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First In-Person WALS in Two Years

Anna Huttenlocher Presents Research on Inflammation Resolution and Wound Repair

BY TAMAR JACOBSOHN, NICHD

The Wednesday Afternoon Lecture Series (WALS) has been videocast-only since the start of the COVID-19 pandemic more than two years ago. But on April 6, 2022, NIH welcomed Anna Huttenlocher, a professor of pediatrics and medical microbiology and immunology at the University of Wisconsin at Madison (Madison, Wisconsin), as the first in-person WALS presenter since the last in-person lecture was held on March 4, 2020.

A return to the lecture series' traditional format allowed for in-person discussion, face-to-face interactions with staff, and questions after the event. More than 30 people attended the lecture in Lipsett Amphitheater (the number of people allowed to attend an event is limited for now). About 200 others watched live via NIH VideoCasting.

"[Huttenlocher is] really passionate about fueling, educating, mentoring, and launching the next generation of scientists and physician–scientists," said Deputy Director and Acting Scientific Director of the National Institute of Neurological Disorders and Stroke **Nina Schor** during her introductory remarks.

Huttenlocher's research focuses on understanding the basic molecular mechanisms that regulate cell movements in

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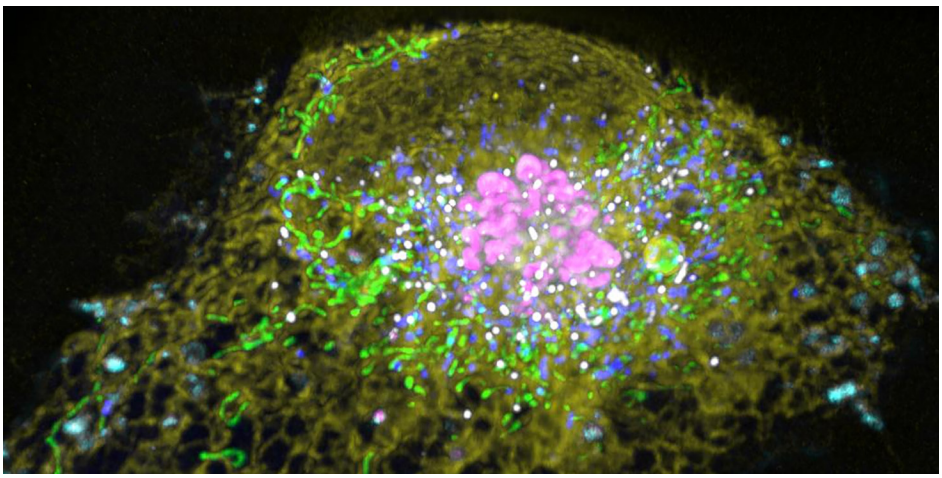
Demystifying Medicine Explores Origin of Life

Evolutionary Biologist and Cell Biologist Share Their Views

BY DEVIKA BOSE, NEI



CREDIT: JENNIFER LIPPINCOTT-SCHWARTZ, HHMI

Jennifer-Lippincott-Schwartz uses a variety of advanced imaging techniques to better understand how cells function in different organs. Shown: Hyperspectral imaging that shows different color signals for six types of membrane-bound organelles in an eukaryotic cell: endoplasmic reticulum, Golgi, lysosome, lipid droplet, peroxisome, and mitochondria.

Four billion years ago, life arose on Earth from nonliving matter. About two billion years later, more complex and multicellular life forms began to emerge. Scientists continually debate how life began, but two of them— evolutionary biologist Nick Lane and cellular biologist **Jennifer Lippincott-Schwartz**—shared their theories with an audience that had gathered (online) for a Demystifying Medicine seminar on "The Origin of Life."

Energy flow shaped evolution: Nick Lane, who is a professor of evolutionary biochemistry at University College London (London), talked about how energy flow has shaped evolution. The focus of his research is on chemiosmosis, the process of moving ions

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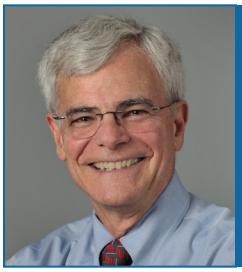


My Time as Deputy Director for Intramural Research: What the Future Holds

BY MICHAEL GOTTESMAN, DDIR

I'm excited that the next Deputy Director for Intramural Research (DDIR) will bring new energy to NIH's intramural research program (IRP). In preparation for the transition to new leadership—including a new NIH Director—I have worked closely with NIH scientific and clinical directors to identify four areas of challenges and opportunities that will need to be addressed.

Increase support for the NIH Clinical Center

Although laboratory science is the foundation of the NIH IRP, the clinical translation of basic research at the NIH Clinical Center (CC) is what makes us the National Institutes of Health. The highly collaborative nature of the clinical and translational research conducted at NIH—first-in-human clinical trials, specialized resources, free clinical services that remove socioeconomic barriers to research and care, a focus on rare and refractory diseases, and a priority to train clinician–scientists—makes NIH both unique and endangered.

Recent challenges aggravated by the COVID-19 pandemic include a declining hospital census at the CC, staffing shortages, and a reduction in research pharmaceutical services. Such challenges highlight the need for new approaches to support the CC, which is now funded through fees that ICs pay to use CC resources for their research; "taxes" levied on all ICs and the Office of the NIH Director to cover maintenance, salaries, and utilities; and a capital investment fund. There is an urgent need to establish a stable funding mechanism to provide appropriate support that is responsive to inflationary changes and surge capacity during biomedical emergencies while fostering initiatives that promote innovative research.

Improve NIH infrastructure: new facilities and maintenance

The NIH IRP comprises facilities in six U.S. states but mostly in Maryland and primarily in Bethesda, where more than 100 buildings are spread across 310 acres. Many of the buildings on the Bethesda campus date back to the 1940s and 1950s; older parts of the CC date back to the 1950s. The National Academies' Committee on Assessing the Capital Needs of the NIH stated in their 2019 report ("Managing the NIH Bethesda Campus Capital Assets for Success in a Highly Competitive Global Biomedical Research Environment") that "The buildings and facilities at the NIH Bethesda campus are in need of significant improvement and upgrading to sustain their current mission and ongoing functionality."

The CC's new Surgical, Radiology, and Laboratory Medicine wing, which is scheduled for completion in 2028, is a first step in the critical upgrading of NIH translational research facilities. For NIH to remain competitive and able to lead health care improvements for the American people, we must upgrade other facilities and build new ones that can house and support biomedical discoveries and innovative technologies. We need a facility that will allow for the translation of laboratory discoveries into preclinical models to prepare for first-in-human clinical research studies in the CC; facilities to enable bioengineering advances that are essential for responding to public health emergencies and for developing a new generation of therapeutics; and "smart" and "green" buildings.

Stimulate trans-NIH collaborations

Given the vast scope of intramural research and the NIH's talent pool and other resources, we can do much more to encourage and support a myriad of exciting collaborative programs and projects. The NIH Office of Intramural Research (OIR) promotes shared resources, convenes the trans-NIH scientific interest groups, develops policies that encourage team science and collaborative activities, and uses the NIH Director's Challenge and Innovation Funds to stimulate and coordinate collaborations among 24 independent, IC-based intramural programs. We have diverse—and advanced—imaging facilities, high-throughput screening resources, and centrally managed recruitment programs for tenure-track investigators that encourage collaboration (Earl Stadtman Investigators, Lasker Clinical Research Scholars, and Distinguished Scholars). My hope is that the new DDIR will not only continue to support collaborative activities, but will also find new ways to expand and enhance them.

Expand diversity, equity, inclusion, and accessibility (DEIA) efforts

We are broadening DEIA in the IRP in many ways. The OIR works closely with the Chief Officer for Scientific Workforce Diversity, the NIH Office of Equity, Diversity, and Inclusion, the Women

Scientists Advisors, the NIH Equity Committee, the NIH UNITE initiative, and several other key NIH entities that are united in DEIA initiatives. OIR programs that have enhanced DEIA efforts the most include the Earl Stadtman Tenure-Track Investigators recruitment program, which has recruited talented individuals from traditionally marginalized groups; the Lasker Clinical Research Scholars Tenure-Track Program, which is 58% women; the Distinguished Scholars Program, launched in 2018 to recruit early and midcareer scientists dedicated to building a more diverse community of scientists at NIH; the Reasonable Accommodation Program, amended in 2020 to reaffirm the NIH's responsibility in regard to accessibility for scientists with disabilities; the NIH Academy on Health Disparities, which offers postbacs the tools to address health-disparity issues; and many programs initiated and supported by the Office of Intramural Training and Education to provide opportunities for a more diverse population of trainees ranging from high-school students to postdoctoral fellows.

In addition, all NIH principal investigators are expected to explain to their Boards of Scientific Counselors and the Central Tenure Committee how they foster and promote a culture of belonging and inclusion within their labs and the NIH research community. I am confident that new leadership will continue to ensure that the IRP incorporates the principles of DEIA in all aspects of its mission of research and training.

Although my replacement has not yet been identified, I am sure that the new DDIR will help the IRP become better than ever. In the meantime, I fully intend to continue working with all of you as we make improvements in the IRP. I trust that even more progress will be made when the baton is passed to NIH's next DDIR. ●

NEW SIG: Consciousness Research

Will we ever be able to quantitatively measure and to understand the nature of consciousness? Research on consciousness has been considered one of the most challenging disciplines in science today. The new NIH Consciousness Research Interest Group will provide a platform for NIH scientists and staff and the extramural community to discuss, discover, collaborate, and stimulate the research of the science of consciousness. Topics can include neuroscience, psychology, and medicine. Main activities include scientific seminars and meetings to assess the current state of science and to stimulate and inform the future research needs.

SAVE THE DATE: NIH inaugural Consciousness Research Seminar Series, Wednesday, August 10, 2022, 11:00 a.m.–12:00 p.m. Eastern Time. It will feature two outstanding scientists and experts in this field: Joseph E. LeDoux (New York University), a recipient of the Karl Spencer Lashley Award and a member of the National Academy of Sciences; and Christof Koch (Allen Institute for Brain Science in Seattle), who was a professor at the California Institute of Technology for 27 years and best known for his work on the neural basis of consciousness. To register, go to https://bit.ly/3MB2zEC.

Co-chairs **Ann Berger** (CC) and **Dan Xi** (NCI); advisor **Eric Wassermann** (NINDS). For more information and instructions for joining the LISTSERV newsletter, go to https://go.usa.gov/xuKrT or contact Ann Berger (aberger@cc.nih.gov) or Dan Xi (xida@mail.nih.gov).

NEW SIG: Metastasis Scientific Interest Group

The goal of the newly formed Metastasis Scientific Interest Group will be to support metastasis-related research at the NIH. The SIG will accomplish this goal by increased communication among research groups through monthly meetings, seminars, and workshops. Activities will initially be held virtually but may transition to a hybrid virtual and in-person format in the future. The Metastasis SIG, through an invited seminar series, will cover current developments in metastasis-related research, increase opportunities for intramural-extramural networking, foster potential collaborative efforts, develop novel clinical interventions, and enhance the ability to recruit highly qualified trainees for NIH laboratories. In addition, the Metastasis SIG plans to host a biannual symposium to permit trainees to present their research to the NIH community and network with invited extramural speakers. Membership in the Metastasis SIG will be open to all interested individuals within the NIH. Acting steering committee members (NCI): **Kent Hunter** (chair), **Glenn Merlino**, **Lalage Wakefield**, **Pat Steeg**, **Li Yang**, **Meera Murgai**, **Rosie Kaplan**, and **Jonathan Hernandez**.

Meetings will be held online for the foreseeable future, on the last Wednesday of each month, 4:00–5:00 p.m. Eastern Time. For more information about the SIG and LISTSERV newsletter, visit https://go.usa.gov/xuKrD or contact Kent Hunter (hunterk@mail.nih.gov). ●

For a full lists of scientific interest groups, go to https://oir.nih.gov/sigs/.

From the Fellows Committee

Training Opportunities in Tech Transfer

BY LARISA GEARHART-SERNA, NCI

Many fellows at the NIH share an interest in developing innovative new drug targets, diagnostics, therapies, and technologies and finding ways to move them from the bench to the bedside. But what does it take to bring innovations into the public realm? The answer often lies in technology transfer.

Technology (tech) transfer is the process by which new inventions and innovations created in an institution's labs are turned into products and commercialized. The NIH has several tech-transfer offices, some of which serve multiple institutes such as the Technology Transfer Center (TTC) in the National Cancer Institute (NCI). If learning about and being a part of advancing today's discoveries into tomorrow's medical care sparks your interest, lean in—NCI's TTC offers three training programs for fellows.

