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COVID-19 SIG

Anthony Fauci Outlines Lessons Learned from COVID-19

BY SUNITA CHOPRA, NCI

As the novel coronavirus SARS-CoV-2 has swept through the world over the past two and a half years, it has infected more than half a billion people with COVID-19 and has caused nearly six and a half million deaths globally. The National Institute of Allergy and Infectious Diseases (NIAID) helped develop safe and effective mRNA COVID-19 vaccines and therapeutics. On September 15, 2022, the COVID-19 Scientific Interest Group hosted a virtual lecture by NIAID Director **Anthony Fauci**, who has served as advisor to seven U.S. presidents and has dealt with major public health challenges including HIV-AIDS, Ebola, and COVID-19.

In his "Pandemic Preparedness and Response: Lessons from COVID-19" talk, Fauci shared some lessons learned:

Global information sharing and collaborations are essential. The sharing of reagents, surveillance data, convalescent and patient samples, real-world clinical data, and genomic data has been extremely important in our ability to address the many problems that have arisen over the past 2 1/2 years.

Leveraging existing clinical-trials networks is important. Four NIAID-funded HIV clinical trials were merged

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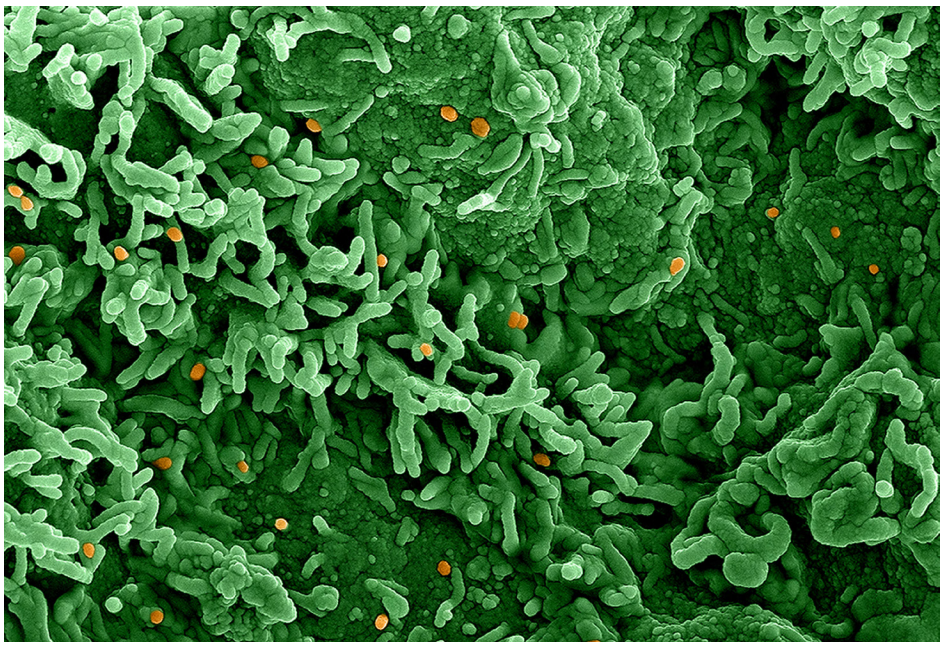
An Old Virus Gets New Attention

Worldwide Outbreak Puts a Fresh Focus on Monkeypox Research

BY MICHAEL TABASKO, OD



CREDIT: NIAID INTEGRATED RESEARCH FACILITY (FORT DETRICK, MARYLAND)

Colorized scanning electron micrograph of monkeypox virus (orange) on the surface of infected Vero E6 cells (green). The Vero cell line is established from kidney epithelial cells of the African green monkey..

For decades, monkeypox has been exclusively endemic to parts of Central and West Africa. But in 2003, 3-year-old Schyan Kautzer of Dorchester, Wisconsin, developed flu-like symptoms and a painful rash of raised welts after being bitten by her pet prairie dog. She was the first person diagnosed with monkeypox in the Western Hemisphere, followed by more than 70 suspected or confirmed cases in six midwestern states reported to the Centers for Disease Control and Prevention (CDC). And the likely culprits? Infected Gambian pouched rats imported from Ghana. The rodents were housed next to a shipment of prairie dogs that in turn became infected

CONTINUED ON PAGE 12

CONTENTS

Data: Not Just Another Four-Letter Word

BY NINA F. SCHOR, M.D., PH.D., DDIR

As I think about the new mandate for managing and sharing scientific data, which goes into effect on January 25, 2023, I can't help but think about the character Data, played by Brent Spiner on *Star Trek: The Next Generation*. He was critical to the crew of the *Starship Enterprise* because he could manage and share data. But his usefulness diminished when he managed it in a way that did not answer the questions being asked or when he shared it in language that seemed unintelligible.

Similarly, it is simple to say that anyone whose research is funded by the federal government should manage their data and make them accessible. Indeed, the concept of proper data management and sharing underscores the importance of accountability, transparency, scientific rigor, and research integrity in serving the overarching goal of improving human health and well-being and is a critical component of team science. But what does "data management" mean and at what stage, how, and with whom should data best be shared?

First, the new Data Management and Sharing Policy (DMS Policy) will require every intramural and extramural investigator conducting NIH-funded research that will generate scientific data to develop and have approved a DMS plan. Intramural plans for each institute and center (IC) will be reviewed and approved by that IC's scientific director or designee. Investigators and project leads will need to submit a DMS plan for ongoing and new research. In addition, clinical research protocols must include a plan along with other materials submitted for IC initial scientific review.

Extramural plans will be reviewed and assessed by NIH program staff.

In the data-management portion of the plan, the investigator will need to make clear what types of data are to be archived and shared; what the relevant metadata are and what methods were used to generate and acquire them; what software and other tools are needed to access and work with them; and, if relevant, what "standards" (things like unique identifiers, data dictionaries, and formats) apply to these data. In the data-sharing portion, the investigator must specify the repositories in which data will be archived as well as the way they are findable and identifiable. The investigator should also provide a timeline for depositing data in an accessible repository. More information on creating and writing such a plan can be found at https://sharing.nih.gov/data-management-and-sharing-policy/planning-and-budgeting-DMS/writing-a-data-management-and-sharing-plan.

Given the rate at which science and technology change, DMS plans are not cast in stone forever. They can be updated, revised, rereviewed, and reapproved during the lifetime of any given project.

The spirit of this policy is, I believe, already part of the DNA of any credible science or scientific institution. Unlike many industries, the biomedical research enterprise has forever thrived on challenging its findings. It has tested and retested and specified methods and shortcomings in published papers. Many scientific communities have long shared information in accessible databases across laboratories. They have also harmonized pre-database data so that they can be credibly and productively added to existing databases. But I am afraid that even the best mom-and-apple-pie approach poses challenges when we consider the details of implementation.

For example, datasets have become larger and larger in size. (Think of imaging and microscopy datasets.) If a clinical research dataset includes imaging, pathology, physiology, body-fluid chemistry, history, and physical examination data, in what repository can all that information be stored and how can it be shared so that users can easily find everything in one place? Please forgive the pun, but something tells me the digital weather in Bethesda is about to get much "cloudier" as supersized datasets outgrow NIH's data-storage infrastructure and must be sent to remote storage systems, a.k.a. the cloud.

No one is asking investigators to put whole laboratory notebooks or their patients' entire electronic medical records in accessible databases. But at what point in the processing, analyzing, and managing effort should scientific data become sharable? The short answer is "by the time of publication." What about negative data that are not likely to be published in conventional journals? And how will we deal with the deficiencies of science literacy (a problem that is at least partially of our inadvertent making) in those who, along with the scientific community, will have access to the data but not necessarily to the science education and reasoning skills to understand them?

Although NIH has been working for many months to develop, disseminate, and implement strategies and instruments to

facilitate data management and sharing, there remains much work to be done in ensuring and enabling compliance with this policy by the January 25, 2023, deadline. For those who work at NIH, the Office of Intramural Research (OIR) will serve as a resource and facilitator, enabling ICs to empower their investigators.

But make no mistake—the need to solve anticipated as well as unanticipated challenges will mean that this process is iterative and continuously improving. Like all such processes, it will proceed most smoothly and efficiently if done as a team sport. The OIR stands ready to be its hub, and we know we can count on the intramural research programs of every IC to share data as well as best practices and tips for overcoming challenges as we render this process optimal for our science, our patients and their loved ones, our country, and our international colleagues. Like Data, we must keep the mission of our "Enterprise" at the forefront and tailor our process and product to its accomplishment. ●

For more information, go to https://sharing.nih.gov/data-management-and-sharing-policy. Address questions for OIR to Charles Dearolf (dearolfc@mail.nih.gov). For an overview of NIH DMS policies go to https://sharing.nih.gov; for the latest news and events on the policies, go to https://sharing.nih.gov/news-events.

Nina F. Schor, who has been the Acting DDIR since August 1, 2022, became the official DDIR on November 6, 2022.

Independent Research Scholar Program

Expanding Diversity, Supporting Early-Career Independence

BY PETER MANZA, NIAAA

When Tasha Morrison at the National Institute of Arthritis and Musculoskeletal and Skin Diseases first heard about the NIH Independent Research Scholar (IRS) program, she thought it might be an opportunity to build on her postdoctoral work. Now in her third year of the program, which is designed to bolster diversity in the biomedical workforce and provide a launchpad for trainees to land higher positions, Morrison has gained a new perspective on research.

She's honed administrative skills, managed a budget, and supervised trainees. "I don't think I would have had those tools otherwise."

The IRS program was established in 2019 to address a key weakness within ongoing efforts to combat disparities in research: Representation of minority groups remains poor at the highest levels of the scientific enterprise despite recent inroads in attracting diverse trainees. Unlike the Distinguished Scholars Program, which hires diverse candidates directly to tenure-track positions, the IRS is geared toward scientists earlier in their career—the first four years of their postdoctoral fellowship—to offer participants a bridge period of semi-independent training before they apply to higher-level jobs.

By starting earlier with trainees, the hope is to tackle inequities in science from the ground up. "It's going to catalyze a self-reinforcing community of diversity," said **Carl Hashimoto**, who administers the program with **Charles Dearolf** and **Rena Rodriguez**. "There [are] going to be ripple effects."

Scholars are hired to a time-limited position with salary and benefits, and awarded resources to run their own lab, including startup funds and support for two postbaccalaureate fellows. Over three years, successful candidates must carry out a research proposal independent from their current advisor while working with mentors to create a career-development plan. Scholars also participate alongside tenure-track and tenured investigators in faculty meetings and other activities at their institute or center (IC).

