

Theodore Pierson Named New VRC Scientific Director

Flavivirus Pioneer Hopes to
Expand Innovation, Creativity

BY GUILLERMO RAIMUNDI RODRIGUEZ

THEODORE PIERSON, CHIEF OF THE Viral Pathogenesis Section (VPS) and the Laboratory of Viral Diseases at the National Institute of Allergy and Infectious Diseases, is excited for the next chapter at the Vaccine Research Center (VRC). He can now be found at the center as its newly appointed Scientific Director (SD), where he eagerly joins what he describes as an “exceptionally collaborative organization” and considers how to define the next series of scientific problems that they will work together to solve, building upon an impressive 20-year foundation that led the VRC to develop life-saving measures currently available to address pandemic as well as endemic public health threats.

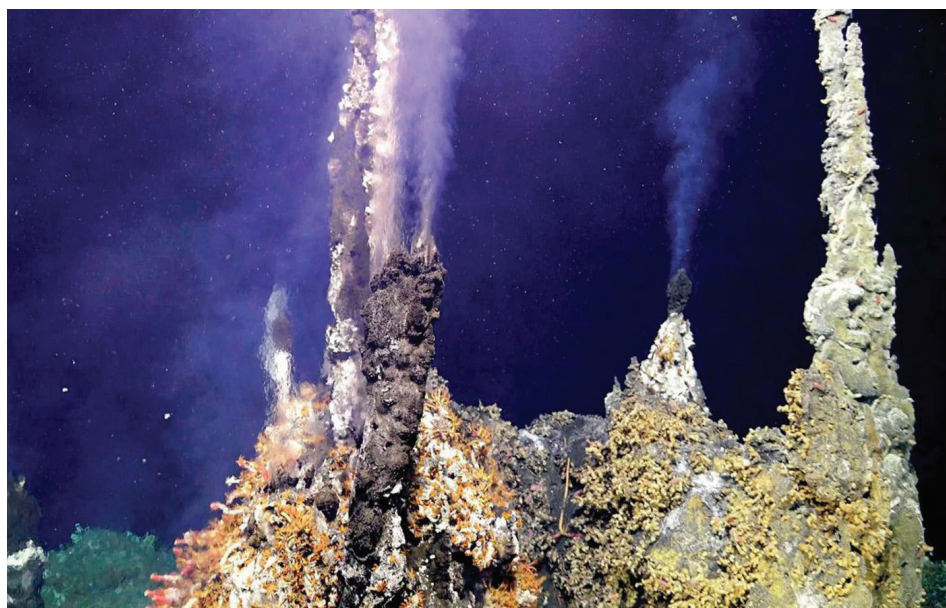
According to Pierson, the VRC is an ideally structured organization that performs basic research in multiple areas, including virology, structural biology, immunology, and vaccine development. The VRC has unique expertise and capabilities to design, develop, manufacture, and perform first-in-human clinical trials of vaccines and antibodies against a large and diverse portfolio of pathogens. This includes well-established threats to global health, such as HIV-1, influenza, malaria, and a

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On the Origin of Life

Scientist and Author Nick Lane Provides His Unique Perspective

BY VICTORIA TONG, OD



Hydrothermal system at Axial Seamount

CREDIT: D. KELLEY, UNIVERSITY OF WASHINGTON/NSF-OOI/WHOI

FOUR BILLION YEARS AGO, LIFE SPRANG UP FROM A NONLIVING EARTH.

Perhaps the source of life was a “warm little pond” that Charles Darwin mused about more than a century and a half ago, teeming with all the necessary chemical ingredients for the first living organisms to form. Or perhaps life preexisted in the universe, and space-hardy microorganisms arrived on our planet via a meteoroid one fateful day.

Nick Lane, professor of evolutionary biochemistry at University College London, favors a different idea. Lane, author of five books exploring the origins and evolution of life, posits that deep-sea hydrothermal vents provided an ideal environment in which the first cells could have emerged.

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What Is Leadership? (I'm Glad You Asked)

BY NINA F. SCHOR, DDIR

OVER THE COURSE OF MANY YEARS, I have thought a lot about leadership. What is leadership? What skills, insights, and character traits does it require? How does it differ from management? Or from administration? And how should we best choose leaders? Are there “biomarkers” for or predictors of excellence in leadership?

Being a leader is not something one learns to do overnight; nor is it something that only comes with a high rank and an official title. Leadership is a philosophy, a way of life, and a method through which one mentors and inspires people, shapes and develops complex programs, and implements a vision for a project or organization.

Leadership is best acquired gradually through successively larger and more complex portfolios of responsibility. It requires being ready to have the currency by which you are judged be the success of those you lead, not your own successes.

There are some at NIH who aspire to leadership and do not readily see opportunities or do not see the potential in themselves to fulfill their aspirations. On behalf of them, I ask my colleagues in leadership to be encouraging, empowering mentors and sponsors for these future leaders.

There are others who see opportunities and do not feel they are given an equitable chance at their attainment. This problem will only change with effective partnership. Those who feel this way must be enabled to speak out and must do so. Those with the knowledge and the power to assess potential for and assign leadership

positions must mentor, offer individual critique and counsel, and delegate without micromanagement.

Still others, very few in number but big in negative impact, view leadership as a self-aggrandizing, empire-building opportunity to control others. All of us must recognize the potential of such behavior to destroy a whole institution, even as it elevates an individual, and to impede the progress of science and medicine — enterprises that depend increasingly on cross-disciplinary teamwork and cooperation.

In my view, some important guiding principles underlie great leadership. I list them here.

1) Listen well and read between the lines. The best leaders are working even when they are theoretically not. What separates the outstanding leader from the merely satisfactory one is having the vigilance to recognize the rare times when someone or something not quite straightforward is involved.

2) Learn from everyone and everything. As an academician of a certain age, when I think of those I see as mentors, it strikes me that many of them would never have used that word to characterize our relationship. They just did what they did. I was an observer, a cataloguer of what I would or would not someday make my own approach. But all were nevertheless mentors.

3) Value all components and contributions. Everyone on your team will bring something different to the table. Finding the fit between what you need and what each team member has to offer

is part of the job of the leader, as is helping those whose talents do not fit your vision ultimately find a situation in which they do. The bar should be high for a standing ovation but low for respect, guidance, and kindness.

4) Thought without action is useless. Everyone loves a policy and a plan. But if they are not enforced and enacted, they don't do anyone any good!

5) Acting without thought is worse. As a leader, you will never do what everyone wants you to do. But your actions should devolve from your thoughts so that, over time, your rationale is transparent and your consequent actions are predictable and consistent to those you lead.

6) There will be things you sweat. But sweat is not blood. There is no job worth doing that does not include some elements of drudgery and unpleasantness. For me, it is reviewing budget spreadsheets! For others, it is having critical, challenging conversations. These are necessary elements of leadership and often a means to an important end. You will sweat them much less if you constantly remind yourself and think of them in the context of that end game. Mind the roadmap and the operations, but keep your eye and your heart on the vision and mission.

7) Development is forever. If there ever comes a time in life when one stops developing, I hope I never reach it! Learn, grow, admit mistakes and missteps, and always take periodic stock of effects and outcomes so you can disclose, discuss, and enact a midcourse correction.

WALS 2023–2024 Season: A Sneak Peek

BY DIANA GOMEZ, OD

8) If you look in the mirror and can't laugh at the person who looks back at you, the ballgame is over. (Laugh. A lot.)

This is perhaps the most important guiding principle. When the stakes are high and the stakeholders many and varied, it can be very easy to mistake your leadership role for your “self” and to take yourself too seriously. You may have become a leader, but you remain a human. You will make mistakes, say things you later regret, and feel embarrassed from time to time. It will be therapeutic for you—and instructive and empowering for those you lead—if you remain humble and can admit and sometimes see the humor in your missteps. By all means, preserve your privacy; but share your “self” with those you lead from time to time and allow yourself to laugh at that inner human.

Leadership is not for the faint of heart. It has huge impact but gets awarded no impact factors. It builds new programs and initiatives, but there are no prizes for such organizationally matrixed achievements. It ignites, fuels, and sustains innovation, growth, and cooperation and applauds from backstage those who ultimately get the applause. But without it, NIH cannot reach and sustain its full potential.

We must make opportunities for all members of our community to develop and try on for size their potential and predilection for leadership, and we must be honest with them about the importance of a measure of selflessness in that enterprise, lest we be rudderless in the future. ●

NIH'S HIGHEST-PROFILE LECTURE program, the NIH Director's Wednesday Afternoon Lecture Series (WALS), launches its 2023–2024 season on September 13. Most lectures will be held in person on Wednesdays at 2 p.m. ET in Lipsett Amphitheater in Building 10. All events will be broadcast and archived via NIH VideoCast.

In a prelude to the upcoming season, the National Institute of Diabetes and Digestive and Kidney Diseases and the WALS Office will co-sponsor the annual John Daly Lecture on September 6. Speaking is Bryan Roth, the Michael Hooker Distinguished Professor of Pharmacology at the University of North Carolina School of Medicine (Chapel Hill, North Carolina). Roth is recognized for his discoveries and inventions in the general areas of molecular pharmacology, GPCR structure and function, and synthetic neurobiology.

The William E. Paul Lecture presented by Diane Mathis from Harvard Medical School (Boston, Massachusetts) kicks off the official WALS season on September 13. The Mathis lab studies T-cell differentiation, tolerance and autoimmunity, and translating mechanistic studies on mouse models to normal and diseased states in humans.

Next up is the annual G. Burroughs

Mider Lecture by **Dale Sandler**, Chief of the NIEHS Epidemiology Branch, on September 20, in the heart of NIH Research Festival week.

Rounding out the first month of the WALS season will be Heran Darwin, professor in the Department of Microbiology of New York University Langone Health (New York), on September 27. Darwin's lab is studying how *Mycobacterium tuberculosis*, the causative agent of tuberculosis, has become arguably the most successful pathogen on earth.

This next season is special as we adjust to the post-pandemic environment. We are bringing back the trainee lunch with the speakers and the post-lecture receptions. Lunches are limited to five to six trainees, so please contact the WALS Office if you're interested in attending.

Each WALS season includes some of the best-known names in biomedical and behavioral science to keep NIH investigators abreast of the latest and most important research being conducted in the United States and beyond. All speakers are nominated by the NIH community.

Visit <https://oir.nih.gov/wals> for the full schedule. For updates and to receive notice of future events, subscribe to the WALS LISTSERV electronic mailing list at <https://list.nih.gov/cgi-bin/wa.exe?SUBED1=WALS&A=1>. ●

And don't miss the NIH Research Festival, September 18–22, 2023.

NIH Research Festival
Lectures, posters, food,
music, and more
September 18–22, 2023
Building 10



From the Fellows Committee

NIH's National Library of Medicine Offers a Wealth of Resources

BY LARISA GEARHART-SERNA, NCI

WHAT STARTED IN 1836 AS A SMALL collection of medical literature in the office of the United States Army Surgeon General has evolved into the world's largest biomedical library. That, of course, is the NIH National Library of Medicine (NLM), which now boasts a multitude of products and services and a globally admired collection spanning ten centuries, reflecting remarkable depth and breadth. These resources and collections are available to researchers, healthcare professionals, librarians, publishers, and the public.

What you might not know, however, is that the NLM has many offerings that are curated to serve the intramural research community at NIH. Read on for information about the top NLM offerings for trainees, as well as NIH scientists and staff.

General discovery

The digital era has been kind to the NLM, leading to the creation of well-known resources such as MEDLINE, ClinicalTrials.gov, and PubMed. NLM's collection and reach have grown dramatically over the years, and they now partner with more than 20 countries and a wide variety of consumers and health professionals around the world. While it may seem daunting to sort through and discover all that you have access to, not to worry—begin your journey on the NLM Data Discovery site, where you can filter search results and find the most accessed NLM products and most accessed material within the full catalog.