Technology Transfer Ambassadors Program (TTAP)

TTAP is a free training program for NCI and TTC client institute postdoctoral fellows and others seeking to enhance their current research activities with hands-on training in invention development and commercialization. The time commitment is 5–8 hours/week for one year. The experience is valuable toward a variety of nontraditional career paths, including tech transfer.

"Through TTAP, I was able to shadow a technology-transfer manager from the NCI TTC and assist with prosecution of a patent application," said **Huimin Chen**, a member of TTAP's inaugural class. "The hands-on experience showed me what the future job entailed and convinced me that it was something I would enjoy and be good at."

Similarly, **Suna Gulay French** came into TTAP as a fourth-year postdoc in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. "This valuable experience basically led to my current career path," she said. "The program got me further interested in the legal and business side of science."

Chen is now a patent agent at a law firm and attending law school at Georgetown University. Gulay French is a tech-transfer manager with the NCI TTC.

Transition to Industry Fellowship (T2I)

Some of you may feel the urge to explore research and commercialization from industry's perspective. The TTC T2I fellowship aims to support NCI postdocs for two years as they advance an invention in the lab toward clinical trials, regulatory milestones, and subsequent commercialization.

It "allowed me to learn about the industry setting and entrepreneurship as well as to continue to develop my invention," said **Eric Wei**, one of the inaugural T2I fellows. "I was able to learn about the decision-making process that is involved in early drug discovery and development."

Trainees take courses—including from NIH's Foundation for Advanced Education in the Sciences—in technology transfer, business development, entrepreneurship, and grantsmanship. Applicants must be NCI postdocs or research fellows and an inventor on a patent or patent application or working on a project for which a patent or patent application has been filed or is recommended for filing. The time commitment is full-time (80% lab research, 20% commercialization) for two years. "The skills that I gained through the fellowship have been invaluable in helping me to quickly integrate into my current role," said Wei, now a senior scientist in lead discovery at Hengenix Biotech (Milpitas, California).

Advancing Innovations through Mentorship (AIM)

TTC's third program, AIM, uses customer and stakeholder interviews to provide valuable insight on how to translate technologies from the lab into the marketplace. The time commitment is around 8 hours per week for three months.

"These interviews were a great way for us to learn about the…issue that our technology is trying to address and to have discussions about how to best integrate our solution into the current treatment workflow and the ecosystem of the market.," said NCI Staff Scientist **Sabina Kaczanowska**, a former AIM team member. "The knowledge that I gained...is invaluable as I lead efforts to translate our technology into the clinic."

If you are interested in invention development, commercialization, or entrepreneurship, take advantage of these three training opportunities. If not part of the NCI or TTC client ICs, you can still request to participate in TTAP, learn about tech transfer through NIH FAES TECH courses, or reach out to your own tech-transfer office. ●

For more information, go to:

* Technology Transfer Ambassador Program (TTAP): https://techtransfer.cancer.gov/abouttc/ambassadors
* Transition to Industry Fellowship (T2I): https://techtransfer.cancer.gov/transition-industry-fellowship-t2i
* Advancing Innovations through Mentorship (AIM): https://techtransfer.cancer.gov/nci-advancing-innovations-through-mentorship

Larisa Gearhart-Serna is a postdoctoral fellow in the National Cancer Institute's Technology Transfer Center.

Norman Sharpless Steps Down as Director of the National Cancer Institute

FROM NIH NEWS RELEASE

Norman E. "Ned" Sharpless

Norman E. "Ned" Sharpless announced in early April that he has decided to step down from his position as director of the National Cancer Institute (NCI), a position he has held since 2017. He continued as NCI director through April 29, 2022, to allow for a thorough transition. NCI Principal Deputy Director **Douglas R. Lowy** began serving as NCI's acting director effective April 30, 2022.

"Working at the National Cancer Institute has been the highlight of my career, and I am honored to have had the chance to serve my country in this role, alongside so many talented scientists and administrators," Sharpless said. "I leave this job knowing that the talent and passion present at NCI, across the Biden-Harris administration and throughout the cancer-research community will continue to fuel tremendous progress for people with cancer in the years ahead."

Sharpless was sworn in as the 15th director of NCI on October 17, 2017. He also served as acting commissioner for food and drugs at the U.S. Food and Drug Administration (FDA) for seven months in 2019, before returning to the NCI directorship.

"During my time in the federal government, I have been inspired by the ways that researchers, caregivers, advocates, and survivors have broken down silos to collaborate and embrace new ways of working together to solve some of the toughest problems in cancer," Sharpless said.

At NIH, Sharpless has championed health equity; developed important programs in data science, including the Childhood Cancer Data Initiative; and advocated forcefully for policies to ensure continued support for investigator-initiated research in cancer and diversity in the cancer research workforce. Amid the calls for racial justice in the summer of 2020, he led the creation of NCI's Equity and Inclusion Program.

"Dr. Sharpless's ability to manage complex problems has been invaluable to several NIH initiatives, including the agency's response to the COVID-19 pandemic and improving equity and inclusion, and in his role as chair of the NIH Clinical Center Governing Board," said Acting NIH Director **Lawrence A. Tabak**. "Dr. Sharpless's absence will surely be felt by his colleagues at NCI and beyond. But I have the utmost confidence in Doug Lowy's leadership of NCI during this transition period. He is a seasoned and thoughtful leader who will guide the institute with a steady hand until a permanent director is appointed by the president."

Lowy served as NCI's acting director from April 2015 to October 2017, after the resignation of **Harold Varmus**, and again in 2019 while Sharpless served as acting commissioner of FDA. ●

NIH ABBREVIATIONS

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

NCI's Quest for a Successful HIV Vaccine

Clinical Trial on the Way

BY DIPTADIP DATTAROY AND LARISA GEARHART-SERNA, NCI

Since the beginning of the AIDS epidemic, scientists at the National Cancer Institute (NCI) have made several pivotal discoveries in HIV and AIDS and AIDS-associated cancers. The quest for a successful vaccine began soon after HIV was identified in the 1980s. Four decades later, NCI senior investigator **Genoveffa Franchini** is close to finding a vaccine approach to prevent HIV infection and AIDS—a disease that has now killed more than 36 million people worldwide, according to the World Health Organization.

The current standard of care for HIV is lifelong antiretroviral therapy, a prohibitively expensive option for many patients. It suppresses the viral infection but does not eradicate the virus from the body, leaving patients susceptible to relapse of infection. Despite the efforts of many over the past few decades, development of an effective vaccine against HIV has remained elusive.

HIV vaccine research groups focusing on the induction of neutralizing antibodies—a small subset of immunoproteins that bind to a virus particle and block the infection—have had generally disappointing results. Franchini's studies, however, suggest that the effort to induce neutralizing antibodies, using an inflammatory adjuvant and inflammatory vaccine platforms, may have contributed to the ineffectiveness of previous methods, because they induce too many target cells that help HIV thrive.

Instead, her lab has developed a new vaccine technology that takes advantage of another subset of immunoproteins known as non-neutralizing antibodies. These antibodies, as their name suggests, do not neutralize virus particles directly, but flag them for destruction by the body's immune cells. Today, Franchini's research has opened new avenues to prevent HIV and other retrovirus-mediated human diseases.

Working with the NCI Technology Transfer Center (TTC), her team has been collaborating with researchers from Sanofi Pasteur through a Cooperative Research and Development Agreement since the 1990s. The joint effort has led to the development of a genetically engineered poxvirus (also known as a viral vector) to deliver HIV genetic material into cells. This invention led to a phase 3 HIV vaccine trial (RV144 trial) in Thailand with 16,000 volunteers. The trial demonstrated significant, yet limited, protection against HIV infection. For the first time, the vaccine was found to reduce the risk of HIV infection in humans by 31.2%.

To improve vaccine efficacy, Franchini's lab has been collaborating with researchers from New York University (NYU) in New York, and in 2017, reported the invention "V1/V2a gp120 Immunogen to Augment Protective V2 Responses" to NCI TTC. With the help of the TTC team, this invention is currently undergoing patent prosecution in the United States, Australia, Canada, and Europe. In 2019, TTC established an inter-institutional agreement with NYU that allowed NCI to take the lead on development and commercialization efforts for the new vaccine technology.

In collaboration with NYU, Franchini and colleagues used a truncated version of the gp120 immunogen to generate a new vaccine that conferred up to 70% protection against simian immunodeficiency virus infection, which is closely related to HIV, in macaque monkeys (*iScience* **24:** 102047, 2021).

Based on these data, the NCI is now planning to tailor this vaccine against HIV and conduct a phase 1 clinical trial in healthy human volunteers in collaboration with the Walter Reed Army Institute of Infectious Diseases (WRAIR) in Silver Spring, Maryland. Healthy participants will be randomized into two study arms, with no placebo control subjects, as an open-label design. The study sites will be the NCI clinic, in the NIH Clinical Center, and the WRAIR clinical facility. Recently, the TTC executed a material transfer agreement with WRAIR to transfer vials of Sanofi Pasteur's ALVAC-HIV for use as part of the vaccine regimen. If results of the phase 1 study are positive, NCI and WRAIR researchers will plan phase 2 clinical-efficacy studies of the V1-deleted gp120 protein.

This HIV vaccine is a prime example of how scientists can use technology-transfer resources to advance their research and collaborate with both academic and industry partners to further develop promising NIH technologies. The NCI is currently seeking industry partners to launch phase 2 and 3 clinical trials for this vaccine with the hope of bringing it to market. ●

For more details, contact NCI TTC Technology Transfer Managers Wendy Patterson (wendy.patterson@nih.gov) and Ricquita Pollard (ricquita.pollard@nih.gov).

Diptadip Dattaroy, a former postdoctoral fellow in the NCI's TTC, is now a licensing manager for the Technology Commercialization Office at George Washington University. Larisa Gearhart-Serna is a postdoctoral fellow in NCI's TTC.

Unfolding the Mystery of Transformer-like Proteins

Lauren Porter's Research on Fold-switching Proteins

BY NATALIE HAGEN, NCATS

For decades it was thought that when proteins fold, they assume only one stable structure that performs a specific function. For example, the unique structure of the protein hemoglobin allows it to transport oxygen from the lungs to the tissues. This one-sequence-one-fold paradigm is attributed to NIH's **Christian Anfinsen**, who won the 1972 Nobel Prize in Chemistry. His work established a connection between the amino acid sequence that makes up a protein and its three-dimensional shape that dictates the protein's biological function.

Stadtman Tenure-Track Investigator Lauren Porter's research on fold-switching proteins challenges the ubiquity of this one-sequence-one-structure paradigm. "Fold-switching proteins are like Transformers, like Optimus Prime," said Porter, referring to the hero of the science fiction franchise of shapeshifting humanlike robots. "Sometimes he's a robot, and sometimes he turns into a car. He uses both of his structures and both of his functions to fight crime." Similarly, the proteins she studies have multiple stable structures and functions.

During her college days, when Porter majored in physics and math, her dad was diagnosed with stage IV lymphoma. Seeing him go through rounds of chemotherapy influenced Porter to pursue her Ph.D. in biophysics at Johns Hopkins University (Baltimore), where she hoped she could use her knowledge to contribute to better medical treatments.

During her graduate training, she became interested in fold-switching proteins and their association with cancer and other diseases. She pursued that interest through her postdoctoral training and as a research scientist at the Howard Hughes Medical Institute's Janelia Research Campus (Ashburn, Virginia) before joining NIH in 2019 with a primary appointment at the National Library of Medicine (NLM) and a secondary one at the National Heart, Lung, and Blood Institute.

She is developing methods that predict fold switching from genomic sequences. Her team validates those predictions using circular dichroism (a form of spectroscopy that uses polarized light to study the structure of molecules), and characterizes the properties of fold-switching proteins.

There are about 220 million unique protein sequences and scientists have only identified the protein structure for about 58,000 of them. Current methods predict protein structure but are unable to predict fold switching.

Porter looks at these proteins from as many perspectives as possible, such as using high-throughput analysis to evaluate how good their predictions are and when they fail. Her group will soon begin to study protein dynamics by analyzing the intermediate steps of fold switching to get a clearer picture of how these proteins are able to change their three-dimensional structures. Another method to better understand fold switching is mutational analysis, in which multiple sites on the protein are mutated and researchers observe which mutations hinder the protein's ability to switch conformations.

