, joined NIMH as a Stadtman Investigator and NIH Distinguished Scholar.

Research focus: The brain's neuromodulatory systems, such as the endogenous opioid system, play a role in modifying synaptic integration, a process by which neurons process incoming signals and convert them to output signals.



PAYEL SEN, NIA



HUGO TEJEDA, NIMH



JOEL VEGA-RODRIGUEZ, NIAID

(Endogenous opioids, such as endorphins and dynorphins, are produced by the body and act on opioid receptors throughout the central nervous system to relieve pain and regulate anxiety and mood.) My group focuses on the role of neuromodulation within motivational and emotional neural circuits in processing information and orchestrating behavior. We are also identifying changes in neuromodulators (such as opioid receptors) and synaptic integration in limbic circuits of animal models of psychiatric disorder symptom clusters to identify novel therapeutic targets and increase our understanding of conventional therapies.

What attracted you to the program?

The NIH provides a stimulating, supportive environment in which one can focus on their basic science. Simultaneously, the research-focused clinical environment facilitates reverse and forward translational research influenced by basic science.

JOEL VEGA-RODRIGUEZ, PH.D., NIAID

Chief, Molecular Parasitology and Entomology Unit, National Institute of Allergy and Infectious Diseases

Came to NIH: In 2018 as a Stadtman Investigator and NIH Distinguished Scholar.

Research focus: My team is studying the biology of malaria parasites (protozoa of the genus *Plasmodium*) during two vulnerable times in their lifecycle: when they are sexually reproducing in the mosquito midgut; and when the mosquito injects the parasitic sporozoites into the human host. We are investigating the role of vector and host factors for parasite infectivity and the molecular mechanisms required for *Plasmodium* sexual reproduction in the mosquito. Our long-term goal is to identify new targets that could be exploited for malaria interventions including chemotherapy, vaccine development, and transgenic mosquitoes.

What attracted you to the program?

It gave me the opportunity to establish a unique research program to study the transmission of malaria by mosquitoes as part of a diverse and vibrant scientific community at the NIH. The exceptional resources available at the NIH foster the advancement of my scientific and professional career as well as those of my trainees.



EMILY VOGTMANN, NCI-DCEG



ALEXANDRA WHITE, NIEHS



FAUSTINE WILLIAMS, NIMHD

EMILY VOGTMANN, PH.D., M.P.H., NCI-DCEG

Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Joined NIH: In 2013 as a Cancer Prevention Fellow and later a research fellow; became Stadtman Investigator in 2018 and an NIH Distinguished Scholar in 2019.

Research focus: I am investigating the association between the human microbiota and cancer risk and how the microbiota may mediate associations between exposures and cancer risk. My team is looking at the effects of cancer risk factors, such as tobacco use, betel quid use (chewing betel nuts), alcohol intake, and diet, on microbial communities. We are also studying risk and lifestyle factors for head-and-neck and lower gastrointestinal cancers. We are characterizing the fungal component of the microbiota and its relationship to cancer risk.

What attracted you to the program?

As a postdoctoral fellow, I was closely involved in the development of the microbiome research program, where we evaluated sample-collection methods, laboratory handling, bioinformatics, and statistical analysis methods. I applied for the Stadtman program to continue this work and to start an independent research program using optimized methods to study the impact of the human microbiome on cancer risk.

ALEXANDRA WHITE, PH.D., M.S.P.H., NIEHS

Environment and Cancer Epidemiology Group, National Institute of Environmental Health Sciences

Came to NIH: In 2015 as a postdoctoral fellow; became a Stadtman Investigator in 2019.

Research focus: My research focuses on the role of air pollution and environmental chemicals, individually and in combination, in breast-cancer risk. My research aims to identify novel and modifiable environmental exposures related to cancer risk and explore underlying biologic mechanisms. Currently my group is investigating the role of air-pollution components and other environmental chemical mixtures in relation to epigenetics, breast-tissue characteristics, and cancer incidence. This work will identify environmental carcinogens for which exposure can be mitigated either with policy changes or individual-level interventions.

What attracted you to the program?

NIH has unparalleled resources and outstanding scientists. It provides the ideal opportunity to conduct cutting-edge science.

FAUSTINE WILLIAMS, PH.D., NIMHD

Health Disparities and Geospatial Transdisciplinary Research Lab, National Institute on Minority Health and Health Disparities

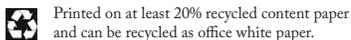
Came to NIH: In 2018 as a Stadtman Investigator and NIH Distinguished Scholar.

