THE NIH CATALYST

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Annals of NIH History: Lantern Slides

BY MICHELE LYONS, OD

There's a lot of hands-on work in a museum, much of it involving dust and some sneezing. But the thrill of holding and preserving something created by someone decades before you were born is what keeps a curator reaching for dust masks. Recently, I went through many such masks cleaning and photographing 199 lantern slides from the National Cancer Institute's (NCI's) Tissue Culture Section dating from the 1940s through the 1960s. And I loved every minute.

Lantern slides, also known as glass slides, are constructed by binding a positive emulsion of an image on a glass plate. Sometimes the image is matted like a painting and sometimes it is allowed to run to the edge of the glass plate. Then another glass plate is placed on top and the visual sandwich is stuck together by taping around the edges. The images were viewed using a projector. Lantern slides became popular in the late 19th century as photography developed, although "magic slides" with hand-painted images and drawings to entertain or educate date back to the 17th century.

This particular collection of lantern slides chronicles the contributions of the NCI Tissue Culture Section (TCS), which was begun by **Wilton Earle** in 1937. **Virginia Evans** took over as chief upon Earle's death in 1964, and **Katherine Sanford** replaced Evans when she retired in 1973. Sanford retired in

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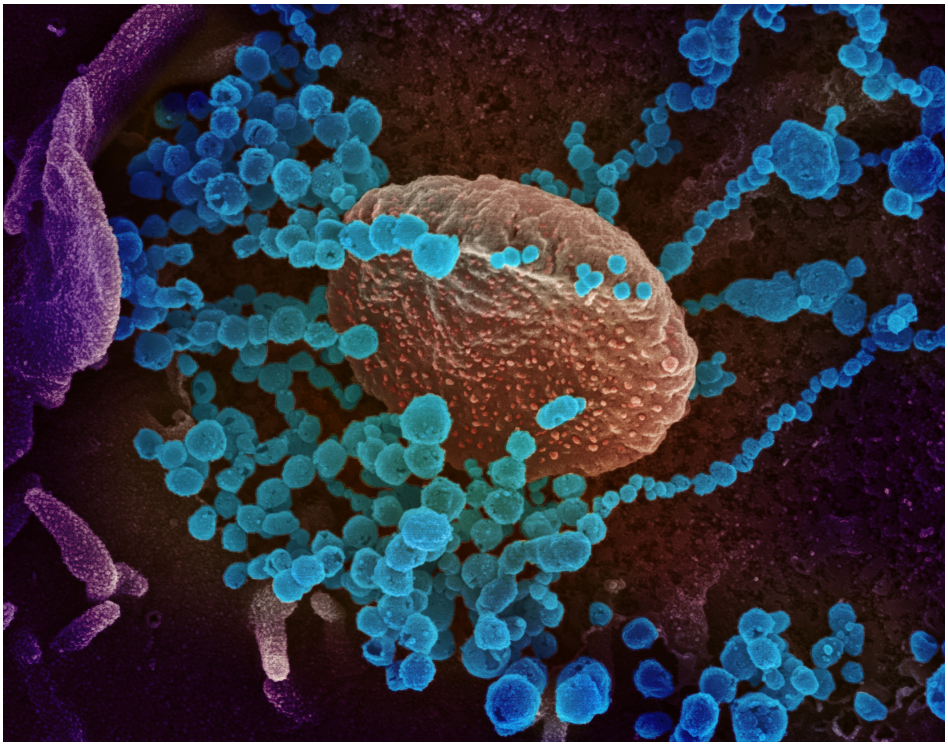
An Amazing Two-Day Banquet of COVID-19 Research Presentations

BY NIH CATALYST WRITERS



CREDIT: NIAID ROCKY MOUNTAIN LABS

This scanning electron microscope image shows SARS-CoV-2 (round blue objects) emerging from the surface of cells cultured in the lab. SARS-CoV-2, also known as 2019-nCoV, is the virus that causes COVID-19. The virus shown was isolated from a patient in the United States.

The two-day "NIH/FDA COVID-19 Research Workshop," held virtually in October 2020, showcased what scientists at NIH and FDA are doing to fight SARS-CoV-2, the virus that causes COVID-19. The workshop took the place of the NIH's annual research festival, which was cancelled this year due to the COVID-19 pandemic.

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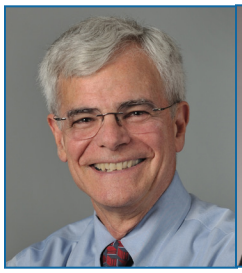


Prioritizing Mental Health and Wellness

BY MICHAEL GOTTESMAN, DDIR, AND SHARON MILGRAM, OD

The past 10 months have been challenging for many of us. With the outbreak of COVID-19, we have had to endure unprecedented challenges and adjust to sudden disruptions in our lives. We have had to worry about the pandemic while juggling dependent care and work, cope with loneliness and isolation while physically distancing from our loved ones, and manage major work disruptions, often all at once with little precedent to rely on. As our second wave of COVID-19 cases and the cold weather arrive, we face even more challenges. Now, more than ever, it is critical that we all be cognizant of our mental health and wellness and of the well-being of our friends and colleagues.

Where are the data? According to the CDC, 40.9% of adults in the United States reported struggling with adverse mental health or substance abuse just a few months into the pandemic. Alarmingly, younger individuals, aged 18–24 and 25–44 and individuals from marginalized communities reported significantly higher rates of adverse experiences (*MMWR Morb Mortal Wkly Rep* **69:**1049–1057, 2020).

A meta-analysis of studies on COVID-19 and mental health showed significant increases in stress, depression, anxiety, and post-traumatic stress disorder across the globe. In some cases the increases were over four- to sixfold. In this analysis, the most vulnerable groups were women, younger individuals, and students (*J Affect Disord* **277:**55–64, 2020).

Although primarily focused on work-life impact, NIH's "COVID-19 Impact Survey Results" showed that 40.7% of intramural respondents have caretaking responsibilities, and 40.3% have reported lower job productivity (the rate for trainees is much higher at 69.4%). It is not surprising that many trainees (38%), especially those who conduct laboratory-based research (52.9%), believe that the pandemic will negatively affect their careers. About half of the trainees indicated that they could not effectively conduct their work via telework (49.1%) and have experienced negative effects due to physical separation from their co-workers (51%).

> Now, more than ever, it is critical that we all be cognizant of our mental health and wellness and of the well-being of our friends and colleagues.

Supporting Our Colleagues. While we need to support all those around us, we need to be especially mindful of our more vulnerable colleagues—our trainees, individuals from marginalized communities, women, caretakers, and even those who conduct laboratory-based research. Because much lab work has been slowed, researchers have to come to campus to be catch up and be productive. That means dealing with the stress of possible exposure to COVID-19, too.

We also need to be attentive to our international colleagues, who may be facing additional stressors. They are especially likely to be isolated from their family and friends and have to navigate a culture different from their own in an uncertain environment. Some even face unacceptable discrimination based on their national origin and are uncertain about their future in this country.

Additionally, check in with colleagues who seem down, sluggish, or agitated. With the change in the weather and shorter daylight hours, they may be suffering from seasonal affective disorder on top of the stressors of the pandemic.

What Can We Do? First, we need to take care of ourselves. We need to prioritize our physical and mental health and explore various resources available to us. NIH's intranet site "NIH Guidance for Staff on Coronavirus" (https://employees.nih.gov/pages/coronavirus) is an excellent resource and includes links to "Wellness Resources" (click on "Your Health") as well as to the Employee Assistance Program (click on "Contacts"). The Office of Intramural Training and Education has informative webinars on developing resilience and on mental health and wellness. The webinars are open to everyone,

and you can attend the live sessions or watch the recorded sessions.

Second, engage in and provide social support while physically distancing. Organize and participate in virtual small-group social activities. For example, have a lab or branch meeting dedicated to conversing about how everyone is dealing with the stressors (without discussing science or business). Touch base with colleagues on a regular schedule, through a buddy system or informal virtual coffee. NIH also has many affinity groups (https://www.training.nih.gov/you_are_not_alone), and it serves a community support system.

Third, take time to rest and recharge. We all need some time for ourselves, and it is okay to take a break. Encourage others to take some time off as well. Importantly, research shows that frequent exposure to social media and news related to COVID-19 increases anxiety and stress-related symptoms. Consider "unplugging" by putting down personal devices and spending time without technology (*Plos One*, **15**:e0231924, 2020).

So please join us in prioritizing our mental health and wellness and supporting our colleagues this winter. Reach out for help, connect with your colleagues and friends, and unplug and recharge. In order to keep our community strong, we all need to be well. ●

Sharon Milgram is the director of the Office of Intramural Training and Education.

NEWS FROM AND ABOUT THE SCIENTIFIC INTEREST GROUPS

Two New SIGs

New SIG: Religion, Spirituality, and Health

The new Religion, Spirituality, and Health Scientific Interest Group (RSH-SIG) aims to foster communication, promote collaboration, and facilitate the exchange of information, understanding, and resources concerning the impact of religion and spirituality (R/S) on health and health outcomes. The SIG will also further the understanding of research on the intersection of R/S and health in order to promote cura personalis, or "care for the entire person," including in the areas of prevention, treatment, and recovery from addiction and other diseases and health conditions.

By delivering lectures and hosting networking events and symposia, the RSH-SIG will serve as a resource for the broader NIH and professional community including providing information on R/S terms, measurement tools, and interventions. The RSH-SIG is open to all persons within the NIH and associated agencies as well as others who share an interest in the intersection of R/S and health. Beginning in February 2021, the group will meet for seminars and discussions on the second Tuesday of each month, 2:00–3:00 p.m. The meetings will be held virtually for the foreseeable future. The first meeting will be held virtually on February 9, 2021, with **Francis Collins** giving a talk titled "Harmonizing the Spiritual and Scientific Worldviews."

For more information and instructions for joining the RSH-SIG LISTSERV, visit the RSH-SIG webpage at https://oir.nih.gov/sigs/religion-spirituality-health-scientific-interest-group. For questions, please contact **Joan Romaine** at joan.romaine@nih.gov.

NEW SIG: Rural Health

The NIH Rural Health Interest Group (RHIG) is a transdisciplinary group of scientists at NIH institutes, centers, and offices who provide scientific leadership, vision, and support to strengthen rural-health research. The RHIG seeks to build and foster a community of intramural and extramural NIH staff with a common interest and expertise in rural-health disparity issues; and to develop a safe environment for the mutual exchange of knowledge and experience. The group provides a trans-NIH forum for sharing and examining programs, initiatives, and strategies that are aligned with the NIH mission, and seeks to enhance and accelerate research among diverse populations in rural areas and geographical regions of the country.

The RHIG encourages career and professional development of both NIH staff and grant recipients. It serves as a resource to NIH staff for creating and implementing innovative scientific and training programs designed to improve the health of rural communities that are underserved and underrepresented in the biomedical sciences. It's critical to build upon the current evidence-based programs to fully understand the conditions that precipitate poor health and well-being of the growing diverse rural populations. The next generation of interventions needs to be developed and implemented to improve health outcomes for all. The RHIG holds meetings and seminars and recommends topics and speakers for a range of events including the annual NIH Rural Health Seminar. For more information, visit https://oir.nih.gov/sigs/rural-health-interest-group. ●

For more information on SIGs and a list, go to https://oir.nih.gov/sigs.

Greening the Scientific Community

Green Labs Update

BY NICKOLAS CHU, NICHD

MAKING YOUR LAB MORE environmentally friendly doesn't require drastic changes. Green Labs Program participants shared that even taking small steps such as monitoring water usage in the lab can make a difference. Another environmentally friendly method is replacing water baths with aluminum beads, a thermal-conductive media. Not only do such measures cut down on water consumption, they also eliminate a breeding ground for potential microbial contamination. Other steps that nearly everyone can take include using other "green" products, recycling, and reducing energy use.

Many everyday products found in both offices and labs have green alternatives. Hand soap, for example, can be replaced with a biodegradable product that is certified for reduced environmental impact. Paper notebooks can also be swapped out for environmentally friendly products made of bagasse (fibrous residue that remains after crushing sugarcane or sorghum stalk) or stone (a combination of calcium carbonate and limestone). Regular paper towels can be replaced with the unbleached variety. Many of these alternatives can be purchased through the NIH Supply Center making it especially easy to go green.