Fold switching seems to be a specific mechanism of regulation that enables cells to respond to their environment very quickly. Having a protein that already exists switch to a different form is a faster and more efficient form of regulation than transcribing and translating a whole new protein. Some of these proteins will exist in both forms at equilibrium, whereas others switch forms in response to specific triggers such as changes in pH or temperature.

CREDIT: CHIA-CHI "CHARLIE" CHANG, OD

Lauren Porter's research focuses on fold-switching proteins, many of which are associated with diseases such as cancer, autoimmune disorders, and bacterial and viral infections.

A number of fold-switching proteins are associated with cancer, autoimmune disorders, and bacterial and viral infections. However, without fully understanding how these mercurial proteins work, it is difficult to make targeted treatments.

"My hope is down the road, therapeutics could be developed that target fold-switching proteins and force them to stay in one conformation or favor one conformation," said Porter. "If by the end of my lifetime there was even one therapeutic based on this, that would be amazing." ●

Read a longer version of this article online at https://irp.nih.gov/catalyst/v30i3/unfolding-the-mystery-of-transformer-like-proteins.

Natalie Hagen is a postbaccalaureate research fellow in the National Center for Advancing Translational Sciences. She is leaving NIH in May 2022, to pursue a Ph.D. in molecular biology at the Perelman School of Medicine at the University of Pennsylvania (Philadelphia).

Intramural Research Briefs

CREDIT: NHGRI

NHGRI: Illustration representing the missing bases (or letters) being inserted into a DNA sequence.

NHGRI, NLM: COMPLETE HUMAN GENOME SEQUENCED

In a milestone scientific achievement, researchers have successfully published a complete human genome sequence. Twenty years after the first draft of a human genome sequence was generated by the Human Genome Project, which was 92% complete, this new version closes the remaining gaps. Named Telomere-to-Telomere CHM13 (T2T-CHM13), the genome adds nearly 200 million base pairs to the approximately three billion pairs that comprise the human genome.

The study was undertaken by the T2T consortium which included leadership from NHGRI, the University of California at Santa Cruz (Santa Cruz, California), and the University of Washington (Seattle, Washington). Playing a critical role in the project were many trainees and early-career researchers from several universities across the country as well as the Howard Hughes Medical Institute (Chevy Chase, Maryland) and the National Institute of Standards and Technology (Gaithersburg, Maryland). Six papers discussing the accomplishment were published in *Science*.

The new T2T-CHM13 will help studies reveal how people's DNA differs, and it will aid the understanding of the genetic contribution to certain diseases.

The discoveries were made possible by two new sequencing methods, which enabled the researchers to generate precise and accurate sequences from a single molecule of DNA.

"Now that we can clearly see everything, we are one step closer to understanding what it all means," said **Adam Phillippy**, whose research group at NHGRI led the finishing effort. (NIH authors: S. Nurk, S. Koren, A. Rhie, M. Rautiainen, C. Jain, A.M. McCartney, N. Hansen, G.G. Bouffard, S.Y. Brooks, A.C. Young, V.V. Maduro, J.C. Mullikin, V.A. Schneider, F. Thibaud-Nissen, B.P. Walenz, C. Xiao, and A. M. Phillippy, *Science* **376:**Issue 6588, 2022)

[BY SATABDI NANDI, NIA]

NHLBI: HYDRATION MAY REDUCE LONG-TERM CARDIAC RISK

Scientists at NHLBI have found that consuming sufficient amounts of fluids not only supports essential body functioning but may also reduce the risk of severe heart problems later in life.

In a retrospective review, investigators analyzed data from over 15,000 individuals ages 45 to 65 who shared information from medical visits over a 25-year period. Those analyzed did not have diabetes, obesity, or heart failure at the beginning of the study. The research team then assessed the hydration status of the participants by looking at blood serum sodium, which increases as the body's fluid levels decrease.

The authors found that serum sodium concentrations above 142 milliequivalents per liter in middle age were associated with increased risks for developing left ventricular hypertrophy and heart failure later in life. While fluid guidelines vary based on the body's needs, the researchers recommended a daily fluid intake of 6 to 8 cups for women and 8 to 12 cups for men. (NIH authors: N.I. Dmitrieva, D. Liu, C.O. Wu, M. Boehm, *Eur Heart J* ehac138, 2022; DOI:10.1093/eurheartj/ehac138)

[BY MICHAEL TABASKO, OD]

NEI: PERIPHERAL VISION ATTENTION NOT DRIVEN BY TINY EYE MOVEMENTS

How does a basketball player keep their eyes on the person guarding them while also noticing where their teammates are positioned? Scientists have been trying to understand how our brains support covert attention, which is the ability to keep track of things in our peripheral vision. Some have speculated that tiny, involuntary, zig-zagging eye movements known as microsaccades might be the cause. A discovery by NEI researchers offers new evidence to reject this theory, with broad implications for the science of attention.

Previous research has found many examples of brain signals that control covert attention, including in the superior colliculus, deep in the brain. But some were skeptical: What if these brain signals were not actually responsible for covert attention and instead were caused by the microsaccades that occur whenever you look steadily at one location?

To find out, NEI scientists tested covert attention by training rhesus macaques (*Macaca mulatta*) to keep their eyes fixated on one part of a screen while also tracking objects that appeared in the periphery. The researchers measured microsaccades with an eye camera while recording activity from the superior colliculus. Crucially, they found that brain activity related to covert attention happened before any eye movements occurred and could even happen without microsaccades at all.

These findings provide insights that could spark future research on attention disorders. (NIH authors: G. Yu, L.N. Katz, and R.J. Krauzlis, *eLife* **11:**e74168, 2022; DOI:10.7554/eLife.74168)

[BY PETER MANZA, NIAAA]

NIDDK: TARGETING FAT-CELL SIGNALING MAY HELP TREAT METABOLIC DISEASE

NIDDK scientists and colleagues have discovered that selectively activating a class of cell surface receptors known as guanine nucleotide binding protein, alpha q polypeptide (Gq)–coupled receptors on fat

cells improved impaired glucose tolerance and insulin resistance in type 2 diabetes (T2D).

Adipocytes (fat cells) play an important role in the development of T2D. Obesity increases the breakdown of fat, a process known as lipolysis, which causes excessive amounts of free fatty acids (FFA) to be released into the blood. Increased plasma FFA concentrations lead to the accumulation of fat in other tissues, which contributes to the impaired glucose tolerance and insulin resistance seen in metabolic disease.

The investigators analyzed mouse and human adipocytes that were altered to enhance Gq signaling. Compared with control cells, the modified cells showed inhibited lipolysis and improved glucose uptake. Improved metabolic effects were mimicked in vivo using mice that were obese and mice that were genetically modified to be insulin resistant. Activating the Gq signaling pathway had beneficial metabolic effects independent of insulin action.

The authors note that these findings may lead to the development of new therapies that selectively activate Gq-coupled receptors to treat T2D and related metabolic disorders. (NIH authors: T. Kimura, S.P. Pydi, L. Wang, D. Haspula, Y. Cui, H. Lu, O. Gavrilova, and J. Wess, *Nat Commun* **13:**Article number 1652, 2022; DOI:10.1038/s41467-022-29231-6)

[BY MICHAEL TABASKO, OD]

NINDS, NICHD, NIA: NEWLY DISCOVERED MOLECULAR PATHWAY IN TWO NEURODEGENERATIVE DISORDERS

Scientists from two independent research teams have discovered a molecular pathway that could be a potential therapeutic target to treat amyotrophic lateral sclerosis (ALS) and some dementias such as frontotemporal dementia (FTD), Alzheimer disease, and certain encephalopathies.

ALS and FTD are two neurodegenerative disorders that have been linked to mislocalized transactive response DNA binding protein 43 (TDP-43), where instead of being primarily located in the nucleus of the cell, where genes are activated, it collects outside the nucleus in multiple neurodegenerative diseases.

The mislocalization of TDP-43 alters the genetic instructions for *UNC13A*, a gene that is important for maintaining the connections between neurons and has been shown to be a risk factor for both ALS and FTD.

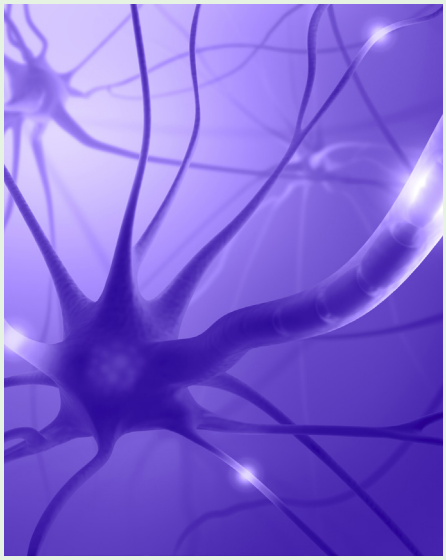
A team of NIH researchers and their colleagues used human stem cells and genetic tools to create neurons that made much less TDP-43 protein than normal. This resulted in the appearance of abnormal sequences of *UNC13A* RNA transcripts, in turn reducing the concentration of UNC13A protein and directly linking a well-established risk factor for ALS and FTD with the loss of TDP-43.

At the same time, a research team at Stanford University (Stanford, California) and at the Mayo Clinic (Jacksonville, Florida) found the same effects caused by a loss of TDP-43 on UNC13A (*Nature* **603:**124–130, 2022). Both studies suggest that developing means to increase the concentration of UNC13A may be effective in preventing the death or dysfunction of neurons. (NIH authors: S.E. Hill, Y.A. Qi, S. Seddighi, J.F. Reyes, S.L. Coon, D. Ramos, and M.E. Ward; New York Genome Center ALS Consortium includes NIH members A. Nath, and S. Muljo, *Nature* **603:**131–137, 2022)

[BY MICHAEL TABASKO, OD]

NIA: MACHINE LEARNING SUCCESSFULLY IDENTIFIES ALS SUBTYPES

NIA researchers have developed a set of reliable, ground-breaking machine learning (ML) algorithms that successfully identify and predict clinical subgroups of amyotrophic lateral sclerosis (ALS). ALS, also known as Lou Gehrig's disease, is a progressive neurodegenerative disease that affects motor neurons, which control voluntary muscle movement. Early-stage symptoms include muscle weakness or stiffness; late-stage symptoms include loss of the ability to speak, eat, move, and breathe. ALS represents a collection of overlapping syndromes, and while various systems to classify subgroups have been proposed, it is unclear how accurately these systems reflect the ALS population.



CREDIT: NINDS

NINDS, NICHD, NIA: Illustration of a neuron.

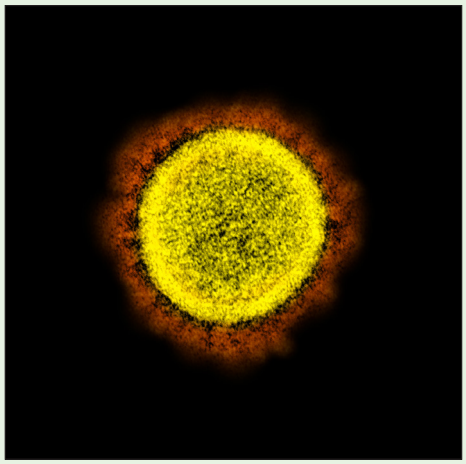
The investigators applied unsupervised, semisupervised, and supervised ML algorithms to data for 42 clinical features collected from a cohort of ALS patients from two regions in Italy. They then replicated their findings on patient data from a separate cohort of individuals with ALS living in another region of Italy.

Of the three algorithms, the semisupervised ML generated the most optimal clustering of ALS patients. These clusters roughly correlated with the six clinical ALS subtypes established by the Chiò classification system (bulbar, respiratory, flail arm, classical, pyramidal, and flail leg). The supervised ML algorithm recognized 11 clinical variables that were important in accurately predicting ALS subtypes. The findings provide insight into the clinical diversity of ALS and could improve clinical care and the design of future clinical trials. (NIH authors: F. Faghri, A. Dadu, M.A. Nalls, and B.J. Traynor, *Lancet Digit Health* 2022; DOI:10.1016/S2589-7500(21)00274-0)

[BY RAGHURAM REDDY, NINDS]

Read longer versions of these briefs at: https://irp.nih.gov/catalyst/v30i3/research-briefs.

COVID-19 Timeline at NIH (March–April 2022)



CREDIT: NIAID

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

March 1: NIH implements a new process for staff to voluntarily report COVID-19 vaccinations received in the community.