"Being in the room with faculty and understanding their viewpoint and opinions has been very helpful for me," said Morrison. "Coming from a postdoc position I wouldn't have had that."

The next application deadline will likely be in February or March 2023. Interested candidates are encouraged to start early and first identify a primary mentor, who will then consult with their IC's scientific director to develop a plan. Dearolf emphasized that applications are judged on three components: quality of the candidate, commitment to diversity, and mentoring and financial support from the IC.

For those selected, including Morrison, the program can open doors. The chance to mentor her own trainees and view science through the lens of an independent investigator has made Morrison a more assertive researcher, emboldening her to advance her scientific career.

"This has made me more likely to ask for what I want and not be silent," Morrison said. "I'm more excited than ever." ●

Peter Manza is a research fellow at the National Institute on Alcohol Abuse and Alcoholism.

Longer version online: https://irp.nih.gov/catalyst/30/6/independent-research-scholar-program.

CHI Reimagined: Call for Collaborative Study Proposals

Providing Advanced Technologies to Intramural Researchers

BY BEN RYAN AND RICHARD APPS, NIAID

The NIH Center for Human Immunology, Inflammation, and Autoimmunity (CHI), which has been in existence for more than 10 years, provides advanced technologies to intramural collaborators who are studying the human immune system. One of CHI's first major studies used a vaccine as a model for assessing immune responsiveness and identified signature subpopulations of immune cells that are predictive of vaccine responsiveness (*Cell* **157:**499-513, 2014). Although there have been a few other studies resulting from intramural-CHI collaborations, many investigators may not realize what CHI has to offer. CHI has recently announced a call for proposals that intramural researchers from any institute or center (IC) may apply for.

A new and improved CHI

CHI has recently revamped its business practices to focus on how it can better support NIH laboratories and enable them to leverage its cutting-edge technologies and informatics support to understand human immune function and pathophysiology. As a trans-NIH initiative, CHI can provide technological resources which are often unavailable to individual laboratories due to costs, complexity, novelty, technological understanding, and expertise. CHI's major technology platforms include sequencing-based technologies, high-dimensional cytometry, and aptamer-based proteomics.

Leadership

In 2022, CHI named **Yasmine Belkaid** as its scientific director and **James Cherry** as its chief of operations. Belkaid, an accomplished researcher in the field of microbiology, first joined CHI as co-director (with **John Tsang**) in 2018. In 2021, she was named chief of the Laboratory of Host Immunity and Microbiome in the National Institute of Allergy and Infectious Diseases (NIAID). Cherry was the scientific program director in the National Cancer Institute's (NCI's) Office of Scientific Operations in Frederick, Maryland, before being recruited to NIAID in 2020 to lead the division of intramural research technologies and serve as the chief of the Research Technology Branch (RTB).

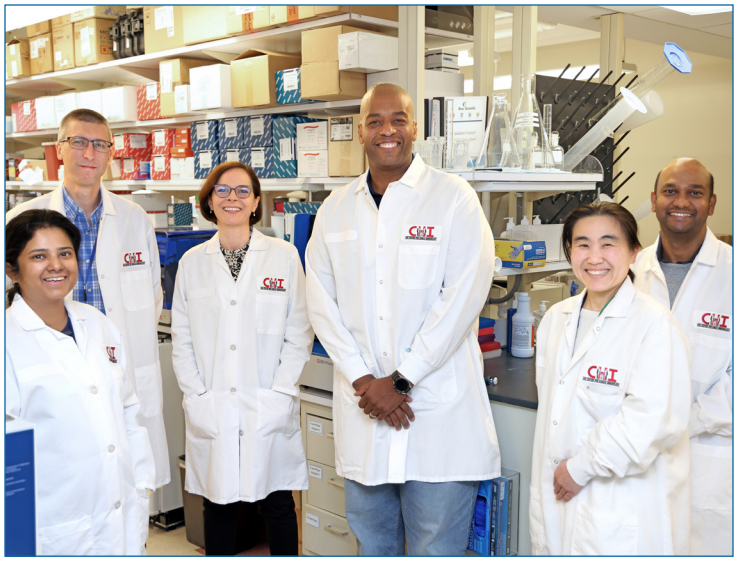
A Scientific Advisory Board (SAB) has been established to help CHI select collaborative projects based on scientific merit. This review process is designed to be transparent with how collaborative projects are selected and what criteria are used. The SAB will ensure that NIH's research spectrum is represented and provide strategic guidance and direction for CHI's scientific priorities and research.

CHI has also forged a close relationship with the RTB to focus on technology development and allow greater access to informatics support through the RTB's Integrated Data Science Section. This new partnership between RTB and CHI will allow for greater collaborative technological expertise and scientific bandwidth.

Call for proposals

On October 3, 2022, CHI announced a call for collaborative scientific study proposals. Intramural investigators from any NIH IC are welcome to apply. Studies would involve tissue samples of particular interest; inter-IC and multi-principal-investigator proposals are encouraged. The application deadline for this round of proposals is November 10. There will be additional project-submission cycles in the coming year. For more information, go to https://www.niaid.nih.gov/research/nih-center-human-immunology-inflammation-and-autoimmunity-chi or contact **Rachel Tracy** (rachel.tracy@nih.gov). ●

Ben Ryan is a program analyst and director of operations at CHI. Richard Apps is a staff scientist at CHI.



CREDIT: CHIA-CHI CHARLIE CHANG, OD

The CHI team provides advanced technologies to intramural collaborators who are studying the human immune system. From left: **Amrita Mukherjee**, **Richard Apps** (staff scientist), **Yasmine Belkaid** (scientific director), **James Cherry** (chief of operations), **Kyu Lee Han**, and **Rohit Farmer**.

New Directors Named for NCI and ARPA-H

New NCI Director: Monica Bertagnolli

ADAPTED FROM NIH NEWS RELEASE (10/3/22)

The National Cancer Institute's (NCI's) 16th director is the first woman to ever hold the position. On October 3, 2022, surgical oncologist **Monica M. Bertagnolli** became the new NCI director, succeeding **Norman E. Sharpless** who stepped down as director in April 2022. Acting NCI Director **Douglas R. Lowy** will resume his role as principal deputy director and will continue his work as chief of the Laboratory of Cellular Oncology in NCI's Center for Cancer Research.

Bertagnolli was previously the Richard E. Wilson Professor of Surgery at Harvard Medical School, a surgeon at Brigham and Women's Hospital, and a member of the Gastrointestinal Cancer Treatment and Sarcoma Centers at Dana-Farber Cancer Institute (all in Boston).

She specializes in treating gastrointestinal cancers and advocates for increasing the diversity of patients enrolled in clinical trials. Earlier in her career, she led the Adenoma Prevention with Celecoxib Trial, which showed that daily use of the nonsteroidal anti-inflammatory drug celecoxib (Celebrex) could lower the risk of precancerous colorectal polyps coming back. Her recent research on the *APC* gene and the role of inflammation in influencing its activity has transformed our understanding of how colorectal cancer develops.

Bertagnolli "is ideally suited to lead NCI at a point in time when opportunities abound for major advancements in cancer research and cancer care," said **Lawrence A. Tabak**, who is performing the duties of the NIH director.

CREDIT: BRIGHAM AND WOMEN'S HOSPITAL

Monica M. Bertagnolli, M.D., became the 16th director of NCI in October 2022.

First ARPA-H Director: Renee Wegrzyn

ADAPTED FROM *NIH RECORD* (10/14/22)

On October 11, 2022, Renee Wegrzyn became the first director of the Advanced Research Projects Agency for Health (ARPA-H), the agency newly established to drive biomedical innovation that supports the health of all Americans.

In announcing his selection on September 12—the 60th anniversary of President John F. Kennedy's "Moonshot" speech—President Joseph Biden talked about his vision for another American Moonshot: ending cancer as we know it. ARPA-H figures prominently among other initiatives to reach that goal.

Biden described Wegrzyn as a leading biomedical scientist and an entrepreneur in synthetic biology with a decade of experience leading multiple biotech projects at the Defense Advanced Research Projects Agency (DARPA). "She's going to bring the legendary DARPA attitude and culture and boldness and risk-taking to ARPA-H to fill a critical need," he said. "Discoveries that save lives, change lives, often start at the lab bench. But then those basic research breakthroughs need to be tested, scaled, and brought to the clinic. This may require unusual partnerships that may require support to get over many obstacles that exist. That's what ARPA-H is designed to do, so the advances can reach all Americans sooner. I predict ARPA-H will emerge as a new and exciting member of America's biomedical ecosystem."

CREDIT: CHRISTOPHER SMITH, HHS

Renee Wegrzyn, Ph.D., became the first director of ARPA-H in October 2022.

ARPA-H was created earlier this year to push the limits of U.S. biomedical and health research and innovation. Public Law 117-103, which was enacted on March 15, 2022, authorized establishment of ARPA-H within the Department of Health and Human Services (HHS). On April 14, HHS Secretary Xavier Becerra transferred ARPA-H to NIH, and on May 25, he formally established ARPA-H as an independent entity within NIH to ensure its ability to operate autonomously and partner across HHS and the wider U.S. government to identify projects that will be transformative and far reaching.

Wegrzyn has professional experience working for two of the institutions that inspired the creation of ARPA-H—DARPA and Intelligence Advanced Research Projects Activity. At DARPA, she was program manager in the Biological Technologies Office, where she leveraged the tools of synthetic biology and gene editing to enhance biosecurity, promote public health, and support the domestic bioeconomy. ●

COVID-19 SIG: Lessons Learned

CONTINUED FROM PAGE 1

to form the COVID-19 Prevention Network, which ran accelerated clinical trials of COVID-19 vaccines and drugs and saved millions of lives.

Prior scientific advances enabled rapid development of COVID vaccines. The speed and efficiency with which the highly efficacious COVID vaccines were developed was due to the extraordinary multidisciplinary effort that involved basic preclinical and clinical science that had been underway out of the spotlight, under the radar screen, even before the COVID-19 pandemic.

Priority- and prototype-pathogen approaches help us prepare for pandemics. A priority-pathogen approach means preemptively making a vaccine for a pathogen, such as Zika and Ebola. A prototype-pathogen approach involves learning from prior experiences with different pathogen families and applying that knowledge of one virus within a family to inform vaccine design for related viruses. Doing this for each of those families will put us in good stead for the next pandemic that we will inevitably face.