Common research resources

Beyond PubMed, the NLM offers a myriad of products and services available to all biomedical researchers both at and outside of the NIH. This includes data sets, tools, and instruction on new methods. While computational molecular biologists and human genome researchers have traditionally found

the various NLM biomedical resources particularly helpful, those same tools can be useful across many different biomedical fields. Those resources include GenBank, Gene Expression Omnibus, Multiple Sequence Alignment Viewer, PubChem, Vector Alignment Search Tool (VAST), and Health Information Technology and Health Data Standards. Visit <https://datadiscovery.nlm.nih.gov> for a full list.

To search for tools, trainees are encouraged to visit <https://eresources.nlm.nih.gov> and use the filters to narrow down results relevant to their specific topic or field. For example, a postdoc conducting research on protein function might access VAST to identify structural similarities within unrelated proteins, potentially discovering new targets and previously unrecognized protein homologues. NLM also provides instruction on using each resource. Go to <https://www.ncbi.nlm.nih.gov/guide/training-tutorials> to learn more.

Other research resources

NLM's own Intramural Research Program has special tools and resources for its staff and for those who collaborate or conduct similar research, including health services and public health research standards, a health statistics tutorial, and databases such as the National Health and Nutrition Examination Surveys. NLM also provides NIH-specific policies and guidelines that may apply to your research. And if you need to take your search further, the library also offers a LocatorPlus Online Catalog to help you find other materials within the library collections.

Education and professional development

As part of its Congressional mandate to acquire, organize, preserve, publish, and make available biomedical and health information to support research and public

health, the NLM shares its vast historical collections with the world through its Digital Collections repository, the popular blog *Circulating Now*, *History Talks*, and an award-winning exhibition program featuring stories about history, society, and medicine drawn from the NLM collections.

NLM is also a great place to go for learning resources and information about training and careers. Search NLM's online tutorials, videos, and other instructional materials on a variety of topics, as well as academic and postgraduate trainings, professional development and continuing education resources, lectures, and exhibitions.

News and updates

If you're looking for news and updates concerning NLM's available resources and similar topics, check out NCBI Insights, NLM Technical Bulletin, and NLM RSS Feeds for News and Webcasts. Stay connected by subscribing to email lists and receive announcements about NLM news and events, data distribution, interlibrary loans and document delivery, publications, literary databases, and terminology. If you have an interest in issues related to clinical- and bio-informatics, keep an eye out for updates from the NIH Trans-NIH Biomedical Informatics Coordinating Committee (BMIC). BMIC was formed over 15 years ago to share information about NIH informatics programs, projects, and plans.

The NLM offers resources galore to help you in your research and professional pursuits. Conveniently explore all it has to offer online, or pay a visit by taking a stroll to the southeast corner of NIH's Bethesda campus.

For more information or questions, email Virginia Meyer, NLM IRP Training Director, at virginia.meyer@nih.gov. ●

Larisa Gearhart-Serna is a former postdoctoral fellow at the National Cancer Institute's Technology Transfer Center and was a member of The NIH Catalyst Editorial Board. She now works in business development and marketing for life sciences investigators at Stanford University (Stanford, California).



NIH Selects Dr. Jeanne Marrazzo as Director of the National Institute of Allergy and Infectious Diseases

FROM NIH NEWS RELEASES

LAWRENCE A. TABAK, ACTING NIH Director, has named **Jeanne M. Marrazzo** as Director of NIH's National Institute of Allergy and Infectious Diseases (NIAID). Marrazzo is currently Director of the Division of Infectious Diseases at the University of Alabama at Birmingham (Birmingham, Alabama). She is expected to begin her role as NIAID Director in the fall. NIAID conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases.

"Dr. Marrazzo brings a wealth of leadership experience from leading international clinical trials and translational research, managing a complex organizational budget that includes research funding and mentoring trainees in all stages of professional development," said Tabak. "I look forward to welcoming Dr. Marrazzo to the NIH leadership team. I also want to extend my gratitude to **Hugh Auchincloss** for serving as Acting Director of NIAID after long-time director Anthony S. Fauci, M.D., stepped down in December 2022."

As NIAID Director, Marrazzo will oversee NIAID's budget of \$6.3 billion, which supports research to advance the understanding, diagnosis, and treatment of infectious, immunologic, and allergic diseases. NIAID supports research at universities and research organizations around the United States and across NIAID's 21 laboratories, including the Vaccine Research Center on NIH's main campus in Bethesda, Maryland, and the Rocky Mountains Laboratories in Hamilton, Montana. NIAID also has a unique mandate to respond to emerging and re-emerging public health threats at home and abroad. The NIAID research response to outbreaks of infectious diseases,

from HIV to Ebola to COVID-19, has led to new therapies, vaccines, diagnostic tests, and other technologies.

Marrazzo's research in discovery and implementation science has focused on the human microbiome, specifically as it relates to female reproductive tract infections and hormonal contraception; prevention of HIV infection using biomedical interventions, including pre-exposure prophylaxis and microbicides; and the pathogenesis and management of bacterial vaginosis, sexually transmitted diseases in HIV-infected persons, and management of antibiotic resistance in gonorrhea.

She has been a principal investigator on NIH grants continuously since 1997 and has served frequently as a peer reviewer and advisory committee member. Marrazzo also has served as a mentor to trainees at all stages of professional development, including on NIH-funded training grants, and was the recipient of the American Sexually Transmitted Diseases Association's Distinguished Career Award, the highest recognition of contributions to research and mentoring in the field.

Marrazzo is a Fellow of the American College of Physicians and of the Infectious Diseases Society of America and is board certified in infectious disease. She earned her bachelor's in biology from Harvard University (Cambridge, Massachusetts); her M.D. from Thomas Jefferson University at Philadelphia; and a Master of Public Health in Epidemiology from the University of Washington (Seattle, Washington). Marrazzo also has chaired the American Board of Internal Medicine (ABIM) Council and the ABIM Infectious Disease Specialty Board. ●



Jeanne Marrazzo is expected to begin her role as NIAID Director this fall.

CREDIT: LEXI COON, UNIVERSITY OF ALABAMA AT BIRMINGHAM

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

Enhanced Potential Pandemic Research: To Do or Not To Do?

Weighing a Way Forward for Controversial Research

BY SEPPIDEH SAMI, CC



CREDIT: STEPHANIE MITCHELL, HARVARD UNIVERSITY

World-renowned infectious disease expert Marc Lipsitch began raising questions about gain-of-function research (GOFR) long before the COVID-19 pandemic. He thinks that with a bit of work and lots of open discussion, we can find an effective means to conduct GOFR.

THE TOPIC OF GAIN-OF-FUNCTION research (GOFR) has garnered much discussion recently in the popular press and also in the scientific literature. How can we accurately weigh the risks and benefits of certain types of GOFR? Can we realistically expect regulatory policies to be fully implemented and adhered to... globally?

World-renowned infectious disease expert **Marc Lipsitch** began raising such questions long before the COVID-19 pandemic. He thinks that, with a bit of work and lots of open discussion, we can find an effective means to conduct GOFR.

Lipsitch, a Professor of Epidemiology and Director of the Center for Communicable Disease Dynamics at the Harvard T.H. Chan School of Public Health (Boston), presented his thoughts on this topic at an NIH-FDA COVID-19 Scientific Interest Group lecture titled “Toward a Reasonable Middle Ground

for Oversight for Enhanced Potential Pandemic Pathogen Research” at the Lipsett Amphitheater on June 30.

“COVID-19 brings new salience to the need to prevent accidental pandemics,” said Lipsitch. “Now is the time to act.” A reasonable middle ground in the scientific community is needed, he said, to ensure that regulation is effective in enabling science that is both informative and safe.

GOFR, where a pathogen is genetically modified to change its function, is largely considered safe, and indeed necessary, to better understand viruses and develop new vaccines. However, a small subset of GOFR, known as GOFROf Concern (GOFROC), is far more controversial.

Ideally conducted under strict oversight and biosecurity measures, GOFROC involves creating enhanced potential pandemic pathogens (ePPP)—microorganisms that are capable of wide, uncontrollable spread in human populations and have been made more virulent or transmissible than their naturally occurring counterparts.

Supporters of GOFROC argue that such work is necessary to assess the pandemic potential of newly emerging viruses and inform public health and preparedness efforts for the next pandemic. Opponents express deep concern that ePPPs, more contagious and deadly than naturally occurring strains, pose significant risks to the public safety and health of millions of people if accidentally released into the environment. They also note that this type of GOFROC does not lead to vaccine development and argue that nearly all of the public health benefits of GOFROC can be achieved in ways that do not increase the risk of an accidental or malicious pandemic.

In his talk, Lipsitch presented compelling reasons why more robust

oversight of GOFROC is necessary and shared a set of reasonable considerations and recommendations that could serve to develop a regulatory framework.

For example, he advocated for a standardized scientific process to review all GOFROC proposals and identify pathogens with the potential to cause a pandemic. That review would be followed by a risk-benefit evaluation of whether to move forward with the research. According to Lipsitch, if the work creates a specific public health benefit that cannot be achieved by safer means, and that public health benefit is large enough to outweigh the risk it creates and is scientifically sound, then it should be approved. “Harm reduction works,” Lipsitch said, adding that such risk evaluation is challenging but not impossible if based on carefully considered and valid criteria. “Perfection is a luxury but we can massively reduce the risks while preserving public health benefits.”

Those beyond the scientific community, such as ethicists, public representatives, and policymakers, should also be involved in the conversation about the risks of research with ePPPs, Lipsitch said. He noted that Congress is currently discussing the issue. “Scientists understandably get concerned when politicians interfere [in] details of research. But politicians have a responsibility for safeguarding public safety...[and] a societal discussion must occur,” he told the *Catalyst*.

“As scientists we have a public trust to do work that is as beneficial as possible and strongly respects [the] public’s concerns about safety,” Lipsitch said. “We need to be very cautious about the work we do and the risks we take, especially when there are more effective ways to reach the same scientific goals as well as public health goals, while maintaining safety.”

Lipsitch's NIH lecture was serendipitous and not part of the COVID-19 SIG's lecture schedule. He happened to be speaking on a panel in downtown Washington, D.C., hosted by the American Enterprise Institute to discuss the lessons learned from the COVID-19 pandemic. Joining him as a panelist was **Emily Ricotta**, who leads the Epidemiology and Data Management Unit at the National Institute of Allergy and Infectious Diseases and is part of the COVID-19 SIG.

"We had the panel discussion on Friday morning, drove up from D.C. on an extremely hot day, then hurried from the NIH Gateway Center to the Lipsett Amphitheater and made it just in time," Ricotta said. "It was all very last minute but a great and rare opportunity for the NIH."

Ricotta added that she hoped to raise awareness about the diversity of expertise necessary to contribute to considerations of GOFROC and a pandemic response.

The lecture drew hundreds of viewers despite being restricted to the HHS intranet. View the archive (HHS-only) at <https://videocast.nih.gov/watch=49969>. ●

At NIH, the Dual Use Research of Concern Institutional Review Entity and the Institutional Biosafety Committee provide rigorous oversight and approval for work that involves potentially infectious agents. Learn more at <https://go.nih.gov/RGLyKkg> and <https://go.nih.gov/x1hyCOF>.

Watch the June 30 American Enterprise Institute panel discussion "Health Scholars on the Impact of COVID-19" at <https://www.c-span.org/video/?529065-2/health-scholars-impact-covid-19>.

Seppideh Sami, making her Catalyst feature debut, is a Training Coordinator in the Patient Support Services Department at the NIH Clinical Center. In her spare time, she enjoys studying the conservation and preservation of the natural world, especially plants.