March 3: The CDC releases updated guidance on when COVID-19 mitigation measures are to be used based on COVID-19 community levels. Both mask wearing and screening and testing are recommended in workplace and community settings when community levels are high. Mitigation measures for high-risk individuals are recommended during medium community levels, and no mitigation measures are recommended during low community levels. HHS will require employees in federal workspaces to comply with the new guidance beginning Sunday, March 6, 2022.

March 4: NIH Acting Director **Lawrence Tabak** emails staff to report U.S cases of COVID-19 are down 37.7% from the previous week and that the percentage of fully vaccinated Americans is now 76.4%. He reviews the CDC mask wearing and screening and testing guidance updated on March 3 and notes that the guidance for healthcare settings such as NIH has not changed. NIH staff working onsite should continue to wear masks until the NIH Coronavirus Response and Recovery Team assesses the impact of the new guidance on NIH. He announces updated density requirements stating that all NIH facilities across the country may begin operating at 1 person per 35 square feet of space.

March 7: NIH Deputy Director for Management **Alfred Johnson** announces that the authorization to use excused absence for hours in which employees are unable to work to care for dependents will expire on March 26, 2022.

March 9: NIAID begins a clinical trial designed to help understand rare but potentially serious systemic allergic reactions to COVID-19 mRNA vaccines.

March 10: An NIH-funded study finds that schools with mandatory masking during the delta variant surge had approximately 72% fewer cases of in-school transmission of SARS-CoV-2 compared with schools with optional or partial masking policies. (Pre-publication release: *Pediatrics* 2022; DOI:10.1542/peds.2022-056687)

March 11: NIH Acting Director **Lawrence Tabak** emails staff to announce that NIH will implement the March 3 CDC guidance for masking on March 14 and screening testing for unvaccinated persons on March 26, based on COVID-19 community levels at all NIH locations. The safety guidance for health care settings with the potential for patient contact has not changed, where masks will continue to be required. NIH adds a preparation section to the Return to the Physical Workplace intranet page with helpful resources, toolkits, and checklists.

March 18: NIH Acting Director **Lawrence Tabak** emails staff announcing that the 10th Virtual Town Hall will be held on April 5 to address the state of the pandemic and answer employee questions about returning to the physical workplace. He mentions this week's Federal Safer Workforce update for safety protocols for visitors to federal facilities based on COVID-19 community levels: When community level is medium or high in a county where a federal facility is located, visitors to that facility should be asked to provide information about their vaccination status or provide proof of a recent negative COVID-19 test. These requirements do not apply to patients or patient visitors. Tabak reports that masking requirements for on-site meetings will follow CDC guidance, and he continues to encourage staff to voluntarily report their vaccination status to the Division of Occupational Health and Safety.

March 21: The NIH Clinical Center (CC) updates its visitation policy to welcome visitors provided they follow hospital requirements, which include screening for COVID-19 symptoms prior to entering the CC, properly wearing the CC-issued medical-grade mask during visits, and maintaining a six-foot distance from others. Masks are required for both adults and children.

March 27: The authorization to use excused absence for hours in which employees are unable to work to care for dependents expires. NIH employees who are unable to complete their normal work hours as a result of dependent care responsibilities, after exercising supervisor-approved flexibilities, are required to use their own approved annual leave, sick leave, or leave without pay, as appropriate.

March 28: All administrative buildings on the NIH Bethesda campus return to their prepandemic building access hours of operation, and approval to come on site is no longer required.

March 29: The CDC recommends additional mRNA COVID-19 boosters for individuals who are moderately or severely immunocompromised or over 50 years of age and received an initial booster dose at least 4 months ago. Those who received the Johnson & Johnson vaccine at least 4 months ago are now eligible to receive a second booster dose using an mRNA COVID-19 vaccine.

March 31: NIAID sponsors a clinical trial to evaluate whether a second COVID-19 booster shot can broaden immune responses in adults who already have received a primary vaccination series and a first booster shot.

March 31: NIAID Director **Anthony Fauci** and his colleagues publish a new perspective that discusses how achieving classical herd immunity against SARS-CoV-2 is unlikely. However, widespread use of currently available public health interventions to prevent and control COVID-19

will enable resumption of most activities of daily life with minimal disruption. (*J Infect Dis*, jiac109, 2022; DOI:10.1093)

March 31: The SARS-CoV-2 Assessment of Viral Evolution program is described in a paper published in *Nature*. The effort was a scientific consortium established by NIAID with faculty from the Mount Sinai School of Medicine (New York) and was designed to provide a real-time risk assessment of SARS-CoV-2 variants on immune protection. (*Nature* 2022; DOI:10.1038/s41586-022-04690-5)

April 1: In his email to all staff, NIH Acting Director **Lawrence Tabak** reviews the March 29 CDC recommendation for additional mRNA COVID-19 boosters for certain individuals. He highlights a new website launched by the Biden administration called COVID.gov that serves as a portal for information on vaccines, tests, treatments, masks, and the latest on COVID-19. Tabak mentions that NIH is making efforts to resume operations of cafeterias, gyms, and other amenities. He reminds all employees to respect one another's decisions to wear or not to wear a mask when mask wearing is optional based on COVID-19 community levels.

April 4: The symptomatic COVID-19 testing car line moves from the Gateway Vehicle Inspection Station (Building 66A) to a tent located east of the B1 cafeteria at Building 10 and will operate Monday–Thursday.

April 4: The *Washington Post* reports how research into long COVID is allowing patients to become partners in it. The NIH received $1.15 billion from Congress to launch the four-year RECOVER initiative to understand long COVID.

April 5: NIH Acting Director **Lawrence Tabak** hosts the 10th Virtual Town Hall to update staff and answer 22 frequently asked questions on the state of the pandemic, workplace flexibilities, and safety guidance. Over 10,000 staff participated in the live event.

April 5: The White House COVID-19 Response Team and HHS public health officials hold a press briefing. CDC Director Rochelle Walensky shares the latest on the state of the pandemic, NIAID Director **Anthony Fauci** discusses the effectiveness of additional booster shots, and HHS Secretary Xavier Becerra provides an update on work to address the long-term impacts of COVID.

April 6: NIH hosts the first in-person Wednesday Afternoon Lecture Series since March 4, 2020, in the Lipsett Amphitheater. The speaker is Anna Huttenlocher (University of Wisconsin at Madison), who delivers a talk titled "Imaging Inflammation Resolution and Wound Repair" to a small, invited audience.

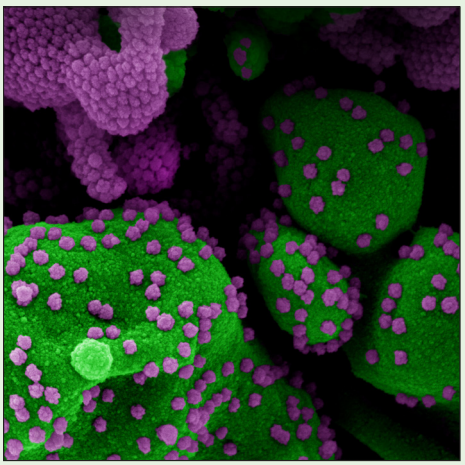
April 10: After two years maximum of telework all NIH staff are able return to work under the HHS Return to the Physical Workplace plan. NIH will continue many of the flexibilities that are outlined in the newly issued HHS Workplace Flexibility Policy.

April 11: The Division of Mail Management Services restarts full mail delivery to all NIH buildings both on and off campus.

April 13: The TSA extends its mask mandate, which was set to expire on April 18, for two more weeks as the CDC monitors the increase in COVID-19 cases. Masks will continue to be required for travel on airplanes, in airports, on buses, and trains, through May 3. On April 18, a federal judge in Florida overturns the CDC mask mandate; the administration plans to file an appeal.

April 15: In an email to all staff NIH Acting Director **Lawrence Tabak** welcomes many employees back to the physical workplace this week. He reports that although the national seven-day average of new COVID-19 cases has increased by 4.9%, hospitalizations and deaths continue to decline. The community transmission levels as reported by the CDC remain low at NIH facilities and Tabak asks staff to be prepared to implement additional workplace mitigation efforts should the community levels change to medium or high.

April 19: The NIH Fitness Centers in Building 53 and Rockledge II reopen for service.



CREDIT: NIAID

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

April 25: The NIH Library reopens its doors for the first time after closing on-site services on March 18, 2020.

April 27: NIH holds a virtual meeting and listening session on the U.S. government's Oversight Framework for Research Involving Enhanced Potential Pandemic Pathogens (ePPP). The meeting's purpose is to get input from stakeholders on the scope of the framework, strategies for minimizing potential biosafety and biosecurity risks, considerations for supporting international ePPP research, and how to balance security with public transparency.

April 29: Acting NIH Director **Lawrence Tabak's** all-staff email reports that yesterday, Moderna asked the FDA to authorize its coronavirus vaccine (which NIH helped develop) for children under 6 for emergency use, making it the first manufacturer to do so. Most NIH locations remain at low in the CDC COVID-19 community levels, except for Framingham, Massachusetts, which at the medium level.

Read a more detailed version of this timeline, complete with links, at https://irp.nih.gov/catalyst/v30i3/covid-19-timeline-at-nih-march-april-2022.

Origin of Life

CONTINUED FROM PAGE 1

across biological membranes and generating an electrochemical gradient, which in turn drives the synthesis of adenosine triphosphate (ATP). ATP is the energy-carrying molecule found in the cells of all living organisms.

He explained how hydrothermal vents on the ocean floor may hold some clues to the origin of life. NASA geochemist Michael Russell proposed that the first life forms started in these vents, which contained hydrogen and methane gases. The vents' pores resemble the outer membranes of cells. A proton gradient forms on the membranes and drives carbon dioxide (CO2) fixation, the process by which plants and algae create energy and food from CO2 in the air. To recreate this reaction, Lane created an origin-of-life reactor (protocell) in the lab. He found that in alkaline hydrothermal conditions, protons could cross the artificial barrier and that protocells with bilayer membranes generate spontaneously. An aqueous environment favors the formation of ATP.

Origin of eukaryotic cells: In the next presentation, Jennifer Lippincott-Schwartz, a former NIH senior investigator and now a senior group leader at Howard Hughes Medical Institute's Janelia Research Campus (Ashburn, Virginia), described her studies on the origin of eukaryotic cells.

When life began to emerge, prokaryotes (single-cell organisms) slowly evolved into eukaryotes (multicellular organisms with a nucleus and other membrane-bound organelles). Lippincott-Schwartz talked about two models of eukaryotic origin: stepwise evolution in which prokaryotic membranes became more complex and evolved into proto-eukaryotes and then eukaryotes; metabolic symbiosis in which two prokaryotic cells interact with each other by providing hydrogen, CO2, gene transfer, and energy. In the latter interaction, archaea (primitive prokaryotes that lack a nucleus) were the host cells and bacteria acted as mitochondria; the pairing resulted in eukaryotic cells.

One difference between prokaryotic and eukaryotic cell membranes is that prokaryotes lack cholesterol and other lipids. Lippincott-Schwartz proposed that the appearance of cholesterol and sphingolipids in the eukaryotic membrane was a turning point in eukaryotic cell evolution. Cholesterol and sphingolipids gives membranes the ability to phase partition protein components, especially at the cell surface and in Golgi membranes. Protein sorting within membranes, in turn, enables more elaborate complex structures, including membrane trafficking pathways and distinct organelles, such as the lysosome, endosome, endoplasmic reticulum, and Golgi apparatus.

Lippincott-Schwartz told the audience that to confirm these theories, she would need to conduct more elaborate experiments and develop mathematical models to study cellular pathways. ●

To watch a videocast of this seminar, presented on March 1, go to https://videocast.nih.gov/watch=44357. For more about the course, go to https://demystifyingmedicine.od.nih.gov. The Demystifying Medicine course, established and run by Irwin Arias, is in its 21st year and aims to bridge exciting developments in medicine with advances in the basic biological and engineering sciences. You can view past videocasts (dating back to 2003) at https://videocast.nih.gov/PastEvents.asp?c=45.

Devika Bose is a molecular biologist and a laboratory technician in the National Eye Institute. She works in Kapil Bharti's lab in the Ocular and Stem Cell Translational Research Section, and uses stem-cell-derived retinal pigment epithelial cells to study different retinal degenerative diseases.