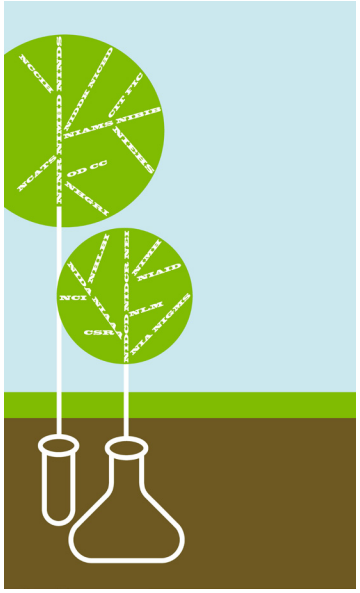
Reusing and recycling what we purchase is another important step toward reducing our environmental impact. While most people recognize that paper should be recycled, other recyclables are often overlooked. For example, NIH uses a Styrofoam take-back program in which vendors will accept Styrofoam items for reuse. Environmentally friendly labs at the NIH often participate in programs like these or choose to repurpose Styrofoam as ice boxes and tube holders.

Another green program is the NIH FreeStuff website (https://stuff.nih.gov), a place to post, search for, and exchange free lab supplies, office equipment, computers, furniture, and more. Used and unused chemicals can also be given away by contacting the NIH's Division of Environmental Protection. When sharing lab equipment is not an option, considerations can be made to shop for products that are environmentally friendly.

One thing to pay attention to is whether a product is made of hazardous materials. For example, to help eliminate the release of toxic substances into the environment during manufacturing, Green Lab participants try to purchase computer monitors that are free of both arsenic and mercury. Labs have also focused on reducing hazardous waste by swapping out radioactive for fluorescent labeling; substituting nontoxic, biodegradable, histological clearing agents for xylene in tissue processing; and disinfecting surfaces with phosphate-free detergents.

Other factors to consider are energy and space usage. For example, large freezers can be replaced with smaller, energy-efficient ultralow temperature freezers, which can save the lab money, too. One lab in the National Institute on Deafness and Other Communication Disorders has coupled their energy-saving freezer with an iPad-based database that helps researchers keep track of the location of inventory and how long freezers are left open.

Going green is a community effort, and doing what you can no matter how small will help in reducing our total environmental impact. In addition to helping the environment, in the long run you may also be saving money. For example, **Minoo Shakoury-Elizeh's** lab (Genetics and Metabolism Section, National Institute



of Diabetes and Digestive and Kidney Diseases) has had great success with dry Western blotting and digital imaging systems. Compared with wet blotting, dry blotting reduces the production of hazardous methanol waste while separating and detecting proteins. In addition, the lab saved more than $11,000 by eliminating the need for purchasing X-ray films and using dark rooms.

Still, there may be some challenges in going green such as a lack of information and trust in green products. Not knowing about alternatives and whether they will even work can discourage many labs from participating. So, it's important that labs share what they know and pass on recommendations for going green. ●

The Green Labs Program has put together a database with alternatives for going green. See the online version of the *NIH Catalyst* for links to resources mentioned in this article: https://irp.nih.gov/catalyst/v29i1/news-you-can-use.

Nickolas Chu, a postbaccalaureate fellow in the National Institute of Child Health and Human Development, is investigating autism gene homologs in zebrafish.

NIAMS Researchers Uncover Clues To Why Some Wounds Don't Heal

Lack of a Certain Protein May Be To Blame

BY STEPHANIE MATHEWS, NIAMS

Unlike acute wounds, such as a paper cut or scraped knee, chronic wounds can take months to heal and leave a person at greater risk for developing infection, chronic pain, and other problems. Slow-healing foot ulcers, a complication of diabetes, are a common type of chronic wound and can put people at risk for limb amputations or early death. Treating diabetic foot ulcers represents a significant challenge to doctors and costs billions of dollars annually in the United States.

In a new study published in *Nature Communications*, researchers identified defects in the wound-healing process that might explain why such wounds heal slower or not at all (*Nat Commun* **11:**4678, 2020; DOI:10.1038/s41467-020-18276-0). The scientists also pinpoint a critical step in the wound-repair pathway that might be a target for developing new treatments for diabetic foot ulcers.

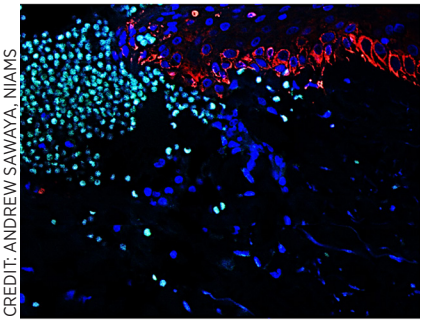
The collaboration included groups led by two established skin biologists: **Maria Morasso**, chief of the Laboratory of Skin Biology at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); and Marjana Tomic-Canic, director of the Wound Healing and Regenerative Research Program at the University of Miami (Coral Gables, Florida). First, the scientists analyzed human tissue samples to identify the molecular culprits responsible for delayed healing. Then they confirmed their findings using specialized laboratory mice. The long-term goal of the work is to find ways to improve chronic wound healing in humans. This collaborative research was made possible by an NIH Bench-to-Bedside and Back Program Award.

Chronic Wounds Struggle to Heal. Wound healing is a normal process that involves four tightly controlled stages: hemostasis (clotting); inflammatory; proliferative (wound rebuilt with new tissue); and maturation (wound fully closes). The inflammatory phase is thought to be the engine that drives the process. During this stage, white blood cells gather at the wound, fight off infection, and recruit other immune cells that promote tissue repair.

Chronic wounds heal slowly because they do not advance through all the phases and seem to get stuck at the inflammatory stage. This can lead to additional complications, such as wound infections or even limb amputations. Scientists don't fully understand why chronic wounds halt at this stage, so it has been difficult to design effective treatments.

Lack of FOXM1 is Key. The scientists studied three different types of healing: injuries in the mouth (fast healing), skin injuries (average healing), and diabetic foot ulcers (slow healing). After collecting human tissue samples, the researchers used a common gene-sequencing technique to take a close look at the specific genes and proteins—collectively known as a transcriptional network—that are involved in wound healing.

Right away, the team noticed transcriptional networks that control white-blood-cell movement and survival were revved up in mouth and skin tissues. Particularly striking was that the tissues were flooded with specialized neutrophils and macrophages, which are essential to wound healing.



CREDIT: ANDREW SAWAYA, NIAMS

Representative image of human skin wound showing neutrophil (light green) recruitment to promote a proper inflammatory response during healing.

A very different picture was revealed in diabetic foot ulcers: Transcriptional networks were weakly activated, and neutrophils and macrophages were absent from the tissue.

Using computer-based software to scan through transcriptional networks, the scientists pinpointed the forkhead box protein M1 (FOXM1), a regulator that triggers the recruitment of white blood cells, as a possible culprit. FOXM1 was suppressed in diabetic foot ulcers but strongly activated in mouth and skin wounds.

The scientists confirmed the role of FOXM1 in wounded diabetic mice and determined that FOXM1 is essential for the healing of wounds. Without it, healing is delayed. The results suggest that finding a way to boost the activity of FOXM1 might lead to a treatment for diabetic foot ulcers and possibly other chronic wounds.

Future Directions. Going forward, the researchers aim to further their understanding of the problem, analyze clinical outcomes, and eventually translate their discoveries into new therapies for diabetic foot ulcers. ●

This article is adapted from one that appeared on the NIAMS "Spotlight on Research" website. You can read the entire article, "Researchers Uncover Clues to Why Some Wounds Don't Heal," posted on November 2, 2020, at https://www.niams.nih.gov/newsroom/spotlight-on-research.

Lantern Slides

CONTINUED FROM PAGE 1

1994. The collection of lantern slides eventually made its way to the Office of NIH History and Stetten Museum.

The TCS was a powerhouse of cell culture research for over 50 years, making important contributions to the methods of cell culturing and our understanding of how cells become cancerous. For example, TCS scientists established the first cloned cell line; created the first cell culture medium with a known chemical composition; developed techniques to grow cultures on cellophane or glass; devised mass suspension cultures for vaccine development; and invented or improved many of the flasks used in cell culturing, including the T flask.

They also pioneered microphotography techniques that enabled them to make detailed images of cancerous and normal cells in various conditions, and photographically documented their techniques and instrumentation. Those images became the basis for this lantern slide collection. A few are shown here and more are in the online version of the *NIH Catalyst*.

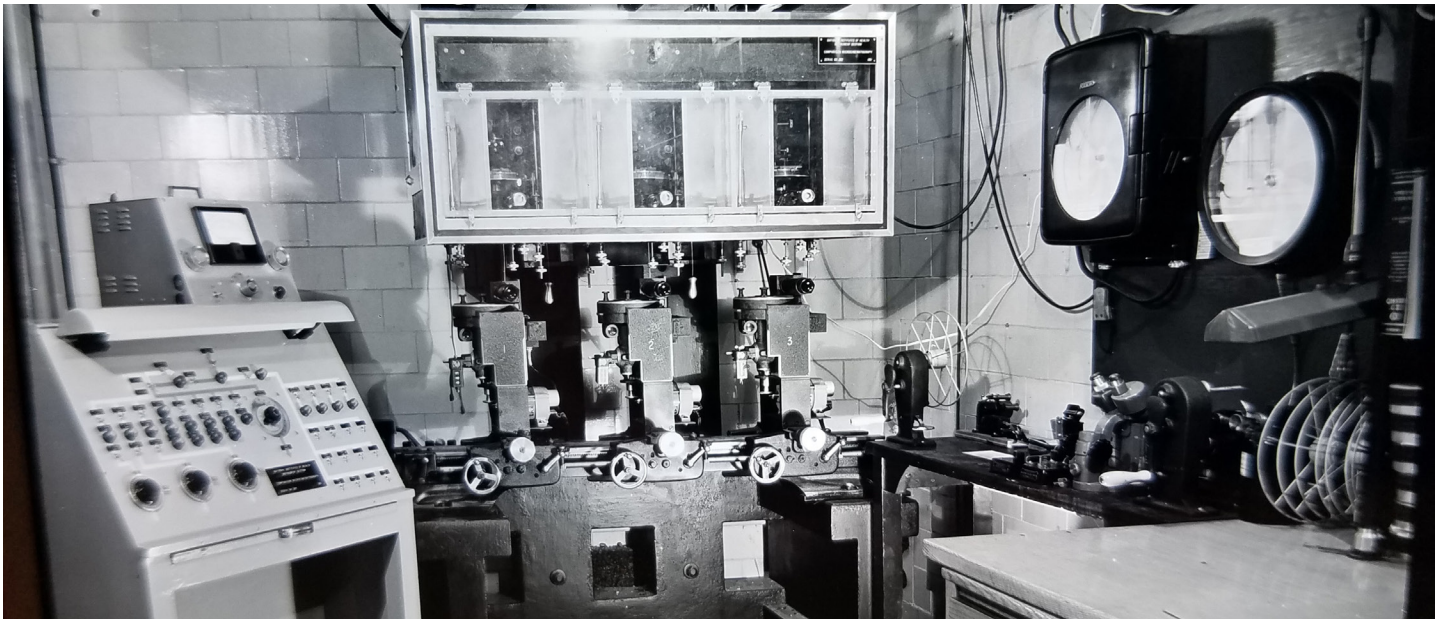
After nearly 80 years, the lantern slides were a bit grimy and the tape on several had loosened or come off. To clean them, I wore white cotton gloves and a dust mask and used Q-tips dipped in deionized water to scrub them, being careful not to get near the tape so that water wouldn't inadvertently get between the glass layers. Then I replaced the tape that needed to be replaced with paper artist tape.

The final step was to photograph them. Scanning both sides of the lantern slides and then aligning the digital images on top of each other is the gold standard, but because I was working at home during the pandemic without a gold standard scanner, my innovative husband rigged a small photography studio in the basement so that I could capture rather good images of the slides. After being photographed, the slides were tucked into archival lantern slide envelopes, put in order, and placed into an archival box.

Now safe for at least another 80 years, what will become of these lantern slides? Their images will be used in a new display that will be installed this summer in the lobby of Building 6, the original home of NCI and the TCS. The display will also feature a few pieces of TCS glassware from our collection. Selections from this large collection were transferred to the Smithsonian's National Museum of American History in 1991, the Smithsonian recognizing the TCS's important contributions to biomedical research.

An online exhibit featuring all of the lantern slides, glassware, and a wealth of information about the TCS and its scientists is in the planning stages. Check the Office of NIH History and Stetten Museum's website at history.nih.gov in the future to see and learn more about these lovely images and the scientific work they represent. ●

Michele Lyons has been the curator in the Office of NIH History since 1995 and wears many hats while documenting NIH's work through collecting scientific and clinical instrumentation, images, documents, and oral histories.



This apparatus was constructed in Building 6 by NCI Tissue Culture Section scientists. It consisted of a double set up of cameras, microscopes, temperature controls, etc. which enabled the researchers to take microphotographs comparing cancerous cells to normal cells at the same time, in the same culture medium, at the same temperature while reacting to the same chemicals.

CREDIT: MICHELE LYONS, OFFICE OF NIH HISTORY

Cleaning lantern slides requires archival paper templates to fold into envelopes for cleaned slides (left), swabs for wiping the slides (center), artist paper tape to reseal the slides (on reel), a non-static brush for a final swipe of cleaned slides (top center), white cotton gloves to keep your body oils off the cleaned slides (right), and deionized water (top). The water does not leave a residue.