We must continue the surveillance of the human and animal interface. About 75% of all new human pathogens—including HIV, influenza, Ebola, and COVID-19—have emerged from animal-reservoir sources. Although we keep an open mind that the origin of COVID-19 may have been from a laboratory accident, the overwhelming evidence now is showing that it was a natural occurrence that was centered in the Wuhan market in China. Evidence indicates that animals brought in from the wild were very likely infected with SARS-CoV-2 that spilled over to humans in the market.

Long-standing systemic health and social inequities drive pandemic disparities. African Americans, Latinos, Native Americans, Alaska Natives, and Pacific Islanders were disproportionately affected by COVID-19. The inequities include discrimination; limited access to and use of health care resources; educational, income, and wealth gaps; and crowded housing conditions that make it difficult to follow prevention strategies such as social distancing.

Misinformation is still the enemy of public health. Misinformation campaigns, conspiracy theories, and fraudulent claims about unproven therapies hindered the dissemination of vaccines. Such misinformation needs to be addressed.

Looking ahead

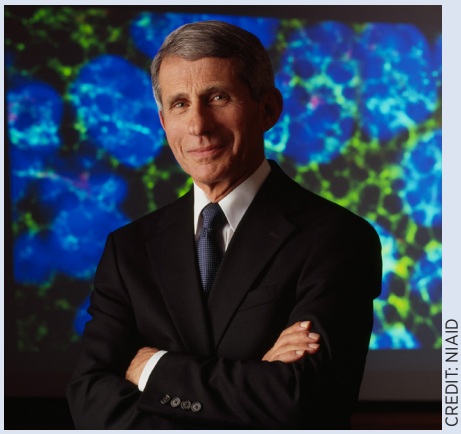
Fauci predicted that it may not be possible to eradicate or eliminate SARS-CoV-2, but believes that it could be controlled at a level that doesn't disrupt our social order or interfere with the economy. "To get there, we believe we have to have the availability of intermittent vaccination," he said. We also need "other things such as respiratory hygiene, attention to ventilation indoors, masking where appropriate, and the availability of effective [antiviral drugs] and monoclonal antibodies."

He hopes that one day we may have a pan-coronavirus vaccine to protect against multiple types of coronaviruses, especially pandemic-causing ones. NIAID is conducting and funding studies on developing universal vaccines and therapeutics, as well as on other pathogens of pandemic concern.

"Emerging infectious diseases have always been with us before we even recorded them," Fauci said in his concluding remarks. "The only way to address them as a global community is to be perpetually prepared. Let's hope that our corporate memory of these lessons does not fade as we put COVID-19 behind us in the future years." ●

To watch the videocast of Fauci's talk, go to https://videocast.nih.gov/watch=45929. To find out more about the COVID-19 Scientific Interest Group, go to https://www.niaid.nih.gov/research/covid-19-sig.

Sunita Chopra is a visiting postdoctoral fellow in the National Cancer Institute's Radiation Oncology Branch, where she studies radiation-responsive coding and noncoding RNA signatures in the blood of whole-body-irradiated animal models.



CREDIT: NIAID

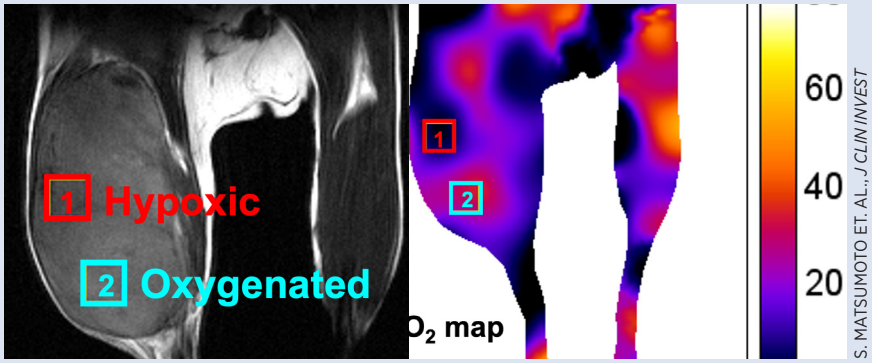
At the COVID-19 SIG virtual meeting, Anthony Fauci talked about lessons learned from the COVID-19 pandemic.

NEWS FROM AND ABOUT THE SCIENTIFIC INTEREST GROUPS

REDOX BIOLOGY SIG:

History of Redox Research at NIH

BY SATABDI NANDI, NIA



NCI and NINDS investigators used a mapping technique to show oxygen gradients in tumors. Left: An MRI of a tumor in a mouse leg. Right: a pulsed electron paramagnetic resonance image of the same tumor showing oxygenated (2) and hypoxic (1) regions (*J Clin Invest* **118:**1965–1973, 2008).

The duality of oxygen was beginning to reveal itself in the 1970s when some scientists were drawing attention to the oxygen paradox—a contentious concept that while oxygen is essential for survival of all aerobic life forms, it can also elicit toxicities through the generation of reactive species known as free radicals.

"As a neonatologist, we knew all about oxygen toxicity," said Senior Investigator **Rodney Levine** at the National Heart, Lung, and Blood Institute (NHLBI). In the 1970s Levine had been treating premature infants whose lungs had been damaged from being ventilated with too much oxygen. Levine's experience was but one vignette in the nascent field of redox biology that would be enriched by a passionate group of investigators who hailed from a range of scientific disciplines.

When they are breathing, all aerobic organisms produce reactive molecules through redox reactions: chemical reactions in which the oxidation number of a molecule, atom, or ion changes by gaining or losing an electron. This normal electron swapping plays a vital role in maintaining functions such as cellular metabolism, molecular signaling, immune response, and the removal of toxins. But those same redox reactions can also be harmful during oxidative stress, a condition of imbalance between free radicals and antioxidant defenses (consisting of small molecules that sacrifice an electron to neutralize free radicals and enzyme systems that degrade reactive species) in the body. Chronic oxidative stress may lead to cardiovascular diseases, cancer, neurodegeneration, and even complications in preterm newborns.

As data surrounding oxygen toxicity accumulated "it was becoming necessary to bring people together to understand the chemistry and biochemistry of it," said **Carol Colton**, who is a neuroscientist at Duke University and was a special expert (1985-1987) in **Daniel Gilbert**'s Reactive Oxygen Species Unit lab at the National Institute of Neurological Disorders and Stroke. In 1987 the pair co-founded The Oxygen Club of Greater Washington, D.C. and its sister organization, the NIH Free Radical Research Scientific Interest Group (SIG).

Colton considers Gilbert "the grandfather of the movement." Gilbert and Rebeca Gerschman were the first to recognize a common free radical mechanism of action in oxygen toxicity and radiation. Gilbert, Colton, and their colleagues would go on to generate seminal work on the role of oxygen in the brain, which led the way in understanding how seizures may come about. The new SIG was among the first transdisciplinary scientific groups dedicated to understanding the role of oxygen, free radicals, reactive oxygen, and nitrogen species across the different fields of biology, physiology, and medicine. It provided investigators the opportunity to learn and network with colleagues at NIH and across the country by organizing lectures, seminars, and meetings.

In 1977, Levine joined **Earl Stadtman's** Laboratory of Biochemistry at NHLBI as a postdoctoral fellow to work on protein turnover. Stadtman was an international redox leader himself and had made major contributions toward understanding the duality of oxygen. His lab both uncovered how oxidation can degrade proteins, and as early as 1960, showed how a free radical played an essential role in cellular metabolism. In 1987, Levine and Stadtman helped found a national society now known as the Society for Redox Biology and Medicine. A wave of new findings in the field led to a lot of excitement and the formation of other oxygen clubs across the country, which began to collaborate.

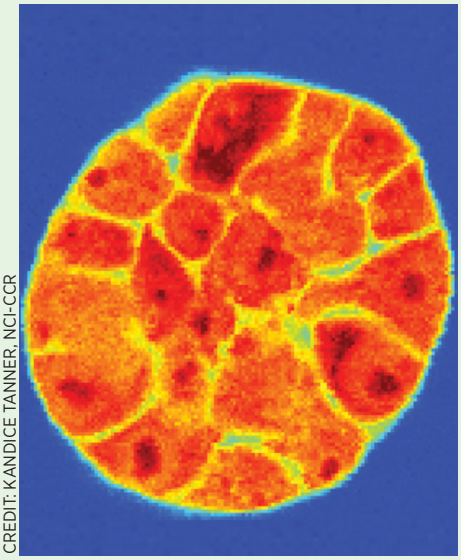
In 2022, the Free Radical Research SIG was rebranded as the NIH Redox Biology SIG and is chaired by National Cancer Institute Stadtman Investigator **Urbain Weyemi**. Weyemi is especially interested in harnessing the dialogue between redox metabolism and genome repair in new ways to treat cancer. ●

For more information about the Redox Biology SIG, go to https://oir.nih.gov/sigs/redox-biology-interest-group or contact Urbain Weyemi at urbain.weyemi@nih.gov.

Satabdi Nandi is a postdoctoral fellow in the Laboratory of Molecular Biology and Immunology in the National Institute on Aging.

Read longer a longer version of this article at https://irp.nih.gov/catalyst/30/6/the-sig-beat-redox-biology-sig.

Intramural Research Briefs



CREDIT: KANDICE TANNER, NCI-CCR

NCI: NCI researchers used Brillouin microscopy to explore how cancer cells' biomechanical properties influence their growth and aggressiveness. Shown: A spheroid of breast cancer cells grown in a three-dimensional matrix; Brillouin microscopy reveals each cell's stiffness (darker red cells are stiffer).

NCI: MECHANICAL PROPERTIES OF CANCER CELLS GIVE INSIGHT INTO METASTASIS

What makes some cancers spread aggressively while others remain harmless for years or decades? One theory is that cancer cells tend to be pliable and can adopt different mechanical properties that are thought to help them slip through tissues and migrate to distant sites in the body. In a recent study, NCI scientists showed how noninvasive techniques can be used to explore how a cancer cell's mechanical properties are shaped by external cues.

According to lead author **Kandice Tanner**, cells' mechanical properties—their stiffness and viscosity, for example—have such a profound influence on their behavior that changes to these properties are likely key to cancer's growth and progression.

The research team assessed the viscoelasticity of cancer cells growing in complex three-dimensional structures with a technique called Brillouin microscopy, which tracks the way light scatters when it hits materials. Paired with a method developed in Tanner's lab called optical tweezer microrheology, which uses microbeads to apply precise forces to the cells, the researchers quantified the mechanical properties at both cellular and subcellular levels.

