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Getting to Know 11 Stadtmans

BY LAURA STEPHENSON CARTER

Meet 11 more investigators who have become part of the Earl Stadtman Tenure-Track Investigator Program, which was launched in 2009 and named for the legendary biochemist who worked at NIH for 50 years. The program is designed to recruit a diverse group of talented, early-career scientists pursuing interests across the biomedical-research spectrum. Before 2009, each institute and center (IC) conducted its own searches to recruit new investigators.

The trans-NIH Stadtman search is an additional hiring effort that may appeal to scientists who might not apply to more narrowly defined positions. When qualified candidates are identified, ICs that wish to increase their strength in the candidates' areas of expertise will invite them for interviews and offer tenure-track positions. Each year, NIH aims to hire upward of 10 researchers through this prestigious program.

Six of the new Stadtmans work in the National Cancer Institute's (NCI's) Center for Cancer Research; two in NCI's Division of Cancer Epidemiology and Genetics; two in the National Institute of Dental and Craniofacial Research; and one works in the National Institute of Allergy and Infectious Disease.

Get to know them a bit in this issue of the *NIH Catalyst*. If you go online, you'll learn even more at https://irp.nih.gov/catalyst/v28i1/getting-to-know-11-stadtmans.

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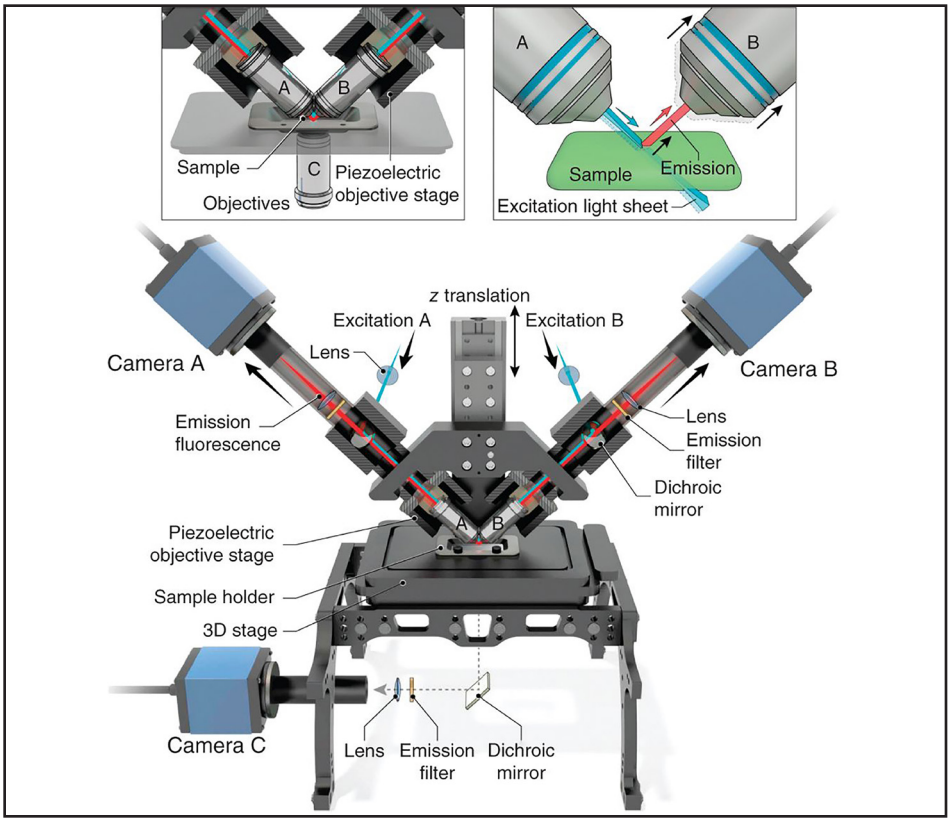
Pushing the Frontiers of Imaging

BY SUSAN CHACKO, CIT



AIM FACILITY, NIBIB

In 2013, Hari Shroff developed the diSPIM, which is a dual light-sheet, fluorescence microscope that acquires two perpendicular views of a sample. It can quickly image live cellular processes—such as viruses moving quickly, cancer cells migrating, and neurons interacting—at high resolution and in 3-D without causing extensive light damage.

The walls are freshly painted, new shelves have been installed, and the microscopes are being moved in. The sparkling new Advanced Imaging and Microscopy (AIM) facility in Building 13 on the NIH Bethesda campus is open for business. It's a trans-NIH core facility that houses, operates, disseminates, and improves noncommercial, prototype optical-imaging systems.

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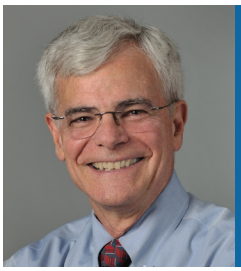


Seeing Is Believing

BY MICHAEL GOTTESMAN, DDIR

Neuroscientists tell us that a large percentage of the information received and processed by the human brain comes through the visual system. It should come as no surprise then that many advances in biological science have resulted from improvements in how instrumentation helps us perceive the physical world, and that advances in data processing have often coincided with improvements in the visual display of information. Microscopy, in particular, has allowed increasing resolution of biological structures, and data processing of increasingly complex datasets has resulted in striking images at the molecular and atomic levels that enhance our understanding of biological events.

The intramural program has always been at the leading edge of developing new approaches to visualize biological phenomena, and some recent investments highlight our desire to remain at the cutting edge. In this brief essay, I will update you on some of the trans-NIH initiatives that illustrate this point.

This issue of the *NIH Catalyst* describes the Advanced Imaging Microscopy (AIM) core, run by **Hari Shroff** (NIBIB). It's a trans-NIH shared resource—available for use by the entire NIH intramural community—that houses, operates, disseminates, and improves noncommercial, prototype optical-imaging systems developed at NIH. (The AIM story begins on page 1.)