What We're Reading

Articles That Capture the NIH's Role in History or Society

"REFLECTIONS ON THE NATIONAL SCIENCE FOUNDATION'S UNDERSTANDING THE RULES OF LIFE PROGRAM: PROCEEDINGS OF A WORKSHOP SERIES"

National Academies of Sciences, Engineering, and Medicine, 2023

<https://doi.org/10.17226/27020>

"One of NSF's Big Ideas addresses what is perhaps the most significant gap in biological knowledge, which is our inability to predict an organism's observable characteristics—its phenotype—from what is known about its genetic makeup and the nature of its environment. . . . That initiative, Understanding the Rules of Life (URoL), seeks to develop a predictive understanding of how key properties of living systems emerge from dynamic interactions operating on multiple levels, including genomic, epigenomic, metabolomic, organismal, and environmental."

"DAVID WALLACE-WELLS: SUDDENLY, IT LOOKS LIKE WE'RE IN A GOLDEN AGE FOR MEDICINE"

New York Times Magazine, June 23, 2023

<https://www.nytimes.com/2023/06/23/magazine/golden-age-medicine-biomedical-innovation.html>

"Hype springs eternal in medicine, but lately the horizon of new possibility seems almost blindingly bright. 'I've been running my

research lab for almost 30 years,' says Jennifer Doudna, a biochemist at the University of California, Berkeley. 'And I can say that throughout that period of time, I've just never experienced what we're seeing over just the last five years.'"

"STEFAN HARRER: ATTENTION IS NOT ALL YOU NEED: THE COMPLICATED CASE OF ETHICALLY USING LARGE LANGUAGE MODELS IN HEALTHCARE AND MEDICINE"

EBIOMEDICINE, April 2023

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10025985/>

"Large Language Models (LLMs) are a key component of generative artificial intelligence (AI) applications for creating new content including text, imagery, audio, code, and videos in response to textual instructions. Without human oversight, guidance and responsible design and operation, such generative AI applications will remain a party trick with substantial potential for creating and spreading misinformation or harmful and inaccurate content at unprecedented scale."

Polishing a Diamond in the Rough

David Lovinger Is NIAAA's New Scientific Director

BY PETER MANZA, NIAAA



CREDIT: NIAAA

As NIAAA's new Scientific Director, Lovinger has identified several targets to help NIAAA combat what he sees as the central challenge in alcohol research: identifying new treatments for alcohol-use disorder.

IN JUNE 2023 NIAAA SELECTED David Lovinger as the institute's new Scientific Director (SD). Lovinger had been Acting SD since January 1, 2022.

A Senior Investigator and Chief of the Laboratory of Integrative Neuroscience, Lovinger has dedicated his career to studying how actions are learned and controlled by the brain—and how behaviors go awry after chronic substance misuse. He is renowned for identifying key molecular targets of alcohol action in the brain, notably the *N*-methyl-D-aspartate glutamate receptor, first published in *Science* in 1989 (*Science* 243:1721-1724, 1989). Lovinger also has worked extensively to uncover how the endocannabinoid system shapes brain function, publishing key findings in journals such as *Nature Neuroscience* (*Nat Neurosci* 5:446-451, 2002) and *Neuron* (*Neuron* 96:1112-1126.e5, 2017).

Yet of his many accomplishments—more than 200 peer-reviewed publications, contributions to numerous books, and honors such as the NIH Director's Award for research—Lovinger first cited his record of mentoring young scientists.

"I've had some amazing graduate students, postdoctoral fellows, and faculty members," Lovinger said, referring to the

more than 50 trainees he has supervised to date. "That's really what I'm most proud of."

Although Lovinger has experience both within the intramural research program (IRP) and extramurally, he ultimately settled into the NIAAA IRP because he sees it as an environment that fosters high-level scientific advances. "You can initiate new research directions nimbly and have the resources to do it. It allows for a lot of creativity," Lovinger said.

Lovinger served as a professor at Vanderbilt University (Nashville, Tennessee) prior to joining NIAAA in 2001. He received a bachelor's from the University of Arizona (Tucson, Arizona) in 1981 and Ph.D. in psychology from Northwestern University (Evanston, Illinois) in 1987. Lovinger currently sits on the editorial boards of the journals *Addiction Biology*, *Neuropharmacology*, *Neuropsychopharmacology*, and *Basal Ganglia* and is the Editor-in-Chief of the journal *Alcohol*.

Colleagues at NIAAA are enthusiastic about Lovinger's appointment. "The program is very fortunate to have recruited such an eminent scientist with many years of experience as an effective leader and as a mentor to junior scientists at all levels," said **Andrew Holmes**, chief of the NIAAA Laboratory of Behavioral and Genomic Neuroscience.

Lovinger has identified several targets to help NIAAA combat what he sees as the central challenge in alcohol research: identifying new treatments for alcohol-use disorder (AUD). Three medications are approved by the FDA to treat AUD, but there is a need for additional treatment options. As a result, NIAAA is heavily focused on medications development and supporting promising new pharmacotherapies such as semaglutide and spironolactone. Yet Lovinger acknowledged compulsive alcohol use is a "multifaceted" condition that requires a comprehensive approach to improve outcomes. Investigating

nonpharmacologic treatments, such as brain stimulation therapy, will be another priority.

"We need new directions of innovative research, with better integration of what we produce," said Lovinger, citing the enduring challenge of merging preclinical research, which is conducted in animal models such as rodents, with clinical research conducted in humans. Part of this effort necessarily involves developing new models that incorporate important facets of human alcohol use and AUD. He further emphasized the importance of maintaining open dialogue and sharing the latest findings between intramural and extramural researchers. "We have to not only communicate our findings better to scientific audiences but also work on getting more information into our group from the outside."

The new SD also hopes to expand the institute's outreach capabilities. NIAAA is tasked with being a knowledge base for the alcohol-research community, providing resources such as *Spectrum*, a triannual newsletter summarizing the latest advances in research and treatment. Lovinger envisions building this platform outward to reach a wider audience of scientists, clinicians, and the public.

In accordance with the NIH's mission to diversify the national scientific workforce, Lovinger stressed that inclusion and equity "at all levels" would remain a core principle of NIAAA moving forward.

By focusing on these key areas, Lovinger hopes that others will take notice of what is one of the smaller, but no less mighty, institutes within NIH.

"The NIAAA intramural program is a real diamond in the rough," said Lovinger. "People from other NIH institutes should look into the research that we're doing. I think they'll be pleasantly surprised at the innovation in many areas of research here."

Peter Manza, a research fellow at the National Institute on Alcohol Abuse and Alcoholism, is a contributing writer for The NIH Catalyst.

On the Origin of Life

CONTINUED FROM PAGE 1



CREDIT: UNIVERSITY COLLEGE LONDON

Nick Lane, author of five books exploring the origins and evolution of life, posits that deep-sea hydrothermal vents provided an ideal environment in which the first cells could have emerged.

Lane presented support for this theory of abiogenesis to an audience gathered in the Lipsett Amphitheater in Building 10 on June 26. The event, sponsored by the Demystifying Medicine course series, the Foundation for Advanced Education in the Sciences, and the Office of Intramural Research, included a reception and book-signing for his latest book, *Transformer: The Deep Chemistry of Life and Death*.

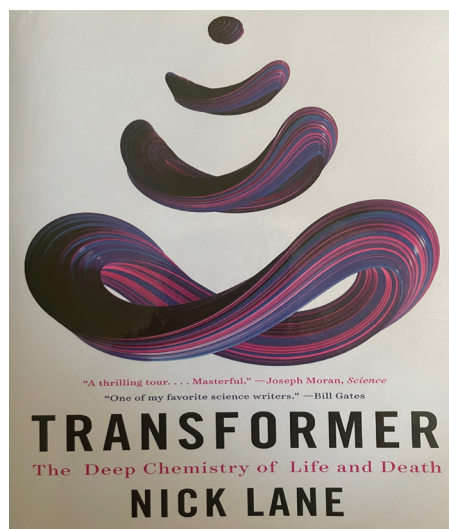
Lane is the first to admit to the unorthodoxy of his ideas. After summarizing his hypothesis—that electricity drives metabolism, which gives rise to genes—he prefaced his deeper dive into the biochemical underpinnings of his theory with a disclaimer: “It’s not the predominant idea in the field,” he said. “I have to warn you upfront that this is slightly heretical.”

Yet Lane builds a solid case for his argument supported by scientific evidence, including experiments he and his research group have carried out, which he detailed in his lecture.

Central to Lane’s work is the idea that life is governed by the flow of energy. This

is as true now as it was billions of years ago, when hydrothermal vents on the ocean floor jetted out highly alkaline fluid, creating a pH gradient after colliding with the acidic ocean water. This pH gradient provided the energy required to drive forward a reaction between the hydrogen gas bubbling out of the vents and the carbon dioxide found in the early oceans, forming molecules vital to life such as lipids, amino acids, and sugars.

In the lab, Lane and his group have been able to simulate this process using a microfluidic chip with acid and alkaline channels flowing through it, which supplies enough energy to drive the reduction of carbon dioxide to other organic molecules. They have also shown that protocells with a lipid bilayer membrane will spontaneously form from a mixture of fatty acids under heated alkaline conditions like those in hydrothermal vents.



Puzzling out how metabolism emerged from these protocells is another area of Lane’s research. Over the past seven to eight years, he and several other research groups have worked to replicate a core set of metabolic pathways shared by all life on Earth, including both bacteria and archaea.

These reactions include glycolysis

and gluconeogenesis, processes in which glucose is broken down and formed; the pentose phosphate pathway, which produces precursors for nucleotide synthesis; the Krebs cycle, which generates and stores energy in the form of adenosine triphosphate; and the synthesis of various amino acids.

Although they have not replicated all these pathways from beginning to end, they have demonstrated that many intermediate steps will occur spontaneously. “It’s no longer hand-waving; this chemistry is favored chemistry. It really will happen if the conditions are right for it,” Lane said.

With the right pieces in place, Lane believes that genes would have naturally arisen from those fundamental metabolic processes, not the other way around.

Although Lane’s theory does not answer all the questions about how life originated, he has provided a feasible pathway for how the earliest forms of life could have evolved from the unique environment provided by hydrothermal vents deep under the sea.

“There’s a lot of missing holes there,” he said. “But there’s also a few markers of a possible path that I would say it’s worth continuing in the lab with these experiments because I think we can nail it.” ●

Victoria Tong, a Pathways editorial intern at The NIH Catalyst, is a sophomore at the University of California at Los Angeles and expects to major in chemistry. She was the editor of the student newspaper at Richard Montgomery High School in Rockville, Maryland. In her free time, she enjoys playing tennis, solving crossword puzzles, and scoping out new restaurants.

TECHNOLOGY TRANSFER

Making the Transfer from Bench to Bedside a Reality

BY NIH CATALYST STAFF AND ADAPTED FROM *THE JOURNAL OF TECHNOLOGY TRANSFER*

THE NIH CATALYST IS COMMEMORATING 30 years of publishing with a series of updates to past coverage. In this issue, we highlight the exceptional evolution of technology transfer at NIH and celebrate how brilliant ideas can be translated to clinical breakthroughs.

Role of public-sector research for new drugs and vaccines

Behind the genesis of any new drug or biomedical innovation is often an intricate backstory, a process historically thought to be carried out in the halls of deep-pocketed private biotech enterprises. However, a new study led by NIH researchers shows that public-sector research institutions (PSRIs), particularly the NIH, play a significant part in the worldwide ecosystem of drug development (*J Technol Transf* 2023; DOI:10.1007/s10961-023-10007-z).

The authors, who include **Sara Dodson** and **Mark Rohrbaugh** from the NIH Office of Science Policy, found that a remarkable 364 drugs approved by the Food and Drug Administration were discovered in whole or in part by PSRIs. NIH tops the list at 27 drugs discovered, which includes the chimeric antigen receptor T-cell cancer-therapy drug Abecma from Bluebird Bio, used to treat multiple myeloma.