Cells can alter their mechanical properties in response to their environment. "We're really probing what a cell senses in the context of a tissue, and we're doing it under different microenvironmental cues that mimic what the cells would see in a living animal," said Tanner. She hopes that biomechanical information might one day help clinicians predict whether a patient's tumor is likely to metastasize and if it does, where metastatic tumors are most likely to emerge. (NIH authors: M. Nikolic and K. Tanner, *Biophy J* **121**:3586-3599, 2022; DOI:10.1016/j.bpj.2022.09.002)

NHGRI, NLM, NIAID: UNIQUE SET OF PROTEINS RESTORES HEARING IN ZEBRAFISH

Through aging and trauma, hearing loss is often caused by the loss of hair cells in the inner ear. Humans can't regenerate them, but some animals, such as zebrafish can. NHGRI researchers have identified a mechanism that could one day translate to humans.

Using a combination of genomic techniques and computational-based machine learning, the investigators found that the regeneration of hair cells in zebrafish relied on a network of transcription factors, which are proteins that can switch genes on and off.

Two families of transcription factors were identified that work together to activate hair-cell regeneration in zebrafish, called Sox and Six. When hair cells die in zebrafish, nearby support cells start changing to become new hair cells in a process called transdifferentiation. Like stem cells, support cells can become other cell types.

First, the Sox transcription factors initiate the regeneration response in surrounding support cells. Next, both Sox and Six cooperate to turn those support cells into hair cells. "This group of zebrafish transcription factors might become a biological target that may lead to the development of novel therapy to treat hearing loss in humans," said lead author **Erin Jimenez**. (NIH authors: E. Jimenez, C.C. Slevin, W. Song, S.C. Frederickson, D. Gildea, W. Wu, A.G. Elkahloun, I. Ovcharenko, and S.M. Burgess, *Cell Genomics* **2**:100178, 2022; DOI:10.1016/j.xgen.2022.100170)

NIDA, NIAAA: POTENTIAL NEW MEDICATION TO TREAT ALCOHOL-USE DISORDER

One size does not fit all when it comes to treating alcohol- and substance-use disorders. There are three medications approved for alcohol-use disorder in the United States, but new research by collaborative teams at NIDA, NIAAA, and the Yale School of Medicine (New Haven, Connecticut) shows promising results for repurposing spironolactone as another potential pharmacotherapy for the disorder.

Spironolactone is used to treat cardiovascular conditions such as hypertension and heart problems. It works by inhibiting hormone receptors found throughout the body that regulate electrolyte balance. Those hormones and receptors might play a role in alcohol use, and the mechanism of action of spironolactone is actively being investigated.

NIDA-led studies found that administering spironolactone decreased bingelike drinking in male and female mice. Concurrently, researchers at Yale led retrospective studies on a large cohort of patients from the United States Veterans Affairs health care system. The scientists found that patients who were prescribed spironolactone for cardiovascular conditions had a marked reduction in self-reported alcohol consumption. According to the authors, the findings support the need for randomized controlled trials of spironolactone in people with alcohol-use disorder. (NIH authors: M. Farokhnia, V. Chuong, M.A. McGinn, S.K. Elvig, E.A. Douglass, L.A. Gonzalez, J.E. Sanfilippo, R.C.N. Marchette, B.J. Tunstall, G.F. Koob, L. Leggio, and L.F. Vendruscolo, *Mol Psychiatry* 2022; DOI:10.1038/s41380-022-01736-y)

[BY DIANNE LEE, NIMH]

NEI, NIAID, NINDS: IMAGING REVEALS DETAILS ABOUT RARE EYE DISEASE

For the first time, NEI scientists have shown how cells across different tissue layers in the living human eye are affected in people with choroideremia, a rare genetic disorder that leads to blindness.

Lead author **Johnny Tam** combined adaptive optics (a technology that enhances imaging resolution) with indocyanine green dye to view live cells in the retina, including light-sensing photoreceptors, retinal pigment epithelium (RPE), and choroidal blood vessels. His team was able to visualize how choroideremia disrupts these tissues, providing information that could help design effective treatments for this and other diseases. The retina's RPE is a layer of pigmented cells essential to the nourishment and survival of photoreceptors.

"One major finding of our study was that the RPE cells are dramatically enlarged in males and females with choroideremia," said Tam. His team also found that enlarged RPE cells can be detected even when using only a commercially available scanning laser ophthalmoscope along with indocyanine green dye. Tam noted that using an existing tool in the clinic could help clinicians identify which patients would benefit the most from therapeutic interventions. (NIH authors: N. Aguilera, T. Liu, A.J. Bower, J. Li, S. Abouassali, R. Lu, J. Giannini, M. Pfau, C. Bender, M.G. Smelkinson, A. Naik, B. Guan, O. Schwartz, A. Volkov, D. Maric, R. Fariss, R.B. Hufnagel, B.G. Jeffrey, B.P. Brooks, W.M. Zein, L.A. Huryn, and J. Tam, *Commun Biol* **5**:article number 893, 2022; DOI:10.1038/s42003-022-03842-7)

NIDDK, NIAID, ORS: CELLS THAT REMEMBER HEPATITIS C VIRUS PROVIDE OPPORTUNITY FOR VACCINE DEVELOPMENT

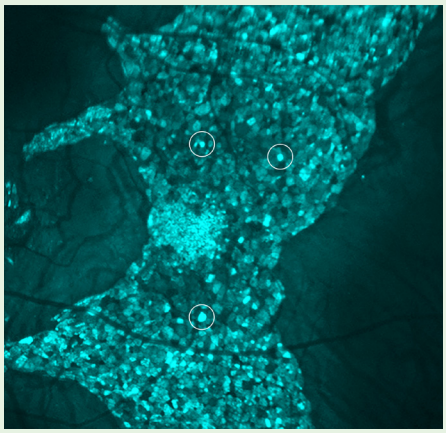
Findings from a study led by NIDDK researchers suggest that vaccines could be developed to protect people from being reinfected with the hepatitis C virus (HCV). The researchers calculated the duration and quality of the natural antibody response against hepatitis C by following HCV-cured patients for up to 18 years. The natural antibody response declined rapidly, with a half-life of about five to seven years. However, some cells continue to remember the virus for decades after the virus was cured. In response to an antigen on the surface of a virus, these long-lived memory B cells are activated and multiply rapidly, differentiating into plasma cells that secrete protective antibodies. The cells' persistence and ability to secrete antibodies suggest that they could be pertinent to the development of future HCV vaccines. (NIH authors: A. Nishio, S. Hasan, H. Park, N. Park, L. Kardava, P. Juneau, S. Moir, M.G. Ghany, and B. Rehermann, *Nat Commun* **13**:5446, 2022; DOI:10.1038/s41467-022-33035-z)

[BY SUSAN BOSWELL-MAIER, NIDDK]

NCATS: NOVEL MOLECULAR COMPOUNDS MAY REVERSE NEUROLOGICAL DISEASE

NCATS researchers and their colleagues at the Icahn School of Medicine at Mount Sinai (New York) have identified small-molecule compounds that reversed the effects of several life-threatening neurodegenerative diseases called lysosomal storage disorders (LSDs) in patient cells and mice. LSDs are caused by inherited genetic defects in which a cell's lysosomes stop breaking down and recycling fats, sugars, and proteins, which can accumulate in the liver and brain. This accumulation eventually causes the energy-producing mitochondria to malfunction. In a recent study, the scientists uncovered new compounds that restored mitochondrial function by activating the tumor necrosis factor receptor-associated protein 1 (TRAP1).

The Mount Sinai researchers first developed assays to identify compounds that increased the expression of Rab9, an enzyme associated with improved lipid storage in a type of LSD known as Niemann-Pick disease type C1 (NPC1). A NCATS team led by **Juan Marugan** then used the test with high-throughput screening facilities to sift through thousands of compounds and determine which ones worked best. The investigators discovered that some compounds activated TRAP1 and made the mitochondria work properly again, and also restarted the lysosome's fat-recycling ability.



CREDIT: JOHNNY TAM, NEI

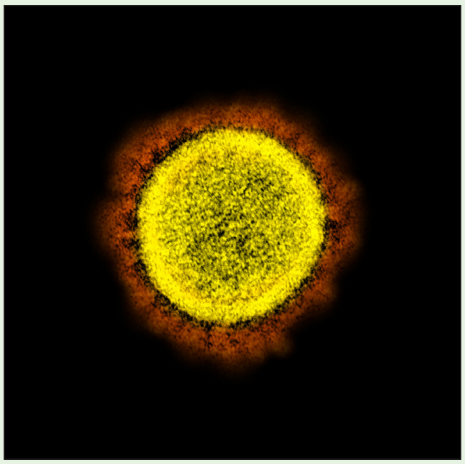
NEI, NIAID, NINDS: Retinal pigment epithelium cells (RPE) in a male participant with choroideremia, showing that enlarged RPE cells can be detected using a multimodal imaging approach (see circled examples).

Additionally, increasing TRAP1 activity in cells from patients with other LSDs also corrected those cell's respective conditions.

Similar dysfunctions in cell recycling and mitochondrial health occur in other neurodegenerative disorders, such as Parkinson disease, amyotrophic lateral sclerosis, and Alzheimer disease. "We believe that this approach could have therapeutic benefits for more mainstream disorders, as well," said Marugan. (NIH authors: R. Calvo, S. Patnaik, R. Mull, P. Dranchack, A. Wang, X. Xu, E. Hughes, N. Southall, M. Ferrer, and J.J. Marugan, *iScience* **25**:104941, 2022; DOI:10.1016/j.isci.2022.104941)

Read longer versions of these briefs, including photos, at https://irp.nih.gov/catalyst/30/6/research-briefs.

COVID-19 Timeline at NIH (September–October 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 in Fort Detrick, Maryland.

September 1: The CDC recommends a single updated booster dose of either the Moderna vaccine for individuals 18 and older or the Pfizer-BioNTech vaccine for individuals 12 and older at least two months following primary or booster vaccination. The original monovalent boosters are no longer authorized for use.

September 2: The CDC updates COVID-19 community levels: Rocky Mountain Laboratories in Hamilton, Montana, moves from medium to low community level. Framingham, Massachusetts, moves from low to medium, and Detroit, Michigan, moves from high to medium. All other NIH locations remain at their current levels.