In addition, you are undoubtedly aware of the recent revolution in cryo-electron microscopy that has allowed true atomic resolution of purified protein preparations. This technology, which was originally developed in part by **Sriram Subramaniam** (formerly at NCI), is now entering more routine use to analyze structures of membrane proteins, protein complexes, and many other difficult-to-crystallize proteins. There are three consortia that have pooled resources to enhance access to these technologies by many more scientists at the NIH. The first, known as MICEF—short for Multi-Institute Cryo-Electron Microscopy (EM) Facility—includes staff from NIDDK, NHLBI, NINDS, and NIAMS who receive support in planning EM experiments, preparing samples, imaging, using equipment, and analyzing data. The MICEF has a new Titan Krios high-resolution electron microscope and a screening electron microscope and other state-of-the-art equipment. This past year, we also established the NIH Intramural Cryo-EM facility (NICE), which has another Titan Krios donated by NCI with research support similar to MICEF, and contributions from NCI, NICHD, NIAID (which has an additional Titan Krios at Rocky Mountain Laboratories in Hamilton, Montana), and NIEHS. The MICEF and NICE consortia are being overseen by NICE Director **Jenny Hinshaw** (NIDDK). The goal is, as equipment comes online, to create a shared facility for use by all intramural scientists.

Another emerging EM molecular-visualization technology is known as cryo-focused ion beam or cryo-FIB. This technique allows the resolution at the molecular level of structures within frozen sections of biological samples such as cells. In its ultimate manifestation, cryo-FIB would allow identification of molecules and molecular assemblies within cellular structures. For cell biologists, this is the final frontier. Several institutes, including NHLBI, NINDS, NIAMS, and NIDDK, are forming a consortium to recruit scientists whose goal will be to develop this technology at the NIH. Space and equipment to begin this enterprise have been identified. There will be more to come.

Finally, I want to remind you about the recent acquisition of a lattice light sheet microscope from Zeiss that will be housed in a facility in NHLBI. **Clare Waterman** and **Xufeng Wu** will oversee the management of this equipment, which projects ultrathin, low-intensity planes of light into a biological sample and boosts image clarity while reducing phototoxicity and photobleaching. The equipment will allow researchers to image live cells and tissues at high resolution and in 3-D for extended periods. There is a user's committee that will determine priority for use, so please let Dr. Wu know of your interest (wux@nhlbi.nih.gov).

And, of course, NIH now has a database of cores, called CREx, that can help you solve any of a myriad of research problems, including the need for high-resolution light and EM imaging (https://irp.nih.gov/our-research/research-resources). Don't forget to check with CREx to find the help that you need (https://nih.scientist.com; you just need your NIH user name and password to access it). ●

20 for 2020: Preserving the NIH in the 21st Century

BY MICHELE LYONS, OFFICE OF NIH HISTORY AND STETTEN MUSEUM

CREDIT: MICHELE LYONS, OD

A lovely Bausch & Lomb Optical Co. Abbe Refractometer could be found in laboratories from the 1920s through the 1940s, and now in the NIH Stetten Museum collection. Let's preserve our instruments from the 21st century too.

If you wanted to outfit a laboratory as it may have looked in the late 1940s, we can help you. We helped Spark Media recreate a "typical" laboratory for their *Partners of the Heart* documentary on Alfred Blalock, Vivien Thomas, and Helen Taussig's development of a surgical procedure to relieve a cyanotic heart defect—cyanosis from Tetralogy of Fallot—saving the lives of "blue babies." We provided the "antique lab equipment" including monocular microscopes, wood test-tubes racks, and even a typewriter. The NIH Stetten Museum has all that and more. (See the movie at https://archive.org/details/PartnersOfTheHeart.)

Maybe you want to recreate a laboratory from the 1990s. We could help a bit with that too. Thanks to a donation from the Office of Research Services' Division of Scientific Equipment and Instrumentation Services, we received instruments helping to document the rise of genetics as a research tool at the NIH, such as an Applied Biosystems GeneAmp PCR System 9700 and a Perkin Elmer DNA Thermal Cycler 480. Remember them?

But if you wanted to know what was happening in biomedical research at NIH in the 21st century, well, we have the first DNA microarray printer at the NIH, which was designed and constructed at the National Human Genome Research Institute, as the core of a microarray collection.

What instruments will museum curators use to explain your work to the public in 2040? How will historians of technology really know how instruments were designed and used if they can't touch them? And if you win a Nobel Prize or a Lasker Award or a National Medal of Science, or even just the admiration and respect of your colleagues, how would your legacy be documented?

The NIH Stetten Museum is in a unique position to preserve the amazing developments of the 21st-century NIH, but it can't do it without your help. So we're looking to collect 20 representative scientific instruments during 2020. Some of the areas we're looking to collect from are high-throughput technologies, imaging technology, 3-D printing, and the use of animals such as zebrafish. Computers and associated technology are also an important collecting area. We're not worried about the size of an instrument or technology, because really big things can be documented in other ways.

What do you think we should be collecting to represent NIH's work of the past 20 years? Do you have anything that fits what we're looking for? Please let me know: **Michele Lyons** at lyonsm@od.nih.gov or 301-496-7695. ●

To learn more about the Office of NIH History and Stetten Museum, go to https://history.nih.gov.

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

From the Fellows Committee

The Prescription for Acing an Interview: Preparation and Practice

BY CRAIG MYRUM, NIA

You've spent years of your life in higher education, honed professional and research skills, and pushed to publish your research. Now, after feeling like applying for jobs was a part-time job in itself, your hard work has paid off and you've been offered an interview. While this interview might be the gateway to continued success, all too often, not enough time is spent preparing for these potentially life-changing meetings with employers. Fortunately, you don't need to look far to find the resources that will help you to ace your interview.