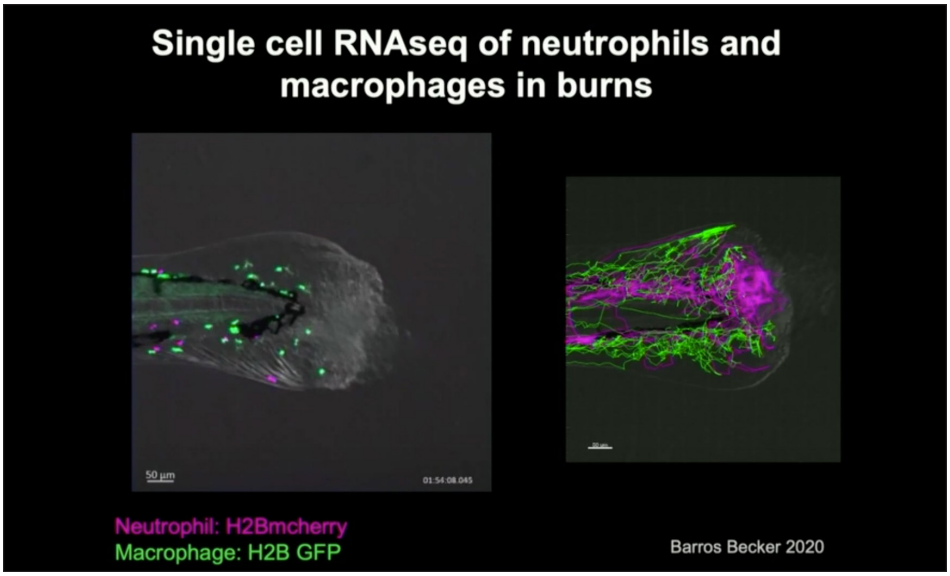
The Demystifying Medicine presenters answered questions from the audience about their views on the origin of life. Clockwise from top left: Win Arias (host and founder of the Demystifying Medicine course), chemist Nick Lane, and cell biologist Jennifer Lippincott-Schwartz.

In-Person WALS Returns

CONTINUED FROM PAGE 1

CREDIT: CHIA-CHI "CHARLIE" CHAN, OD

Anna Huttenlocher, from the University of Wisconsin at Madison, was the first in-person WALS presenter since the onset of the COVID-19 pandemic more than two years ago required NIH to hold its lectures and meetings online only.



CREDIT: FRANCISCO BARROS BECKER, UW-MADISON

A spinning disc confocal microscope was used to produce live images of an uninjured zebrafish tail (left) and one that has a burn injury (right). Anna Huttenlocher's lab found that, after a burn injury, more neutrophils (purple) than macrophages (green) tend to migrate to the wound site (far right of the tail).

the context of wound healing, inflammation, and cancer. Her WALS talk was on neutrophils, which she described for the audience as the "primary cells of the innate immune response [and] the first responders to tissue damage."

Her lab uses zebrafish (*Danio rerio*) as a model system to study the migration and motility of neutrophils, and to understand the balance between their ability to assist with infection and repair as well as their contribution to inflammation. Historically, it was thought that when neutrophils died, they were removed from the site by macrophages, promoting the resolution of inflammation. Huttenlocher's lab found that instead, neutrophils arrive and depart from wound locations and sites of inflammation in a process known as reverse migration.

To determine what regulates reverse migration, her lab is identifying new mechanisms that regulate inflammation resolution. The researchers have studied various models of injury such as cutting the tail or ear of zebrafish or using heat to burn the tail to pinpoint inflammation-resolving pathways. After a burn injury (which destroys collagen organization) the lab found that more neutrophils than macrophages tend to migrate to the burn wound, an indication that macrophages need collagen to do their work, whereas neutrophils do not.

One of the proteins involved in this pathway is the myeloid derived growth factor (MYDGF). During her talk, Huttenlocher described her lab's discovery that depletion of MYDGF leads to increased neutrophils at the wound prolonging inflammation. Given the negative impact of diminished MYDGF activity on regulating neutrophil behavior, the lab proposed the protein as a potential therapeutic target to treat inflammatory conditions.

Going forward, the Huttenlocher research group is working with Huy Dinh, assistant professor in the Department of Oncology at the University of Wisconsin's McArdle Laboratory for Cancer Research. Together, they are trying to understand the diversity in neutrophils and macrophages within interstitial tissues by using live imaging and examining gene expression in individual cells.

For many WALS lecturers, an invitation to speak on campus is about more than just giving a talk—it includes meeting with NIH scientists and trainees. "It was a thrill to meet and talk science in person again," said Huttenlocher in an email interview with this reporter. It was her first in-person lecture in over two years, too. "We may be a bit rusty! But it's fun." During her visit, she had a full day's schedule of meetings with several NIH scientists across campus who are both old friends and colleagues. She also "enjoyed seeing the remaining cherry blossoms and the start of spring." ●

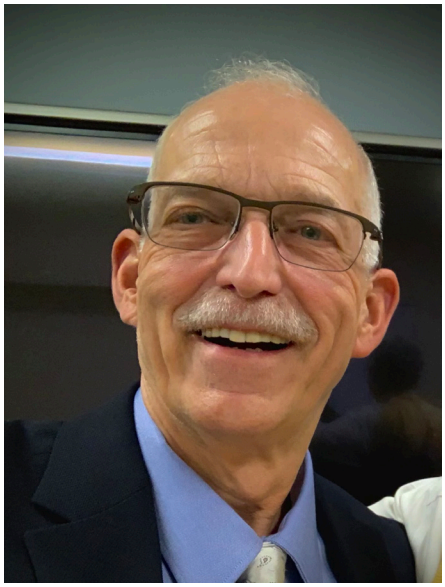
For more on the NIH Director's Wednesday Afternoon Lecture Series and to see which lectures will be in person, go to https://oir.nih.gov/wals. To watch a videocast of the lecture, "Imaging Inflammation Resolution and Wound Repair," held on April 6, 2022, go to https://videocast.nih.gov/watch=44239.

Tamar Jacobsohn is a postbaccalaureate fellow in NICHD's Contraceptive Development Program, which focuses on the development of new contraception measures for men and women. She is applying to medical school and is interested in the intersection of the women's health and mental health fields.

A Glycobiology Pioneer Uncovers the Secrets of Sugar

Profile: John A. Hanover, Ph.D.

BY MICHAEL TABASKO, OD



CREDIT: NIDDK

John Hanover

In autumn 1944 the Nazis blocked food supplies to German-occupied western Netherlands, plunging much of the country into a famine known as the Dutch Hunger Winter. By the time World War II in Europe drew to a close in May 1945 and allied forces liberated the country, over 20,000 people had died and millions of others had suffered from the effects of starvation. The trauma would prove imprinted into Dutch genes. Decades later, people who were in utero during the famine experienced higher rates of diseases such as obesity and type 2 diabetes (T2D). They had inherited what some researchers call the "thrifty gene": Their bodies were conserving energy, as if they were still experiencing famine conditions.

Scientists have since found that stressful environmental factors in the womb might alter the genetic traits of unborn offspring through methylation, an epigenetic process in which cells attach a methyl group to DNA. The addition of a methyl group can silence a gene, whereas removing it can boost a gene's expression. Not only does this process affect a developing fetus, but it also acts on the fetus's immature germ cells, which are precursors to egg and sperm. In the case of children born during the Hunger Winter, the methylation process likely led to insulin resistance and increased their risk—and that of their future offspring—to metabolic disease.

Exactly how cells sense environmental stresses and then signal molecular tools to reprogram DNA is not entirely clear. But understanding this concept might lead to new diagnostics and treatments for populations—such as Native Americans—at higher risk for metabolic diseases. **John Hanover** at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), who knows a thing or two about sugar, might have an answer.

Hanover is chief of NIDDK's Laboratory of Cell and Molecular Biology (LCMB) and has dedicated nearly 40 years of research to glycoscience, the study of glycans. Glycans, also known as saccharides and carbohydrates, are sugar molecules that cloak the surface of all cells and festoon many proteins (glycoproteins), lipids (glycolipids), and other molecules, forming glycoconjugates. "We were focused on an area where there was very little existing knowledge," said Hanover of his early years. Hiding in plain sight for decades, the function of these sugary appendages was largely unknown because of a lack of tools to study them. In the 1980s, Hanover and a handful of intrepid scientists began to unravel their secrets.

Fast forward to today and it turns out that when proteins or other molecules are tagged by certain glycans, it can signal big changes in cell-cell interactions, alter molecular traffic within a cell, and even allow a virus to recognize and infect a host. Scientists now know that glycans are inextricably linked to nearly every facet of cellular biology and implicated in conditions from cancer to neurodegenerative diseases and T2D.

For his outstanding contributions to glycobiology, Hanover received the 2021 Karl Meyer Lectureship Award, the most prestigious international honor bestowed by the Society for Glycobiology each year. He joins prior recipients that include William Lennarz—who mentored Hanover as a graduate student at Johns Hopkins University School of Medicine (JHUSM, Baltimore)—and several scientists at NIH's intramural research program who had an early influence on his career. The Karl Meyer award offers a pulpit to better advocate for a field that hasn't been without challenge during an era in which flashier biomedical specialties such as genomics and epigenetics have often taken center stage. More recently, glycobiology has proven pivotal to discoveries such as antiviral therapies and our understanding of the immune system, and is finally finding its place within the tapestry of biomedical research.

Early influences

Growing up in Tulsa, Oklahoma, Hanover found a connection with the change of seasons and was drawn outdoors to the natural world. He had an insect collection and a small telescope to scan the stars, a hobby he continues today as an amateur astronomer. But it was in high school that a particularly outstanding biology teacher lit a career-commencing spark. "She just opened up my eyes to the joy of biology," said Hanover in a 2009 oral history interview with the Office of NIH History.

He graduated from the University of

To read about other NIH glycobiology researchers, go to https://go.usa.gov/xuPVh.

Tulsa (UT, Tulsa, Oklahoma) in 1976 with a master's degree in chemistry and a bachelor's in biology. It was somewhat of a different path than that of his parents: His mother worked in a bank. His father was a jazz musician, a trombonist, who briefly attended college on a music scholarship, then found a career as a butcher. Perhaps influenced by his father, Hanover himself is an amateur musician: He plays the flute, banjo, guitar, and trombone and loves performing Irish and bluegrass tunes.

During undergraduate studies at UT, he sought a solid grounding in the physical sciences and was told he had a talent for teaching, a skill that would serve him well as a mentor and lecturer in the years to come. He gravitated toward research and began searching for graduate schools.

The next turning point was guided by a molecular biology professor at UT who had done a postdoctoral fellowship with Albert Lehninger, chair of the biochemistry department at JHUSM and author of *Biochemistry*, considered by many a seminal textbook. Hanover's professor advised him that Lehninger's department was the place to go to learn chemistry. Hanover was accepted to JHUSM's graduate program and headed to Baltimore in 1976, a decision that would point him down the glycobiology road.

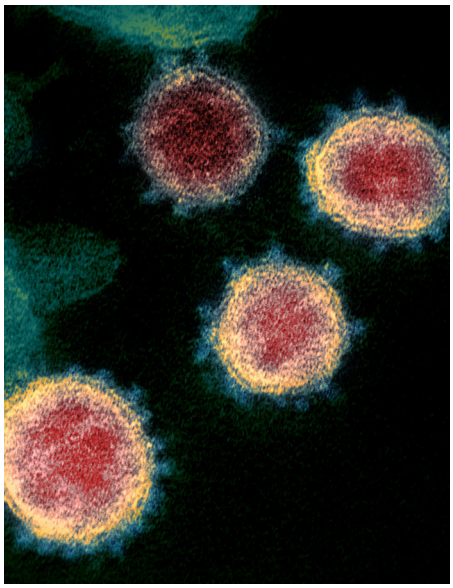
A foundation of mentors

While earning his Ph.D. at JHUSM, Hanover worked closely with Professor of Biochemistry William Lennarz, an impactful mentor whom he remembers fondly. Lennarz had laid the groundwork for much of what is known about glycosylation, the process by which glycans attach to proteins or lipids across cell membranes. He supported Hanover's dissertation on how glycoproteins assemble and arrange themselves on the cell membrane. And while it wasn't popular at the time, they used model systems such as sea urchin embryos (*Strongylocentrotus purpuratus*) and yeast (*Saccharomyces cerevisiae*) to do chemistry alongside genetics and modern biology, which are all methods that the LCMB incorporates today.

Lennarz trained several notable scientists, including Gerald Hart, a friend and contemporary of Hanover's. A few years later when Hart started his own lab he would use one of Hanover's techniques to identify O-linked N-acetylglucosamine (O-GlcNAC), a simple form of glycosylation in which a monosaccharide is attached to a target protein. In the years to come the discovery would largely define both scientists' careers. The O-GlcNAC modification began to show up as a major way for cells to signal changes in key pathways involved in cellular machinery and human disease.