September 2: **Lawrence Tabak** (Performing the Duties of the NIH Director) emails staff with a coronavirus update. He calls attention to this week's FDA authorization (August 31) of the Moderna and the Pfizer-BioNTech COVID-19 bivalent boosters, which are designed to give better protection against circulating omicron BA.4 and BA.5 subvariants, and to the CDC recommendation (September 1) to get one of those vaccines. Tabak notes revised and streamlined content on the NIH Guidance for Staff on Coronavirus intranet site based on the latest information.

September 8: NIH's RADx Tech program issues two new funding opportunities for diagnostic test manufacturers to develop the next generation of COVID-19 tests, with a focus on accessibility. The first is a call to develop accessible over-the-counter tests that can be used by people with disabilities, specifically blindness, low vision, fine-motor-skill difficulties, and aging-related disabilities. The second focuses on improving performance of over-the-counter and point-of-care tests as well as integrating universal design features to ensure ease of use. Products should be ready for commercialization in 12-24 months.

September 9: The CDC updates COVID-19 community levels: Rocky Mountain Laboratories in Hamilton, Montana, moves from low to medium community level. Research Triangle Park in Durham County, North Carolina, moves from high to medium, and Framingham, Massachusetts, moves from medium to low. All other NIH locations remain at their current levels.

September 12: President Joseph Biden announces his intent to appoint **Renee Wegrzyn** as the first director of the Advanced Research Projects Agency for Health (ARPA-H). She started as ARPA-H director on October 11, 2022.

September 15: An NIH-funded research team develops a method to evaluate how mutations in SARS-CoV-2 can affect recognition by antibodies used in rapid antigen tests. Because most rapid antigen tests detect the SARS-CoV-2 nucleocapsid protein (N protein), the team directly measured how mutations to the N protein affected diagnostic antibodies' ability to recognize their target (*Cell* **185:**P3603-3616.e13, 2022).

September 15: NIAID Director **Anthony Fauci** gives a talk to the COVID-19 Scientific Interest Group outlining lessons learned from COVID-19. Watch videocast at https://videocast.nih.gov/watch=45929. Story in this issue of *The NIH Catalyst* starts on page 1.

September 16: The CDC updates COVID-19 community levels: Bayview Research Center in Baltimore, Maryland, and Rocky Mountain Laboratories in Hamilton, Montana, move from medium to low community level and Framingham, Massachusetts, moves from low to medium. All other NIH locations remain at their current levels.

September 16: **Lawrence Tabak** (Performing the Duties of the NIH Director) emails staff with a coronavirus update and encourages eligible employees to get the updated Moderna or the Pfizer-BioNTech COVID-19 bivalent vaccine boosters. Additionally, effective November 1, 2022, NIH asymptomatic testing services will only be offered to staff members with direct patient contact or referred by Occupational Medical Service based on job duties required to keep the workplace safe. Tabak highlights the September 8 RadX Tech announcement about new funding opportunities for diagnostic test manufacturers to develop the next generation of COVID-19 tests.

September 21: The National Science Advisory Board for Biosecurity (NSABB) convenes virtually to discuss its progress in reviewing existing national biosecurity oversight frameworks governing research with enhanced potential pandemic pathogens and dual-use research of concern. The NSABB is a federal advisory committee chartered to provide advice, guidance, and recommendations to the United States government regarding potential biosecurity implications of life sciences research.

September 23: The CDC updates COVID-19 community levels: Rocky Mountain Laboratories in Hamilton, Montana, moves from low to medium community level and Research Triangle Park in Durham County, North Carolina, moves from medium to low. All other NIH locations remain at their current levels.

September 27: A large international study funded by NIH confirms the findings of a previous U.S. study that linked COVID-19 vaccination with an average increase in menstrual cycle length of less than one day (*BMJMedicine* 1:e000297, 2022; DOI:10.1136/bmjmed-2022-000297).

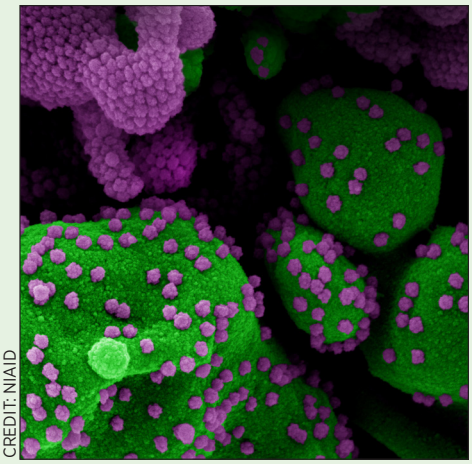
September 30: **Lawrence Tabak** (Performing the Duties of the NIH Director) emails staff with a coronavirus update, reporting a continuing trend of decreasing new case numbers, hospitalizations, and deaths. Starting in October, Tabak will send his coronavirus update email on the second Friday of each month.

October 3: The National Library of Medicine (NLM) resumes Reading Room Operations after having been closed since March 2020 due to renovations taking place in the NLM Building as well as ongoing COVID-19 considerations. NLM welcomes customers by appointment only Monday-Friday from 8:30 a.m. to 5:00 p.m. ET.

October 6: A small NIAID-supported study of eight patients taking the antiviral Paxlovid suggests that COVID-19 rebound is likely not caused by impaired immune responses (*Clin Infect Dis* 2022; DOI:10.1093/cid/ciac663).

October 7: The CDC updates COVID-19 community levels: Research Triangle Park in Durham County, North Carolina, moves from low to medium community level. All other NIH locations remain at their current levels.

October 12: The FDA amends their emergency use authorizations for the Moderna and the Pfizer-BioNTech COVID-19 bivalent vaccine boosters for use in younger age groups. The Moderna COVID-19 bivalent vaccine is authorized for administration at least two months after completion of primary or booster vaccination in children down to six years of age. The Pfizer-BioNTech COVID-19 bivalent vaccine is authorized for administration at least two months after completion of primary or booster vaccination in children down to five years of age.



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 in Fort Detrick, Maryland.

October 14: The CDC updates COVID-19 community levels: Research Triangle Park in Durham County, North Carolina, and Rocky Mountain Laboratories in Hamilton, Montana, move from medium to low community level. All other NIH locations remain at their current levels.

October 14: **Lawrence Tabak** (Performing the Duties of the NIH Director) emails staff with a coronavirus update. He reports that after this week's amended FDA authorization, the CDC now recommends the Pfizer-BioNTech bivalent vaccine booster for individuals five years of age and older and the Moderna bivalent vaccine booster for individuals six years of age and older.

Read a more detailed version of this timeline, complete with links, at https://irp.nih.gov/catalyst/30/6/covid-19-timeline-at-nih-september-october-2022.

NIH ABBREVIATIONS

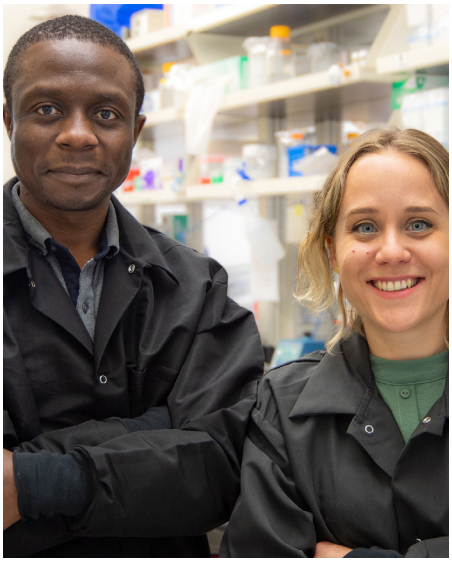
CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
DIPHR: Division of Intramural Population Health Research, NICHD
FAES: Foundation for Advanced 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

Monkeypox

CONTINUED FROM PAGE 1

before being distributed through the exotic pet trade. All confirmed cases of monkeypox in humans were eventually traced to direct contact with those prairie dogs. Within two months the outbreak would fizzle out, along with international attention on the virus.

CREDIT: RYAN KISSINGER, NIAID



CREDIT: AUSTIN ATHMAN, NIAID

Top: **Vincent Munster's** lab in Rocky Mountain Labs (at NIAID's Hamilton, Montana, campus) began studying monkeypox in 2017 when an outbreak appeared in a rural logging community in the Republic of the Congo.

Bottom: Postdoctoral visiting fellows in Munster's lab: **Kwe Claude Yinda** (left) is doing deep-sequencing analyses on monkeypox samples; **Julia Port** is involved in experimental animal modeling of monkeypox virus.

Fast forward to 2022: Since May, the CDC has recorded more than 65,000 cases of monkeypox globally and nearly 24,000 cases in the United States alone. This time, transmission is being driven by human-to-human contact. What makes this outbreak different? The vast majority of cases are affecting interlinked communities of men who have sex with men, although public health officials caution that anyone who has had close contact with an infected person can get the disease.

Vaccines originally developed for smallpox are likely to be effective against monkeypox, too, and scientists are expanding treatment options. But questions remain on precisely how the virus is transmitted, how it might be changing, and what can be done better to combat it. NIH scientists are addressing those gaps in knowledge with new research to improve diagnostics and optimize therapeutics. They are working with colleagues around the globe to understand why this emerging virus is posing new challenges.

The origins of monkeypox outbreaks

In search of monkeypox's elusive human-animal interface and its natural animal reservoir is Senior Investigator **Vincent Munster** at the National Institute of Allergy and Infectious Diseases' (NIAID's) Rocky Mountain Labs in Hamilton, Montana. His team is studying emerging viruses deep in the rainforest of the Republic of the Congo in Central Africa. Back at the lab, they model how changes in the environment or the virus's biology itself may affect transmission.

"How do you truly get in contact with that particular virus?" said Munster, referring to the conditions needed for a zoonotic virus such as monkeypox to jump the species barrier from animal to human. For example, hunters might be more likely to encounter an infected animal in areas where that animal's food sources are more abundant. Monkeypox's natural animal reservoir has yet to be pinpointed, but is widely thought to be rodents, with African rope squirrels, Gambian pouched rats, and African dormice being among the prime suspects.

The first case of human monkeypox was identified in 1970 in a 9-month-old boy in the Democratic Republic of the Congo (DRC) in Central Africa. Clinically, the disease resembles smallpox, but it's not as deadly and there are fewer human-to-human transmissions. A virulent strain known as clade one is prevalent in the rainforests of Central Africa, particularly in the DRC where mortality rates frequently top 10%. Fueling the current global outbreak is a subvariant of clade two, which is a milder strain in West Africa with a mortality rate of less than 1%.