Research focus: Acculturation and social determinants influencing immigrant, migrant, and minority populations' health are particularly challenging. These factors, including sociocultural, environmental, economic, and biological factors and genetics are often interconnected, making them difficult to address. Our research program seeks to understand these complex dynamic factors. Subsequently, the lab has two interrelated research goals. The first is using transdisciplinary methods including system science, geographic information system, and mixture models to understand the complex interactions of factors contributing to the health and health disparities of immigrant, migrant, and minority populations. The second is using our findings to develop and implement culturally appropriate interventions to improve diverse populations' overall health outcomes and reduce health disparities.

What attracted you to the program?

The NIH is the most robust research environment in the world! Working here will provide me resources to pursue my research ideas, which would be difficult to conduct on the outside if I did not secure extramural funds. Another advantage is the opportunity to collaborate with NIH's wide range of researchers as well those outside the NIH. Additionally, the fulfillment of my long-term goal requires expanding my research to understanding the impact of interactions of social, behavioral, and genetic underpinnings of health disparities. I believe there is no better environment for these types of work than the NIH due to its unique nexus of researchers. ●

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CATALYTIC REACTIONS?

IF YOU HAVE A PHOTO OR other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation or confession that scientists might appreciate and that would be fit to print in the space to the right, why not send it via e-mail: catalyst@nih.gov; fax: 301-402-1434; or mail: *The NIH Catalyst*, Building 60, Room 232.

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

READ MORE ARTICLES, AND EXPANDED VERSIONS OF THE ONES IN THIS ISSUE, ONLINE AT <https://irp.nih.gov/catalyst/v29i2>.

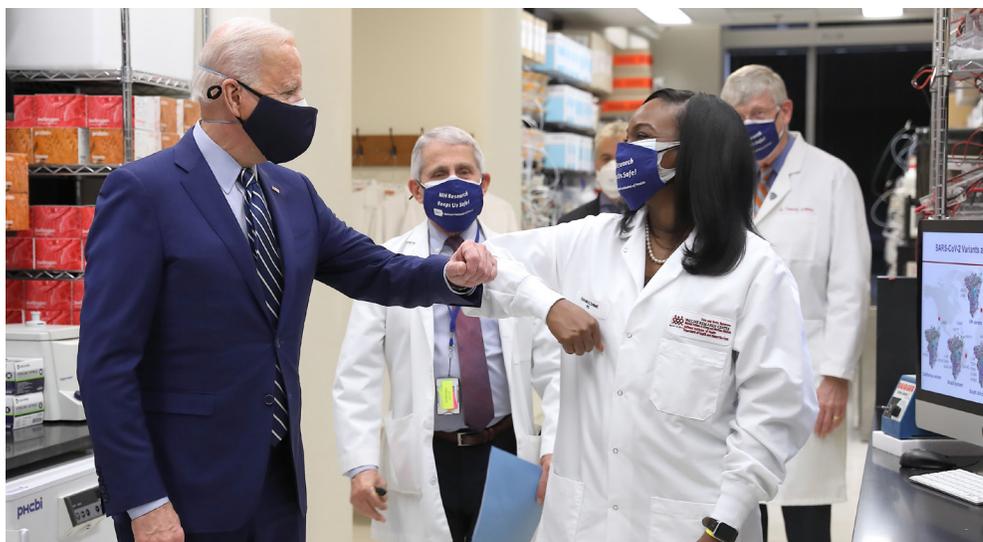
The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH.

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PHOTOGRAPHIC MOMENT

A Visit From the New President



CREDIT: CHIA-CHI “CHARLIE” CHANG, OD

PRESIDENT JOSEPH BIDEN MET WITH SCIENTISTS AT NIH’S VACCINE RESEARCH CENTER (VRC) on February 11, 2021, and then gave a virtual pep talk to NIH staff thanking them for their hard work and outstanding contributions in fighting the COVID-19 pandemic. “On behalf of a grateful nation, I want to thank you and your families for your work and sacrifice,” he said. During his remarks, he also talked about his plans to expand the distribution of COVID-19 vaccines. Here, Biden elbow bumps VRC researcher **Kizzmekia Corbett, who helped develop COVID vaccines, while NIAID Director **Anthony Fauci** (center) and NIH Director **Francis Collins** (right) look on.**

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