For intramural fellows, the natural go-to resource is the Office of Intramural Training and Education (OITE). Its frequent workshops on how to interview for positions in industry and academia and for graduate, medical, or professional schools are an excellent place to start.

"My best advice for preparing for an interview is to learn about the typical interview format—be it industry, academia, or a graduate program—well in advance," said **John Taborn**, an OITE career counselor.

Importantly, the structure of interviews also varies dramatically across disciplines, geographical areas, and institutions. For this reason, trainees can schedule tailored mock interviews with OITE career counselors or pre-med advisors that appropriately prepare them for the type of interview that they will experience. But practicing your interview skills shouldn't stop at a mock interview. Have family or friends ask you questions, use flashcards of common questions, and record yourself—because as we all know, practice makes perfect.

"Learn and practice the STAR interview format—Situation, Task, Actions, and Results—in order to answer behavioral interview questions," advised Taborn. "This approach is very useful when employers and admissions committees ask applicants to describe how they utilized 'soft skills' when they handled past challenges in leadership, collaborations, problem solving, and [or] failures. They want to predict how a candidate will behave in similar situations in the future."

Fortunately, you don't need to look far to find the resources that will help you ace your interview.

A quick internet search on how to interview brings up seemingly endless advice. Some of the more consistent tips included in these lists: Wear something that gives you confidence; bring questions to ask them; be authentic; try to stay calm; follow up with a "thank you"; and do your research ahead of time. This last tip is often one of the most important. Be sure to find out everything you can about that specific organization—through their website and every social media platform. Being familiar with whom you will be meeting and the organization's mission, strengths, and culture will help to demonstrate your interest and preparedness.

"Staying calm" may seem easier said than done, but OITE can help with that, too. "Trainees who participate in OITE's various wellness workshops and programs often incorporate wellness strategies into the interview process," Taborn noted. "These [strategies] help fellows to manage stress and anxiety and interview with more confidence."

If an interview is on the horizon, check out the OITE website. It has information about upcoming workshops (including sessions on the STAR interviewing technique), a link to the OITE Careers Blog (which includes information on interviewing), and archived workshops and programs related to interview preparation. For those applying to positions in industry and academia, additional useful resources can be found in places such as *Science* magazine (https://www.sciencemag.org/careers/how-prepare-interview) and the *Chronicle of Higher Education* website (https://www.chronicle.com/interactives/advice-finder?cid=wcontentgrid#id=top_top).

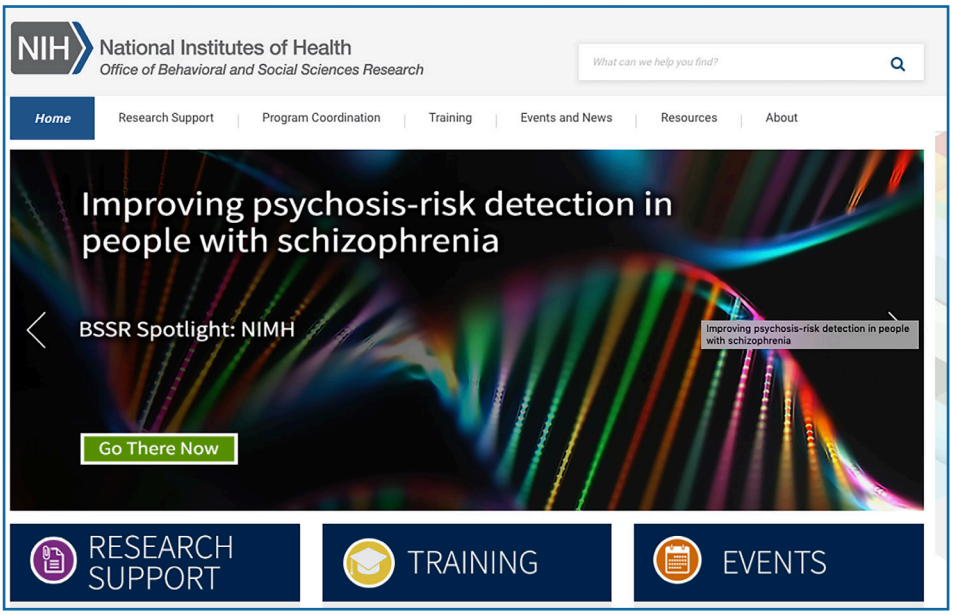
For postbaccalaureate fellows who are applying to professional schools, be sure to visit the websites of professional associations (such as the Association of American Medical Colleges; American Dental Education Association; American Association of Colleges of Osteopathic Medicine; American Public Health Association; and the American Psychological Association), where you can find strategies and resources for interviews.

For some visiting fellows, interviewing in English can be an added challenge. Taborn offered a few suggestions: 1) attend relevant workshops including "English Communication for Visiting Scientists" and "Career Planning for International Scientists" offered by the OITE; 2) participate in OITE discussion groups for building resilience for international scholars; and 3) join the Visiting Fellows committee (https://www.training.nih.gov/felcom/visitingfellows2). ●

For more information, go to OITE's home page at https://www.training.nih.gov/.

Need Help with Your Behavioral and Social Sciences Research?

BY WENDY SMITH, OBSSR



Did you know that the Office of Behavioral and Social Sciences Research (OBSSR) is a resource for coordinating behavioral and social sciences research (BSSR) at NIH? Your research might even fit our portfolio. BSSR includes research topics such as attention, learning, and memory; developmental processes; obesity; disease management (medical errors, adherence, provider-patient interactions); language and communication disorders; bio-psychosocial processes related to mental health; pain, injury, and disability (pathophysiology, functional impairments); sensation and perception; sleep disorders; social processes and determinants; stress, trauma, and resilience; and health and well-being.

The OBSSR is dedicated to enhancing, coordinating, and communicating health-related BSSR across both extramural and intramural programs at the NIH. These efforts include reaching out to investigators, enhancing communications efforts, offering opportunities for funding support, and highlighting intramural accomplishments in the behavioral and social sciences.