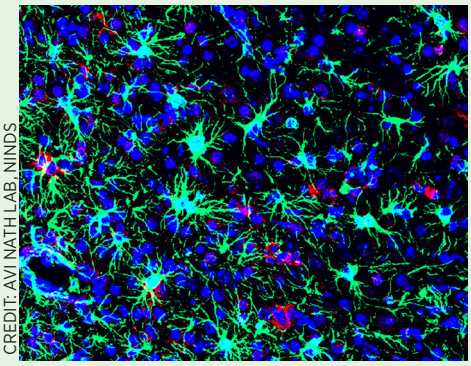
This lantern slide (left) doesn't look like much even after it has been cleaned—note the touches of dirt in the corners. But when the image, held between the glass plates, is lit, stunning luminescent cells appear (right). The Office of NIH History is still in the process of identifying what this slide depicts.

See more images online at:
https://irp.nih.gov/catalyst/v29i1/from-the-annals-of-nih-history.

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

Intramural Research Briefs



CREDIT: AVI NATH LAB, NINDS

NINDS, NCATS: NIH scientists found that the commonly used antibiotic methacycline may be effective at combating the neurological problems caused by Zika virus infections. This is a picture of a Zika-infected mouse brain from the study.

NINDS, NCATS: COMMON ANTIBIOTIC SHOWS PROMISE AGAINST ZIKA INFECTIONS

The global outbreak of Zika virus, primarily spread by the *Aedes aegypti* mosquito, emerged as a public health emergency in 2015 and 2016 with at least 60 countries reporting active cases. When infection occurs during pregnancy, the virus may cross the placental barrier and cause babies to be born with microcephaly (abnormally small heads). Some adults develop severe neurological disorders such as Guillain-Barré syndrome, encephalitis, and myelitis. Scientists in NINDS, in NCATS, and at Georgetown University Medical Center (Washington, D.C.) collaborated on a study that used a high-throughput technique to screen more than 130,000 compounds to identify several inhibitors of Zika virus infection.

The researchers found that the widely available and commonly used tetracycline-based drugs, which includes the antibiotic methacycline, may be effective at blocking Zika virus infection in mice and reduced some of the resulting neurodevelopmental problems. Tetracyclines are FDA-approved drugs that are known to cross the placenta of pregnant women. (NIH authors: R.P.M. Abrams, A. Yasgar, M.-H. Lee, D. Dorjsuren, R. T. Eastman, N. Malik, A.V. Zakharov, W. Li, M. Bachani, K. Brimacombe, J.P. Steiner, M.D. Hall, A. Jadhav, A. Simeonov, and A. Nath, *Proc Natl Acad Sci USA* **117**:31365–31375, 2020)

[BY MANJU BHASKAR, NINDS]

NIEHS: DOUBLE-STRAND DNA BREAKS REPAIRED BY POLYMERASE MU

NIEHS researchers have taken the first snapshot of polymerase mu (Pol-mu) as it bridges a double-strand break (DSB), the most toxic form of DNA damage. Persistently unrepaired DSBs can lead to cancers and other diseases. The findings may aid the understanding of cancer and cancer therapeutics because cancer cells depend heavily on this type of repair. Pol-mu, one of the few enzymes that helps repair these breaks, is capable of handling DSBs that have jagged, unpaired ends. Going forward, the researchers plan to find out how all the enzymes involved in DNA double-strand-break repair work together. (NIH authors: A.M. Kaminski, T.A. Kunkel, L.C. Pedersen, and K. Bebenek, *Nat Commun* **11**:4784, 2020)

[BY MARLA BROADFOOT, NIEHS]

NCI: STUDY OF "EXCEPTIONAL RESPONDERS" YIELDS CLUES TO CANCER AND POTENTIAL TREATMENT

A small percentage of cancer patients are "exceptional responders" because they survive longer than similar patients with advanced disease. NCI researchers, in collaboration with others, found molecular changes in the tumors that may provide some explanation. In nearly a fourth of the 111 exceptional responders who had received chemotherapy, the scientists identified mechanisms behind the efficient response to chemotherapy treatment: the immune system's response to tumors; ability to repair DNA damage; and synthetic lethality (when deficiencies in two or more genes leads to the death of tumor cells during treatment). The researchers noted that further studies are needed. (NCI authors: N. Takebe, J.C. Zenklusen, R. Tarnuzzer, L.M. McShane, J.V. Tricoli, P.M. Williams, I. Lubensky, G. O'Sullivan-Coyne, E.C. Kohn, R.F. Little, J. White, S. Malik, L. Harris, C. Weil, A.P. Chen, C. Karlovich, B. Rodgers, L. Shankar, P. Jacobs, E.F. Edmondson, J.H. Doroshow, B.A. Conley, S.P. Ivy, and L.M. Staudt, *Cancer Cell* **39**:1–16, 2021)

[BY DEBOLEENA GUHARAY]

NIAID RML: EXPERIMENTAL VACCINE PROTECTS AGAINST DEADLY VIRUS

NIAID researchers at the Rocky Mountain Labs (Hamilton, Montana) and colleagues in Europe developed an experimental DNA-based vaccine that is protective against Crimean-Congo hemorrhagic fever virus (CCHFV) in Cynomolgus macaques. The virus, which causes Crimean-Congo hemorrhagic fever, is primarily transmitted by Hyalomma ticks (which are endemic in Eastern Europe, Africa, the Middle East, and parts of Asia) and also through the handling of infected livestock or care of infected patients.

The researchers tested the experimental vaccine, consisting of plasmid expressing the nucleoprotein and viral glycoproteins of CCHFV, on six primates. The vaccinated animals were infected with CCHFV and monitored for six days and did not get sick. Six control animals infected with the virus but not given the vaccine got sick. These results suggest that this vaccine can be advanced to human clinical trials. (NIH authors: D.W. Hawman, K. Meade-White, P.W. Hanley, D. Scott, A. Okumura, and H. Feldmann, *Nat Microbiol* 2020; DOI:10.1038/s41564-020-00815-6)

[BY EMMA ROWLEY, NIAID]

NINDS: THE GUT TRAINS THE IMMUNE SYSTEM TO PROTECT THE BRAIN

The brain has been viewed as an immune-privileged site, meaning that it can tolerate foreign antigens without launching an immune response. New research, conducted by scientists at NINDS and elsewhere, has shown that the meninges (the barrier that protects the brain and spinal cord from pathogens) contain a diverse population of immune cells, some of which are trained to fight infections by first spending time in the gut.

Unexpectedly, the investigators found that large venous sinuses residing in the meninges of healthy mice contained many antibody-producing plasma cells called immunoglobulin A (IgA) cells. These IgA cells are common on barrier surfaces such as the gut or skin.

In the meninges, they help protect the brain from foreign intruders that enter the blood. Compared with the controls, germ-free mice had almost no IgA cells in their meninges. When the researchers reconstituted the gut microbiome in these mice, the population of meningeal IgA cells was restored. This finding suggests that the gut bacteria are important in shaping the antibodies produced by the meningeal IgA cells.(NIH authors: Z. Fitzpatrick, M.L. Negro-Demontel, N. Bouladoux, D.S. Reich, Y. Belkaid, and D.B. McGavern, *Nature* **587**:472–476, 2020)

[BY NATALIE HAGEN, NCATS]

NICHD: GENE IN MICE THAT CONTROLS FOOD CRAVINGS AND DESIRE TO EXERCISE

Scientists at NICHD have identified a gene, *Prkar2a*, in the mouse brain that controls the consumption of palatable foods and the desire to exercise. In the absence of *Prkar2a*, mice reduced their intake of fatty and sugary food, even when given unlimited access to it, and were more likely to exercise. The gene's protein product, RII-alpha, is expressed in the habenular (Hb), a tiny brain region associated with reward processing and motivation. Although the Hb's role has been investigated in substance abuse, its role in obesity and metabolic dysregulation is unclear. The findings from this study could provide useful information for the prevention of obesity, cardiovascular disease, and diabetes. (NIH authors: E. London, J.C. Wester, M. Bloyd, S. Bettencourt, C.J. McBain, and C.A. Stratakis; *JCI Insight* 2020; DOI:10.1172/jci.insight.141670)

[BY SATABDI NANDI, NIA]

NEI: RESEARCH REVEALS NEW ASPECTS OF VISUAL PROCESSING

Color perception, the process by which the brain receives information from cones in the retina and converts the signals into color vision, is largely a mystery. NEI researchers have decoded brain maps of human color perception and learned how color processing is organized in the brain. The scientists used a technique called magnetoencephalography (MEG) that involves placing an array of sensors around the head to noninvasively record the tiny magnetic fields that accompany brain activity. As study participants viewed specially designed color images and reported the colors they saw, the recordings revealed unique patterns of brain activity for each color. The researchers were even able to predict from MEG recordings what color a participant was viewing. The study may also have implications for the development of machine-brain interfaces for visual prosthetics. (NIH authors: I.A. Rosenthal, S.R. Singh, K.L. Hermann, and B.R. Conway, *Curr Biol* **31**:1–12, 2020; DOI:10.1016/j.cub.2020.10.062)

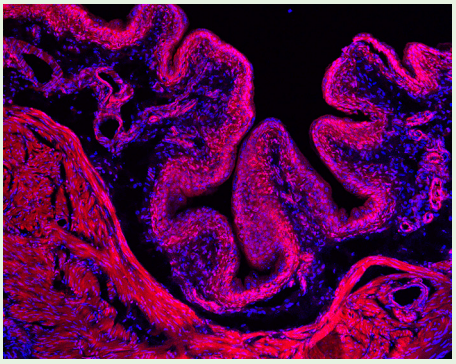
[BY HENRY DIECKHAUS, NINDS]

NIA, NINDS: TWO NERVOUS SYSTEM DISORDERS LINKED TO MUTATION ASSOCIATED WITH HUNTINGTON'S DISEASE

NIH researchers led an international study that discovered a surprising connection between two nervous-system disorders—frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS)—and a mutation in the huntingtin gene (*HTT*), which causes Huntington disease. By comparing the DNA of ALS and FTD patients with DNA from aged-matched healthy individuals, the scientists found repeat expansions in the *HTT* gene in a small subset of ALS and FTD patients, who did not show symptoms of Huntington disease. The authors believe that adding genetic screening for the mutation could increase diagnostic accuracy for patients showing symptoms of ALS or FTD. Clinical trials are underway. (NIH authors: R. Dewan, R. Chia, J. Ding, Y. Abramzon, S. Ahmed, M.S. Sabir, M.K. Portley, A.B. Singleton, T. Tanaka, L. Ferrucci, S.M. Resnick, J.R. Gibbs, S.W. Scholz, and B.J. Traynor, *Neuron* **109**:1–13, 2021)

[BY EIMEAR HOLTON, NIAID]

Read more at: https://irp.nih.gov/catalyst/v29i1/research-briefs.



SCRIPPS RESEARCH INSTITUTE

Researchers discovered that the PIEZO2 gene may help us sense when our bladders are full and it is time to urinate. Shown: Immunofluorescence microscopy image of a mouse bladder (tissue stained red; nuclei stained blue).

NINDS, NCCIH: PIEZO2 GENE HELPS US KNOW WHEN TO URINATE

The *PIEZO2* gene may be responsible for the powerful urge to urinate, accrording to a new study by scientists at NIH and the Scripps Research Institute (La Jolla, California) . The gene helps at least two different types of cells sense when our bladders are full. The study involved both mice and patients who are part of a clinical trial at the NIH Clinical Center. (NIH authors: D. Saade, N. Ghitani, M. Szczot, T. Ogata, C.G. Bönneman, and A.T. Chesler, *Nature* **588**:290–295, 2020)

[BY SATABDI NANDI, NIA]

NIEHS, NCI: BREAST CANCER, AIR POLLUTION LINKED BY NEW MARKER

NIH researchers reported a connection between outdoor air pollution and terminal duct lobular units (TDLUs; epithelial structures within the breast that produce milk), where most breast cancers originate. As women age, their TDLUs naturally shrink and become fewer, a process called involution. Reduced involution is linked to an increased risk of breast cancer. The researchers analyzed more than 1,900 samples of healthy breast tissue, compared the number and size of TDLUs with air-pollution exposure levels, and found that women living in areas with high levels of fine particulate matter held the strongest association with reduced involution. (NIH authors: N.M. Niehoff, A.P. Keil, R.R. Jones, S. Fan, G.L. Gierach, and A.J. White, *Breast Cancer Res* **22**:100, 2020)

[BY ERNIE HOOD, NIEHS]

COVID-19 Timeline at NIH (November–December 2020)

November 6: NIH Director **Francis Collins**, in his "all staff" email, acknowledges that election week brings a level of uncertainty and, during an expanding pandemic, it brings a whole new level of anxiety. He also encourages employees to nurture their health and wellbeing, both mental and physical.