In this study, the term PSRI broadly included universities, research hospitals, not-for-profit research institutes, and government laboratories worldwide that contributed to products approved by the FDA. The term “drug” referred to any product

that received marketing approval from the FDA Center for Drug Evaluation and Research or the Center for Biological Evaluation and Research.

Included were small-molecule drugs, including over-the-counter drugs, protein-based biologic drugs, vaccines, and in vivo diagnostics. Not included were serum-derived biologic drugs, insulin, warfarin, levodopa, or the early vaccines and antibiotics discovered in PSRIs pre- and immediately post-World War II.

The investigators used new and existing methods that captured a broad range of relationships and included drugs receiving FDA approval through 2016. They used four major sources—such as the FDA’s Orange Book, which provides a listing of patents protecting approved drugs—that accounted for a total of 246 drugs. The remaining 118 were identified by other sources such as press announcements, litigation, and conversations with colleagues.

By casting a broad information-gathering net, the authors said that their research provided the most complete compilation of drugs owing their origins to PSRIs.

Particularly noteworthy are the 23 vaccines. Nearly all important, innovative vaccines introduced over the past 30 years were invented by PSRIs, a trend continuing up to the response to the COVID-19 pandemic and including Moderna’s mRNA



NIH’s [intramural licensing impact study](#) describes how the technologies invented at the Intramural Research Program at the NIH generate benefits to public health, economic growth, and the biomedical innovation system.

CREDIT: NIH OFFICE OF TECHNOLOGY TRANSFER

COVID-19 vaccine, which was developed in partnership with NIH.

Indeed, the NIH dominates the list of FDA-approved vaccines, also contributing to the development of vaccines against human papillomavirus (HPV), rubella, pertussis, Type B *Haemophilus influenzae*, rotavirus, and hepatitis A, to name just a few; and these in addition to technology for ensuring vaccine safety.

Similarly, two-thirds of all FDA-approved drugs had their origins in U.S. public-sector-based research. The next most prolific countries—Canada and the United Kingdom—each discovered around 5 percent of the total.

A culture of invention

Technology transfer at NIH goes way back. More than 25 years ago *The NIH Catalyst* (March–April 1997, pages 1–6) reported on NIH inventions, notably, an HIV antibody test developed by the National Cancer Institute’s **Robert Gallo**, and CHAPS, a zwitterionic detergent used in labs worldwide to purify proteins from Leonard Hjelmeland of the *Eumice Kennedy Shriver* National Institute of Child Health and Human Development.



A photo from the 1997 March-April issue of the Catalyst showing the Office of Technology Transfer's Steve Ferguson and some of the products he negotiated.

TECH TRANSFER

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OTT-Licensed Products Approved by FDA in FY 2004

Between 1991 and 2004, FDA approved 23 products based on technologies developed in the NIH Intramural Research Program. The three 2004 newcomers were:

- Paclitaxel-eluting coronary stent system to inhibit restenosis after coronary angioplasty (James Kinsella et al., NIA)
- Generic form of didanosine (ddI) delayed-release capsules in the treatment of HIV infection (Hiroaki Mitsuya et al., NCI)
- Recombinant human keratinocyte growth factor protein, the first and only therapy for the severe mouth sores accompanying myelotoxic therapy for hematologic cancer (Jeffrey Rubin et al., NCI)

A story in the 2005 May-June Catalyst titled "From Bench to Tech Transfer and Back to the NIH Scientist" reported on new technologies developed at NIH including a coronary stent system, a treatment for HIV infection, and novel therapy to address certain side-effects from blood-cancer treatment.

Following the creation of Cooperative Research and Development Agreements in 1986, the NIH Office of Technology Transfer (OTT) patent license royalties exceeded patent expenses for the first time in 1996; and in that 1997 article, **Steven Ferguson**, now a Special Advisor at OTT, commented on how tech-transfer activity directly benefits the scientific community: "Not only does it bring inventions to the bedside, ...money is plowed back into the institutes. It incentivizes the system," he had said.

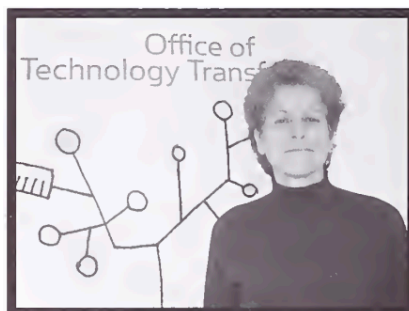
[https://irp.nih.gov/system/files/media/file/2022-01/NIH_catalyst_v05i2_1997-March-April.pdf]

The impact of NIH innovation gains momentum

In June 2023, NIH's long-anticipated intramural licensing impact study was officially released in conjunction with the BIO Annual Meeting and is now posted to a special section of the NIH Community Tech Transfer Website.

The year-long study involved a full download and analysis of NIH licensing data and demonstrates the true impact and power that NIH's intramural licensing program has had in three major areas:

- **Innovation:** NIH licensees cited 148 NIH patents on more than 1,700 patents of their own, and NIH drug discoveries were used in nearly 1,200 clinical trials.
- **Economy:** Sales of NIH licensed products supported an average of nearly 75,000 positions each year between 2001

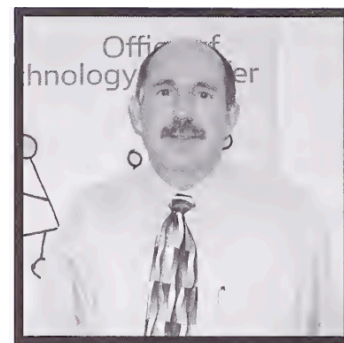


Fran Pollner

Bonny Harbinger

"We have one of the largest tech transfer programs, and we are inundated with requests for training. We now have visitors from Ireland and China—for six months of training, and two groups are coming from India and Hungary. This [interaction] provides us with contacts in these countries to help us place licenses and gives us the opportunity to teach others the way we think tech transfer should be conducted to provide the greatest public health benefit—which is critical to us."

"We have one of the largest tech transfer programs, and we are inundated with requests for training," said Bonnie Harbinger in a 2005 Catalyst article. Harbinger is now Senior Advisor for Innovation in the OIR.



Fran Pollner

Mark Robrbaugh

"The conflict-of-interest issue certainly should not decrease the number of formal collaborations between NIH scientists and industry. The new policy in no way limits such activities as part of one's official duties. Scientists are encouraged to establish such links, select CRADA partners based on their knowledge and working relationships with them. . . . Licensing is another story. The scientists are not involved. They can't make requests on behalf of a company. We keep a wall between them and the financial terms of a license related to what they're doing in the lab."

In an article from the 2005 May-June Catalyst titled "From Bench to Tech Transfer and Back to the NIH Scientist", then-OTT Director Mark Rohrbaugh emphasized that NIH researchers are the heart of tech transfer—from the point of discovery through the successful introduction of a new therapy into clinical practice.

and 2021. Aggregate sales in the United States alone totaled more than \$130 billion through 2021.

- **Health:** More than 26,500 deaths from cervical cancer will be averted in the United States alone as a result of the introduction of the Gardasil HPV vaccine—just one example cited.

"It's an amazing story and it's also our story," said Ferguson. ●

The full report, summary brochure, and case studies can be found at <https://www.techtransfer.nih.gov/reports/public-health-and-economic-impact-study>.

Interested in more tech transfer? On September 22, 2023, at 10 a.m. in Lipsett Amphitheater, Distinguished Investigator **Carlos Zarate** will deliver the 16th Annual Philip S. Chen Jr. Ph.D. Distinguished Lecture on Innovation and Technology Transfer. Zarate is Chief of the Section on Neurobiology and Treatment of Mood Disorders and Chief of the Experiment Therapeutics and Pathophysiology Branch at the National Institute of Mental Health. He will present a talk titled "Developing Novel Medications for Treatment-Resistant Depression and Bipolar Disorder." Watch the lecture online at <https://videocast.nih.gov/watch=49943>.

Theodore Pierson Named New VRC Scientific Director

CONTINUED FROM PAGE 1



CREDIT: NIAID

Theodore Pierson is the Vaccine Research Center's new Scientific Director

growing list of pathogens studied as part of the VRC's large investment in pandemic preparedness.

"There are so many layers of scientific leadership within the center that contribute in critical ways to moving science forward," said Pierson. He believes continued support and integration of those multiple layers of talent and expertise represents a major opportunity to foster a new era of ingenuity and discovery.

Pierson is best known for his 18 years of pioneering work studying how antibodies protect against flaviviruses. Flaviviruses are vector-borne RNA viruses that can emerge unexpectedly in human populations and cause a spectrum of potentially severe diseases including hepatitis, vascular shock syndrome, encephalitis, acute flaccid paralysis, congenital abnormalities, and fetal death (*Nat Microbiol* 5:796–812, 2020).

Pierson received his Ph.D. in immunology from The Johns Hopkins University School of Medicine (Baltimore)

in 2001 under the tutelage of his advisor, Robert Siciliano, where he studied how infection by HIV leads to the induction of viral reservoirs and disease persistence in humans. In 2003 he completed his postdoctoral fellowship at the University of Pennsylvania (Philadelphia) in Robert Doms' lab. There, he developed an interest in what would eventually become his current work—studying the viral immunology of flaviviruses such as the West Nile, Zika, and dengue viruses.

Science by the seashore

In an early memory, Pierson recalls being carried on the shoulders of his father along the shores of the Persian Gulf when he was 4 years old. As the high tide receded, it revealed a bounty of sea life residing on the rocks that would have otherwise remained invisible. Those experiences sparked a lifelong pursuit to understand life, first through the lens of marine biology, which would later inspire him to further appreciate all aspects of the living world. He would go on to complete his bachelor's at Eckerd College (St. Petersburg, Florida), where he was able to study marine creatures such as manatees and pygmy sperm whales.

While at Eckerd, Pierson connected with Guy Bradley, a virologist and immunologist who introduced him to molecular biology and provided an opportunity to learn at the bench. Bradley was among the first to describe HIV virology and infection in children. "Learning from a virologist made [me] a virologist," said Pierson. He considers that time as a pivotal period in which his interests shifted dramatically from marine biology towards viral immunology.

A multidimensional approach

Pierson remarks how his interests have significantly shifted from a reductionist

way of thinking about how antibodies interact with flaviviruses to exploring more translational questions. In recent years, Pierson and others have uncovered a more complex understanding of the multi-dimensional mechanisms involved in how antibodies bind viruses to contribute to immunity (*PLoS Pathog* 4(5):e1000060, 2008; *Sci Transl Med* 12(547):eaaw9066, 2020).

Research surrounding viruses like dengue and Zika is an area in virology and immunology that continues to foster scientific collaboration, according to Pierson. Such NIH-wide projects resulted in multiple joint VRC-VPS projects, including studying Zika vaccine candidates (*Science* 354 (6309):237-240, 2016). In his new role as SD, he hopes to explore solutions to stop the spread of other emerging diseases.

Pierson is an American Academy of Microbiology Fellow and recipient of the NIH Director's Ruth L. Kirschstein Mentoring Award, which reflects his commitment to the next generation of scientists. "I'm very proud of our science and the development of people I've had a chance to interact with. I'm proud of watching them grow beyond how much they believed they could," said Pierson, adding how passionate he is about mentoring the young scientists who come through his lab. "I get to watch that humanity." ●

Guillermo Raimundi Rodriguez was a postbac fellow in the lab of Leah Katzelnick at the National Institute of Allergy and Infectious Diseases, where he studied how a Zika DNA vaccine induces neutralizing antibodies in recipients with varying profiles of dengue immunity. He is currently attending his first year as a virology Ph.D. student at Harvard Medical School (Boston).