In 1981, Hanover began a postdoctoral fellowship with **Ira Pastan** at the National Cancer Institute (NCI). The NCI lab was investigating how receptors on a cell's surface bind to bioparticles such as hormones, proteins, and even viruses to allow entry into the cell, a process known as receptor-mediated endocytosis. It was the dawn of the molecular biology era and of learning to work with DNA. Hanover wanted to be a part of it. At NCI, he noted parallels to the Lennarz lab in the scientific rigor and creativity that Pastan was able draw from his trainees. During lab meetings Pastan would often challenge students to generate their own ideas of what the data meant, an approach that Hanover now uses with his own trainees to stimulate innovation.

By 1984, Hanover had found some scientific success, including a paper in *Cell* describing the kinetics of the protein clathrin as it encircles and moves molecules through a cell membrane, one of the early examples of how endocytosis works (*Cell* **39:**283–293, 1984). In 1985, with Pastan's support, he landed a job at NIDDK's Laboratory of Biochemistry and Metabolism (LBM) and headed in a new direction.



CREDIT: NIAID

Spike proteins (blue) crown SARS-CoV-2, the virus that causes COVID-19. Once the virus enters humans, the spike protein is decorated with sugars that attach to some of its amino acids, forming O-glycans. Loss of key O-glycans may facilitate viral spread to human cells.

The expanding role of glycans

Between 1986 and 1987, Hanover and his former colleague Hart published separate papers showing that O-GlcNAc occurred within a cell's cytoplasm and on the nuclear pore complex (NPC), a semipermeable membrane barrier that regulates the flow of important proteins and genetic information between the nucleus and the rest of the cell. (Hanover's paper: *J Biol Chem* **20:**9887–9894, 1987; Hart's paper: *J Biol Chem* **17:**8049–8057, 1986) Their findings were controversial, almost heretical, and

CONTINUED ON PAGE 23

Restoring Body and Mind

How Bonnie Hodsdon is Expanding the Reach of Occupational Therapy Research

BY ETHAN SMITH, NINR

"Man, through the use of his hands, as they are energized by mind and will, can influence the state of his own health."
—Mary Reilly (1916–2012), an occupational therapist visionary

CREDIT: BILL BRANSON

Bonnie Hodsdon

"Linda" couldn't write her name, and **Bonnie Hodsdon**, an NIH occupational therapist, was trying to help her.

Like many of the patients Hodsdon sees at the NIH Clinical Center, Linda had writer's cramp, a neurological disorder in which the hand muscles involuntarily contract, making daily fine-motor tasks such as writing nearly impossible. Often, just thinking about writing triggered the debilitating muscle contractions. Linda had become accustomed to using a stamp and inkpad to sign consent forms because she couldn't hold a pen. Hodsdon, the chief of the Rehabilitation Medicine Department's Occupational Therapy Section (OTS), was working on a clinical research protocol to test a new assistive-writing device—a hand splint that helped to control muscle contractions in people with writer's cramp as well as other types of focal hand dystonias (hand-movement disorders). After four weeks of training and practice with the device, most patients saw improvement in their ability to write.

And Linda? She was able to write entire pages without stopping.

Developing innovative ways to treat motor disabilities

Physical therapy and occupational therapy, often lumped together, are distinct fields. Physical therapy helps patients recover from an injury, cope with pain, and increase muscle strength, flexibility, range of motion, and endurance. Occupational therapy, on the other hand, aims to improve the quality of life of people—who have undergone surgery or who have cancer or other debilitating disorders—by maintaining or restoring their ability to perform daily, routine tasks. Occupational therapists work with a wide range of people, including those struggling with developmental delays, visual impairments, cognitive changes, behavioral health challenges, and physical disabilities.

Hodsdon first learned about occupational therapy when she was an undergraduate student at the Virginia Commonwealth University (Richmond, Virginia). The summer after her freshman year, she worked in the Lynchburg Training School and Hospital Rehabilitation Center (Lynchburg, Virginia), which housed people with severe physical and mental-health conditions. She was inspired by the occupational therapists who were helping children with cerebral palsy (CP) improve their swallowing techniques so they could eat independently. CP is a group of disorders that affects a person's ability to control their muscles, making movements such as swallowing and maintaining balance and posture difficult.

"Right then and there I thought this is what I want to do," said Hodsdon. She spent the rest of her undergraduate years pursuing a Bachelor of Science degree in occupational therapy and graduated in 1973. She arrived at NIH in 1974 as a staff occupational therapist and worked her way up to becoming chief of the OTS in 1995.

Occupational therapy—a field continuing to evolve

Occupational therapy has its roots in World War I (1914–1918), when reconstruction aides taught wounded soldiers activities like weaving, basketry, and woodworking. In the aftermath of life-changing injuries, these lessons served as new avenues for soldiers to improve their productivity and morale. Early pioneers of the field noticed that these tasks often promoted physical and emotional healing.

Hodsdon's long career in occupational therapy has given her a unique view into how the field has evolved. Licensing in the field began in the 1970s. Until 2008, one needed to earn a bachelor's degree to enter the profession. Now, master's-level training with a greater emphasis on research competency is required to become an occupational therapist. Some programs offer a doctoral degree. Moreover, the field has integrated evidence-based practice, with NIH at the forefront of research, into new, more effective, ways to improve daily functions. For example, Hodsdon designed and tested a finger orthotic (commercially

available) to help support the finger joints of patients with ligamentous laxity, a condition in which hypermobile joints that are very flexible can cause pain.

OTS has grown

As chief of the OTS, Hodsdon has been developing innovative ways to help patients with motor disabilities relearn how to perform daily tasks or adapt to their situation. She specializes in the clinical care of people with arthritis and is involved with research on focal hand dystonia, women's health, congenital muscular dystrophy, and the functional effects of rare or undiagnosed diseases. She has also coordinated collaborative work between occupational and physical therapy by combining biomechanical and neurodevelopmental concepts.

The OTS has also grown in Hodsdon's time at NIH. Previously, the OTS played only a supportive role for various research programs at NIH. Today, all OTS occupational therapists are associate investigators in collaborative research projects. Their activities include designing methods to measure the effectiveness of drug trials or phenotyping rare diseases. Hodsdon's influence has resulted in hiring occupational therapists who have specialized skills, or board certifications, that prepare them to work with patients who have physical disabilities, behavioral health challenges, pediatric diseases, low vision, and lymphedema.

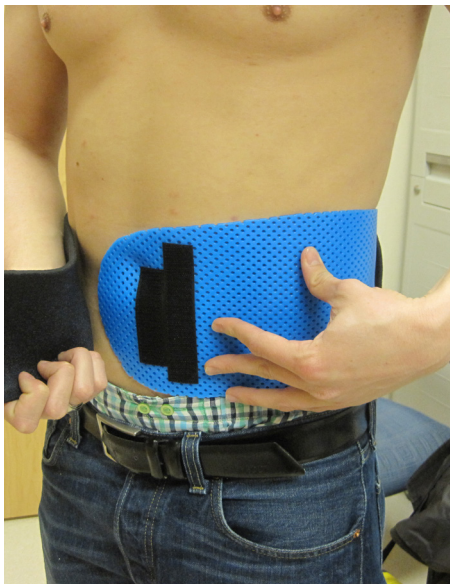
She has also championed new research directions such as the Women's Health Initiative. The initiative includes research on the mental health of women who have primary ovarian insufficiency, which in many cases results in an inability to have children. She is currently working with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and its patients who have androgen insensitivity syndrome and other reproductive disorders and are dealing with psychosocial, sexuality, and body-image issues.

Part of Hodsdon's job involves designing, fabricating, and modifying assistive devices that help patients adapt to their disabilities. People with certain autoimmune disorders, for example, need to wear guards to protect their enlarged spleens. But when she realized that the spleen guards were too cumbersome for children to wear, she designed and fabricated one that allowed them to return to safe and inclusive outside play and sports activities.

Still, there are patients who are very hard to help. In those with cancer, their bone-marrow stem cells—which are needed to produce new blood cells—may be depleted due to the toxic effects of chemotherapy. The depletion can be treated with donated stem cells, but sometimes the donor cells view the recipient's body as foreign and attack in what is known as graft-versus-host disease. In some cases, the hands may be affected and the muscles can tighten and contract over time and be difficult to use. Hodsdon has explored a variety of novel orthotics and strategies to help patients maintain normal function in their hands.

"It's almost nearly impossible [to prevent hand immobilization] in patients who have serious graft-versus-host disease," said Hodsdon. "But we keep trying to figure out what is the next-best design or exercise to do with the next patient to try and keep the hands from becoming immobilized."

Hodsdon, however, is encouraged that NIH and the Clinical Center are conducting research aimed at developing new treatments for those patients and others. She appreciates how the collaborative environment at NIH is providing hope for people with debilitating diseases. She's inspired by the patients themselves, too.



CREDIT: BONNIE HODSDON

Although a spleen guard protects an enlarged spleen, it may too cumbersome for children to wear because it limits their ability to engage in outside play and sports. Bonnie Hodsdon designed and fabricated a spleen guard (shown) that is protective but more flexible than the usual hard, molded-plastic variety.

"I'm mentored daily by my patients who tell me what it's like living with their diagnosis and the functional impact from it," she said. They are "helping me understand further what it is I need to think about to help them regain function or find some meaning or purpose in their daily life." ●

Ethan Smith is a postbaccalaureate fellow in the National Institute of Nursing Research. There, he works on clinical research aimed at developing blood-based biomarkers for traumatic brain injury in military service members and veterans. He is currently preparing applications for graduate school in clinical psychology.

Why Climate Change Is a Health Threat

NIH's New Climate Change and Health Initiative Explores the Risk

BY RAGHURAM REDDY, NINDS

Since 1912, the snow on Mount Kilimanjaro in Tanzania has melted more than 80%. Widespread scientific consensus informs us the Earth's climate is changing, as evidenced by increased global temperatures, warming oceans, and shrinking ice sheets. These climate drivers are bringing about new health risks: Increasing severity and frequency of heat waves leads to more heat-related illnesses and deaths; expanding ranges of disease-carrying insects pose a greater threat to humans; increased exposure to pollen, mold, and other pollutants can worsen allergies and lung diseases such as asthma; higher temperatures can contribute to poor air quality that can exacerbate cardiovascular disease; more flooding events and sea level rise can contaminate water with harmful bacteria, viruses, and chemicals; and more frequent and severe weather events can cause injuries, illness, and even death.

Having noted the implications that climate change has on people's health, NIH developed the NIH Climate Change and Health Initiative to better understand the relationship between climate change and health, reduce health threats from climate change, and build health resilience in individuals, communities, and nations. The National Institute of Environmental Health Sciences (NIEHS) is leading this multi-institute collaborative effort, which includes a seminar series, held virtually. Two of the seminars, both in February 2022, are described here: One featured Robert Bullard (Texas Southern University in Houston); the other, was a joint presentation by Jonathan Samet (Colorado School of Public Health in Aurora, Colorado) and Tami Bond (Colorado State University in Fort Collins, Colorado).

Feeling the pain

In his February 9 talk, Bullard, considered the "Father of Environmental Justice," spoke on "Why Climate Change is a Health Threat." He stressed the importance of understanding the geography of inequality and how ZIP Codes can be powerful predictors of health. While historically, people of color and low-income households have contributed least to climate change, they feel the pain the earliest, the most, and the longest.

Compared with whites, people of color receive less FEMA aid after a natural disaster, tend to live in areas that have a greater risk of flooding, are more likely to die from extreme heat, suffer from more air pollution, and are more apt to live in nature-deprived areas. Bullard currently serves on the advisory council of the President's Justice40 initiative, which seeks to deliver 40% of climate investment benefits to disadvantaged communities.

On February 22, Samet and Bond spoke about "Climate Change, Air Pollution, and Health: What Lies Ahead?" Samet, a pulmonary physician and epidemiologist, investigates the health risks of inhaled pollutants and how they are linked to respiratory diseases and cancer. Bond, an engineer, focuses on combustion, atmospheric chemistry and climate, and the relationship between technology and human choice.

Accelerating climate change

In their presentations, Samet and Bond highlighted the significance of health-effects research and intervention science. They described how increased air pollution (particulate matter, ozone, nitrogen dioxide) may be due to increased energy use that comes from rising temperatures and urbanization and the effect of temperature itself, which drives up ozone production. As urban areas grow, more people will be living in polluted environments and those with fewer resources will be trapped in those harmful locations and will be challenged to adapt. Samet and Bond stressed the importance of understanding how air pollution, the climate, and the natural world exist in a complex feedback system.