November 9: A NIH multicenter, blinded, placebo-controlled randomized clinical trial conducted at 34 U.S. hospitals and involving 479 patients finds that hydroxychloroquine does not benefit adults hospitalized with COVID-19. (*JAMA* 2020; DOI:10.1001/jama.2020.22240)

November 11: According to a *JAMA* "Viewpoint" article by NIAID Director **Anthony Fauci** and colleagues, COVID-19 treatments for people with early infection are needed urgently to speed recovery, reduce the likelihood that they develop severe outcomes, and reduce demand on the health-care system. (*JAMA* 2020; DOI:10.1001/jama.2020.22813)

November 13: In his NIH Director's message, **Francis Collins** announces several research updates for the week: Pfizer announced that early analysis of data on 94 cases in its phase 3 COVID-19 experimental vaccine trial suggests the vaccine is more than 90 percent effective; Moderna signaled that a sufficient number of cases had occurred in the 30,000 participants in their experimental phase 3 trial that the Data and Safety Monitoring Board will be asked to unblind the results in the next few days to assess efficacy; FDA announces that it has issued an Emergency Use Authorization for the Eli Lilly investigational monoclonal antibody bamlanivimab (LYCoV555) for the treatment of mild-to-moderate COVID-19 in non-hospitalized adult and pediatric patients who are at high risk for progressing to severe disease and hospitalization; NHLBI closes the lid on the use of hydroxychloroquine in hospitalized adults with COVID-19, concluding that the drug provides no clinical benefit in this population. In addition, Collins reports that he and many NIH colleagues met virtually with the Bill & Melinda Gates Foundation (BMGF) to consider the COVID-19 vaccine research and development landscape, rapid detection for SARS-CoV-2, and application of lessons learned to future pandemics; to end the two intense days of Zoom science, BMGF's Chris Karp and Collins put together a recorded duet of the famous Beatles song "In My Life," taking liberties with lyrics to add a COVID-19 spin.

November 16: NIH announces that an independent data and safety monitoring board's interim review of data from Moderna's investigational COVID-19 vaccine suggests that the vaccine is safe and effective at preventing symptomatic COVID-19 in adults.

November 19: In his message to NIH staff, NIH Director **Francis Collins** reports on the results of the NIH Workforce COVID-19 Impact Survey Summary.

November 20: NIH has awarded nearly $45 million to expand the research network of the Rapid Acceleration of Diagnostics Underserved Populations (RADx-UP) program. RADx-UP aims to enable and enhance COVID-19 testing of populations disproportionately affected by the disease including African Americans, American Indians and Alaskan Natives, Latinos and Latinas, Native Hawaiians, older adults, pregnant women, and those who are homeless or incarcerated.

November 20: NIH holds its sixth Virtual Town Hall to discuss COVID-19-related issues: https://videocast.nih.gov/watch=40080]

November 20: In his "all staff" email, NIH Director **Francis Collins** cautions people about holiday travel and gatherings and advises people to review the Travel Guidance page on the NIH coronavirus intranet page and to refer to the Centers for Disease Control and Prevention guidance on traveling for Thanksgiving and general guidance about holiday celebrations and small gatherings.

November 23: NIH Director **Francis Collins** performs "Thanksgiving Eve," adding his own final verse to the folk song written by Bob Franke to thank staff and offer hope during these challenging times: "from the Spring to the Fall, you've been heroes one and all, you've answered the calls and the cries. Despite the heavy load, your mission has been hope, you've done all you could to save lives. I am thankful for our NIH heroes!"

November 25: NIAID announces that the fourth iteration of the Adaptive COVID-19 Treatment Trial has begun to enroll hospitalized adults with COVID-19 who require supplemental oxygen. The NIAID-sponsored trial will enroll up to 1,500 patients at approximately 100 sites in the United States and other countries.

November: NIAID Senior Investigator **Elodie Ghedin** begins genetic sequencing of SARS-CoV-2 in NIHers who have tested positive for COVID19 and who have given consent. The goal is to determine what variants of the virus are circulating among NIH staff.

December 4: In his email message to staff, **Francis Collins** announces that HHS, working with NIH and Operation Warp Speed, launched the Combat COVID website: https://combatcovid.hhs.gov. In addition, he announces that NIH has rolled out a new app called My COVID-19 Risks that staff can use to help estimate the risk level of activities based on activity type, zip code, health characteristics, and personal risk tolerance: https://safercovid.org/myrisk/.

December 7: An NIBIB-funded tool helps organizations plan COVID-19 testing; an online calculator computes costs of testing and offers strategies for preventing infections in schools and businesses.

December 11: The FDA issues the first Emergency Use Authorization for a vaccine to prevent COVID-19—to Pfizer-BioNTech.

December 11: NIH announces that the combination of baricitinib, an anti-inflammatory drug, and remdesivir, an antiviral, reduced time to recovery for people hospitalized with COVID-19, according to clinical trial results published in the *New England Journal of Medicine*. The study was

supported by NIAID. (*New Engl J Med* 2020; DOI:10.1056/NEJMoa2031994)

December 15: NIH announces that the FDA granted emergency-use authorization for a rapid at-home COVID-19 test that was developed through the NIBIB RADx initiative and designed by Ellune USA (Valencia, California).

December 16: An observational study has launched to evaluate the short- and long-term health outcomes of SARS-CoV-2 infection in children, including multisystem inflammatory syndrome in children (MIS-C), and to characterize the immunologic pathways associated with different disease presentations and outcomes.

December 16: Vaccine Research Center (VRC) Director **John Mascola** is named a 2020 Washingtonian of the Year. Mascola and the VRC codeveloped a COVID-19 vaccine with Moderna, building on fundamental research on coronavirus vaccines by **Barney Graham**, **Kizzmekia Corbett**, and their colleagues.

December 17: A vaccine advisory group to the FDA votes that the benefits of the Moderna COVID-19 vaccine outweigh the risks for use in individuals 18 years of age or older.

December 17: Two randomized, controlled phase 3 clinical trials have begun evaluating investigational monoclonal antibodies for their safety and efficacy in treating people hospitalized with moderate COVID-19.

December 18: HHS Secretary **Alex Azar's** email to HHS and NIH staff announces that "[T]hanks to coordination by Operation Warp Speed and CDC, 2.9 million doses of Pfizer's vaccine were shipped to more than 1,500 sites across America, everywhere from the shores of Guam to the northeastern corner of Maine. This coming week, we have allocated another approximately 2 million doses of Pfizer's vaccine. On top of that, the FDA has signaled that it plans to authorize the NIH/Moderna vaccine immminently, and we have allocated approximately 5.9 million doses of that product to jurisdictions to ship next week."

December 18: In NIH Director **Francis Collins**'s email to NIH staff, he announces that NIAID is starting two randomized, controlled phase 3 clinical trials for monoclonal antibody treatments in hospitalized patients with moderate COVID-19. NIAID also launched an observational study this week to evaluate health outcomes of SARS-CoV-2 infection in children including MIS-C in children. The study is part of a research effort led by NHLBI and NICHD to understand MIS-C.

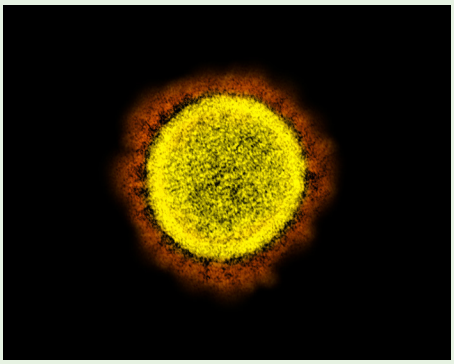
December 18: The FDA issues an Emergency Use Authorization to Moderna for its COVID-19 vaccine, which was co-developed with scientists at NIAID's Vaccine Research Center.

December 21: NIH has awarded eight research grants to develop approaches for identifying children at high risk of MIS-C, a rare and severe aftereffect of COVID-19 or exposure to the virus that causes it.

December 21: NIH has awarded over $107 million to support new, nontraditional approaches and reimagined uses of existing tools to address gaps in COVID-19 testing and surveillance. The program also will develop platforms that can be deployed in future outbreaks of COVID-19 and other infectious diseases.

December 22: Preliminary results of a phase 3, randomized, placebo-controlled clinical trial testing the investigative neutralizing monoclonal antibody LY-CoV555 in hospitalized COVID-19 patients is published today in the *New England Journal of Medicine*. The antibody did not provide clinical benefit compared with placebo. (*New Engl J Med* 2020; DOI:10.1056/NEJMoa2033130)

December 22: NIH ACTIV trial of blood thinners pauses enrollment of critically ill COVID-19 patients. Among critically ill COVID-19 patients requiring intensive-care-unit support, therapeutic anticoagulation drugs did not reduce the need for organ support. Enrollment continues for moderately ill hospitalized COVID-19 patients in the trials. NIH and other organizations are funding the trials.



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.

December 22: At the NIH COVID-19 Vaccine Kick-Off Event, six frontline health-care workers at the NIH Clinical Center received the Moderna COVID-19 vaccine codeveloped by researchers at the NIH Vaccine Research Center. HHS Secretary **Alex Azar**, NIH Director **Francis Collins**, NIAID Director **Anthony Fauci**, and Office of Research Services Director **Colleen McGowan** also received the vaccine.

December 22: Pregnant women in their third trimester are unlikely to pass SARS-CoV-2 infection to their newborns, according to a study funded by NIH. (*JAMA Netw Open* **3:**e2030455, 2020)

December 22: NINDS neuroscientists isolate promising mini antibodies against COVID-19 from a llama. (*Sci Reports* **10:**Article number 22370, 2020)

December 28: The NIH Division of Occupational Health and Safety opens a vaccine clinic to provide NIH health-care workers with the Moderna COVID-19 vaccine.

December 28: A phase 3 trial of Novavax investigational COVID-19 vaccine opens and will enroll up to 30,000 volunteers. NIAID and HHS's Biomedical Advanced Research and Development Authority are funding the trial.

December 30: An NIH study uncovers blood-vessel damage and inflammation in COVID-19 patients' brains but no infection. (*New Engl J Med* 2020; DOI:10.1056/NEJMc2033369)

December 30: A peer-reviewed report on Moderna COVID-19 vaccine confirms that the vaccine is 94.1% effective. (*New Engl J Med* 2020; DOI:10.1056/NEJMoa2035389) ●

Amazing Two-Day Banquet

CONTINUED FROM PAGE 1

Introduction: Sharing COVID-19 Research

BY MEGAN KALOMIRIS, NIAID

October 31st is a date often associated with spooky costumes and eating candy, but it holds additional significance this year—it was the 80th anniversary of President Franklin Delano Roosevelt's 1940 dedication of the National Institute of Health's (yes, it was singular back then) Bethesda campus. Roosevelt's vision for NIH was to use science to protect the health of Americans, and 80 years later during the midst of the COVID-19 pandemic, the NIH is still doing just that.

To show how much the NIH is using science to fight SARS-CoV-2, the virus that causes COVID-19, the COVID-19 Scientific Interest Group (SIG) organized a two-day workshop where NIH and FDA scientists could share the results of their research. The "NIH/FDA COVID-19 Research Workshop" was held virtually (via WebEx) on October 29 and 30 and took the place of the NIH's annual research festival, which was cancelled this year due to the COVID-19 pandemic.

The event featured roughly 135 presentations including 56 talks and 79 flash talks representing some 250 labs working on COVID-19 projects. National Institute of Allergy and Infectious Diseases (NIAID) Director **Anthony Fauci** kicked off the first day with an overview of our current knowledge of SARS-CoV-2 and described therapeutic treatments being tested and vaccine trials taking place. In a similar fashion, NIH Director **Francis Collins** opened the second day by congratulating the researchers presenting their work.

"This was an amazing two-day banquet," said Deputy Director for Intramural Research **Michael Gottesman** in his closing remarks at the end of the workshop. He noted that almost all the talks described research that involved collaborations.

President Roosevelt's "dream of how this institution could contribute…against the next worldwide pandemic," has come true, Collins said. "And you all are part of that."

Videocasts are available at:

Day 1, General Session: https://videocast.nih.gov/watch=40137
Day 1 Flash Talks: https://videocast.nih.gov/watch=40167
Day 2, General Session: https://videocast.nih.gov/watch=40138
Day 2 Flash Talks: https://videocast.nih.gov/watch=40168

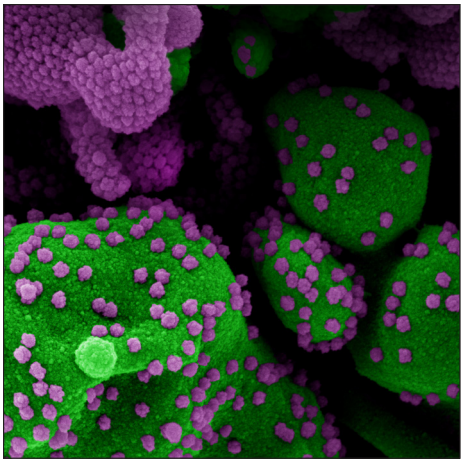
Megan Kalomiris is a postbaccalaureate fellow in the Laboratory of Infectious Diseases (National Institute of Allergy and Infectious Diseases).