Santa Ono Shares His Scientific Journey at Annual Jeang Lecture

BY VICTORIA TONG, OD

CREDIT: UNIVERSITY OF MICHIGAN, OFFICE OF THE PRESIDENT



FROM NIH TRAINEE TO SCIENTIST

to university president, Santa Ono's path has not been a linear one.

"It was meandering, as you can see," said Ono, alluding to his time at a multitude of universities in three countries. "But I have to tell you, I feel very blessed to have been at each of these incredible institutions. Each stop has shaped me as a person. And I've met some incredible people that have really shaped who I am along the way."

Ono, now the 15th president of the University of Michigan (Ann Arbor, Michigan), shared his career journey at the Annual Kuan-Teh Jeang Memorial Lecture at the Lipsett Amphitheater on June 5.

The lecture series celebrates the legacy of "**Teh**" Jeang, a beloved and accomplished virologist at the National Institute of Allergy and Infectious Diseases who advocated for greater Asian American representation in scientific leadership. Each lecture features a scientific leader of Asian heritage.

Appointed in October 2022, Ono is the first person of Asian descent to lead the University of Michigan. He has extensive experience in both academic administration and scientific research: an immunologist and vision researcher by training, he previously served as the president of the University of British Columbia (Vancouver) as well as the University of Cincinnati (Cincinnati), and he has also held faculty positions at Johns Hopkins University (Baltimore), Harvard

University (Cambridge, Massachusetts), University College London (London), and Emory University (Atlanta).

During his talk, Ono emphasized the importance of the mentors who shaped him on his journey to becoming president of the University of Michigan. He credited his professors at the University of Chicago during his undergraduate years, as well as his mentors and colleagues at McGill University and Harvard University during his graduate and postdoctoral years, for fueling his passion for biomedical research. Working and learning alongside these individuals gave him the opportunity to explore a variety of research areas, including herpesviruses, genes linked to susceptibility and resistance to type 1 diabetes, and immune-response genes.

One of these mentors happened to be from the NIH. During his undergraduate years, Ono spent a summer at the National Cancer Institute in Frederick, Maryland, working in the lab of the virologist **Harvey Rabin**, who was studying primate versions of herpesviruses. These versions were of interest due to their similarity to the Epstein-Barr virus in humans, which is associated with multiple types of cancer. "He played a very important role in getting me excited about molecular biology," Ono said.

After his graduate studies at McGill and postdoctoral fellowship at Harvard, Ono was recruited to be an Assistant Professor of Medicine at Johns Hopkins University. There, he began to become interested in eye research, with a focus on studying inflammation of the eye at a molecular and cellular level.

After leading research groups at Harvard and University College London, Ono began his transition from concentrating on his academic research to entering the world of academic administration, or what he jokingly referred to as the "dark side." While he was at University College London, the provost of Emory University at the time, Earl Lewis,

reached out to him and invited him to join Emory's Office of the Provost. "He took a gamble on me," Ono said.

Ono accepted the offer, taking on the title of Senior Vice Provost at Emory. While there, Ono continued with his research on the eye, but on Lewis' encouragement, he also seriously began to consider branching off to pursue the administrative side of academia. "I started to think about the importance of universities in the education of the next generation of researchers and professors," Ono said. "And so, he [Lewis] drew me into administration."

Ono next became provost and then president of the University of Cincinnati before being recruited to become president of the University of British Columbia.

After sharing his own journey, Ono highlighted how NIH grants have been essential for advancing scientific research at the University of Michigan. For example, an NIH grant supported the launch of a firearm-safety research center to reduce firearm-related injuries. With support from the NIH and the Social Security Administration, the university has also been running a longitudinal study of aging that surveys a representative sample of more than 20,000 Americans every two years.

Translational science continues to be a major focus for the University of Michigan. With a recently awarded \$71 million grant from the NIH, the university can invest more resources into translating biomedical research into treatments for patients. "It's not just bench research that's ongoing. [The NIH] has also helped us enhance our ability to translate from the bench to the bedside," Ono said.

Established in 2014, the Kuan-Teh Jeang Memorial Lecture is sponsored by the NIH Office of Intramural Research and the NIH Office of Equity, Diversity, and Inclusion. Watch the Santa Ono lecture at <https://videocast.nih.gov/watch=49797>. ●



70 Years Onward, the NIH Clinical Center Remains a Beacon of Hope

BY VICTORIA TONG, OD



CREDIT: NIH OFFICE OF HISTORY AND STETTIN MUSEUM

Construction of the Clinical Center, which was the 10th building constructed at NIH, began in the late 1940s. In this photograph, Building 1 is shown with the beginnings of construction of the Clinical Center behind it.

STANDING IN FRONT OF THE TOWER-ing red brick exterior of Building 10 for the first time can be a daunting experience. Fourteen stories tall at its highest, with more than 10 miles of corridors, occupying more than 3 million square feet, Building 10 is home to the NIH Clinical Center, the world’s largest hospital dedicated solely to clinical research.

Yet even more impressive than the millions of bricks in its structure are the incredible achievements that have taken place within its walls.

Since its opening in July 1953, the Clinical Center has served more than 500,000 patients who have volunteered to participate in clinical research studies. This partnership between patients and scientists

has led to countless medical breakthroughs, including the first time a cancerous solid tumor was cured with chemotherapy and the development of the first antiretroviral drug to treat HIV and AIDS.

To commemorate the 70th anniversary of the Clinical Center, former NIH Director **Francis Collins** delivered a Grand Rounds lecture in the Lipsett Amphitheater on June 28. Collins divided his talk into two parts, beginning by presenting many of the medical milestones that have occurred at the Clinical Center before describing his hopes for its future directions.

Collins peppered his talk with examples of the Clinical Center’s recent major advances. Noting the emergence of immunotherapy as a field, he recognized the work carried out by **Steven Rosenberg**, the Chief of Surgery at the National Cancer Institute. Rosenberg has pioneered several immunotherapy treatments for cancer patients, including a therapy where tumor-infiltrating lymphocytes, which can recognize and destroy specific tumor cells, are isolated from the patient, grown to large numbers in the lab, and then reinfused into the patient.

Collins also highlighted research done by Senior Investigator **John Tisdale** and Lasker Scholar **Courtney Fitzhugh** at the National Heart, Lung, and Blood Institute. Tisdale and Fitzhugh have explored the use of gene therapy to treat and potentially even cure sickle-cell anemia. In this experimental treatment, a viral vector is used to insert a corrected copy of the sickle-causing gene into bone marrow cells.

Collins mentioned numerous advancements in infectious disease research as well, noting **Nancy Sullivan’s** leadership in the development of a vaccine for Ebola and the teamwork displayed in the Clinical Center to treat a nurse from Texas who



CREDIT: NIH OFFICE OF HISTORY AND STETTIN MUSEUM

A patient and clinician enjoy the sunlight in the original Clinical Center solarium.



CREDIT: NIH OFFICE OF HISTORY AND STETTIN MUSEUM

This photograph shows the Clinical Center patient waiting area in the early years.

had contracted Ebola in 2014.

The Clinical Center has been home to a multitude of advancements in mental health research. Collins spotlighted the ketamine research conducted by **Carlos Zarate**, the chief of the Experimental Therapeutics and Pathophysiology Branch at the National Institute of Mental Health. Zarate's work has demonstrated that ketamine can rapidly reduce symptoms of depression in individuals who have not responded to other treatments.

Then there's the Clinical Center's international recognition for studying rare diseases. Sharing his own lab's experience with researching progeria, a rare form of premature aging, Collins spoke of the importance of natural history studies to investigate the development of a disease over time before moving forward to consider

possible therapeutics. The Undiagnosed Diseases Program, founded in 2008 by **William Gahl**, a senior investigator at the National Human Genome Research Institute, has admitted more than 1,500 patients and has since expanded to become the Undiagnosed Diseases Network, with 12 clinical sites nationwide.

Looking towards the future, Collins presented several areas for progress for the Clinical Center. A common theme was expanding the infrastructure on campus to better support ongoing research, which is already underway with two new cell-processing facilities scheduled to open within the next year and the Roy Blunt Center for Alzheimer's Disease and Related Dementias having opened last September.

Collins was excited by the potential of precision medicine, which involves tailoring



CREDIT: NIH OFFICE OF HISTORY AND STETTEN MUSEUM

The Clinical Center was constructed as a research hospital in which laboratory research and clinical investigations involving patient care were paramount. This photograph shows the Clinical Center entrance lobby in the early years. The Warren Grant Magnuson Clinical Center has grown over the years, adding facilities and centers, and is considered the one of the largest clinical research facilities in the world.

prevention and treatment to the individual patient. The NIH *All of Us* research program has been collecting data from hundreds of thousands of individuals, including their genome sequences and information about their lifestyle and environment, to build a diverse database that future research studies at the Clinical Center can draw upon.

After a whirlwind tour of the Clinical Center's past accomplishments and future endeavors, Collins expressed his deep appreciation for the privilege of being involved with the Clinical Center. He referred to it as a "House of Hope," a place where many patients come to as a best hope for treatment after conventional medical care has not come up with the answers, even though there is no guarantee that an experimental protocol will be effective for them.

"The people that we are most grateful to are the patients who have come here and put their trust in us," Collins said. "They were willing, even if it wasn't going to help them, to know that we were going to learn something that might help the next person."



CREDIT: NIH OFFICE OF HISTORY AND STETTEN MUSEUM

The Clinical Center (Building 10) at NIH was constructed for long-term patients. A reflecting pool was included to urge in-patient use. The nurses accompanied patients and family outside for fresh air and sun. Building 10 was constructed as a research hospital and combines research laboratories with patient care.

Watch Collins' talk at <https://videocast.nih.gov/watch=49881>.

The Magnuson Act's Continuing Legacy

BY VICTORIA TONG, OD

Warren G. Magnuson, a congressman from Washington, was a dedicated advocate for medical research who, among his legislative accomplishments, co-sponsored a bill in 1937 to create the National Cancer Institute (NCI). In appreciation of his years of support, the Clinical Center was renamed the Warren G. Magnuson Clinical Center in 1980.

Magnuson also contributed to the NIH more indirectly. Eighty years ago, he proposed the Chinese Exclusion Repeal Act, also known as the Magnuson Act, which allowed Chinese immigrants to enter the United States for the first time since the Chinese Exclusion Act of 1882, which effectively had banned immigration from China.

Although the Magnuson Act abolished the outright exclusion of Chinese immigrants, it was more of a symbolic act than a complete liberalization of admitting Chinese people into the country. This served as a starting point for gradually easing restrictions on Chinese immigrants. Subsequent legislation nudged open the door further for Chinese scientists to train and do research in the United States and at the NIH.

One such scientist was **Min Chiu Li**, who came to the United States in 1947 and joined the NCI in 1955. Li studied choriocarcinoma, a highly malignant form of cancer that develops in the placenta. By treating patients with a chemotherapy drug called methotrexate, to the point that not only their visible tumors disappeared but also the concentration of hCG in their blood normalized, Li and his colleagues were able to send the cancer into complete remission, marking the first cure of a solid tumor using chemotherapy. For his work, Li won a Lasker Award in 1972.

Another trailblazer at the NIH was **Jacqueline Whang-Peng**. Whang-Peng was born in Jiangsu province, China, earned her medical degree in Taiwan, and joined the NCI in 1960, where she focused on cytogenetics, or the study of chromosomes and their effect on cell behavior.

CONTINUED ON PAGE 21 ►

FEATURE



A Tale of Two Labs: Quality Control of Cellular Membranes

An NIH Homecoming for Ramanujan Hegde

BY ANNELIESE NORRIS, NCI

CREDIT: MRC LABORATORY OF MOLECULAR BIOLOGY



Manu Hegde highlighted the vast diversity of membrane proteins and various past ideas of how those proteins are inserted. Hegde and colleagues use biochemical and structural approaches to reveal the machinery involved in these processes and visualize them “in action” at different steps.