Human activities are accelerating climate change at a pace never before seen. Combustion pollutants from the burning of fuels such as wood and natural gas can cause eye, nose, and throat irritation, lung disease, cancer, and cardiovascular and respiratory diseases. Samet and Bond acknowledged that although fixing the climate is a daunting task, we must start somewhere. They emphasized the need to continue efforts to clean up combustion pollutants and seek cleaner forms of energy such as solar power. We must also look at climate change through lens of justice and health equity, understand the environmental conditions that patients face, and support community groups all over the country to create a more sustainable future. ●

To read more about the NIH Climate Change Initiative, visit https://www.nih.gov/climateandhealth. To view videocasts of these talks and others in the seminar series, go to https//www.niehs.nih.gov/research/programs/geh/events/index.cfm.

Raghuram Reddy is a postbaccalaureate fellow in the National Institute of Neurological Disorders and Stroke, where he is analyzing the role of primary cilia in Parkinson disease and glioblastoma. When he completes his fellowship in 2022, he plans to attend medical school.

Biologics Regulation and Research

The People and Work of Buildings 29 and 29A

BY DAVID DERENICK, OD, AND KATIE WATTS

CREDIT: OFFICE OF NIH HISTORY AND STETTEN MUSEUM

John Finlayson worked on Factor VIII, an essential blood-clotting protein, sometimes called anti-hemophilic factor (not licensed until 1966). Shown: Finlayson (left) and lab technician Mimi Reyes in 1963 in Building 29, first floor.

CREDIT: ROB TUCHER

Historic American Buildings Survey photograph taken of Building 29, North Elevation.

Two historic buildings on the NIH Bethesda, Maryland, campus will soon be demolished to make way for new structures that can accommodate modern laboratories. But never fear, the stories of the important research that went on in those buildings will be preserved on a new website hosted by the Office of NIH History and Stetten Museum.

The Biologics Standards Laboratory Building (Building 29, which opened in 1960) and the Biologics Standards Laboratory Annex (Building 29A, which opened in 1967) are nationally significant to the history of medicine and public health. Within their laboratories, NIH and FDA scientists helped to conquer some of the world's deadliest infectious diseases. In their regulatory role, the two agencies licensed vaccines, antitoxins, blood products, and other biologics to ensure their safety and effectiveness. In 2014, the FDA Center for Biologics Evaluation and Research moved from Buildings 29, 29A, and 29B (which opened in 1994) to the FDA White Oak campus in Silver Spring, Maryland. Buildings 29 and 29A have been vacant since then; Building 29B was renovated and is now occupied by NIH intramural researchers from three institutes.

After careful study, NIH determined in 2020 that Building 29 and Building 29A are functionally obsolete and that it would be cost prohibitive to rehabilitate them and impossible to resolve the physical constraints of the buildings. The Section 106 review process of the National Historic Preservation Act of 1966 requires federal agencies to identify and assess the effects its actions may have on historic buildings on their property. NIH consulted with the Maryland Historical Trust and local organizations and agreed that before the buildings were demolished, photographic surveys would be completed as well as a public website that showcased the significant science and individuals associated with the two buildings. Some of the most well-known medical and infectious-disease researchers of the 20th century worked in these buildings, as did the key administrators and others who supported their work.

Although replacing Buildings 29 and 29A is a high priority for NIH, it may be several years before the buildings are demolished. NIH's Office of Research Facilities must finish decommissioning the buildings and planning the demolition.

The Office of NIH History and Stetten Museum, the FDA History Office, and a number of others—including architects, photographers, historians, and a website programmer—teamed up to mitigate the loss of the buildings. A new website—which features the stories of the people, the labs, and the work conducted in the two buildings between 1960 and 2014—is now live on the Office of NIH History and Stetten Museum website at https://go.usa.gov/xudV6. ●

David Derenick, an architect in the Office of Research Facilities, is the NIH Federal Preservation Officer. Katie Watts is a principal investigator in history and architecture at Gray and Pape, Inc., a consulting company with headquarters in Cincinnati, Ohio, and a regional office in Richmond, Virginia, where she resides.

Recently Tenured


CLINT T. ALLEN, NIDCD


JOHN BROGNARD, NCI-CCR


JONATHAN HOFMANN, NCI-DCEG


YUICHI MACHIDA, NCI-CCR


QUAN YUAN, NINDS

CLINT T. ALLEN, M.D., NIDCD

Senior Investigator and Chief, Section on Translational Tumor Immunology, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders

Education: Texas A&M University, College Station, Texas (B.S. in biochemistry); Clinical Research Training Program (CRTP), Head and Neck Surgery Branch, NIDCD (fellowship); Texas A&M University Health Science Center College of Medicine, Bryan, Texas (M.D.)

Training: Surgical internship and resident in Otolaryngology–Head and Neck Surgery, Washington University in St. Louis (St. Louis, Missouri); surgical fellow in laryngology, University of Washington (Seattle)

Came to NIH: In 2006 for CRTP fellowship in NIDCD; returned to NIDCD 2013 as an investigator

Outside interests: Running; woodworking; traveling

Website: https://www.nidcd.nih.gov/about/staff/clint-t-allen-md

Research interests: I am interested in the immunologic aspects of neoplastic development and progression, with a focus on head and neck epithelial neoplasms. My lab is studying different combinations of immunotherapy for human papillomavirus (HPV)–positive or –negative head and neck cancer. We explore mechanisms of resistance to immunotherapy mediated by genetic and microenvironment factors and translate these finding into novel phase 1 and phase 2 studies that are performed at the NIH Clinical Center. My being a surgeon–scientist facilitates my access to clinical specimens for study in the laboratory and rapid translation of new findings into the clinic in collaboration with several intramural medical oncology groups.

We are trying to understand 1) how tumor heterogeneity can be overcome with combination immunotherapy approaches using both T cells and natural killer cells to maximize response and clinical benefit (*J Immunother Cancer* **9:**e002128, 2021); and 2) how the immunosuppressive tumor microenvironment can be overcome to unleash the potential benefit of existing or new immunotherapies. Ultimately, our findings could lead to better ways of safely combining immunotherapies based on rational, mechanism-driven approaches.

Several of our studies focus on neoadjuvant administration of immunotherapy to improve recurrence-free survival in patients with newly diagnosed, advanced-stage head and neck cancer.

Our program also translates many of our findings to the examination of a rare disorder called recurrent respiratory papillomatosis (a disease characterized by recurrent wartlike growths on or around the vocal cords). We are one of the few programs worldwide to study this disease and have completed several clinical trials investigating both repurposed and novel, first-in-human immunotherapies. We are studying a therapeutic vaccine that activates T-cell immunity against HPV infection (*NPJ Vaccines* **6:**article 86, 2021). Early clinical results have been promising.

JOHN BROGNARD, PH.D., NCI-CCR

Senior Investigator, Laboratory of Cell and Developmental Signaling, Center for Cancer Research, National Cancer Institute

Education: James Madison University, Harrisonburg, Virginia (B.Sc. in chemistry); Johns Hopkins University, Baltimore (M.Sc. in biotechnology); University of California at San Diego, San Diego, California (Ph.D. in biomedical sciences)

Training: Postdoctoral fellow, Salk Institute for Biological Studies (San Diego)

Before coming to NIH: Group leader, Cancer Research UK Manchester Institute (Didsbury, England)

Came to NIH: First as a summer intern with an NCI basic-research program (1993–1995), then as a research technician at the NCI-affiliated SAIC-Frederick, and later as a research associate in NCI (1999–2002); returned in 2016 as a tenure-track Stadtman Investigator

Outside interests: Spending time outdoors with his sons playing soccer and tennis; hiking; fishing; skiing

Website: https://irp.nih.gov/pi/john-brognard

Research interests: I investigate genetic and molecular pathways that contribute to the development of cancers. The major focus of my lab is elucidating cancer-associated kinases in the unexplored human kinome (complete set of protein kinases encoded in the genome). Of the 538 kinases in the human kinome, approximately 300 have not been explored in depth, but we know—from cancer genomic-sequencing studies—that they are implicated in cancer. We hope to identify novel kinase drivers and develop new drugs targeting these kinases so that we can expand the number of cancer patients who can benefit from precision-medicine-based therapies. Collectively, our research should identify new genetic drivers, targets for therapeutic intervention, and novel mechanisms of tumorigenesis.

We use bioinformatics and functional genomic approaches to initially identify novel cancer-associated kinases. We then proceed to decipher the molecular mechanisms by which these kinases promote tumorigenesis. We then develop compounds (small molecule catalytic inhibitors or proteolysis-targeting chimeras) to target our most promising kinase drivers. We use in vivo patient-derived xenograft mouse models to assess the efficacy of these new drugs, with the overall goal of bringing new therapies to the clinic for cancer patients.

Specifically, we are defining novel kinase drivers in squamous cell carcinomas and exploring the mechanisms by which these kinases promote cancer. For example, we identified the protein kinase TNIK as a promising therapeutic target in lung squamous-cell carcinoma, the second most prevalent type of lung cancer, and defined a novel mechanism in which TNIK regulates the Merlin protein to promote lung tumorigenesis (*Cancer Discov* **11:**411–1423, 2021).

JONATHAN HOFMANN, P.H.D., M.P.H., NCI-DCEG

Senior Investigator, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Education: Carleton College, Northfield, Minnesota (B.A. in English); School of Public Health, University of Washington, Seattle (M.P.H. in environmental and occupational health; Ph.D. in epidemiology)

Training: Postdoctoral fellow (2009–2011), then research fellow (2011–2015), Occupational and Environmental Epidemiology Branch, NCI-DCEG

Came to NIH: In 2009 for training; became an investigator in 2015

Outside interests: Running; gardening; spending time outdoors with his family and their dog Evie

Website: https://dceg.cancer.gov/about/staff-directory/hofmann-jonathan

Research interests: My research is helping to advance our understanding of the role of agricultural exposures, per- and polyfluoroalkyl substances (PFAS), and other risk factors in the development of various cancers. I focus on multiple myeloma and renal cell carcinoma (RCC), the most common form of kidney cancer. I am also investigating the biological mechanisms underlying multiple myeloma and progression from its precursor, monoclonal gammopathy of undetermined significance (MGUS).

Pesticides, endotoxins, and other agricultural exposures have been associated with risk of various cancers, although the biological mechanisms underlying these associations are not well understood. I am the principal investigator of the Biomarkers of Exposure and Effect in Agriculture (BEEA) study within the Agricultural Health Study. Field work for the BEEA study ended in 2018; we collected biospecimens (including blood, urine, buccal cells, and house dust) and updated information about pesticide use and other agricultural exposures of more than 1,600 farmers in Iowa and North Carolina. In a recent investigation in BEEA, we confirmed an excess of the myeloma precursor MGUS in farmers and identified novel associations with several pesticides, including permethrin, a widely used pyrethroid insecticide previously linked to an increased risk of multiple myeloma (*Environ Health Perspect* **129:**17003, 2021).

I am also investigating the risk of RCC and other cancers in relation to exposure to PFAS, a diverse class of synthetic chemicals that are highly persistent in the environment. In a recent investigation in a cohort with PFAS exposures comparable to that of the general population, we found that elevated levels of perfluorooctanoic acid, a commonly detected and widely studied PFAS, were associated with an increased risk of RCC (*J Natl Cancer Inst* **113:**580–587, 2021).

YUICHI MACHIDA, PH.D., NCI-CCR

Senior Investigator, Developmental Therapeutics Branch, Center for Cancer Research, National Cancer Institute

Education: Nagoya University, Nagoya, Japan (B.S., M.S., and Ph.D. in biotechnology)

Training: Postdoctoral fellowship, Brigham and Women's Hospital, Harvard Medical School (Boston); research associate, University of Virginia (Charlottesville, Virginia)

Before coming to NIH: Associate professor of pharmacology, Mayo Clinic College of Medicine and Science (Rochester, Minnesota); senior associate consultant II–research, Division of Oncology Research, Department of Oncology, Mayo Clinic (Rochester, Minnesota)

Came to NIH: In January 2022

Outside interests: Skiing; playing tennis; listening to music

Website: https://irp.nih.gov/pi/yuichi-machida

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Recently Tenured

CONTINUED FROM PAGE 21

Research interests: DNA damage is the major source of mutations and genomic instability, which are the hallmarks of cancer.My lab an I are studying the proteases involved in DNA repair and their roles in maintaining genomic stability.