Session 1: Tracking, Diagnostics, and Prevention

BY FRANCES FERNANDO, NICHD

Stadtman Investigator **Kaitlyn Sadtler** (National Institute of Biomedical Imaging and Bioengineering) explained how the trans-NIH COVID-19 Serosurvey team mapped the pandemic with SARS-CoV-2 seropositivity. They used mail-in blood-sampling kits to detect antibodies to the SARS-CoV-2 spike protein among 10,000 donors. Preliminary results are expected to be published soon; the study is continuing with follow-up measurements through summer 2021.

Kaiyuan Sun, a postdoctoral fellow at the Fogarty International Center, talked about his research on transmission risk. His group analyzed data from Hunan, China, that evaluated 1,178 SARS-CoV0-2 infected individuals and their 15,648 close contacts. His team found that 80% of secondary transmissions can be traced back to 15%



CREDIT: NIAID

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

of SARS-CoV-2 infections and that a typical SARS-CoV-2 infection peaks just before the symptoms appear, with about 50% of the transmission occurring in the pre-symptomatic phase. The highest rate of transmission was household contact, followed by extended family, social or community, and health-care contact. Controlling the virus through non-pharmaceutical interventions requires case identification, isolation, and population-level intervention methods.

To introduce two talks on vaccines, **Barney Graham**, the deputy director of NIAID's Vaccine Research Center, explained how the mRNA-1273 vaccine rapidly controls SARS-CoV-2 infection in the upper and lower airways of nonhuman primates. Product development with Moderna and clinical evaluation began in record time. The vaccine received FDA's Emergency Use Authorization approval on December 18, 2020.

Neeltje van Doremalen from NIAID's Rocky Mountain Labs in Montana, presented preclinical studies of ChAdOx1 nCoV-19, an adenovirus-vectored vaccine that encodes the spike protein of SARS-CoV-2 and prevents pneumonia in rhesus macaques. The vaccine, now in clinical trials, was developed at the University of Oxford (Oxford, England) in partnership

with AstraZeneca.

On the hunt for COVID-19 biomarkers, NIAID investigators may be on to something, according to clinical infectious disease fellow **Michael Abers**. His team analyzed concentrations of 66 biomarkers in 175 Italian patients with COVID-19 and identified 12 biomarkers that were significantly associated with mortality from SARS-CoV-2 infection.

Yu Zhang (NIAID) presented findings from a recently published *Science* article regarding the genetic determinants of susceptibility to severe COVID-19 infection. (*Science* **370:**eabd4570, 2020). After an analysis of over 1,000 whole-genome sequencing and whole-exome sequencing of COVID-19 patients, Zhang and colleagues determined that COVID-19 severity could be explained by mutations in type I interferon (IFN) response genes.

Frances Fernando is a postbaccalaureate fellow in the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Session 2: Virology 1: Replication, Evolution, and Host Factors

BY NATALIE HAGEN, NCATS

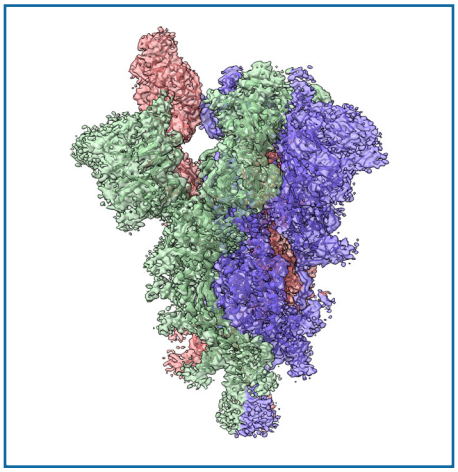
"We are very much learning about COVID-19, but one area that we still lack is [understanding its] cell biology," explained **Nihal Altan-Bonnet**, a senior investigator at the National Heart, Lung, and Blood Institute and one of eight presenters in this session.

She explained that it was once thought that beta-coronaviruses, such as SARS-CoV-2, exit cells via the secretory pathway. However, when her lab used the drug brefeldin A to block transport out of the cell via that pathway, she found that the viruses were still able to escape by taking advantage of lysosomes to aid in their egress.

Blake M. Warner, an assistant clinical investigator in the National Institute of Dental and Craniofacial Research, studies the role of saliva in the infection and transmission of SARS-CoV-2. His lab determined that salivary epithelial clusters had high expression of angiotensin converting enzyme 2 (receptors that allow SARS-CoV-2 to enter cells), that salivary glands were infected with the virus in autopsy tissue samples from SARS-CoV-2 positive individuals, and that the virus can replicate within the salivary glands. The lab also found that mask use reduces expulsion of this potentially infectious saliva tenfold.

The session ended with a presentation by **Emily M. Lee**, a scientist in the 3D Tissue Bioprinting Laboratory at the National Center for Advancing Translational Sciences. To mimic the complexity of tissues in the human body, the lab is developing a variety of 3D platforms in which biofabricated tissues imitate tracheobronchial, small airway, and alveolar lung tissues in vitro and can be used to improve disease modeling, and for drug toxicology and efficacy studies.

Natalie Hagen is a postbaccalaureate research fellow in the National Center for Advancing Translational Sciences.



CREDIT: TONGQING ZHOU, NIAID

Tongqing Zhou (Session 3) is exploring how the virus uses pH changes along the endosomal pathway to bind to ACE2 and evade immune surveillance. Shown: Cryogenic electron microscopy image of the structure of the SARS-CoV-2 spike protein with three subunits colored green, blue, and pink. The receptor-binding domain in the pink subunit is shown in the "up" position ready for binding to the receptor.

Session 3: Virology II: Structure, Function, and Inhibition of Viral Proteins

BY SUNITA CHOPRA, NCI

A dozen scientists presented their research on trying to understand SARS-CoV-2 infections by investigating the structure, function, and inhibition of viral proteins. Of particular interest was the spike protein that binds to the human receptor acetylcholine esterase 2 (ACE2), which enables the virus to enter cells.

Presenters included **Dominic Esposito** (Frederick National Lab), who is optimizing the production of large amounts of spike proteins to supply to NIH scientists investigating the structure of the SARS-CoV-2 virus. Staff scientist **Tongqing Zhou** (NIAID) is exploring how the virus uses pH changes along the endosomal pathway to bind to ACE2 and evade immune surveillance. **Adam Olia's** (NIAID) finding that the spike protein unfolds slowly at neutral pH and rapidly refolds at low pH may have implications for spike-based vaccines. Senior investigator **Mitchell Ho** (National Cancer Institute, NCI), whose lab specializes in isolating single-domain antibodies (also called nanobodies) from camels, presented data showing three nanobodies that effectively inhibited interaction between SARS-CoV-2 and ACE2. **Venkata Dandey** from **Mario Borgnia's** lab (National Institute of Environmental Health Sciences) also presented data on four humanized nanobodies that displayed varying degrees of potency in blocking virus interaction with ACE2. Because of their small size, nanobodies can be used in treatments, especially ones administered by an inhaler.

An interesting study from the lab of **Peter D. Sun** (NIAID), presented by staff scientist **Jinghua Lu**, showed how binding SARS-CoV-2 to ACE2 enzymes increased

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Amazing Two-Day Banquet

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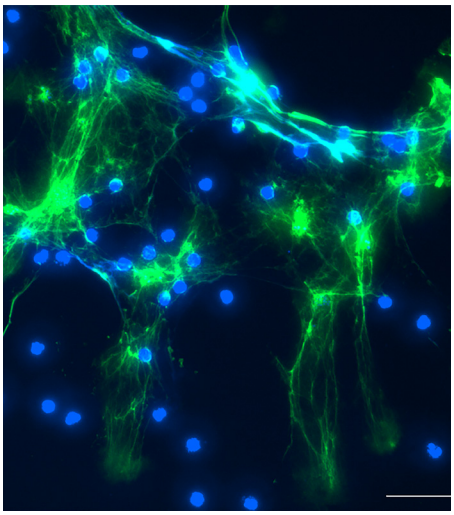


CREDIT: YOGEN KANTHI, NHLBI ; KNIGHT LAB (U MICHIGAN)

Yogen Kanthi (NHLBI) discussed his work (Session 4) on how neutrophils are hyperactivated during a COVID-19 infection. Shown: Serum from patients with COVID-19 triggers healthy human neutrophils to undergo NETosis (green-citrullinated histone H3, a marker of NETosis; blue-DNA).

enzymatic activity. These results shed new light on the pathogenesis of COVID-19.

Nadya Tarasova (NCI) described how she used the Biowulf supercomputer to run virtual screens on synthetic compound libraries containing upward of a billion different structures; 190 hits were verified as SARS-CoV-2 protein ligands that are promising drug candidates and powerful chemical biology tools. The other presenters also described their efforts to use structural biology to unlock the mysteries of SARS-CoV-2 and how to fight it.

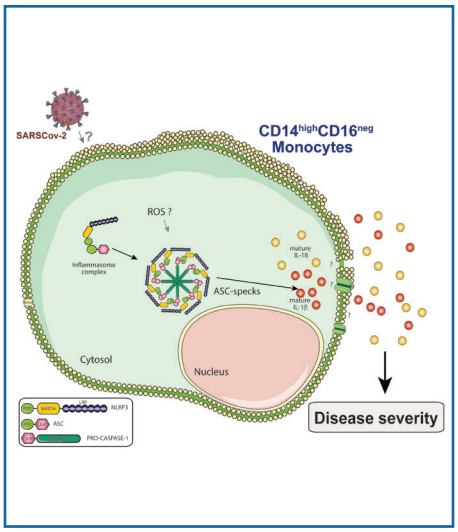
Sunita Chopra is a visiting postdoctoral fellow in the National Cancer Institute's Radiation Oncology Branch.

Session 4: Clinical Manifestations and Pathogenesis

BY ETHAN SMITH, NINR

Temesgen Andargie, a research fellow in the National Heart, Lung, and Blood Institute's (NHLBI) one of 11 presenters, discussed his research demonstrating that cell-free DNA (cfDNA), which is released into the bloodstream by damaged cells, can help predict which hospitalized COVID-19 patients will need to go to the intensive care unit (ICU) and who might eventually die. Previous research has shown that cfDNA is detected in lung-transplant recipients whose bodies reject the organ, but before they develop symptoms. Andargie's group found that in hospitalized COVID-19 patients, ICU patients have a sixfold increase of cfDNA from different tissue types in their blood compared with non-ICU patients. They also found that at admission, cfDNA is strikingly increased in COVID-19 patients who eventually die compared with those who recover.

Lasker Clinical Research Scholar **Yogen Kanthi** (NHLBI) discussed his work on how neutrophils are hyperactivated during a COVID-19 infection. When neutrophils die, they release neutrophil extracellular traps (NETs), bundles of sticky DNA that trap foreign microbes and can serve as building blocks for blood clotting. In COVID-19, hyperactivated neutrophils contribute to blood clots in the lung and lung damage. Kanthi's group discovered that COVID-19 induces the production of prothrombotic autoantibodies that may contribute to NETs and blood clotting. They are interested in treating COVID-19 with dipyridamole, an FDA-approved medication that prevents blood clotting. Kanthi launched a clinical trial to test the efficacy of the drug in patients with COVID-19.



CREDIT:SILVIA L. LAGE AND EDUARDO P. AMARAL, NIAID

Silvia Lucena Lage (Session 5) described how the NLRP3 inflammasome is activated in a type of monocyte, called CD14highCD16-, circulating in the blood of COVID-19 patients, seems to contribute to COVID-19-associated hyper inflammation and severity. (ROS=reactive oxygen species; ASC-specks=Apoptosis-associated speck-like protein.)

Ben Afzali, a Stadtman Investigator in the National Institute of Diabetes and Digestive and Kidney Diseases, discussed how SARS-CoV2 activates the complement system (part of the immune response) in infected lung epithelial cells and how the complement proteins and COVID-19 together activate T cells in the lungs. In patients with severe COVID-19, the inflammatory response remains ramped up, changing the composition of RNA inside T cells and putting those T cells in a dangerous state of hyperactivation. Afzali's group found that activated T cells switch on the vitamin D response pathway, which later initiates the shutdown of the immune response. People with a deficiency of vitamin D are more susceptible to contracting COVID-19 and also to developing more severe disease. The study data predicted that therapy with vitamin D, possibly in combination with steroids, may aid in the resolution of hyperinflammation in severe COVID-19.