NIH WELCOMED THE RETURN OF A familiar face, Ramanujan (Manu) Hegde, now Group leader at the MRC Laboratory of Molecular Biology (Cambridge, United Kingdom), who delivered a Wednesday Afternoon Lecture Series (WALS) talk titled “How Cells Make Membrane Proteins” on June 14, 2023.

There was no shortfall of accolades. “Instant classics, the kind of work that students will read about in textbooks,” is how NICHD Section Chief of Microbial Pathogenesis **Matthias Machner** described Hegde’s tome of work in his welcoming remarks. “[Hegde] has shaped the field of protein biochemistry and cell biology not only through his marvelous research but also by mentoring over 55 trainees.”

Hegde earned his bachelor’s degree at the University of Chicago (Illinois), followed by an M.D. and Ph.D. at the University of California at San Francisco. He went on to join a lab as part of the National Cancer Institute’s (NCI’s) scholars program and

later, in 2002, as a Principal Investigator at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) in the Cell Biology and Metabolism Program.

Today, Hegde is a leader in the field of protein biogenesis and quality control and has won numerous awards and honors, including election to the European Molecular Biology Organization in 2013 and the Royal Society in 2016.

An old friend

Though no stranger to the NIH community, Hegde hadn’t set foot on campus since he left for the UK in 2011. To him, this WALS lecture represented more than just a talk. He was able to meet former friends and colleagues, share stories, and reminisce about his time working on campus. He reconnected with **Harris Bernstein** (National Institute of Diabetes and Digestive and Kidney Diseases), **Roberto Weigert** (NCI), **Juan Bonifacino** (NICHD) and others whom he knew from the protein trafficking scientific interest group. “It was very nostalgic to come back,” said Hegde. “Bethesda has changed a huge amount, [and some] NIH buildings no longer exist, so former colleagues are now in new places.”

Hegde spoke fondly of his time at NIH, highlighting how he worked with numerous people, including Irwin “Win” Arias, Scientist Emeritus at NICHD and the brainchild behind the Demystifying Medicine lecture series, which seeks to bridge the gap between clinical work and basic science, in which Hegde had lectured during his time at NICHD.

As a PI at NIH, Hegde expanded his interests in membrane protein insertion

and biogenesis—topics that piqued his interest in graduate school but which he would not begin serious work on until after five years at NIH. Hegde’s other research passion is understanding protein quality control, a crucially important process to eliminate improperly made proteins. Both those interests were heavily influenced by work he did at NIH—research which he continues to this day.

A unifying model for membrane-protein insertion

Membrane-embedded proteins are required hardware for molecules to translocate, or move across, cellular membranes. In his WALS talk, Hegde highlighted the vast diversity of membrane proteins and various past ideas of how those proteins are inserted. Such embedded proteins contain hydrophobic segments that must be inserted into the membrane as they are synthesized. Hegde and colleagues used biochemical and structural approaches to reveal the machinery involved in these processes and visualize

them “in action” at different steps (*Nature* 584:630–634, 2020; *Nature* 611:161–166, 2022; *Nature* 611:167–172, 2022). This work allowed Hegde to propose a unifying model for how a diverse range of membrane proteins are inserted across all organisms.

Hegde has an “instinct for important biological questions,” said Machner. Indeed, 25 years ago Hegde co-wrote a review (*Cell* 91:575–582, 1997) that speculated how the machinery for membrane protein insertion might work—concepts for which he has since provided experimental evidence.

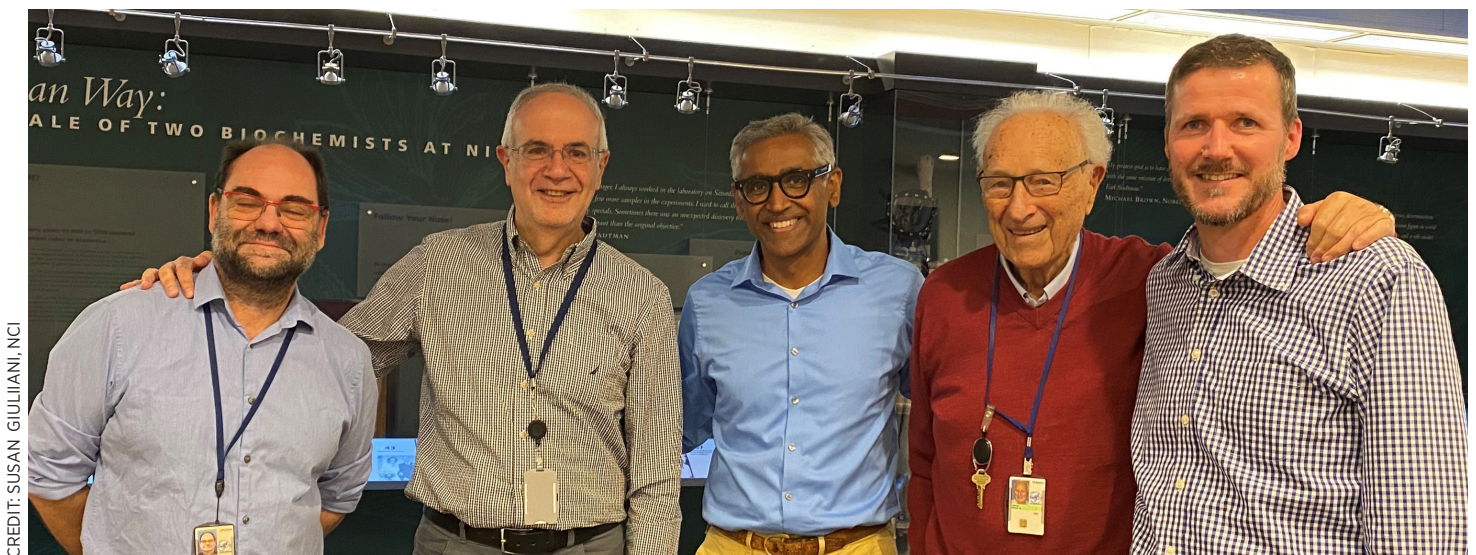
Understanding how cells make membrane proteins is fundamentally important to human health and disease, explained Hegde. “Membrane proteins are how cells engage and communicate with their surroundings. Most drugs target membrane proteins, so understanding exactly how they are made, delivered to the correct place, and turned over might provide new opportunities for manipulating their abundance or function for therapeutic benefit,” he said.

A new adventure

Hegde noted that the MRC Laboratory of Molecular Biology has provided a welcoming environment, and he enjoys the closeness of that community. “There are only about 50 research groups, and at lunch everyone goes to the canteen and interacts with one another,” said Hegde. “It’s easy to discuss ideas, papers, or a recent seminar. Cambridge is a charming town, and moving to a new country has been an adventure.” The amicable Hegde is even enjoying the fickle British climate. “It’s perfect weather,” he said with a smile.

To watch a videocast of Hegde’s lecture, go to <https://videocast.nih.gov/watch=46093>. ●

Anneliese Norris, a postdoctoral fellow at the National Cancer Institute, is working on HIV dynamics and replication. In her spare time, she enjoys reading and building with LEGO construction toys.



CREDIT: SUSAN GIULIANI, NCI

At his WALS lecture, Hegde reconnected with old colleagues and friends. Shown left to right: **Roberto Weigert**, Juan Bonifacino, Manu Hegde, Irwin Arias, Matthias Machner.



Intramural Research Briefs



CREDIT: NHGRI

NHGRI, CC: Mitochondria convert food and oxygen into energy. Genomic variants in more than 350 genes have been linked to mitochondrial disorders.

NHGRI, CC: WEAKER IMMUNE RESPONSE TO VIRAL INFECTIONS IN CHILDREN WITH MITOCHONDRIAL DISORDERS

Children with mitochondrial disorders (MtD) may have difficulty fending off and recovering from viral infections, according to a study led by NHGRI scientists. The study was one of the first to investigate how B cells, which produce antibodies in response to viral infections, are affected in human MtD.

The investigators performed single-cell RNA sequencing in peripheral blood cells of children with MtD to analyze gene activity and found biomarkers of cellular stress directly related to mitochondrial dysfunction. “We think that B cells in these patients undergo cellular stress when they turn into plasma cells and produce antibodies,” said senior author **Peter McGuire**. “The B cells are too fragile due to their limited energy, so they are unable to survive the stressful conditions.”

The authors noted that their findings have broad implications not only for understanding the role of mitochondrial dysfunction in the human immune response, but also for finding targeted treatments for children with MtD, who have weaker immune responses and are at risk for life-threatening infections. (NIH authors: E.M. Gordon-Lipkin, P. Banerjee, J.L.M. Franco, T. Tarasenko, S. Kruk, E. Thompson, D.E. Gildea,

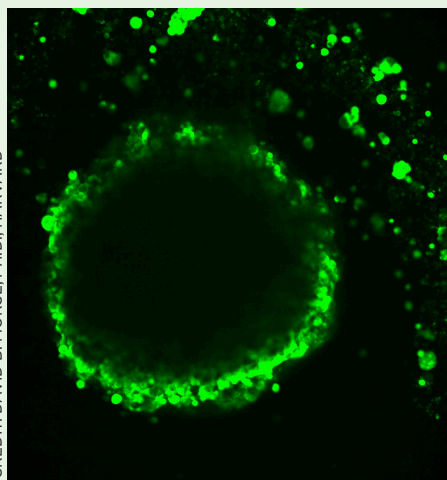
S. Zhang, T.G. Wolfsberg, NISC Comparative Sequencing Program, W.A. Fiegel, and P.J. McGuire, *Front Immunol* 14:1142634, 2023; DOI:10.3389/fimmu.2023.1142634)

[BY: SEPPIDEH SAMI, CC]

NCATS, NCI, CC: TUMOR CELL'S LOCATION AND ENVIRONMENT AFFECT ITS IDENTITY

A cell's location and environment within a cancerous tumor can strongly influence which genes are active, according to a new study co-led by NCATS scientists. To explore that concept, **Craig Thomas**, Leader of NCATS' Chemistry Technology group, and his colleagues developed a new system that pairs a fluorescent dye with the ability to unravel an individual tumor cell's genetic activity. “Two cells can be genetically identical but have different cellular identities, meaning different genes are turned on because of their location and environment,” said Thomas.

Some of their findings confirmed old suspicions. Others provided new insights: With the help of 3D models of ovarian cancer tumors, the researchers found that gene activity in cells at or near a tumor's surface differed from that of cells closer to the tumor center. They also found evidence of metastasis activity on the surface and of cancer cells finding ways to work against the immune system.



CREDIT: DAVID B. MORSE, PH.D., HARVARD

NCATS, NCI, CC: Image shows differences in cell layers' fluorescent-dye uptake in a model of high-grade serous ovarian cancer.

By better understanding how tumors are structured, clinicians could potentially identify treatment strategies focused on specific areas in tumors, which could lead to improved therapies for cancers, neurological disorders, and other site-dependent diseases. (NIH authors: D.B. Morse, A.M. Michalowski, M. Ceribelli, D. Riley, T. Davies-Hill, T. Voss, S. Pittaluga, J. Liu, and C.J. Thomas, *Cell Syst* 14:464-481.E7, 2023; DOI:10.1016/j.cels.2023.05.003)

[BY STEVEN BENOWITZ]

NHGRI: PRIMITIVE SEA CREATURE PROVIDES CLUES TO AGING AND HEALING

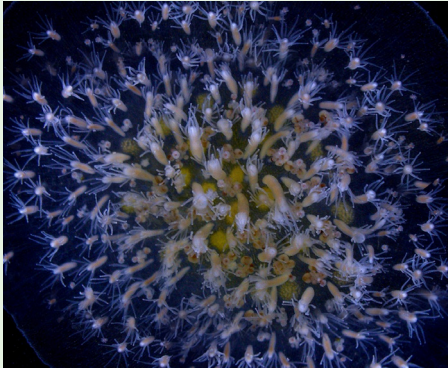
NHGRI scientists and their colleagues demonstrated how a tiny sea creature, *Hydractinia symbiolongicarpus*, is capable of entirely regenerating itself by reverting differentiated cells back into stem cells when the organism is wounded. This finding provides insight into cellular signaling pathways that might similarly promote healing in more complex animals, including humans.