Listening Tour: OBSSR has begun a series of visits to intramural researchers, programs, and branches. This "listening tour" is designed for OBSSR staff to hear about issues and explore potential ways to provide support to behavioral and social sciences researchers and their projects. Challenges already identified in conducting BSSR include difficulty in finding expertise and collaborators and a lack of networking activities. OBSSR is exploring ways to assist by developing resources for identifying collaborators and creating "meet and greet" and other networking opportunities. If you are interested in having OBSSR associate director **Wendy Smith** meet with you or your team, contact OBSSRIRP@nih.gov.

Funding Support: OBSSR has participated in the NIH Bench-to-Bedside Program awards since 2009 and has funded an average of one award per year and provided bench-to-bedside support to several programs (https://cc.nih.gov/ccc/btb/). In addition, OBSSR has been able to provide some direct support to programs requesting assistance. Feedback from previously and currently supported IRP investigators has helped OBSSR understand what kinds of support can be most helpful.

"The OBSSR helped us in a fundamental fashion with our 'Molecular Foundations of Human Pain' program," said NIH Clinical Center scientist **Michael J. Iadarola**. "This program is focused on understanding the human 'nociceptome' and all the genes expressed in sensory neurons related to transduction of painful stimuli, understanding human genetic disorders of pain sensation by including behavioral phenotyping, and identifying new non-opioid molecular targets for pain control. The aid of OBSSR was an immense and timely contribution that is deeply appreciated."

OBSSR is developing a standardized process for intramural programs to request funding support. For more information or questions, email OBSSRIRP@nih.gov.

LISTSERV: To identify BSSR investigators and share information, OBSSR is creating a LISTSERV email list of NIH intramural behavioral and social sciences researchers and fellows. The goal is to be able to facilitate communication and dissemination of information such as activities, funding opportunities, and networking events. For information on the LISTSERV or how to join it, email OBSSRIRP@nih.gov. ●

To learn more about OBSSR, go to https://obssr.od.nih.gov. To arrange a visit as part of the OBSSR IRP listening tour, explore funding opportunities or other resources support, have questions answered, and get clarification as whether your program or research topics are related to BSSR, contact OBSSRIRP@nih.gov.

Recognizing 35 Years of Progress in Sjögren Syndrome Research

NIDCR Hosts a Special Grand Rounds to Celebrate

BY CATHERINE EVANS, NIDCR

CREDIT: CHIA-CHI CHARLIE CHANG

The presenters at the "Celebrating 35 Years of Sjögren's Syndrome Research at NIDCR" special grand rounds included (from left) Bruce Baum, Caroline Shiboski, Kathy Hammitt, Martha Somerman, Blake Warner, Janice Lee, and Steven Taylor.

Most of us know the parched sensation of dry mouth, whether from dehydration, side effects of medicine, nervousness, or something else. The dryness is usually fleeting, but not for people with Sjögren syndrome, an autoimmune disease that causes dry mouth and dry eyes. By attacking the salivary and tear glands, the syndrome interferes with taste, chewing, and swallowing, and it boosts the risk for cavities, tooth loss, and oral infections. Although there is not yet a cure for the syndrome, the symptoms can be treated.

In 1984, the National Institute of Dental and Craniofacial Research (NIDCR) established a clinic (in the NIH Clinical Center) to evaluate people with salivary dysfunction and to better understand and find more effective treatments. To mark the clinic's 35th anniversary, NIDCR hosted a special grand rounds in November 2019 to trace the past, present, and future of research on the condition. Today, clinical studies on dry mouth disorders and Sjögren syndrome continue in the NIDCR Dental Clinic in the Clinical Center.

NIDCR Director **Martha Somerman** introduced the first speaker, NIDCR Scientist Emeritus **Bruce Baum**, who along with **Phil Fox** established the first dry-mouth clinic in the United States. "Dr. Baum's vision is why we're here today," Somerman said. "His pioneering work in the field, including the first-ever salivary-gland gene therapy tested in humans, helped build the groundwork for our current intramural and extramural research to understand and treat Sjögren's syndrome."

Salivary disorders such as Sjögren syndrome affect up to four million Americans, most of them women. The condition's cause is unknown and it can significantly disrupt a person's quality of life by interfering with the enjoyment of food and hindering speech. Soon after Baum's arrival at NIDCR in 1982, he and Fox began seeing patients with salivary-gland disorders. In 1984, they established the NIDCR Dry Mouth Clinic, which later became the NIDCR Sjögren's Syndrome Clinic. Their aim was to evaluate patients with dry mouth to better understand how Sjögren syndrome develops and to test treatments.

Their work led to the FDA approval of pilocarpine to prevent or treat dry mouth in people with Sjögren syndrome as well as dry mouth in people who have been treated with radiation therapy for head and neck cancer. This oral medication stimulates the salivary glands to make more saliva. Although the drug helps some people, not everyone finds relief.

"It's so discouraging to see a patient and only be able to say, 'There's nothing I can do for you,'" Baum said.

So he turned to the idea of using a non-disease-causing virus to deliver a corrective gene directly into a damaged gland to restore the flow of saliva. In 2012, the results of the first trial in 11

humans with radiation-induced dry mouth showed that five participants had increased salivary flow that persisted in some cases for up to four years. A second trial using a slightly different viral delivery vehicle is ongoing, and Baum's NIDCR successors, **John Chiorini** and **Blake Warne**r, will soon launch a third trial to test the therapy's efficacy in Sjögren syndrome.

Next, Kathy Hammitt, who has the syndrome and is a patient advocate and vice president of medical and scientific affairs at the Sjögren's Syndrome Foundation, introduced the Foundation's CEO, Steven Taylor. "For a long time, I felt like mine was one of the few voices in a dark space," Hammitt said. "Steven Taylor brought in light when he arrived at the Sjögren's Syndrome Foundation, which has grown exponentially over the last 16 years."