Ethan Smith is a postbaccalaureate fellow in the National Institute of Nursing Research.

Session 5: Host Response and Immunology

BY JUNE GUHA, NIAID

In this session, 10 scientists dis-cussed their work; several are highlighted here. **Yvonne Baumer**, a staff scientist in **Tiffany Powell-Wiley's** lab (NHLBI) talked about the impact of socioeco-

nomic disparities and neighborhood deprivation on COVID-19 severity and outcome. COVID-19 disproportionately affects African Americans and individuals residing in lower-resourced neighborhoods. Powell-Wiley's team determined that the more disadvantaged neighborhoods people were from, the greater the decrease in certain toll-like receptors (TLRs), which are recognition molecules for multiple pathogens. A decrease in TLR2 in particular was associated with decreased expression of monocyte TLR2, a phenomenon associated with decreased survival in pneumonia.

Phillip Swanson (NIAID) talked about the efficacy of one of the messenger RNA (mRNA) vaccine candidates, mRNA-1273, which was codeveloped by Moderna and NIAID's Vaccine Research Center. The vaccine includes mRNA, encoding the full-length SARS-CoV-2 spike protein, encapsulated in a lipid nanoparticle that enables the mRNA to enter human cells. Swanson and his colleagues demonstrated that mRNA-1273 induces a strong T-cell helper type 1 (Th1) response in adults regardless of age. The vaccine received FDA's Emergency Use Authorization approval on December 18, 2020.

Silvia Lucena Lage (NIAID) described how the NLRP3 inflammasome is activated in a type of monocyte, called CD14highCD16-, circulating in the blood of COVID-19 patients. Her findings suggest that the activation of the NLRP3 inflammasome in circulating CD14highCD16- monocytes contributes to the severity of COVID-19-associated hyperinflammation and could potentially represent a target for host-directed therapies (therapies that interfere with host cell factors rather than acting directly on a pathogen) against COVID-19.

June Guha is a visiting fellow in NIAID.

Session 6: Animal Models and Vaccines

BY CHARLESICE HAWKINS, OITE

ANIMAL MODELS ARE INVALUABLE for understanding the mechanisms of the immune response and for predicting how well treatments and vaccines will work in humans. Several scientists talked about the different kinds of animal models they are using in their COVID-19 research.

Emily Speranza (NIAID) explained how her team compared subgenomic RNA from lung samples of African green monkeys inoculated with either active SARS-CoV-2 or an irradiated inactive form of the virus. Her team found that replication of the virus in the lungs appears to occur at high levels only in pneumocytes, while macrophages drive the inflammatory response.

Routes of SARS-CoV-2 transmission are also a major concern. Postdoctoral fellow **Julia Port** (NIAID Rocky Mountain Labs), using a Syrian golden hamster model, found that intranasal and aerosol exposure—compared to oral or fomite exposure—led to more severe COVID-19. Increased virus titers in the lungs and trachea were also observed with aerosol exposure; and airborne transmission was more efficient than fomite transmission.

Another NIAID researcher, **Ji Hyun Lee**, is using computed tomography (CT) and positron emission tomography (PET) imaging to characterize SARS-COV-2 in the golden hamster model. Also using the golden hamster model is FDA scientist Prabhuanand Selvaraj, who found that SARS-CoV-2 infection induces protective immunity that prevents re-exposure and limits transmission. Another FDA scientist, Meseda Clement, is using both mouse and hamster models is quantifying the immunogenicity of different forms of SARS-CoV-2 spike proteins.

In experimental mice, **Lydia Roberts** (NIAID RML) found that CD4+ and CD8+ T cells display unique antigen specificity depending on their location in the lung. With the same mouse model, **Forrest Jessop** (NIAID RML) used imaging to demonstrate metabolic perturbations among infected animals and characterized how SARS-CoV-2 manipulates the host metabolism.

CREDIT: NIAID

Several of the researchers giving presentations work in this Integrated Research Facility at NIAID's Rocky Mountain Laboratories campus in Hamilton, Montana.

Staff scientist **Shelly Robertson** (NIAID RML) is working with Jackson Laboratories to assess disease susceptibility in a range of mouse strains crossed with the K18-hACE2 transgene. Other innovative work is being carried out across NIH and FDA to improve vaccine efficacy, availability, and delivery. For example, NIAID staff scientist **Baoshan Zhang**, working with mice, is developing rapid and efficient vaccine platforms that use self-assembling nanoparticle immunogens to stimulate strong immune responses and provide protection against SARS-CoV-2 (*Sci Rep* **10:**article number 18149, 2020). ●

Charlesice Hawkins is an administrative trainee in the Office of Intramural Training and Education.

A Destiny in Neuroendocrine Oncology

Profile: Jaydira del Rivero, M.D.

BY SUSAN CHACKO, CIT

"What we do for ourselves dies with us. What we do for others and the world remains and is immortal." Albert Pike

Jaydira del Rivero is one of the world's few specialists in rare cancers that originate in the body's neuroendocrine system, which is made up of specialized cells that make hormones in response to neurological signals. Her goal is to treat these tumors in a holistic way—using a biological approach as well as taking the whole patient into consideration.

Such neuroendocrine tumors (NETs) make up less than 1% of cancer cases in the United States each year, but have a higher death rate than most cancers, as described in a *JAMA Oncology* Viewpoint essay she co-authored (*JAMA Oncol* **6:**21–22, 2020). NETs affect both children and adults and can occur in any organ but are most common in the small intestine, pancreas, and lungs. Many people do not develop symptoms until the cancer is far advanced, making the treatment very challenging. Because most medical centers have limited experience with these tumors, patients often need to travel far for diagnosis and treatment at specialized cancer centers.

Very few treatment options were available until 2010. Despite the development of additional therapies over the last few years, there are still only a handful of FDA-approved therapies, some of which benefit only a few patients. Many questions remain: Why has the incidence of NETs increased dramatically over the past decade (better diagnosis or environmental factors)? How should these tumors be classified? Which treatment should be offered to which patients and when? How long should treatment be continued? When should combination treatments of two or more therapies be used? And, foremost, can new treatments be developed that improve the survival and quality of life for the patients?

Followed her passion. Del Rivero grew up in Veracruz, Mexico, in a family in which her generation was the first to go to college. "Girls are usually taught to cook," she said. But her mother pushed her to focus on her studies instead. Her older brother encouraged her to follow her passion no matter what. "'With hard work and perseverance, you can be anything you want. You can do it,'" she recalled him telling her when she was growing up.

After getting her M.D. from the University of Veracruz medical school (Veracruz, Mexico), doing internships in Mexico, and taking courses to be licensed in the United States, she did a residency in internal medicine at Woodhull Medical Center/New York University–Langone Medical Center (New York). In 2011, she came to NIH for an interinstitute endocrinology fellowship and then did a medical oncology fellowship in NCI before becoming an assistant research physician in 2017. Having training in both oncology and endocrinology was unusual and made her "uniquely suited to pursuing the treatments of these patients," said her collaborator **Nitin Roper**, who was an oncology fellow with her and is now an NCI physician–scientist early investigator. "She was all about neuroendocrine tumors from day 1," he said.

Making a difference. Del Rivero's clinic is part of NCI's Rare Tumor Initiative, headed by NCI staff scientist **Karlyne Reilly** and senior investigator **Brigitte Widemann**. They collaborate extensively

Jaydira del Rivero

JAYDIRA DEL RIVERO, M.D.

Assistant Research Physician and Director Rare Tumor Clinic, Center for Cancer Research, National Cancer Institute

Website: https://ccr.cancer.gov/Developmental-Therapeutics-Branch/jaydira-del-rivero

Born: Veracruz, Mexico

Education: University of Veracruz, Veracruz, Mexico (M.D.)

Training: Internal medicine residency, Woodhull Medical and Mental Health Center/New York University–Langone Medical Center (New York); NIH interinstitute endocrinology fellowship (NICHD, NIDDK, and NIDCR); medical oncology fellowship in NCI

Came to NIH: In 2011 for training; became assistant research physician in 2017

Selected professional positions: Board of Directors of the North American Neuroendocrine Tumor Society

Outside interests: Performing different styles of dancing, most recently bhangra masala, a type of folk dancing from India; exercising

with other NCI scientists including senior investigator **Yves Pommier**, who describes del Rivero as "an extraordinary team player…and an extremely efficient clinician."

The NIH intramural research program "has a unique infrastructure to study the natural history and [to do] treatment studies of rare cancers in depth, with cutting-edge research from bench to bedside that allows us to understand the biology and pathophysiology of these rare cancers [as well as to] make a difference in the lives of these patients," said del Rivero. "We have the ability to longitudinally and comprehensively follow patients over time, to extensively collect tissue samples and perform imaging studies. We are fortunate to have a superb behavioral group who work[s] with patient-related outcomes."

For the natural history studies, del Rivero's group collects data about the patients including demographics, clinical characteristics, familial genetics with adequate genetic counseling, patterns of disease progression, response or lack of response to therapeutic interventions, disease recurrence, and overall survival. The goal is to develop effective therapies for these cancers, but their rarity makes it difficult to find patients for studies. It can take up to three years to enroll just 76 patients in one of the trials.

Targeted therapies. Drug development requires successful testing with preclinical in vitro and in vivo models before moving to clinical trials, but very few cell lines were available for NETs. In 2017, del Rivero developed the first cell lines for a rare tumor, adrenocortical cancer (ACC). Now, organoids (tissue cultures derived from patient tissues) can be used to screen and identify new drugs and eventually lead to personalized treatment for these patients. An ongoing collaboration with Roper and **Suresh Kumar** (staff scientist in Pommier's branch) led to the first organoids developed for ACC drug screening and treatment. The data are being validated, and del Rivero expects to publish her findings in the near future.

Del Rivero is about to launch several clinical trials to study targeted therapies for NETs. One of these is a phase 1/2 study of two drugs for inoperable gastroenteropancreatic neuroendocrine tumors in collaboration with **Frank Lin** (Lasker Clinical Research Scholar at NCI-CCR). The study has just been approved and will open for enrollment soon. She is also a co-chair of a National Clinical Trials Network study, a prospective, multi-institutional phase 2 trial evaluating treatments for two types of rare tumors that develop in adrenal gland tissue—advanced pheochromocytoma and paraganglioma NETs. Her codevelopment of the protocol for the natural history study of rare solid tumors is another scientific milestone that could translate to effective new treatments.

Del Rivero "is uniquely poised to conduct these clinical trials given her expertise in both oncology and endocrinology" and significant scientific contributions will emerge with the new data from these projects, said Widemann.

Del Rivero gratefully acknowledges the mentorship of Pommier, Widemann, **Ravi Madan** (senior clinician, NCI-CCR), **James Gulley** (senior investigator, NCI-CCR), and **Anish Thomas** (Lasker Clinical Research scholar, NCI-CCR). She, in turn, is mentoring junior staff, trainees, and others and giving "them opportunities to present patients, to review patients with her, to present abstracts, and to participate in paper writing, said Widemann. "She's a very good teacher and educator."

Long hours working with seriously ill patients for whom there may not be a cure can be emotionally and physically draining, so del Rivero manages her stress with "any kind of dancing and exercise," most recently bhangra masala, a type of folk dancing from India.

Del Rivero's beloved older brother passed away when she was 19 and she chokes up when talking about his consistent support. The loss has made her more empathetic to her patients and gives her a deeper understanding of the emotional burdens on their families, she said. Del Rivero is a "wonderfully committed and compassionate and caring physician," said Widemann. She is "not just thinking of what research study a patient may be eligible for, but what is the best treatment for" each.

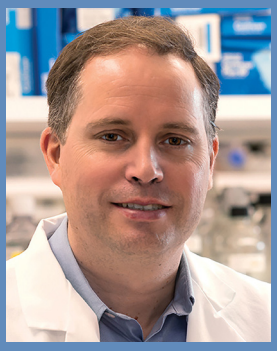
Pinned to the board behind del Rivero's desk are letters from grateful patients about their journeys with cancer. "I see [those] and I have the motivation that I need to do better," she said. "I need to improve their own lives, their life expectancy, and their quality of life. NIH is just an amazing place and I'm just grateful it's given me the opportunity to do that." ●

Scientist Susan Chacko, in the Biowulf cluster group at the Center for Information Technology, leads a team of scientists who install and maintain scientific programs on Biowulf, helps intramural researchers implement large-scale computational research projects, and provides one-on-one support.