Hydractinia are made up of a long trunk with a head and mouth at its tip. When the head is separated from the trunk, it is able to regrow a brand-new body with the help of highly versatile cells called i-cells. In this new study, the investigators found that although stem cells are absent in the heads of uninjured animals, the cells reappeared in the separated head tissue and were able to drive regeneration.

The research team used RNA sequencing to identify several genes activated in head tissue adjacent to the injury—genes typically associated in other organisms with an aging-related process called senescence. When the scientists deleted those genes, the modified animals were unable to produce the stem cells necessary for tissue regeneration and died when their heads were separated from their trunks. “We still don't understand how senescent cells trigger regeneration or how widespread this process is in the animal kingdom,” said study author **Andy Baxevanis**.



CREDIT: MADDISON HARMAN,
WHITNEY MARINE LABS



NHGRI: *Hydractinia symbiolongicarpus*, a small, tube-shaped animal that lives on the shells of hermit crabs, is capable of entirely regenerating itself by reverting differentiated cells back into stem cells when the organism is wounded.

“Fortunately, by studying some of our most distant animal relatives, we can start to unravel some of the secrets of regeneration and aging.” (NIH author: A.D. Baxeavanis, *Cell Rep* 42:112687, 2023; DOI: 10.1016/j.celrep.2023.112687)

[BY CODY R.K. CONRAD, NIAID]

NIA, NINDS: PROTEINS IN PLASMA PORTEND RISK OF DEMENTIA

Scientists from NIA and NINDS and their colleagues have discovered that several proteins present in plasma at middle age are linked to developing dementia later in life.

In order to better understand the association of proteins with such a protracted disease, plasma samples from 10,981 middle-aged participants were analyzed over a 25-year period. Analysis of 4,877 proteins revealed that 32 were associated with increased dementia risk, after adjustment to rule out other contributing factors.

The investigators discovered that near-term dementias were linked to distinct biological pathways compared with long-term dementias. One protein, GDF15, was found to have a particularly strong association with all stages of the disease. And analysis of an immune pathway revealed that the protein SERPINA3 may contribute to the development of Alzheimer’s disease (AD).

Finally, a machine-learning analysis demonstrated that predicting future dementias

using the identified dementia-associated plasma proteins was significantly improved when assessed with other contributing factors. This research highlights the need for additional study into AD and dementia pathways outside of the well-known amyloid, tau, and neurodegenerative mechanisms. (NIH authors: K. Walker, M. Duggan, Z. Peng, and R. Gottesman, *Sci Transl Med* 2023; DOI:10.1126/scitranslmed.adf5681)

[BY CODY R.K. CONRAD, NIAID]

NIEHS: WOMEN TREATED FOR BREAST CANCER MAY AGE FASTER THAN CANCER-FREE WOMEN

Past studies suggested that women who overcome breast cancer are at elevated risk for age-related disease. But biological aging, or the general health of your body’s cells, can be difficult to define. In a recent study, NIEHS investigators explored this concept further by tracking naturally occurring chemical modifications made to DNA, called DNA methylation. Small variations in methylation are linked to an increased incidence of age-related illness and mortality risk.

The scientists examined methylation changes by drawing blood from 417 women over eight years. Half of the women developed and were treated for breast cancer during that time, and the other half remained cancer-free. Blood samples were examined using three different “methylation clocks” to determine the effect of breast cancer on biological aging.

The results showed that women treated for breast cancer had accelerated biological ages across all three methylation clocks compared with their cancer-free counterparts. When sorted by treatment type, the researchers found that surgery had little effect, but that radiation therapy was strongly associated with faster biological aging, even after controlling for other factors such as race and tumor type.

While these findings shed some light on how breast cancer can increase risk of age-related disease, the researchers noted that

modern radiation therapy remains effective and that patients should discuss all possible treatment options with their doctors. (NIH authors: J.K. Kresovich, K.M. O’Brien, Z. Xu, C.R. Weinberg, D.P. Sandler, and J.A. Taylor, *J Natl Cancer Inst* 2023; DOI:10.1093/jnci/djad117)

[BY JONATHAN CHU, NIAID]

NCI: CELLS PREPARING FOR MITOSIS CAN REVERSE THEIR DECISION TO DIVIDE

In cancer, the cell cycle becomes dysregulated when cancer cells enter the cycle and undergo the process of mitosis at a greater rate than normal cells. NCI researchers led by Stadtdman Investigator **Steven Cappell** recently published new research in *Nature* that found cells preparing to divide can reverse that decision, calling into question long-held beliefs about cell division.

When cells receive growth-promoting signals, called mitogens, they enter the cell cycle and prepare to divide. Scientists have traditionally thought that beyond a certain point known as the restriction point, a positive feedback loop between mitogen signaling and proteins that govern cell division led to an irreversible progression of the cycle toward mitosis. However, Cappell’s group showed that upon loss of mitogen signaling, some cells could return to a resting state even after reaching the restriction point.

The researchers found that cell-cycle regulators CDK4 and CDK6 promoted synthesis of the protein cyclin A2, which in turn induced cell division. In experiments with different kinds of cells, repressing that process at any time before mitosis allowed cells to exit the cell cycle and halt mitosis.

These findings point toward a new model that is more dynamic and reversible and may inform future cancer therapies that target cell division. (NIH authors: J.A. Cornwell, A. Crncec, M.M Afifi, K. Tang, R. Amin, and S.D. Cappell, *Nature* 619:363–370, 2023)

[BY STEPHEN ANDREWS, NCI]



Recently Tenured



SHANSHAN ZHAO, NIEHS



JINWEI ZHANG, NIDDK



KATHERINE L. GRANTZ, NICHD

SHANSHAN ZHAO, PH.D., NIEHS

Senior Investigator, Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences (NIEHS)

Education: Peking University, Beijing, China (B.S. in applied mathematics); University of Iowa, Iowa City, Iowa (M.S. in biostatistics); University of Washington, Seattle (Ph.D. in biostatistics)

Training: Postdoctoral Research Fellow at the Fred Hutchinson Cancer Research Center, Seattle (2012-2014)

Came to NIH: In 2015 as a Tenure-Track Investigator, NIEHS

Outside interests: Gardening; painting; spending time with family

Website: <https://irp.nih.gov/pi/shanshan-zhao>

Research interests: My main research interest is to develop novel statistical methods to discover how humans' interaction with the physical and social environments influence their health and well-being. By developing and applying powerful statistical tools, my group aims to elucidate the etiology of various health outcomes through assessing risk factors and further building robust risk prediction models.

Toward achieving this overarching goal, we use a dynamic approach by integrating statistical methodological developments and collaborative population-based studies through two aspects. First, we develop

general statistical methods for disease risk assessment, with a focus on methods for time-to-event outcomes. Many biological studies follow time-to-occurrences for multiple events, such as the onset of diseases or death, which motivated us to develop joint models for multivariate time-to-event outcomes (*Lifetime Data Anal* 24:3-27, 2018; *J Am Stat Assoc* 116:1330-1345, 2021). These methods enable researchers to take a lifetime history of related health outcomes into account for accurate prediction of future diseases.

Second, we develop statistical methods for cancer and environmental epidemiological studies, motivated by our collaborations with other NIEHS researchers. An area of special interest is developing statistical methods for various issues in environmental mixtures analysis to account for the synergy and interaction between components of high dimensionality and high correlation (*J Expo Sci Environ Epidemiol* 30:149-159, 2020).

JINWEI ZHANG, PH.D., NIDDK

Senior Investigator, Laboratory of Molecular Biology (LMB), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Education: Peking University, Beijing, China (B.S. in biochemistry and molecular biology); University of Wisconsin at Madison, Madison, Wisconsin (Ph.D. in biomolecular chemistry)

Training: Postdoctoral training in molecular biophysics, Howard Hughes Medical Institute, Chevy Chase, Maryland; the Fred Hutchinson Cancer Center, Seattle (2009-2011); and the National Heart, Lung, and Blood Institute (2011-2015)

Before coming to NIH: Research Associate, Howard Hughes Medical Institute, and Fred Hutchinson Cancer Center

Came to NIH: In 2011 as a Research Fellow at the National Heart, Lung, and Blood Institute, then in 2015 as a Stadtman Tenure-Track Investigator in the LMB, NIDDK

Outside interests: Traveling with family; table tennis

Website: <https://www-mslmb.niddk.nih.gov/zhang/zhanglab.html>

Research interests: My lab focuses on understanding the structure, recognition, and mechanisms of host and viral noncoding RNAs (ncRNAs). The COVID-19 pandemic occurred against the backdrop of a rapid expansion of our knowledge of ncRNAs—the “dark matter” of our genome. The extraordinary efficacy of the mRNA vaccines was in part enabled by decades of basic research into RNA structure, stability, modification, and translation, attesting to the critical importance of fundamental RNA research to public health.

However, wider application of ncRNAs is still severely limited by our rudimentary, largely descriptive understanding of these versatile molecules. Despite clear evidence of the importance of RNA structure to function, there is little 3D structural information available for most complex ncRNAs, which precludes our understanding of their mechanisms of action. My lab aims to bridge this critical gap in knowledge by elucidating the fundamental principles of RNA structure, dynamics, and interaction, using multidisciplinary approaches that combine atomic-resolution structural analyses with advanced biochemical, biophysical, and single-molecule methods.

Our recent work has uncovered how two ncRNA archetypes—the tRNA and



double-stranded RNAs (dsRNAs)—mediate stress responses, viral replication, and antiviral immunity. For tRNAs, we first visualized and elucidated how widespread bacterial ncRNAs termed T-box riboswitches recognize the 3D structure and aminoacylation state of their tRNA partners using complex, form-fitting RNA-RNA interactions, to sense and respond to amino acid starvation (*Nat Struct Mol Biol* **26**:1094–1105, 2019; *Nat Struct Mol Biol* **26**:1114–1122, 2019). We uncovered and elucidated a novel form of host tRNA parasitism by retroviruses including HIV-1, where the major viral protein Gag directly and specifically binds host tRNAs to slow down Gag migration toward the plasma membrane, in order to optimize viral replication (*Cell Host Microbe* **29**:1421-1436, 2021).

For dsRNAs, we revealed how adenovirus virus-associated RNAs function as decoys of dsRNAs to disable human antiviral protein PKR (*Nat Commun* **10**:2871, 2019), and how the widely used S9.6 monoclonal antibody picks out DNA-RNA hybrids in R-loops from the abundant dsRNAs (*Nat Commun* **13**:1641, 2022).

These research findings and our future ones will open new RNA-based avenues to treat bacterial and viral infections and autoimmune and inflammatory diseases as well as to spur novel biotechnological applications including RNA sensors, switches, and catalysts.