"Our vision is to create a community of patients, health-care professionals, and researchers to join together to conquer the complexities of understanding, diagnosing, and treating Sjögren's," said Taylor, who has been with the foundation since 2003.

The Sjögren's Syndrome Foundation sponsors patient-support groups, raises awareness among the public and scientists, and funds research. These efforts have enabled successes such as shortening the time to diagnosis from six to just under three years. The Foundation's ongoing efforts include drafting clinical-management guidelines for health-care professionals, leading discussions on developing biomarkers and novel diagnostics, formulating classification criteria, and engaging with the FDA on approval of therapies.

Caroline Shiboski, the Leland A. and Gladys K. Barber Distinguished Professor in Dentistry at the University of California at San Francisco, spoke next about her work since 2003 with the NIDCR-funded Sjögren's International Collaborative Clinical Alliance (SICCA). The collaborative of nine research groups in seven countries has enrolled and evaluated more than 3,500 participants to develop a data and biospecimen registry and biorepository for the research community, as well as classification criteria for Sjögren syndrome.

"The heterogeneity of Sjögren's syndrome, as well as the lack of effective systemic treatments, highlights the need for a personalized and targeted approach," Shiboski said. Her group is proposing to perform transcriptomic analysis, in particular, single-cell mRNA sequencing, to identify disease subtypes and to search for biological targets for more effective therapies. The genetic information will be made available via the SICCA registry to scientists worldwide.

The final speaker was **Blake Warner**, who's chief of NIDCR's Salivary Disorders Unit, which conducts basic and clinical research. Understanding the syndrome is challenging, he said, because a "variety of pathological processes underlie a shared clinical presentation."

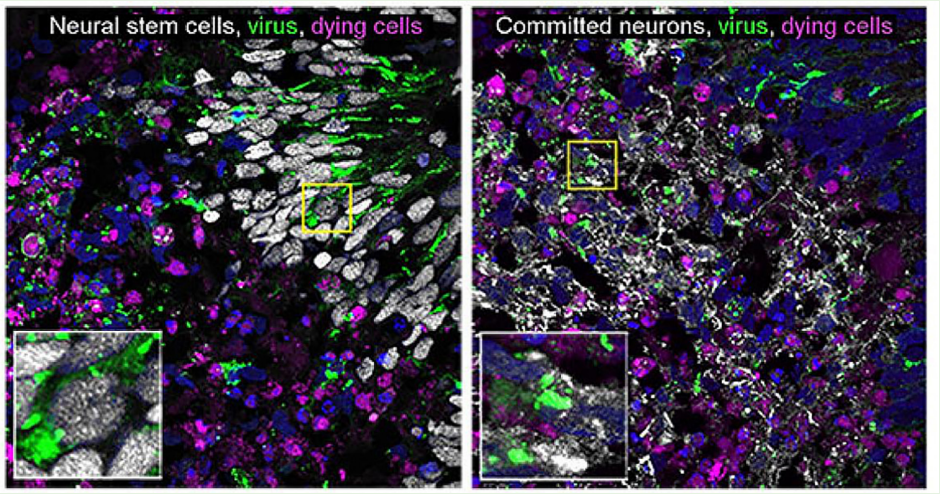
Warner's group works with a multidisciplinary team of experts in oral medicine, pathology, rheumatology, and ophthalmology to provide research-driven clinical assessments of patients with dry mouth. The aim is to solve questions about salivary-gland biology, autoimmunity, and treatment targets.

Recent work by Warner's team to examine patients' salivary-gland tissue revealed that the Janus kinase-signal transducers and activators of transcription (JAK-STAT) molecular-signaling pathway, which is implicated in autoimmunity, appears to be overactive in a subset of patients with Sjögren syndrome. Warner's group will soon launch a clinical trial, at the NIH Clinical Center, to test an FDA-approved JAK-STAT inhibitor, tofacitinib, in Sjögren syndrome patients. (Tofacitinib is a product of John O'Shea's lab in the National Institute of Arthritis and Musculoskeletal and Skin Diseases; see https://irp.nih.gov/catalyst/v25i1/innovations-john-o-shea-and-arthritis-drug.)

"As you've heard today, our progress over the past 35 years in understanding Sjögren's syndrome couldn't have been possible without collaborations among researchers, multiple NIH institutes and centers, and patients," said NIDCR Clinical Director **Janice Lee** at the end of the program. "These partnerships will be critical as we look forward in coming years to the goal of better treatments and a cure." ●

To learn more about the Sjögren's Syndrome Clinic, go to https://www.nidcr.nih.gov/health-info/sjogrens-syndrome/sjogrens-syndrome-clinic. To watch a videocast of the "Celebrating 35 Years of Sjögren's Syndrome Research at NIDCR" special grand rounds, held November 15, 2019, go to https://videocast.nih.gov/launch.asp?28871.

Intramural Research Briefs



CREDIT: NIAID

NIAID: These images taken from cerebral organoids infected with the La Crosse virus show infected cells (green) and cells that are dying from infection (magenta). The left image also shows neural stem cells (white) that have the potential to become neurons; these cells are rarely dying. In contrast, the image on the right shows committed neurons (white), many of which are shown to be dying.