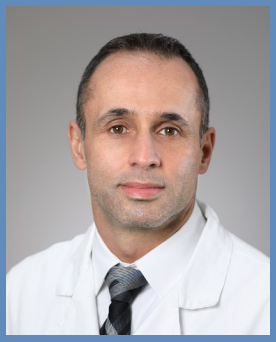
Recently Tenured

ISAAC BROWNELL, NIAMS

JILL KOSHIOL, NCI-DCEG



CHRISTOPHER J. WESTLAKE, NCI-CCR



KAREEM ZAGHLOUL, NINDS

ISAAC BROWNELL, M.D., PH.D., NIAMS

Senior Investigator and Head, Cutaneous Development and Carcinogenesis Section, Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Education: University of Maryland at College Park, Maryland (B.S. in electrical engineering and in mathematics); Baylor College of Medicine, Houston, Texas (Ph.D. in molecular and cellular biology; M.D.)

Training: Transitional residency program, Christus St. Joseph Hospital (Houston, Texas); residency in dermatology, New York University School of Medicine (New York); postdoctoral fellowship, Sloan-Kettering Institute (New York)

Before coming to NIH: Attending physician and instructor in dermatology, Memorial Sloan-Kettering Cancer Center (New York)

Came to NIH: In 2011 as investigator and head, Cutaneous Development and Carcinogenesis Section, Dermatology Branch, NCI (program transferred to NIAMS in 2017)

Outside interests: Enjoys hiking, international travel, and storytelling

Website: https://www.niams.nih.gov/about/directory/isaac-brownell-md-phd

Research interests: I study the regulation of cutaneous stem cells and the molecular pathogenesis of skin cancer. Specifically, my team is investigating the development and maintenance of Merkel cells (neuroendocrine cells in the skin that sense light touch) and Merkel-cell carcinoma, a rare and very lethal type of skin cancer.

Using mouse genetics, we investigate the signals that regulate skin stem cells. We further use mouse models to study targets identified by high-dimensional oncogenomic analysis of human skin tumors. Collaborating with the National Center for Advancing Translational Science, we also use high-throughput screening techniques to identify novel therapeutic targets and treatments for skin cancers. In collaboration with oncologists in the National Cancer Institute, I conduct early-phase clinical trials treating skin cancer.

I contributed to the clinical development of avelumab, a novel immunotherapy drug to treat Merkel-cell carcinoma. The clinical trial was successful and resulted in the 2017 FDA approval of avelumab to treat this cancer (*Lancet Oncol* **17:**1374–1385, 2016).

JILL KOSHIOL, PH.D. NCI-DCEG

Senior Investigator, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Education: William Jewell College, Liberty, Missouri (B.A. in biology; B.S. in composition/piano performance); University of North Carolina at Chapel Hill, School of Public Health, Chapel Hill, North Carolina (MSPH and Ph.D. in Epidemiology)

Training: Cancer Prevention Fellow in NCI-DCEG

Came to NIH: In 2005 for training; became Earl Stadtman Investigator in 2010

Outside interests: Making and writing music; playing keyboard and singing with her church praise band; staying active and being outdoors; looking forward to partner dancing again (especially salsa)

Website: https://irp.nih.gov/pi/jill-koshiol

Research interests: I am interested in developing a better understanding of hepatobiliary cancers, which are linked to both infections and inflammation. The etiology of biliary tract cancers, which are rare in the developed world, is poorly understood. But there are hotspots where these cancers constitute a major public health burden. Biliary tract cancers have a multifactorial etiology, and inflammation is likely central in the carcinogenesis process. My work is identifying previously unknown risk factors such as aflatoxin (carcinogens produced by certain molds). Identification of such determinants, as well as biomarkers, may lead to new opportunities for cancer prevention and early detection particularly in high-risk areas. (*JAMA* **313:**2075–2077, 2015; *Gastroenterology* **153:**488–494, 2017)

Chile is one such high-risk area.

Gallbladder cancer (GBC) is a leading cause of cancer death in Chilean women. To investigate the epidemiologic and molecular predictors of gallbladder dysplasia and cancer, my team initiated the Chile Biliary Longitudinal Study. The high rates of GBC and gallstones in Chile provide a unique opportunity to test several emerging hypotheses that are difficult to examine in other populations. (*Am J Epidemiol* 2020; DOI:10.1093/aje/kwaa199)

I am the principal investigator for the Shanghai Biliary Tract Cancer Study. I also lead and collaborate on other studies.

CHRISTOPHER J. WESTLAKE, PH.D., NCI-CCR

Senior Investigator and Head, Membrane Trafficking and Signaling Section, Laboratory of Cell and Developmental Signaling, Center for Cancer Research, National Cancer Institute

Education: University of Guelph, Guelph, Canada (B.Sc. in biological science); Queen's University, Kingston, Canada (Ph.D. in biochemistry)

Training: Postdoctoral research fellow, Genentech (South San Francisco)

Came to NIH: In 2011 as tenure-track investigator in NCI-CCR

Outside interests: Spending time with his family; playing ice hockey; playing guitar

Website: https://irp.nih.gov/pi/christopher-westlake

Research interests: My laboratory studies the regulation of cellular membrane transport critical in development and normal homeostasis. We are trying to understand the role of membrane-trafficking regulators in ciliogenesis and ciliary signaling including the Hedgehog signaling pathway, which regulates many processes in vertebrate embryonic development. Defects in primary cilium formation and function are important in ciliopathies and are linked to cancer.

Specifically, we are investigating the role of the Rab small GTPase proteins and associated trafficking regulators in the transport of ciliary cargo to the developing and mature cilium. Using cell and zebrafish models, we have discovered mechanisms for how ciliogenesis is initiated, characterized new regulators of cilium assembly, identified novel ciliary trafficking pathways, and connected these processes to human disorders (*Dev Cell* **50:**229–246, 2019; *Nat Commun* **10:**428, 2019; *Cell Rep* **20:**384–396, 2017; and *Nat Cell Biol* **17:**228–240, 2015).

Our findings also provide insight into the basic biological processes of membrane trafficking that are affected in a wide range of human diseases. For our cellular imaging studies, we use cutting-edge approaches including live-cell and super-resolution microscopy, transmission electron microscopy, focused-ion-beam scanning electron microscopy, and correlative light and electron microscopy.

KAREEM ZAGHLOUL, M.D., PH.D., NINDS

Senior Investigator, Functional Neurosurgery Section, National Institute of Neurological Disorders and Stroke

Education: Massachusetts Institute of Technology, Cambridge, Massachusetts (B.Sc. in electrical engineering and in computer science); University of Pennsylvania, Philadelphia (M.Sc. in bioengineering; Ph.D. in neuroscience; and M.D.)

Training: University of Pennsylvania: postdoctoral training in experimental psychology, residency in neurosurgery, and fellowship in functional neurosurgery; University of Bonn (Bonn, Germany): fellowship in epilepsy surgery

Came to NIH: In 2010 as staff physician; became tenure-track investigator in 2013

Outside interests: Spending time with family

Website: https://irp.nih.gov/pi/kareem-zaghloul

Research interests: My interests and training have spanned the fields of systems neuroscience, electrophysiology, electrical engineering, and clinical neurosurgery. My team focuses on examining the neural mechanisms involved in the formation of human memories. We gather information in the course of treating patients with epilepsy and movement disorders by recording neural signals directly from the brain.

For patients with epilepsy, clinical recordings captured from intracranial subdural electrodes (placed on the brain) and depth electrodes (inserted into the brain) are important tools for accurately defining areas of epileptic and functional cortex. These recordings offer a distinct opportunity to collect neurophysiologic data and to explore how those data correlate with a variety of cognitive functions. We are specifically investigating single-neuron and oscillatory activity to understand the neural mechanisms that underlie the formation of human episodic memory. We are mapping the distributed patterns of activity that occur across the brain when an item is stored in memory. We are also trying to understand how these patterns of activity reactivate when an item is remembered and how connections among different areas of the brain coordinate these changes across several regions (*Science* **367**:1131–1134, 2020).

For patients with movement disorders, deep-brain stimulation surgery provides us an opportunity to learn about how subcortical structures, such as the basal ganglia, may participate in learning and decision making. We similarly examine oscillatory and single-unit neuronal activity to understand how these structures may coordinate with the cortex.

In addition, we are also examining how information stored and conveyed among brain regions may provide important insights into how pathological activity, such as in epilepsy, may originate and spread through the brain.

Characterizing the Skin Microbiome, One Genome at a Time

Julie Segre Delivers the Anita Roberts Lecture

BY SUNITA CHOPRA, NCI

We often associate microbes with disease. But the Human Microbiome Project has shown that people live in a mutually beneficial relationship with trillions of microbes on and in their bodies. Human diseases affecting the mouth (cavities) and gastrointestinal tract (inflammatory bowel disease) as well as more complex diseases such as premature birth or type 2 diabetes are associated with alterations in the microbiome. And now, clinical studies are investigating whether those modifications might even drive some features of disease.

Senior Investigator **Julie A. Segre** (National Human Genome Research Institute, NHGRI), who is exploring the skin microbiome, explained the dichotomy in her Anita Roberts Lecture, "Human Microbiome: Friend or Foe," on November 3, 2020. She uses genome sequencing and computational methods to characterize the healthy skin microbiome to better understand the pathology of and design novel therapies for skin-related disorders such as atopic dermatitis (AD), or eczema.

So far there is no cure for AD although symptoms can be treated with topical application of emollients, corticosteroids, and antimicrobials. Segre's lab, however, is investigating what causes it. She discovered that, in AD, there is a decrease in the skin's microbial diversity and an increase in two species of the Staphylococcus bacteria—*S. aureus* and *S. epidermidis*. In collaboration with her long-time clinical partner, **Heidi Kong** (National Institute of Arthritis and Musculoskeletal and Skin Diseases), Segre's lab found that topically applying Staphylococcal strains from patients with severe flare-ups of AD cause skin and immune changes in mice; strains from patients with milder disease cause no symptoms in mice. Segre envisions developing patient-tailored treatments by understanding the basic mechanisms of host-microbial interactions in mice first.

The skin microbiome also includes a diversity of fungi, which Segre is also studying. In particular, she is focusing on *Candida auris*, a fungus that is emerging as a global health threat because it is multi-drug resistant and has caused outbreaks in nursing homes, according to the Centers for Disease Control and Prevention. First seen in patients in 2008 in Asia, Africa, and South America, *C. auris* has spread throughout the world. The fungus can colonize skin for months to years; it can easily spread; and it also causes difficult–to–treat bloodstream infections. In a recent study, Segre's team explored the spread of *C. auris* in a nursing facility to identify sites of colonization and changes in the skin microbiome associated with colonization. She hopes that these insights will help to halt the spread of this emerging human fungal pathogen (*Open Forum Infect Dis* **6**(Suppl 2):S25–S26, 2019).

She counsels young investigators and researchers to develop quantitative skills and build collaborations, advice she has followed herself. Among her quantitative skills is the ability to use computational tools effectively. "I was not afraid to take ownership of analyzing the humungous amount of data that sequencing experiments generate," she said. And she has had many successful long-term collaborations: with Kong; **Yasmine Belkaid** (National Institute of Allergy and Infectious Diseases, NIAID), who developed the mouse models that Segre used and is trying to understand the mechanisms controlling host–microbe interactions on the skin and in the gut; **Helen Su** (NIAID), who is evaluating the microbial colonization of patients with primary immune deficiency; and many others.

Julie Segre

In addition to performing cutting-edge science, Segre is committed to nurturing a more inclusive and diverse workforce. She is a founding member of the NIH Anti-Harassment Committee and the NIH Equity Committee. She also acknowledges the support of the Women Scientists Advisors in advocating for women scientists at NIH. ●

The "Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH" honors Roberts, who known for her groundbreaking work on transforming growth factor–beta. To watch a videocast of Segre's lecture go to https://videocast.nih.gov/watch=37780.

Sunita Chopra, a visiting postdoctoral fellow in the National Cancer Institute's Radiation Oncology Branch, studies radiation–responsive coding and noncoding RNA signatures in blood. She plans to transition into a writing–intensive career after finishing her training at NIH.

Lisa Cooper's WALS Dyer Lecture on Global Health Equity

Public Health Disparities, Humanism, and COVID-19

BY FRANCES FERNANDO, NICHD

"We are only as healthy as the least healthy person in our society." –Lisa Cooper

For Lisa Cooper, COVID-19 health disparities are the result of both infectious disease and social pandemics. In her recent *JAMA* editorial, "A New Kind of Herd Immunity," she describes social deprivation as an infection, similar to COVID-19, that spreads within communities and is invisible. At the heart of her humanistic messaging is the collective responsibility that we all have to each other and the interconnectedness of our lives, our social structures, and our institutions (*JAMA* **323:**2478–2480, 2020).

Documenting Health Disparities. Awarded the MacArthur Foundation Fellow's grant in 2007, Lisa Cooper was one of the first scientists to document disparities in the quality of relationships between physicians and patients from socially-at-risk groups. She has dedicated her career to researching and developing innovative interventions targeting the needs of marginalized populations that are experiencing health disparities.