KATHERINE L. GRANTZ, M.D., M.S., NICHD

Senior Investigator, Epidemiology Branch, Division of Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Education: Duke University, Durham, North Carolina (B.S. in biology); Virginia Commonwealth University, Richmond, Virginia (M.D.); NIH Clinical Research Training Program at the University of Pittsburgh, Pittsburgh (M.S. in Clinical Research)

Training: Obstetrics and Gynecology residency, University of North Carolina,

Chapel Hill (2000-2004); Maternal-Fetal Medicine fellowship, Magee-Womens Hospital, University of Pittsburgh (2006-2009); IRTA postdoctoral fellowship, Epidemiology Branch, Division of Population Health Research, NICHD (2009-2011)

Before coming to NIH: Maternal-Fetal Fellow at Magee-Womens Hospital, University of Pittsburgh

Came to NIH: In 2009 as an IRTA postdoctoral fellow at NICHD, then as a Research Fellow in 2011

Outside interests: Running; going on nature walks with my husband and three daughters; attending our children's sports games and dance recitals; traveling; reading

Website: <https://irp.nih.gov/pi/katherine-grantz>

Research interests: I am an obstetrician and maternal-fetal medicine specialist who leads a research program on clinical management of pregnancy complications, including aberrant fetal growth, when to deliver a high-risk pregnancy, and labor and delivery management. Findings from my research have informed over 28 national and international clinical guidelines with evidence-based practice recommendations. An expert in the field of fetal growth, I am responsible along with a multidisciplinary team for an effort that generated fetal-growth percentile charts in a diverse U.S. population for clinical practice (*Am J Obstet Gynecol* **213**:449.e1-449.e41, 2015; *Am J Obstet Gynecol* **226**:576-587, 2022). I led development of a first-ever fetal-growth velocity calculator (*Am J Obstet Gynecol* **219**:285.e1-285.e36, 2018; *Am J Obstet Gynecol* **227**:916-922, 2022) for clinical use as well as development of twin fetal-growth percentile charts (*Am J Obstet Gynecol* **215**:221.e1-221.e16, 2016).

My work addresses the clinical challenge of differentiating constitutionally small-for-gestational-age from fetal-growth restriction, which is associated with increased morbidity and mortality. An emerging area uses 3D ultrasound

that provides more detail than the standard 2D ultrasound in determining fetal fat and lean tissue volumes. My group is among the first to have accumulated a large collection of fetal 3D volumes from a racially and ethnically diverse pregnancy cohort with repeat ultrasounds spanning the length of gestation in the Fetal 3D Study (*Am J Epidemiol*, in press). Detection of fetal volume and body-composition changes in fetuses that are growth restricted or growing excessively has potential to inform clinical management, such as increased antenatal monitoring to prevent stillbirth or changes in maternal nutrition to prevent excess fetal fat accumulation.

My team is also addressing labor and delivery management to prevent medically unnecessary cesarean section deliveries, an issue declared as a national priority because cesarean section delivery is a risk factor for severe maternal morbidity and mortality (*Obstet Gynecol* **122**:33-40, 2013; *Obstet Gynecol* **124**:57-67, 2014; *Obstet Gynecol* **131**:345-353, 2018). More recently, I lead a multicenter randomized clinical trial in the Study of Pregnancy And Neonatal Health (SPAN) to determine the optimal timing of delivery for uncontrolled gestational-diabetes-complicated pregnancies to prevent neonatal complications. •

The Magnuson Act's Continuing Legacy
CONTINUED FROM PAGE 16

The NIH has since benefited from the descendants of Chinese immigrants, such as **Maryland Pao**, the clinical director of the National Institute of Mental Health, whose parents came to the United States from China in the mid-1950s. In this way, the legacy of the Magnuson Act lives on through the generations of Chinese immigrants and their children who have continued to make significant contributions to the NIH community.

Four New Clinical Directors at the Helm

ADAPTED FROM INSTITUTE ANNOUNCEMENTS

AMONG THE 23 OF THE 27 NIH institutes and centers with intramural programs, 20 have a clinical research program, each led by a clinical director. This past year saw the addition of four new appointments, and five others are expected in the coming year, a reflection of a next generation of leadership sweeping across the NIH. We feature the four most recently appointed here.

James L. Gulley, M.D., Ph.D.

NCI

James Gulley was appointed NCI Clinical Director in July 2023. He is an internationally recognized expert in cancer immunotherapy with a strong interest in prostate cancer. He received his medical degree and a Ph.D. in chemistry from Loma Linda University, Loma Linda, California, then completed his residency in internal medicine at Emory University in Atlanta. He joined the NCI in 1998 as a medical oncology fellow. He became senior clinical staff in 2001, and in 2013 he was appointed chief of the CCR Genitourinary Malignancies Branch and Director of the Medical Oncology Service.

Gulley has been an investigator on more than 200 clinical trials and has published more than 350 papers. He has been involved in the clinical development of multiple cancer vaccines, including the FDA approval of treatments for Merkel cell carcinoma, bladder cancer, and renal cancer. And he has received multiple awards including the 2011 Presidential Early Career Award for Scientists and Engineers.



In his new role within the NCI, Gulley will oversee the day-to-day operations of more than 350 active clinical trials as well as all regulatory aspects of the clinical program, such as protocol approval and regulatory compliance. He will also continue his role as Co-director of the CCR Center for Immuno-Oncology and as a senior investigator focusing on developing innovative, investigator-initiated clinical trials using immunotherapy.

NCI Director **Monica Bertagnolli** noted that Gulley's appointment "comes at a meaningful time in NCI's intramural research program, as we are working intently to streamline our regulatory approval processes to accelerate CCR clinical trials and to expand our patient base to ensure access for all patient groups to our cutting-edge trials. With Dr. Gulley's expertise and vision, we will continue to provide innovative and personalized care to the many patients we are privileged to care for at the NCI Clinical Center and drive research advances to benefit people with cancer everywhere."

Lorenzo Leggio, M.D., Ph.D.

NIDA

Lorenzo Leggio was selected and appointed NIDA Clinical Director in May 2023. He is recognized nationally and internationally in the addiction field for his broad clinical-practice and clinical-research background. The thrust of his clinical work has been the treatment of alcohol- and substance-use disorders and on the medical consequences of alcohol-use



disorder, notably alcohol-associated liver and cardiovascular diseases. He has pioneered work on the role of the microbiome-gut-liver-brain axis, on the role of neuroendocrine pathways in addiction, and on medication development via human laboratory studies and clinical trials as well as translational and reverse-translational experimental medicine approaches in animal models.

Leggio was recruited to the NIH in 2012 as a tenure-track clinical investigator (joint NIAAA/NIDA), where he is also on the medical staff as a senior attending physician. He was promoted to senior investigator in 2018 and in this capacity, he continues to hold a joint NIDA/NIAAA faculty appointment. At NIDA, Leggio was the founder and chief of the Translational Addiction Medicine Branch and also serves as the NIDA deputy scientific director.

Leggio received his M.D. and Ph.D. from the Catholic University of Rome and Agostino Gemelli University Hospital (Rome), where he also completed his residency and board in internal medicine. He was a postdoctoral research associate in Psychiatry and Human Behavior at Brown University (Providence, R.I.), where he joined the core faculty as Assistant Professor and Principal Investigator in 2010.

"Dr. Leggio brings to the role superb research, leadership, organizational, managerial, and mentoring skills along with the requisite scientific vision and standing within the field to help the NIDA intramural research program carry out its mission," said NIDA Director **Nora Volkow**. "Dr. Leggio has already made significant contributions to NIDA, and I look forward to seeing what more he will do in the Clinical Director role."

Joshua M. Levy, M.D., M.P.H.

NIDCD

Joshua Levy was appointed NIDCD Clinical Director in April 2023. He was previously an associate professor of otolaryngology and associate vice-chair of research at Emory University School of Medicine (Atlanta), Department of Otolaryngology-Head and Neck Surgery.



At Emory, Levy led multidisciplinary research teams, treated patients, and conducted basic- and clinical-research studies. His work focused on improving the diagnosis and treatment of aspirin-exacerbated respiratory disease (AERD), a chronic condition that causes almost 100% of patients to lose their sense of taste and smell. His research includes studies of biomarkers to diagnose and possibly treat AERD by altering the pathways that lead to debilitating symptoms. He also worked as the Clinical Studies Director for the NIH COVID-19 Rapid Acceleration of Diagnostics (RADx) Point-of-Care Technologies Research Network to verify and validate COVID-19 tests.

Levy will oversee NIDCD's clinical and translational research program aimed at developing novel diagnostic and therapeutic strategies for disorders affecting hearing, balance, taste, smell, voice, speech, and language. Under his leadership, the program will provide clinical training opportunities for future clinician-scientists. He also will head NIDCD's new Sinonasal and Olfaction Program, in which a multispecialty team will explore basic

science discoveries that have the potential to advance treatments for patients.

Originally from Maryland, Levy received a bachelor's degree from Cornell University (Ithaca, New York). He earned a medical degree at Tulane University School of Medicine (New Orleans) and completed his residency in otolaryngology-head and neck surgery at Tulane University Hospital (New Orleans) in 2015. His fellowship training in rhinology, sinus, and skull base surgery was performed at Oregon Health & Science University in Portland, Oregon. Levy holds a master's degree in public health from the Tulane University School of Public Health and Tropical Medicine (New Orleans) and most recently, he earned a master's degree in clinical research at Emory University's James T. Laney School of Graduate Studies.

"I am so pleased to welcome Dr. Levy to lead innovative clinical and basic research in NIDCD's robust intramural clinical program," said NIDCD Director **Debara Tucci**. "As a recognized clinician-scientist and board-certified otolaryngologist, he has the vision to integrate multidisciplinary teams to improve treatments for disorders of human communication."

Christopher Koh, M.D. M.H.Sc.

NIDDK

Christopher Koh was appointed NIDDK Clinical Director in December 2022. His research is both clinical and translational and is focused on liver disease. This includes assessing novel therapeutics, improving understanding of



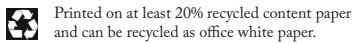
the pathogenesis of rare liver diseases, and characterizing liver disease in unique populations. Koh had been serving as the Acting Clinical Director since October 2020, managing high-quality clinical research and patient care in NIH's Clinical Center.

Koh earned his Doctor of Medicine from Saba University School of Medicine in Saba, Dutch Caribbean, and holds a Master of Health Science from Duke University School of Medicine, Durham, North Carolina. After completing fellowships in gastroenterology and hepatology at the University of Maryland School of Medicine at Baltimore and NIDDK, Koh became an NIDDK staff clinician in the Liver Diseases Branch in 2013.

Among his many accomplishments, Koh has served in leadership roles in the NIDDK as Director of the Hepatology Fellowship Program and of the Gastroenterology Fellowship Program. He is the recipient of NCI and NIDDK Director's Awards and the NIDDK Nancy Nossal Scientific Mentoring Award; the author of more than 100 articles and book chapters; and a member of several editorial boards for gastrointestinal and hepatology journals. In addition to his Clinical Director duties, Koh continues to lead research on liver disease caused by chronic hepatitis D virus infection as a Senior Research Physician in NIDDK's Liver Diseases Branch.

"I am grateful to Dr. Koh for providing a seamless transition while diligently serving as acting clinical director these past two years," said NIDDK Director **Griffin Rodgers**. "I highly respect his expert frontline clinical skills, outstanding management, and impressive policy acumen and look forward to continuing to work with him in this capacity." ●

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CATALYTIC REACTIONS?

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

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

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PHOTOGRAPHIC MOMENT

NIH Zebrafish Research Included in U.S. Postal Service’s “Life Magnified” Stamps

A MICROSCOPY IMAGE created by NIH researchers is part of the “Life Magnified” stamp panel issued on August 10 by the United States Postal Service. The NIH zebrafish (*Danio rerio*) image, which was taken to understand lymphatic vessel development in the brain, merges 350 individual images to reveal a juvenile zebrafish with a fluorescently tagged skull, scales, and lymphatic system.

“Zebrafish are used as a model for typical and atypical human development. It is surprising how much we have



in common with zebrafish,” said **Diana Bianchi**, Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), which generated the

image. “NIH research affects our lives every day. My hope is that this postage stamp will help spur conversations and appreciation for the importance of basic science research.”

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