NIAID: CEREBRAL ORGANOID MODEL PROVIDES CLUES ON HOW TO PREVENT VIRUS-INDUCED BRAIN-CELL DEATH

NIAID scientists at the Rocky Mountain Laboratories in Hamilton, Montana, have determined that La Crosse virus (LACV), which can cause inflammation of the brain in children, affects brain cells differently depending on their developmental stage. Neurons evolve from neural stem cells and during development commit to becoming neurons. The study shows that uncommitted neural stem cells generally survive LACV infection, whereas LACV often kills neurons. The study also shows that neurons infected by LACV can be rescued by interferon. (NIH authors: C.W. Winkler, T.A. Woods, B.R. Groveman, A.B. Carmody, E.E. Speranza, C.A. Martens, S.M. Best, C.L. Haigh, and K.E. Peterson, *J Neuroinflammation* **16:**229, 2019; DOI:10.1186/s12974-019-1614-1)

NIMH: SIDE EFFECTS MILD, BRIEF WITH SINGLE ANTIDEPRESSANT DOSE OF INTRAVENOUS KETAMINE

NIMH researchers found that a single, low-dose ketamine infusion was relatively free of side effects for patients with treatment-resistant depression. The researchers compiled data on side effects from 163 patients with major depressive disorder or bipolar disorder and 25 healthy control subjects. Out of 120 possible side effects evaluated, 34 were found to be significantly associated with the treatment. Eight occurred in at least half of the participants: feeling strange, weird, or bizarre; feeling spacey; feeling woozy or loopy; dissociation; floating; visual distortions; difficulty speaking; and numbness. None persisted for more than four hours. No drug-related serious adverse events, cravings, propensity for recreational use, or significant cognitive or memory deficits were seen during a three-month follow-up. To overcome the limitations associated with side effects and intravenous delivery, ongoing research efforts seek to develop a more practical rapid-acting antidepressant that works in the brain similarly to ketamine. (NIH authors: E.E. Acevedo-Diaz, G.W. Cavanaugh, D. Greenstein, C. Kraus, B. Kadriu, C.A. Zarate Jr., and L.T. Park, *J Affect Disord* 2019; DOI:10.1016/j.jad.2019.11.028)

NCATS, NCI: PROMISING DRUG COMBINATION AGAINST LETHAL CHILDHOOD BRAIN CANCERS

NCATS and NCI researchers, along with scientists from other institutions, have devised a new plan of attack against a group of deadly childhood brain cancers collectively called diffuse midline gliomas (DMG), including diffuse intrinsic pontine glioma, thalamic glioma, and spinal cord glioma. The researchers showed that a combination of the two drugs—panobinostat and marizomib—was more effective than either drug by itself in killing DMG patient cells grown in the laboratory and in animal models. Their studies also uncovered a previously unrecognized vulnerability in the cancer cells that scientists may be able to exploit to develop new strategies against the cancer and related diseases. (NIH authors: K.M. Wilson, M. Ceribelli, X. Zhang, P.J. Morris, D.Y. Duveau, A.M. Michalowski, P. Shinn, R. Guha, M. Ferrer, C. Klumpp-Thomas, S. Michael, C. McKnight, Z. Itkin, E.H. Raabe, L. Chen, and C.J. Thomas, *Sci Transl Med* **11:**Issue 519, eaaw0064, 2019; DOI:10.1126/scitranslmed.aaw0064)

NICHD: HIGH AMOUNTS OF SCREEN TIME BEGIN AS EARLY AS INFANCY

Children's average daily time spent watching television or using a computer or mobile device increased from 53 minutes at age 12 months to more than 150 minutes at 3 years, according to an analysis by researchers at NICHD and two institutions in New York State. By age 8, children were more likely to log the highest amount of screen time if they had been in home-based child care or were born to first-time mothers. The researchers analyzed data from the Upstate KIDS Study. Mothers of nearly 4,000 children who took part in the study responded to questions on their kids' media habits when they were 12, 18, 24, 30, and 36 months of age. They also responded to similar questions when the children were 7 and 8 years old. The findings suggest that interventions to reduce screen time could have a better chance of success if introduced early. (NIH authors: M.-H. Trinh, R. Sundaram, S.L. Robinson, and E.H. Yeung, *JAMA Pediatr* 2019; DOI:10.1001/jamapediatrics.2019.4488)

Read more online:
https://irp.nih.gov/catalyst/v28i1/research-briefs

NEI: USING ARTIFICIAL INTELLIGENCE FOR QUALITY CONTROL OF STEM CELL–DERIVED TISSUES

BY KATHRYN DEMOTT, NEI

Researchers from the National Eye Institute (NEI) and the National Institute of Standards and Technology (NIST) have used artificial intelligence (AI) to evaluate stem cell–derived "patches" of retinal pigment epithelium (RPE) tissue for implanting into the eyes of patients with age-related macular degeneration (AMD), a leading cause of blindness.

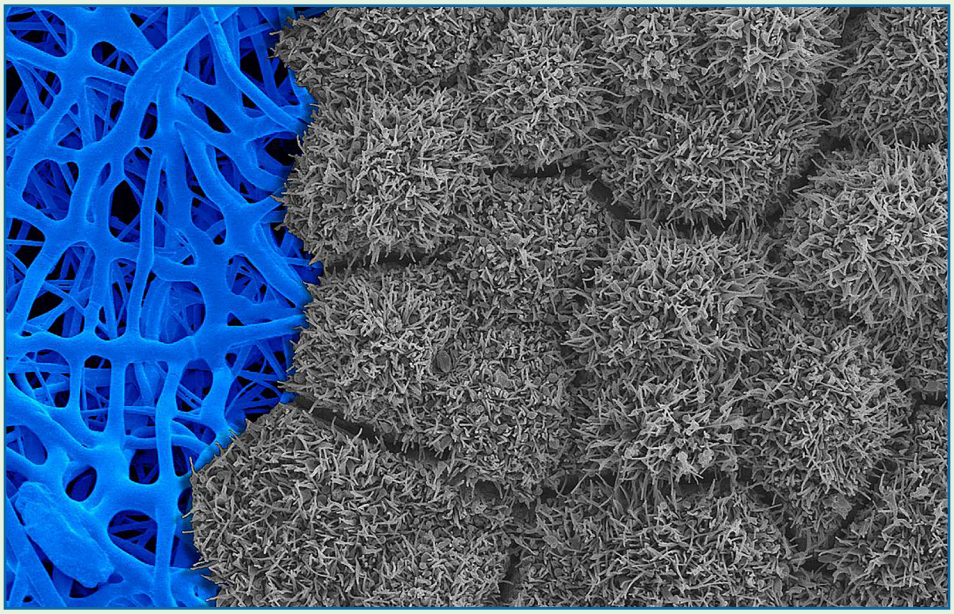
"This AI-based method of validating stem cell–derived tissues is a significant improvement over conventional assays, which are low-yield [and] expensive and require a trained user," said **Kapil Bharti**, a senior investigator in NEI's Ocular and Stem Cell Translational Research Section.