Rapidly diagnosing the first cases of an outbreak is a critical step in arresting its advance. In collaboration with African academic and conservation groups, Munster's Viral Ecology Section (VES) lab has been conducting long-term studies on Ebola and the role of fruit bats, a natural reservoir of the disease. The NIAID team provides training, equipment, and the reagents needed for diagnosis while their partners in Africa provide the laboratory and clinical infrastructure. In 2017, the VES added monkeypox to their list of diagnostic capabilities when an outbreak of that virus appeared in a rural logging community in the Republic of the Congo. "Everywhere you can expect a virus to emerge, we need to ensure that we have appropriate diagnostics," said Munster, noting that the frequency of small monkeypox outbreaks in Africa had been increasing in recent years.

Improving disease surveillance

Some scientists have suggested that the current monkeypox strain originated from a Nigerian outbreak in 2017 that continued to lurk in the human population before being exported by travelers in recent years. A project led by Ghanaian scientist **Irene Owusu Donkor** may help shed some light on that theory. Donkor was a postdoctoral fellow in Munster's lab (2019-2020) and worked on Lassa virus before returning to her native country. She's now partnering with the VES team on an extensive serosurvey in Ghana to analyze blood samples collected from people across the country before the current monkeypox outbreak began. The presence of poxvirus antibodies in those samples could indicate that there was already widespread circulation and show which parts of the population historically get exposed to monkeypox.

Munster's lab is also testing the environmental stability of the virus to understand how well it holds up under different conditions. Monkeypox spreads through direct contact with an infected person's bodily fluids (such as saliva, respiratory droplets, and semen) or via sores or scabs. People are considered infectious from the onset of flu-like symptoms or rash until the scabs have fallen off (typically 2-4 weeks). But scientists don't yet understand whether it is transmitted by respiratory droplets and how long contaminated surfaces such as bedding remain infectious. Virologists like Munster hope that identifying new routes of transmission will better inform public health messaging.

New diagnostics

More precise diagnostics are needed to enhance epidemiological studies. A team led by Senior Investigator **Daniel Douek** at NIAID's Vaccine Research Center (VRC) is developing new monkeypox-specific assays that distinguish between individuals who have been infected with a poxvirus and those who were vaccinated against monkeypox or variola (smallpox). Both viruses are part of the genetically similar Orthopoxvirus genus, as is the less dangerous vaccinia virus, from which today's poxvirus vaccines are derived.

CREDIT: IRENE OWUSU DONKOR

Ghanaian scientist **Irene Owusu Donkor** (right), a former postdoc in Munster's lab, and current Munster team member **Bob Fischer** are performing small-rodent field work in Ghana.

Orthopoxviruses have a distinct feature: Infection confers cross-immunity to other orthopoxviruses. But for how long, we don't know. Current blood tests are unable to discriminate between a history of infection and vaccination. A more sensitive assay would help researchers determine to what degree prior vaccination against or infection with any of the orthopoxviruses is protective against monkeypox.

Smallpox preparedness aids monkeypox response

Our arsenal of monkeypox treatments is a result of years of drug development and having stockpiled them for a potential bioterrorist event. Following the 9/11 and anthrax terrorist attacks in 2001, concerns mounted that smallpox could be resurrected and used as a biological weapon. Smallpox was declared eradicated in 1980 following worldwide programs that used a weakened vaccinia vaccine. That vaccine, labeled Dryvax in the United States, was highly effective but could have severe side effects in immunocompromised individuals or those with conditions such as eczema. A safer vaccine that was well tolerated by the entire population was needed.

NIAID subsequently worked with the Biomedical Advanced Research and Development Authority to support the development of a modified vaccinia virus ankara (MVA) vaccine platform known as JYNNEOS. This next-generation vaccine, which is safe for people with weakened immune systems, was approved in 2019 by the United States Food and Drug Administration (FDA) for smallpox and monkeypox. Data from European studies have also shown that it can be used as post-exposure prophylaxis within 4 days and can be considered up to 14 days after exposure due to monkeypox's long incubation period.

Clinical trials underway

According to **Emily Erbelding**, director of NIAID's Division of Microbiology and Infectious Diseases, we still need to learn more about how to improve the tools we already have. JYNNEOS stockpiles are limited, and NIAID-supported trials will determine whether one-fifth the dose administered intradermally (two subcutaneous injections is the standard regimen) results in a safe and effective immune response—a strategy that would stretch the vaccine supply fivefold. That strategy has already been authorized by the FDA for adults and eight trial sites—including one at the NIH Clinical Center—across the country are recruiting volunteers to provide

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Monkeypox

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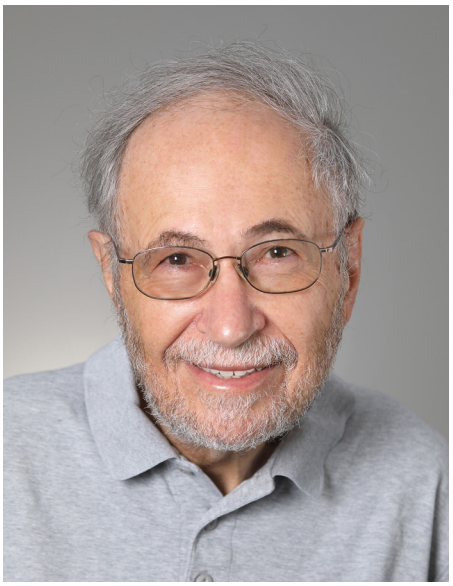


CREDIT: CHIA-CHI CHARLIE CHANG, OD

Since coming to NIH in 1966, **Bernard Moss** has elucidated every step in the life cycle of pox viruses from cell entry to gene expression to DNA replication and assembly of infectious particles. His group is studying the monkeypox virus now.

more data on intradermal administration that would support licensure.

The antiviral tecovirimat (Tpoxx), a drug developed with NIAID support, was FDA-approved in 2018 to treat smallpox. Preclinical trials have found the drug has a good safety profile and targets a protein shared by both variola and monkeypox. Recruiting study participants is suddenly easier as a result of the 2022 monkeypox outbreak, and two new NIAID-supported clinical trials in the United States as well as the DRC will test the safety and efficacy of Tpoxx in humans. The trials are expected to provide data on how long people remain infectious whether or not they receive antivirals.

A changing virus

How is monkeypox evolving? NIAID Distinguished Investigator **Bernard Moss**, chief of the Genetic Engineering Section, is working on figuring that out. Since he came to NIH in 1966, Moss has elucidated every step in the life cycle of pox viruses from cell entry to gene expression to DNA replication and assembly of infectious particles.

"Our first interest in monkeypox was to try to understand why the Central African clade was more virulent than the West African clade," said Moss. His lab uses an animal model known as a castaneous (CAST) mouse, which is highly susceptible to Orthopoxvirus infection, as well as African dormice. In a soon-to-be-released paper, his lab found the Central African clade was significantly more lethal than the West African clade in CAST mice. Studies are now underway to test whether the virulence of the 2022 strains is any different.

Working with monkeypox requires stringent safety precautions. Moss's Biosafety Level 3 laboratory in Building 33 is specially equipped to conduct research on select agents that have the potential to pose a severe health threat. The facility is monitored by round-the-clock security guards and video surveillance and access requires additional clearances.

New technologies

Vaccinia was the first virus to be engineered as a recombinant vaccine. Moss, along with his former postdoctoral fellow **Enzo Paoletti**, were the first to show that a vaccina virus could be modified to protect against other pathogens. Their two papers were published simultaneously (Moss's paper: *Proc Natl Acad Sci USA* **79:**7415-7419, 1982; Paoletti's paper: *Proc Natl Acad Sci USA* **79:**4927-4931, 1982). Moss further showed that a recombinant vaccinia virus could protect chimpanzees against hepatitis B (*Nature* **311:**67-69, 1984). Years later, leading up to the development of the JYNNEOS vaccine, Moss and his collaborators published a study demonstrating that the MVA platform could be safely used to protect monkeys from monkeypox (*Nature* **428:**182-185, 2004).

MVA can be difficult to manufacture however, and there are possibilities for new vaccines. Moss is working with Senior Investigator **Nancy Sullivan** at the VRC in collaboration with the pharmaceutical company Moderna to evaluate the immunogenicity of novel mRNA vaccines for monkeypox.

Current guidance to control the 2022 outbreak has focused on temporarily changing social behaviors while vaccination efforts are ramped up. There are signs that the strategy is working. Case counts have declined since August and behavior surveys show that individuals are taking steps to protect themselves and their partners from monkeypox. But Moss cautions continued vigilance. In 2003 monkeypox did not become widespread. Given the scope of the current outbreak, he warns of the possibility that we might not be so lucky this time. If the virus were to establish itself in the animal population, future outbreaks could become more common.

"One would have to consider that would be a very bad result of this epidemic if monkeypox would resolve in humans but continue as a reservoir in North American animals," Moss said. ●

CREDIT: GEORGE KATSAFANAS, NIAID

Patricia Earl and **Jeffrey Americo**, members of NIAID's Genetic Engineering Section, study monkeypox in a Biosafety Level-3 containment laboratory. Photograph taken through a window from outside the lab.

How to Be an Antiracist

NIH Big Read Discussion with Ibram X. Kendi

BY AMRITA MANDAL, NICHD

After a two-year hiatus due to the COVID-19 pandemic, the NIH Big Read resumed its annual lectures on September 27, 2022, with a virtual presentation by Ibram X. Kendi, author of the New York Times #1 bestseller *How to Be an Antiracist* (2019). Kendi is an award-winning author, a distinguished historian and antiracist scholar, and the founding director of the Center of Antiracist Research at Boston University (Boston). The event featured Kendi in conversation with National Institute on Minority Health and Health Disparities (NIMHD) Director **Eliseo J. Pérez-Stable**.

In his book, Kendi takes us through his journey of coming to understand the true meaning of antiracism. He believes that the opposite of "racist" is "antiracist" and there is no neutral middle ground of "not racist." An antiracist believes that problems are rooted in power and policies and confronts racial inequities. Kendi explained that we all have the responsibility to consistently self-examine our daily practice and take actionable measures toward creating an antiracist world.