Her work as a general internist, social epidemiologist, and health-services researcher was inspired by witnessing the effects of social deprivation on the health of people in Liberia, where she grew up. Although she came from an affluent family—her father was a surgeon, her mother a university librarian, and she (Cooper) attended a private international school—others in neighboring communities weren't so fortunate. She couldn't understand why so many others in her country were poor and had limited access to food, health care, and education. Her sensitivity to such inequities has driven her to a career in promoting social justice in medicine.

After earning her M.D. in 1988 from the University of North Carolina School of Medicine (Chapel Hill, North Carolina), she began an internal medicine residency at the University of Maryland hospitals (Baltimore) at the height of the opioid and HIV/AIDS epidemics. She was struck by how so many patients were suffering the same way people in her country had. They lacked the social foundations and institutional support to be healthy; they had limited or no access to education; and their communities were beset by high rates of poverty, violence, and crime. Cooper was determined to learn what she could do alleviate health disparities.

In 2010, she founded, and now directs, the Johns Hopkins Center for Health Equity, which strives "to advance effective health-system and community practices and policies that will achieve health equity in the United States and around the world," according to its website.

WALS Lecture. On October 28, 2020, Cooper presented (virtually) the annual Rolla E. Dyer lecture, which is part of the Wednesday Afternoon Lecture Series (WALS). In her talk, "Deep and Wide: The Voyage to Discover Local and Global Health Equity," she described the health-inequity crisis; how targeted interventions are helping; the ability of health-care organizations to address the needs of marginalized communities; and how the COVID-19 pandemic has disproportionately affected them.

She has developed interventions at multiple levels—from individuals and their families; to providers and organizations; to communities and policy-making organizations—that are helping little by little. Among her many initiatives are a patient program to improve engagement, activation, and empowerment in the medical interview; communication-training programs for physicians; and interventions targeting primary-care teams.

Lisa Cooper

Ultimately, Cooper hopes that scientists and society can temper skepticism with optimism as we progress toward eliminating health disparities in the treatment of COVID-19 and other health conditions. ●

The WALS Rolla E. Dyer series honors the former NIH director and noted infectious disease physician. Each year, the Dyer series features an internationally renowned researcher who has contributed substantially to the infectious-disease field. To watch Lisa Cooper's Dyer lecture go to https://videocast.nih.gov/watch=36083.

Frances Fernando is a postbaccalaureate fellow in the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

IN 2019 (NOT INCLUDED LAST YEAR)

James Victor Dingell (died December 21, 2019, at 88), who retired in the late 1990s, worked in research at NIH in the 1950s and early 1960s, returned in 1975, and worked in three institutes.

Robert Dobie (died September 4, 2019, at 74) was a clinician at the Clinical Center and the director of extramural research (1999–2002) at the National Institute on Deafness and Other Communication Disorders. He studied the effects of noise exposure and aging on hearing.

Daniel Samuel Zahrko (died May 2, 2019, at 88) was the director of Pharmacokinetics and branch chief of Pharmacology in NCI until 1992.

IN 2020

Duane Alexander (died February 14, 2020, at 79) was the director of the National Institute of Child Health and Human Development (NICHD) from 1986 to 2009. He oversaw many achievements including the demonstration of the safety and efficacy of amniocentesis for prenatal genetic diagnosis; the establishment of newborn screening programs; and the reduction of sudden infant death syndrome rates.

Gertrude Axilrod (died April 10, 2020, at 103) was a biochemist and technical information specialist in NCI's Dermatology Branch (1960s) and worked at elsewhere NIH until 1982.

Arthur A. Campbell (died March 10, 2020, at 96), best known for his contributions to fertility research, was deputy director of NICHD's Center for Population Research (1968–1994).

Nikolai Chub (died January 10, 2020, at 59), a neurophysiologist in the National Institute of Neurological Disorders and Stroke for 28 years, pioneered the understanding of the mechanisms regulating the genesis and organization of motor activity in the developing spinal cord.

John Thomas Crawford (died September 23, 2020, at 71) joined NIH in 1978 and was a medical photographer for 34 years. His pictures were used to find the treatment for AIDS. He also photographed the first gene-therapy treatment at NIH.

Murray Eden (died August 9, 2020, eight days shy of his 100th birthday), a pioneer in biomedical engineering, was the director of what later became the intramural research program at the National Institute of Biomedical Imaging and Bioengineering for 18 years. He retired in 1994.

Thomas Guy Fanning (died March 25, 2020, at 76) was a microbiologist at NCI from 1984 to 1990. His later research centered on endogenous retroviruses and on characterizing the 1918 influenza virus. His wife, **Giesela Heidecker**, worked for many years at NCI-Frederick on HIV.

Isaiah "Josh" Fidler (died May 8, 2020, at 83), who founded the MD Anderson Department of Cancer Biology, led the metastasis program at NCI-Frederick from 1975 to 1983.

Miriam Gershfeld (died October 18, 2020, at 89, from complications of COVID-19) spent 20 years as a medical librarian at the National Library of Medicine, and was also a chemistry technical information specialist at NIH's Center for Scientific Review before retiring in 2001. Her husband, **Norman**, worked for 40 years as a physical chemist at NIH.

John Giovanelli (died May 5, 2020, at 89), who began his NIH career in 1965 as a principal investigator in the greenhouse laboratory of General and Comparative Biochemistry, retired in 1995.

Harvey Gralnick (died February 3, 2020, at 82), who came to NIH in the 1960s, was chief of hematology and oncology at the Clinical Center before retiring in 2001. He was an expert on von Willebrand disease, a blood-clotting disorder.

Jerome "Jerry" Green and Marie Röder Green (died two weeks apart—Jerry on April 20, 2020, and Marie on May 1, 2020; both were 91 and both succumbed to COVID-19) were longstanding citizens of NIH. Jerry was an associate director and a division director at NHLBI and then the director of research grants before retiring in 1995. Marie was a lab researcher in NCI and discovered a technique to easily detect carcinogens in lipstick dyes.

Donald E. Henson (died September 29, 2020, at 85) was an internationally renowned pathologist and cancer researcher at the NCI Laboratory of Pathology in the 1970s and among the first to show that nuclear magnetic resonance imaging could detect cancer in living animals.

Larry K. Keefer (died September 11, 2020, at 80) held research and leadership positions in NCI (1971–2015) and made major contributions to the understanding of the chemistry of carcinogenic nitrosamines and landmark discoveries that led to the field of nitric oxide becoming one of the major fields in biomedical science.

Richard "James" King (died March 30, 2020, at 52), the NIH Library's Information Resources and Services Branch Chief (2009-2020), was the 2014 Federal Librarian of the Year.

Leonard Laster (died October 24, 2020, at 92), an accomplished gastroenterologist and later an academic administrator, conducted research at the National Institute of Arthritis, Metabolic, and Digestive Diseases from 1954 to 1973.

Philip Leder (died February 2, 2020, at 85), among the world's most accomplished molecular geneticists, was an undergraduate intern in the National Heart Institute in the 1950s and returned in 1962 as a postdoc with **Marshall Nirenberg**, who won the Nobel Prize in 1968. Leder's work with Nirenberg elucidated the triplet nature of the genetic code. Leder helped set the stage for the revolution in molecular genetic research that he would continue to lead for the next three decades. In 1980, he left NIH to become the founding chairman of Harvard Medical School's Genetics Department.

István (Stephen) Oroszlán (died May 9, 2020, at 92, from complications of COVID-19) was best known for his groundbreaking research that played a central role in the development of HIV protease inhibitors. He was a postdoctoral fellow at NCI in the 1960s, returned in 1976, and directed the Laboratory of Molecular Virology and Carcinogenesis at NCI-Frederick (1983 to 1995) .

Ida Stephens Owens (died February 24, 2020, at 80), the first African American woman to earn a doctoral degree from Duke University, was internationally known for her contributions to the understanding of the genetics of drug metabolism. She came to NIH in 1968 for training, started her own laboratory in NICHD in 1975, and retired in 2017.

Nora Meehan Quade (died November 24, 2020, at 51) was a nurse in medical surgery and most recently in research at the NIH Clinical Center.

David J. Remondini (died May 7, 2020, at 88), a legendary scientific review officer at NIH's Center for Scientific Review (1977–2013), became a volunteer in the Office of NIH History after he retired. He curated a unique collection of grant reviews dating back to the 1950s and the birth of the field of molecular genetics.

Umberto Saffiotti (died September 8, 2020, at 90) joined NCI in 1968. His work on cancer causation included efforts to regulate environmental carcinogens and contributed to the establishment of the Occupational Safety and Health Administration and the Environmental Protection Agency.

Joseph Scotto (died August 5, 2020, at 81), a biostatistician and epidemiologist, worked in the NCI Biostatistics Branch (1962–1992). He applied his expertise toward the development of population-based studies of skin cancer.

Ulrich Klaus Siebenlist (died August 4, 2020, at 68), an internationally recognized molecular immunologist, did his postdoctoral training in **Philip Leder's** (see obit) lab at both the NIH and Harvard Medical School. In the 1980s, Siebenlist became an investigator in the National Institute of Allergy and Infectious Diseases (NIAID) and was later a section chief in the Laboratory of Molecular Immunology.

Gilbert Howlett Smith (died July 6, 2020, at 81), an NCI senior investigator, retired as scientist emeritus in June 2020. He came to NCI as a staff fellow in 1965 and became a senior investigator in 1970. His proposal of tissue-specific stem cells was far ahead of its time and is now a foundation in developmental biology.

Herbert Tabor (died Aug 20, 2020, at 101), a senior principal investigator in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) until his death, was the world's foremost authority on the enzymatic pathways of polyamines, as well as an esteemed editor of the *Journal of Biological Chemistry* for 40 years. He was chief of NIDDK's Laboratory of Biochemistry and Genetics until 1999. His wife, **Celia**, who died in 2012, was a physician–scientist at NIDDK and an expert on the biosynthesis of polyamines. The two started work together at NIH in 1952.

Leslie Ungerleider (died December 11, 2020, at 74), chief of the Laboratory of Brain and Cognition at the National Institute of Mental Health, joined NIH in 1975. She studied how the brain processes visual information and made the landmark discovery, with a colleague, of two cortical visual systems—one for object recognition and the other for visuospatial perception.

Richard "Bud" Veech (died February 2, 2020, at 85), considered by many to be the father of metabolomics and of the field of ketones as it relates to longevity, was chief of the Laboratory of Metabolic Control in the National Institute on Alcohol Abuse and Alcoholism (NIAAA). He was a true hero as well, having narrowly survived a plane crash in New Hampshire in 1968 and risking his life to save others on board. He began his 50-year career at NIH shortly thereafter, first as a medical officer in NIMH and then in NIAAA in 1974. Among his key discoveries was that beta-hydroxybutyrate, also known as a ketone body (generated naturally by the liver when a person fasts or is starving) could "super-charge" metabolism by increasing the potential energy of adenosine triphosphate.

Leo von Euler (died December 17, 2020, at 89, of an illness related to COVID-19,) who retired from NIH in 1987, was a pathologist and former deputy director of the National Institute of General Medical Sciences.

Forrest Fielding Weight Jr. (died November 14, 2020, at 84), a molecular and cellular neurobiologist, started working at NIH in the 1960s. He spent his career researching the physiology and pharmacology of the nervous system.

Flossie Wong-Staal (died July 8, 2020, at 73), a major figure in the discovery of HIV and the first to clone the virus, discovered molecular evidence of microvariation in HIV, which led to the use of "drug cocktails" to manage AIDS. She worked at NCI (1973-1990), first as a visiting fellow in **Robert Gallo's** lab, then as a senior scientist. She was section chief of the NCI Laboratory of Tumor Cell Biology (1982-1990) and left NIH to start a Center for AIDS Research at the University of California San Diego.

Leepo Cheng Yu (died April 28, 2020, at 80, who worked at NIH for 36 years, was an expert on the molecular architecture of muscle fibers, and lab chief in the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Dmitri Vitalievich Zaykin (died December 28, 2020, at 54), an internationally recognized statistical geneticist, joined the Biostatistics Branch at the National Institute of Environmental Health Sciences in October 2004. Some of his most impactful work related to understanding and modeling the balance between spurious and real findings in high–throughput genetic data, such as genome–wide association studies. ●

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PHOTOGRAPHIC MOMENT

Vaccine at Last

At NIH's COVID-19 Vaccine Kick-Off Event, held on December 22, 2020, six frontline health-care workers at the NIH Clinical Center received the Moderna COVID-19 vaccine that was codeveloped by researchers at the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center. In addition, Health and Human Services Secretary **Alex Azar**, NIH Director **Francis Collins**, NIAID Director **Anthony Fauci** (pictured), and Office of Research Services Director **Colleen McGowan** also received the vaccine. On December 28, NIH opened its clinic to begin vaccinating NIH health-care workers. Read the online article for information on vaccination plans for NIH staff at https://irp.nih.gov/catalyst/v29i1/photographic-moment.

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