"Our approach will help scale up manufacturing and will speed delivery of tissues to the clinic," added Bharti, who led the research along with Carl Simon Jr. and Peter Bajcsy of NIST.

Cells of the RPE nourish the light-sensing photoreceptors in the eye and are among the first to die from geographic atrophy, commonly known as "dry" AMD. Photoreceptors die without the RPE, resulting in vision loss and blindness.

Bharti's team is working on a technique for making RPE replacement patches from AMD patients' own cells. Patient blood cells are coaxed in the lab to become induced pluripotent stem cells (iPSCs), which can become any type of cell in the body. The iPSCs are then seeded onto a biodegradable scaffold where they are induced to differentiate into mature RPE. The scaffold-RPE "patch" is implanted in the back of the eye, behind the retina, to rescue photoreceptors and preserve vision. The patch worked in an animal model, and a clinical trial is planned.

The researchers' AI-based validation method used deep neural networks, an AI technique that performs mathematical computations aimed at detecting patterns in unlabeled and unstructured data. The algorithm operated on images of the RPE obtained using quantitative bright-field absorbance microscopy. The networks were trained to identify visual indications of RPE maturation that correlated with positive RPE function.



CREDIT: NATHAN HOTALING, NCATS

Scanning electron micrograph showing induced pluripotent stem cell–derived retinal pigment epithelium tissue (gray) cultured on a fiber-based scaffold (blue).

Those single-cell visual characteristics were then fed into traditional machine-learning algorithms, which in turn helped the computers learn to detect discrete cell features crucial to the prediction of RPE tissue function.

The method was validated using stem cell–derived RPE from a healthy donor. Its effectiveness was then tested by comparing iPSC-RPE derived from healthy donors with iPSC-RPE from donors with oculocutaneous albinism disorder and with clinical-grade stem cell–derived RPE from donors with AMD.

In particular, the AI-based image analysis method accurately detected known markers of RPE maturity and function: transepithelial resistance, a measure of the junctions between neighboring RPE; and secretion of endothelial growth factors. The method also can match a particular iPSC-RPE tissue sample to other samples from the same donor, which helps confirm the identity of tissues during clinical-grade manufacturing.

"Multiple AI methods and advanced hardware allowed us to analyze terabytes and terabytes of imaging data for each individual patient and do it more accurately and much faster than in the past," Bajcsy said. ●

(NIH authors: N.A. Hotalin, Q. Wan, R. Sharma, A. George, and K. Bharti, *J Clin Invest*, 2019; DOI:10.1172/JCI131187)

Read more intramural research summaries online at: https://irp.nih.gov/catalyst/v28i1/research-briefs

Stadtman Investigators

EFSUN ARDA, NCI-CCR

ELI BORITZ, NIAID

ELIZABETH (LISA) KHAYKIN CAHOON, NCI-DCEG

EFSUN ARDA, PH.D., NCI-CCR

Research focus: Understanding the genomic basis of cell-fate determination, differentiation, and gene networks that maintain cell identity.

What is one of your "greatest hits"?

With the help of my colleagues, I showed that the hormone-producing cells—such as insulin-secreting beta cells—in the human pancreas continue their maturation after birth; specific gene-expression programs are turned on after the age of 10. (*Cell Metab* **23:**909–920, 2016; DOI:10.1016/j.cmet.2016.04.002)

How did you get into your career?

Growing up, I was always fascinated by the invention stories of famous inventors and scientists and loved experimenting with whatever I could find at home. My mother was a nurse practitioner, and I spent a great deal of time following her in the hospital and her colleagues in clinical laboratories. I think subconsciously that experience made me focus on biology and medicine. During grad school, I discovered the field of systems biology, and the idea of understanding how a system functions as a whole appealed to me.

Would you like to tell us anything else?

NIH is a great place to kick start your career as a junior scientist. I am grateful and honored to be part of this community.

ELI BORITZ M.D., PH.D., NIAID

Research focus: Elucidating the immunologic and virologic mechanisms that allow HIV to persist; contributing to global efforts toward curative therapies for HIV infection.

What is one of your "greatest hits"?

In my best first-author paper, we used a combination of sequencing tools to track replicating HIV and the persistence of HIV-infected cells in people who had natural control of HIV. We discerned the contributions of many cellular processes operating in vivo, and were pleasantly surprised to see how predictably our fundamental understanding of CD4 T-cell immunology could be mapped onto virologic data from distinct anatomic and functional immune compartments. (*Cell* **166**:1004–1015, 2016; DOI:10.1016/j.cell.2016.06.039)

How did you choose a career in your field?

My interest in a physician–scientist's career grew from a love of the natural world that began in childhood. David Attenborough's *Life on Earth* television series was an inspiration. I considered branching away from HIV at multiple points during my career but could never shake my fascination with it and its interactions with the immune system.

What about you might be surprising?

During my 20s, I spent much of my free time playing competitive Ultimate Frisbee.

ELIZABETH (LISA) KHAYKIN CAHOON, PH.D., M.H.S., S.M., NCI-DCEG

Research focus: Investigating cancer and precancer risks conferred by environmental sources of radiation exposure including: 1) studies of preventable risk factors that modify the relationship between ultraviolet radiation and the risk of skin cancer and other cancers; and 2) studies that address unanswered questions about people exposed to ionizing radiation such as after the Chernobyl accident (1986) and after the atomic bombings in Japan (1945).