Looking at racism through a historical lens, Pérez-Stable and Kendi discussed the interweaving of the science on race, class, and racism; social and cultural beliefs; and the policies that bind them. In this respect, Pérez-Stable introduced the research NIH is undertaking to better understand the impact of racism on health conditions, as well as the myriad social constructs that contribute to racial and ethnic health disparities. Kendi emphasized that to eliminate these disparities and to create a healthier society, we need to shift the focus of research from culture and/or the behavior of certain racial groups to investigating "policies and practices and conditions that are actually causing…racial health disparities."

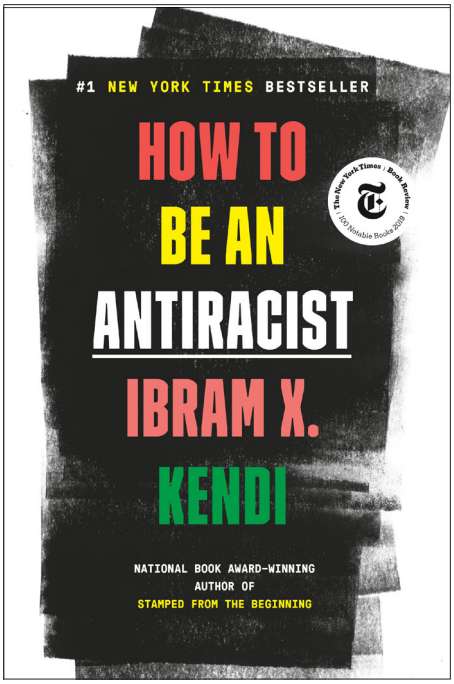
NIH is taking steps in that direction. Pérez-Stable described the NIH UNITE initiative, which was launched in February 2021 by then-NIH-Director **Francis Collins**. UNITE aims to identify and address structural racism within the NIH-supported and greater scientific community. Kendi expressed his excitement over this initiative and mentioned how the work of NIH scientists has been critical to racial equity since the mapping of human genome, in 2003, established that "race does not exist from a biological [or] scientific standpoint." From then on, it could be said definitively that "race is a fiction and racism is a fact," he said.

Marie Bernard, a UNITE co-chair and NIH's Chief Officer for Scientific Workforce Diversity, talked about how UNITE's Anti-Racism Steering Committee is addressing racial and ethnic equity in the NIH internal workforce. She asked whether Kendi had any general advice for the committee.

He suggested that the committee try to "figure out ways—whether it's through focus groups or extended interviews—to really understand how people are being treated or how they're feeling [and] see what impact the interventions are having."

It is important "for everyone at [NIH] to realize that these equitable initiatives are actually beneficial to the [NIH's] work [and will] create better science [and] equitable teams," Kendi said. "This is not just to create equity. This is to create a better NIH."

In his book, Kendi used cancer as a metaphor for racism. "We can survive metastatic racism," he wrote. "Saturate the body politic with the chemotherapy or immunotherapy of antiracist policies that shrink the tumors of racial inequities, that kill undetectable cancer cells."



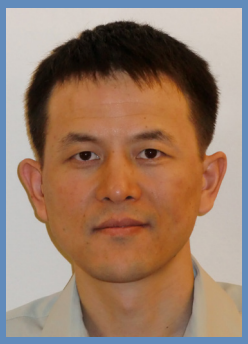
The cancer of racism is fast spreading in our society, but Kendi dreams of a future in which humanity wins against all odds and the sun will rise again in an antiracist world. "As individuals if we are willing to transform ourselves, and look deeply at ourselves, [then] we'll be able to transform our [biomedical centers] for the better." ●

The 2022 NIH Big Read was presented by the NIH Library, the Foundation for Advanced Education in the Sciences, the Office of the NIH Director, NIH UNITE, and NIMHD.

Amrita Mandal, a postdoctoral visiting fellow in the Eunice Kennedy Shriver *National Institute of Child Health and Human Development, studies lipid signaling in eukaryotes.*

Recently Tenured

YEKA APONTE, NIDA



HAIMING CAO, NHLBI

MARC GHANY, NIDDK

STAVROULA (VOULA) MILI, NCI-CCR

NAOKO MIZUNO, NHLBI

YEKA APONTE, PH.D., NIDA

Senior Investigator and Chief, Neuronal Circuits and Behavior Section, National Institute on Drug Abuse

Education: Universidad Central de Venezuela in Caracas, Venezuela (B.Sc. in biology); University of Freiburg in Freiburg, Germany (Ph.D. in natural sciences)

Training: Postdoctoral training at the University of Freiburg and the Janelia Research Campus, Howard Hughes Medical Institute (Ashburn, Virginia)

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

Outside interests: Traveling the world; learning about different food cultures; preparing elaborate meals; hiking; and watching soccer

Website: https://irp.nih.gov/pi/yeka-aponte

Research interests: Obesity and opioid overuse are global epidemics and major causes of death. Public awareness of the addictive properties of food and opioids has been growing progressively throughout the last decade. Both overeating and substance overuse are disorders by which individuals learn rewarding associations between stimuli (such as highly palatable foods and opioids) and outcomes.

My laboratory is investigating how specific neurons modulate the rewarding and addictive nature of food and opioids. We study this topic at the level of neuronal circuits in the context of behaviors, cell types, and synaptic connectivity. Using the mouse as our model system, we apply optogenetics and chemogenetics to manipulate neuronal circuits in awake, behaving mice. In addition, we use a combination of electrophysiology, fluorescence endomicroscopy, and behavioral assays to elucidate the neuronal basis of survival behaviors, such as feeding and nociception (detection of painful stimuli), and determine how these behaviors are disrupted in both eating and substance-overuse disorders.

Recently, we found that neurons in the brain's lateral hypothalamic parvalbumin region orchestrate pain behaviors in mice. We demonstrated their potential as a novel target for analgesic treatment (*Elife* **10:**e66446, 2021). In addition, we found that certain lateral hypothalamic GABAergic neurons that express leptin receptors drive appetitive behaviors in mice (*Cell Rep* **36:**109615, 2021). In another study, we manipulated three hypothalamic neuronal populations that had well-known effects on feeding and found that each type had distinct—and sometimes unexpected—effects on food consumption and reward. The complexity of hypothalamic feeding regulation can be used as a framework to characterize how other neuronal circuits affect hunger and help us identify potential therapeutic targets for eating disorders (*Curr Biol* **31**:3797-3809.e5, 2021).

Ultimately, understanding the mechanisms regulating food intake and the rewarding and addictive nature of food will enhance our ability to battle disorders such as obesity, diabetes, anorexia, bulimia, and substance overuse.

HAIMING CAO, PH.D., NHLBI

Senior Investigator, Laboratory of Obesity and Metabolic Diseases, National Heart, Lung, and Blood Institute

Education: Harbin Normal University in Harbin, China (B.S. in biology; M.S. in genetics); University of Nevada in Reno (Ph.D. in biochemistry)

Training: Postdoctoral training at the School of Public Health, Harvard University (Boston)

Came to NIH: In 2011 as a Stadtman Investigator in NHLBI

Outside interests: Reading about history, philosophy, and culture

Website: https://irp.nih.gov/pi/haiming-cao

Research interests: The worldwide obesity epidemic—along with an array of obesity-related disorders, particularly diabetes, fatty liver, and cardiovascular

diseases—has become a major public health threat in the 21st century. The molecular and pathological basis by which obesity induces metabolic disorders, however, remains only partly understood, hampering the development of effective therapies against these debilitating diseases.

My group is studying the complex regulation of energy metabolism and uncovering its significance in metabolic physiology and the pathogenesis of metabolic disease. Our current knowledge of energy metabolism is mostly based on studies of protein-coding genes, which constitute less than 2% of the human genome. Examinations of the human transcriptome in recent years have revealed that over 85% of the human genome is transcribed, and human cells express tens of thousands of long, noncoding RNAs (lncRNAs). In humans, lncRNAs are at least three times as prevalent as protein-coding genes, and many lncRNAs overlap disease-associated genetic variants, suggesting that they might have important physiological functions.

We demonstrated that a large number of lncRNAs could function as vital metabolic regulators in mice (*Cell Metab* **2:**455-67, 2015; *Cell Rep* **14:**1867-187, 2016; and *Cell Metab* **24:**627-639, 2016). Our findings also suggest that energy metabolism-associated lncRNAs may have systemic regulatory effects, and that the dysregulation of these lncRNAs could be the underlying cause of many metabolic abnormalities.

We recently produced humanized mice in which the mouse liver cells are replaced by human hepatocytes (essentially, these mice carry a human liver). Using this powerful model, my lab has demonstrated that many human-specific lncRNAs regulate critical signaling networks in human metabolism and their dysregulation could play a role in the pathogenesis of human metabolic diseases (*Nat Commun* **11:**45, 2020; and *J Clin Invest* **131:**e136336, 2020).

MARC GHANY, M.D., M.H.SC., NIDDK

Senior Investigator and Chief, Clinical Hepatology Research Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases

Education: Royal College of Surgeons in Ireland, Dublin, Ireland (M.D.); Duke University, Durham, North Carolina (M.H.S. in clinical research)

Training: Residency in internal medicine at Hospital of Saint Raphael (New Haven, Connecticut); fellow, gastroenterology and hepatology, Tulane University (New Orleans)

Before coming to NIH: Clinical instructor in gastroenterology and hepatology, Department of Medicine, Tulane University

Came to NIH: In 1996 as medical staff fellow in NIDDK; in 2000 became a staff physician, Liver Diseases Branch, NIDDK; became tenure-track investigator in 2015

Outside interests: Enjoys cycling, sailing, and cooking

Website: https://irp.nih.gov/pi/marc-ghany

Research interests: My career has centered on understanding the natural history and therapy of the hepatitis B and C viruses. These two viruses are major causes of cirrhosis and liver cancer. My clinical and translational team examines how the host, viruses, and environment interact to affect infection outcomes. We perform translational studies in the laboratory and conduct clinical trials to evaluate novel ways to manage or cure these chronic viral infections. Through my research, I am trying to understand how certain therapies work or why they fail and identify new treatment approaches. The ultimate goal is to improve the care and outcomes of patients with chronic viral hepatitis.

Specifically, my research focuses on 1) defining the host, viral, and environmental factors that determine the natural history and outcome of hepatitis B and C infections; 2) developing and evaluating novel, more effective therapies for chronic viral hepatitis B and C; and 3) understanding mechanisms of action of therapy and predictors of treatment response.