We are examining how cells resolve replication conflicts with DNA-protein crosslinks (DPCs) to prevent genomic instability and tumorigenesis. My group at the Mayo Clinic was one of the laboratories that contributed to the discovery of SprT-like N-terminal domain (SPRTN), a nuclear metalloprotease that is important for repairing DPCs at DNA replication forks (*Cell Cycle* **11:**3395–3402, 2012).

Mutations in the *SPRTN* gene cause Ruijs-Aalfs syndrome, a rare genetic disease characterized by genomic instability, progeria, and early onset of liver cancer. We generated a mouse model with reduced expression of the *Sprtn* gene that recapitulated the phenotypes of Ruijs-Aalfs syndrome and exhibited accumulation of DPCs in the liver, in which tumors were later formed (*Nat Commun* **5:**5744, 2014). We found that spontaneous DPCs are produced frequently yet removed efficiently by a mechanism involving SPRTN (*Nucleic Acids Res* **45:**4564–4576, 2017).

We are also investigating the effect of DPC repair inhibition on chemotherapies in order to develop strategies to sensitize tumors to chemotherapeutic drugs and identify types of tumors that are susceptible to DPC-inducing or protein-trapping drugs. We found that SPRTN-deficient cells are hypersensitive to camptothecin, suggesting that inhibition of DPC repair mechanisms could enhance the toxicity of DPC-inducing chemotherapeutic drugs (*Nucleic Acids Res* **45:**4564–4576, 2017). Another study showed that a protein called FAM111A plays an important role in mitigating the effects of protein obstacles on DNA replication forks and thereby influences sensitivities to chemotherapeutic drugs (*Nat Commun* **11:**1318, 2020). We are currently investigating the function and regulation of these DPC proteases.

QUAN YUAN, PH.D, NINDS

Senior Investigator, Dendrite Morphogenesis and Plasticity Unit, National Institute of Neurological Disorders and Stroke

Education: Lanzhou University, Lanzhou, China (B.S. in biology); University of Pennsylvania, Philadelphia (Ph.D. in biology)

Training: Postdoctoral training in developmental and behavioral neurobiology, University of California at San Francisco (San Francisco), Howard Hughes Medical Institute

Came to NIH: In 2013 as an Earl Stadtman Tenure Track Investigator

Outside interests: Traveling; hiking; slowly building up a rock and fossil collection

Website: https://irp.nih.gov/pi/quan-yuan

Research interests: My lab and I are using *Drosophila melanogaster* as a model to understand how experience and genetic programming interact to shape the structural and functional connectivity of neuronal circuits during brain development.

We are interested in neuronal dendrites, the branchlike structures that receive sensory signals from the surrounding environment or synaptic input from connected partner cells. The elaborate dendritic arborizations are genetically controlled, often unique to the specific neuronal type, and sensitive to experience and activity. Although neuroscientists have been captivated by dendrite morphogenesis and plasticity for decades, we are still trying to figure out what the cell- and context-specific mechanisms are.

Previously, I established a genetic model in Drosophila larvae for performing systematic in vivo analyses on dendrite plasticity. I identified homeostatic structural plasticity as a major contributor to neurons' compensatory responses toward alterations in synaptic inputs.

Our work has revealed visual-experience-induced homeostatic plasticity targeting dendritic filopodia (thin protrusions in neurons at early developmental stages) regulates synapse number and dendrite size in the developing Drosophila larval visual circuit (*Nat Commun* **9:**3362, 2018). We also isolated molecular signatures associated with the neuronal adaptive responses (*Cell Reports* **25:**1181–1192.e4, 2018). Our follow-up studies uncovered a pair of carriers mediating neuron-glia lipid trafficking and offered molecular insight into how glia-derived factors help regulate brain lipid homeostasis, which is closely linked to human neurodevelopmental disorders and neurodegenerative diseases (*Nat Commun* **12:**article number 2408, 2021).

We conducted another study to help us understand how cholinergic neurotransmission (linked to many neuropsychiatric disorders in humans) in the central nervous system contributes to neural plasticity. We demonstrated that the temporal regulation of nicotinic acetylcholine receptor (nAchR) subunits during development is critical for the structural and functional maturation of cholinergic synapse in the Drosophila central nervous system (*Proc Natl Acad Sci USA* **118:**e2004685118, 2021). These findings offer us opportunities to further explore the nAchR receptor complex, discover the key factors modulating cholinergic transmission, and better model related human psychiatric disorders. ●

Hanover
CONTINUED FROM PAGE 15

To read about other NIH glycobiology researchers, go to https://go.usa.gov/xuPVh.

represented a paradigm shift that would not be widely accepted for many years. Prevailing dogma at the time said that glycosylation was restricted to the cell's outer membrane, and the new discovery suggested that glycans might play a role in controlling access to the RNA factory sequestered inside the nucleus. At the time, the Hart and Hanover labs were the only ones using an enzyme-based assay trick that Hanover had developed in graduate school to visualize O-GlcNAc within the cell. Hanover went on on to characterize and clone the first nuclear pore glycoprotein.

From 1988 to 1990, his lab would also be the first to identify the enzymes that catalyzed the cycling of O-GlcNAc to its protein targets, such as those guarding the NPC. Further work by Hanover and others would establish O-GlcNAc as critical in maintaining the stability of the NPC. Improperly glycosylated proteins can dysregulate the NPC, which has been associated with DNA damage resulting in several diseases. Clinical trials are exploring potential treatments for neurodegenerative conditions by targeting the enzymes that control O-GlcNAc cycling.

Hanover became chief of LBM's Cell Biochemistry Section in 1991 and the chief of NIDDK's Laboratory of Biochemistry and Biology in 1994. As technology advanced, glycobiologists began using tools such as mass spectrometry to identify new glycans and glycoconjugates. By the late 1990s, genomic sequencing led to discoveries revealing how glycans functioned in model organisms such as *Caenorhabditis elegans* and *Drosophila melanogaster*, opening the floodgates to new research possibilities. In 1997, Hanover's postdoctoral fellow, **William Lubas**, was the first to isolate and clone O-GlcNAc-transferase (OGT), an enzyme found in abundance in the pancreas. OGT responds to elevated blood glucose concentrations by boosting O-GlcNAc activity (*J Biol Chem* **14:**9316–9324, 1997).

In 2010, Hanover became chief of LCMB, and ongoing research there has since linked the OGT glucose-sensing pathway to the development of T2D. Hanover credits that work to close collaboration with several talented scientists including **Dona Love** (NIAID), **Michelle Bond** (National Institute of General Medical Sciences), and **Lara Abramowitz** (NIDDK).

New technologies and new directions

So, if O-GlcNAc activity does indeed respond to environmental stresses such as hunger and diet, might it also play a role in reprogramming the DNA of future generations? Hanover's team has been grappling with this question for nearly 15 years. They may have found the answer by using new enzyme-based tools. "We see a dramatic change in DNA methylation if we block the cycling of O-GlcNAc in mice," said Hanover of his lab's new findings. "This link between transgenerational information transfer and nutrients, it's sort of the Holy Grail of epigenetics." The LCMB plans to submit their data for publication this year.

An advocate for glycobiology at NIH

When Hanover first came to NIH, the IRP was a "hotbed of glycobiology research," he said. **Elizabeth Neufeld**, **Victor Ginsburg**, and **Roscoe Brady** had already made important contributions to our understanding of how carbohydrates play a role in cellular signaling and disease. Hanover found support from senior researchers such as **Gilbert Ashwell** and **Vincent Hascall**—both former Karl Meyer awardees (**Stuart Kornfeld** was another NIH recipient)—who would help him establish the Glycobiology Scientific Interest Group (SIG), which remains active today.

Now with nearly 300 published papers, Hanover remains highly involved as an advocate for the NIH intramural glycoscience community. He lectures both locally and internationally, helped develop one of the nation's first courses dedicated solely to glycoscience at NIH's Foundation for Advanced Education in the Sciences, and remains involved with several professional organizations and committees.

"Many of his ideas have helped to advance glycobiology right here, creating a very vibrant community within the intramural program," said **Kelly Ten Hagen** (National Institute of Dental and Craniofacial Research, NIDCR). Ten Hagen represents a new batch of investigators at NIH who are pushing the boundaries of glycoscience research. Her recent collaboration with NIH Acting Director **Lawrence Tabak** (NIDCR) resulted in a study that found glycosylation of the SARS-CoV-2 spike protein influences how the virus recognizes and infects human cells (*Proc Natl Acad Sci USA* **118:**e2109905118, 2021)

Today, Hanover takes great pride in mentoring the next generation of glycobiology researchers. Many of his trainees are pursuing successful careers and are uncovering how glycan-mediated pathways are involved in everything from cancer to immune deficiencies and the differentiation of stem cells.

What's next for Hanover? He hopes to move the lab in new directions with his DNA methylation work. "I don't like to rest on our laurels," he said, adding that all the new knowledge gained in glycobiology hasn't yet made it into the general biochemical textbooks—and that there's much more to be discovered. "I still open the journals and learn something every day, even after studying this for 40 years." ●

Read a longer version of this article online at https://go.usa.gov/xu5HP.

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National Institutes of Health
Building 60, Room 232
MSC 4730
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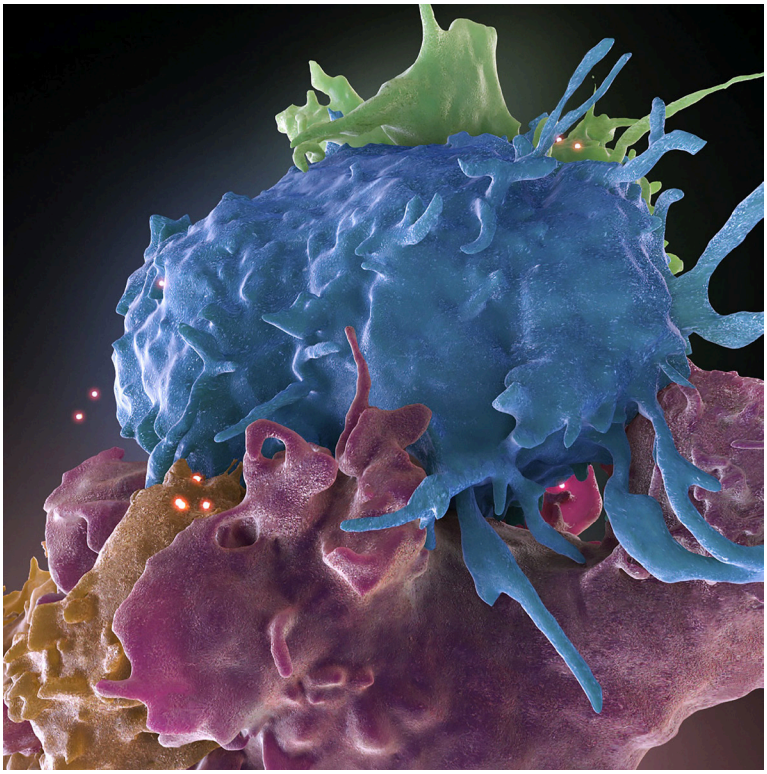
PHOTOGRAPHIC MOMENT

HIV-Infected and Uninfected Immune Cells Interact



CREDIT: DONALD BLISS, NLM; SRIRAM SUBRAMANIAM, NCI

HIV infected (blue, green) and uninfected (brown, purple) T cells interacting. One cell (brown) has wrapped an extension around its uninfected neighbor (purple) to reach an infected cell (blue). Data from focused ion beam scanning electron microscopy. ●

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Address correspondence to:
Building 60, Room 232, NIH
1 Cloister Court
Bethesda, MD 20892
Ph: 301-402-1449
Fax: 301-402-1434
e-mail: catalyst@nih.gov

The NIH Catalyst online:
https://irp.nih.gov/catalyst

PUBLISHER
MICHAEL GOTTESMAN
Deputy Director for Intramural Research, OD

EDITORS
JOHN I. GALLIN
Chief Scientific Officer, CC, and NIH Associate Director for Clinical Research
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CONTRIBUTING WRITERS
DEVIKA BOSE
DIPTADIP DATTAROY
DAVID DERENICK & KATIE WATTS
LARISA GEARHART-SERNA
NATALIE HAGEN, TAMAR JACOBSOHN
RAGHURAM REDDY, ETHAN SMITH
MICHAEL TABASKO
RESEARCH BRIEFS: PETER MANZA, SATABDI NANDI, RAGHURAM REDDY, MICHAEL TABASKO

PHOTOGRAPHERS/ILLUSTRATORS
DONALD BLISS & SRIRAM SUBRAMANIAM
BILL BRANSON, BONNIE HODSDON
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