We demonstrated that, in patients with chronic hepatitis C, the innate immune system contributes to a successful response to direct-acting antiviral therapy (*Hepatology* **68:**2078-2088, 2018). For chronic hepatitis B, new biomarkers are needed to better stratify risk and select patients for therapy. In a recent multinational consortium study, we tested two biomarkers and compared them to conventional biomarkers of hepatitis B virus replication and disease activity. We found that the novel markers offered limited advantages over currently approved assays in characterizing the phase of chronic hepatitis B but may have a role in assessing the efficacy of antiviral agents that are being developed (*Hepatology* **74:**2395-2409, 2021).

Further research on chronic hepatitis C will involve collaborations to define the clinical, virological, histological, and immunological outcomes following cure of the disease. Additional research on chronic hepatitis B will require conducting clinical trials to evaluate novel more effective therapies.

CONTINUED ON PAGE 18

Recently Tenured

CONTINUED FROM PAGE 17

STAVROULA (VOULA) MILI, PH.D., NCI-CCR

Senior Investigator, Laboratory of Cellular and Molecular Biology, Center for Cancer Research, National Cancer Institute

Education: National Kapodistrian University, Athens, Greece (B.Sc. in biology); Mount Sinai School of Medicine of New York University, New York (Ph.D. and M.Phil. in biomedical sciences)

Training: Postdoctoral training, Yale University (New Haven, Connecticut) and University of Virginia (Charlottesville, Virginia)

Came to NIH: In 2012 as a Stadtman Investigator

Outside interests: Figuring out how to raise two boys; trying to stay fit with minimal effort

Website: https://irp.nih.gov/pi/stavroula-mili

Research interests: I am studying RNA localization—how and why cells transport specific messenger RNAs (mRNAs) to predetermined locations. A large fraction of mRNAs do not distribute diffusely in the cytoplasm of cells but adopt a variety of distribution patterns through passive or active transport to a variety of subcellular destinations. The roles fulfilled by these intricate localization mechanisms are largely unknown.

My group has spearheaded the study of mRNAs that are targeted to protrusive regions of migrating mammalian cells. This protrusion-localization pathway is controlled by disease-related factors such as the tumor-suppressor protein APC, whose mutation or loss initiates the majority of colorectal cancers, and the FUS protein, which is mutated in cases of amyotrophic lateral sclerosis and other neurodegenerative diseases (*Nature* **453:**115-119, 2008; *J Cell Biol* **216:1**015-1034, 2017).

Our research is revealing that mRNA location can provide a partner-selection mechanism for proteins that can engage with multiple, mutually exclusive interacting partners. In such cases, the specific location of the mRNA and co-translational events that happen at the site of synthesis provide important determinants for selecting among multiple potential partners and thus for specifying the functional potential of the encoded protein (*EMBO J* **39:**e104958, 2020).

We are investigating the physiological relevance of these mechanisms in normal tissue function and in the context of cancer metastasis, and we are examining their broader implications regarding the regulation of protein function.

NAOKO MIZUNO, PH.D., NHLBI

Senior Investigator, Laboratory of Structural Cell Biology, National Heart, Lung, and Blood Institute

Education: University of Tokyo (B.S. in pure and applied sciences; M.S. in life sciences); University of Tokyo and University of Texas Southwestern Medical Center in Dallas, Texas (Ph.D. in biophysics)

Training: Research fellow, NIAMS

Came to NIH: In 2007-2011 as research fellow; returned to NIH as Stadtman Investigator in 2020

Before returning to NIH: Independent Group Leader, Max Planck Institute of Biochemistry (Martinsried, Germany)

Outside interests: Traveling; building furniture

Website: https://irp.nih.gov/pi/naoko-mizuno

Research interests: My lab was initiated in 2012 at the Max Planck Institute of Biochemistry and relocated to NIH (NIAMS-NHLBI joint appointment) in 2020. We are investigating the molecular mechanisms governing specialized cell shapes, such as those of neurons, activated immune cells, platelets, and certain cancer cells. We use several techniques—in situ cellular cryoelectron tomography in combination with interdisciplinary techniques such as single-particle cryoelectron microscopy, X-ray crystallography, in vitro reconstitution, and cellular light microscopy—to visualize the key factors determining different cell morphologies.

We are elucidating the molecular actions of how neurons are created. These highly polarized cells form an intricate network of dendrites and axons. In one study, using primary neuronal cell cultures from hippocampus and thalamus explants of mouse embryos, we obtained a roadmap of events showing local protein synthesis selectively taking place at axon branches, allowing them to serve as unique control hubs for axon development and downstream neural network formation (*J Cell Biol* **4:**221(4):e202106086, 2022).

We are also exploring precise mechanisms of how the involved molecular players crosstalk with each other in order to define cell shape. By doing so, we can find molecular clues for cellular defects. We use a technique, which we call "bottom-up analysis," to elucidate how building blocks regulate themselves or each other in a binary or synergistic fashion at a molecular resolution. This strategy helped us to solve several functional mysteries in cellular homeostasis (*Science Adv* **7:**eabe9716, 2021; *elife* **9:**e56110, 2020; *Cell* **179:**120-131.e13, 2019; *Nat Commun* **9:**4684, 2018; *Nat Cell Biol* **20:**1172-1180, 2018).

"Behind-the-Mask" Project

Real Stories About Life During the COVID-19 Pandemic

BY GABRIELLE BARR, OD

Collecting historical materials around current cataclysmic events or catastrophes always seemed to be the experiences of others, a session at a conference, a single lecture in graduate school. When I joined the Office of NIH History and Stetten Museum (ONHM) in April 2020, COVID-19 had already begun to wreak havoc around the globe.

With NIH at the helm of scientific research surrounding the novel pathogen SARS-CoV-2, it was apparent that my small office would need to document the activities and pursuits of NIH's 27 institutes and centers to capture the experiences of its 40,000 employees. "Behind the Mask: Real Stories from NIH Staff About Life During the COVID-19 Pandemic" originated as a web portal in English and Spanish in the summer of 2020 in which NIH staff could reply to a series of questions and submit photos, videos, artwork, objects, and other materials that relayed their personal pandemic stories. We began conducting short, curated interviews via Microsoft Teams and Zoom the following fall and formal oral histories a year later as a more targeted means for NIH staff to share their contributions to NIH's COVID-19 response and reflect upon how the new virus has influenced their daily living.

The oral and written accounts from more than 300 scientists, administrators, health care practitioners, trainees, and support personnel have focused on NIH's COVID-19 studies; NIH's partnerships with industry, academia, and other government agencies for cracking medical mysteries like multisystem inflammatory syndrome in children and long COVID and tackling social issues like vaccine hesitancy and health disparities; and NIH's efforts to address mental-health and substance-abuse problems that the pandemic has exacerbated.

Many have recollected what it has been like to be responsible for others during these turbulent times whether that meant shaping NIH COVID policies or meeting the individual needs of colleagues and subordinates. Nearly all discussed acclimating to a changed work environment, which ranged from performing duties entirely from home to following strict guidelines on campus, and how NIH employees had to band together quickly to put certain measures in place such as screening, testing, and vaccine dissemination to make possible what had previously been considered routine operations. These accounts also revealed the private and communal struggles Americans have faced these past few years and are testaments to the resilience and ingenuity NIHers have demonstrated in contending with adversity.

At previous jobs, I fleshed out the historical narrative of national traumas, but the incidents always felt distant and the people unknown. With COVID-19, it has been different. I have had the opportunity to connect with those who have participated in this project, sympathizing with their losses, relating to their fears, congratulating them on their successes and milestones, laughing at their anecdotes and jokes, admiring their sacrifices and will to volunteer on behalf of NIH and communities, and marveling at their vast array of hobbies that have allowed them to cope with the stresses the pandemic has evoked. Each of us at the ONHM who has been involved with the "Behind the Mask" project has felt deeply humbled that our NIH colleagues have trusted us with their candor and emotions and recognize the gravity of being stewards of these stories for years to come.

The ONHM will continue collecting for the "Behind the Mask" project through January 2023. For information on submitting your story, giving short interviews, or donating objects, go to https://history.nih.gov/display/history/Behind+the+Mask or contact history@nih.gov. ●

Gabrielle Barr is the archivist at the Office of NIH History and Stetten Museum.

CREDIT: HELENE LANGEVIN, NCCIH

"Painting and music are some of the things that sustained me during the pandemic," NCCIH Director **Helene Langevin** wrote in an email to the author. "I find both very calming and uplifting—even when the stress is piling up around us." Shown: Langevin's watercolor painting "Rock Point."

See more photos and instructions for accessing COVID-19-related oral histories and donated objects at https://irp.nih.gov/catalyst/30/6/from-the-annals-of-nih-history.

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

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

LONGER ARTICLES AND MORE PHOTOS ONLINE AT https://irp.nih.gov/catalyst/30/6-0.

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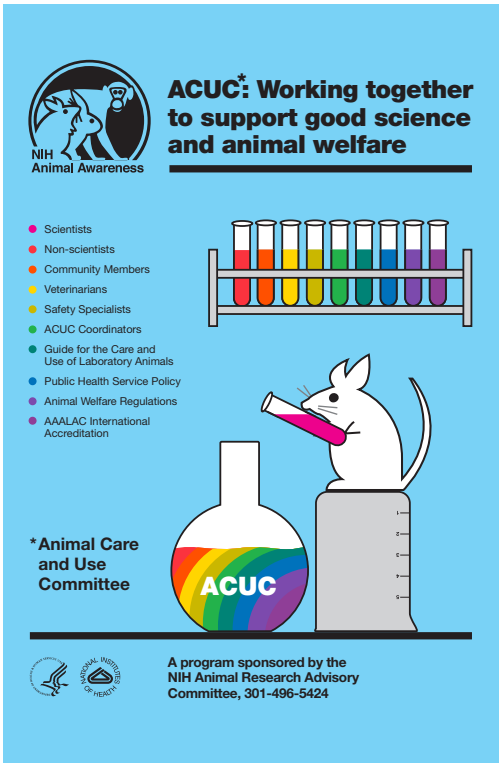
Honoring Research Animals



CREDIT: OFFICE OF ANIMAL CARE AND USE, OD

NIH's 6th Annual Animal Celebration and Reflection Ceremony, on September 21, 2022, was held to honor and express gratitude for the contributions research animals have made to exceptional biomedical research advances. The event was hosted by Deputy Director for the Office of Intramural Research **Richard Wyatt** who chaired the Animal Research Advisory Committee for nearly 30 years, and featured remarks from several other scientists. To watch the videocast, go to https://videocast.nih.gov/watch=46033. ●

Read more online at https://irp.nih.gov/catalyst/30/6/photographic-moment.

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