What is one of your "greatest hits"?

My group was the first to determine that the risk of Kaposi sarcoma was elevated among HIV-infected men who had a diagnosis of nonmelanoma skin cancer and in those living in locations with high ambient ultraviolet radiation at the time of HIV diagnosis (*J Natl Cancer Inst* **109(**5):djw267, 2017; DOI:10.1093/jnci/djw267).

How did you choose your career?

I knew that I wanted to help people live happier, healthier lives. When I discovered the field of epidemiology, it seemed like a perfect fit for my love of mathematics and problem solving.

What about you might be surprising?

I am originally from Tbilisi, Georgia. My family immigrated when I was a child.

Stadtman Investigators

STEVEN CAPPELL, NCI-CCR

ANUPAMA KHARE, NCI-CCR

MITCHELL MACHIELA, NCI-DCEG

STEVEN CAPPELL, PH.D., NCI-CCR

Research focus: Understanding how cells make the decision to proliferate; exploring regulatory circuits in normal cells and how they are rewired in mutations and cancer.

What is one of your "greatest hits"?

The identification of the point of no return for cell-cycle commitment. This discovery has implications for our basic understanding of the cell cycle and for new drugs being developed to target proteins involved in cell-cycle commitment. (*Nature* **558:**313–317, 2018; DOI:10.1038/s41586-018-0199-7)

How did you wind up in your current field?

Growing up, I wanted to become a marine biologist. I was inspired by nature documentaries such as the Discovery Channel series *Shark Week* as well as scuba diving trips to the Caribbean. In college, I learned about how marine corals and marine sponges produce toxins and other natural products that inhibit the growth of nearby marine organisms. Some of these marine natural products have anticancer properties and were being developed as new chemotherapies.

What about you might be surprising?

I've swum with great white sharks (Cape Town, South Africa), picked up a rattlesnake with my bare hands (in the Mojave Desert), and was charged by a grizzly bear (in Alaska).

ANUPAMA KHARE, PH.D., NCI-CCR

Research focus: Using systems-biology approaches to study the molecules and mechanisms that underlie complex microbial behaviors including polymicrobial interactions; identifying the determinants of the early steps of the evolution of antibiotic resistance and characterizing these as potential targets for novel antimicrobials.

What is one of your "greatest hits"?

In my postdoctoral work, I established a framework to analyze all the cellular pathways that underlie a specific interaction between two different bacterial species, unlike most previous studies that focused on only one class of molecules. Gaining such a systematic understanding of interactions among bacterial species is a first step toward developing novel therapies to modulate clinically important microbial communities. (*PLoS Genet* **11**:e1005715, 2015)

How did you choose your career?

My parents are both scientists (as is my brother), which may explain how my love for science first started. Mathematics and science, especially biology, were my favorite subjects in school. I really enjoyed learning about Mendelian genetics in high school; more in-depth exposure to cell biology, evolution, and genetics in college fueled my interest in molecular biology, especially as it pertains to microbiology.

MITCHELL MACHIELA, SC.D., NCI-DCEG

Research focus: Studying the role of germline variation and somatic mosaicism in cancer risk; conducting and analyzing genetic association studies to elucidate the underlying genetic architecture of pediatric and common adult cancers.

What are some of your "greatest hits"?

One is a web tool I developed to help scientists study how inherited variants correlate with each other and how these correlation patterns vary by ancestry. The tool, LDlink, was intended to be a simple online reference for lab biologists and expanded from there. LDlink is available at http://ldlink.nci.nih.gov and has had over 280,000 pageviews and users from 145 different countries. (*Bioinformatics* **31:**3555–3557, 2015; DOI:10.1093/bioinformatics/btv402)

My personal favorite is one of the first papers I published at NCI as a research highlight on genome-wide association studies in dogs. It was a fun change of pace to write an article on man's best friend that included details on Frisbee catching, narcolepsy, and extending a paw to help humans map complex diseases. The crowning achievement was getting a picture of my PI's dog as the cover photo. It was certainly one of my greatest hits. (*Genome Biol* **15:**105, 2014; DOI:10.1186/gb4166)

CONTINUED ON PAGE 12

Stadtman Investigators

NATALIE PORAT-SHLIOM, NCI-CCR

SERGIO RUIZ MACIAS, NCI-CCR

ROXANE TUSSIWAND, NIDCR

NATALIE PORAT-SHLIOM, PH.D., NCI-CCR

Research focus: Using light and microscopy of hepatocytes in the liver, to understand how cells sense and adapt to changes in nutrients and how nutrient availability affects organelle dynamics and cell metabolism.

What is one of your "greatest hits"?

My group discovered that in exocrine tissues (such as sweat, salivary, and mammary glands), mitochondria have a conserved distribution and consist of distinct populations that exhibit different dynamic properties and functions. I developed intravital microscopy approaches for imaging cells in intact tissues of live, anesthetized mice. (*iScience* **11:**440–449, 2019; *Cell Rep* **9:**514–521, 2014; *Cell Syst* **4:**277–290, 2017; *Hepatology* **64:**1317–1329, 2016)

What will be the impact of your work?

Using intravital microscopy to observe biological processes in live animals at high resolution, we can reveal the dynamic nature of cellular processes. This approach is powerful in disease models such as cancer.

Would you like to tell us anything else?

The environment has great impact on cells and also on scientists. Collaborative, communicative, and supportive space is the recipe for creative, high-quality science.

SERGIO RUIZ MACIAS, PH.D., NCI-CCR

Research focus: Using human and mouse embryonic stem cells as well as mouse embryos to study cell plasticity, pluripotency, and differentiation to get a better comprehension of embryonic development, cell transformation, and cancer.

What is one of your "greatest hits"?

When I was a staff scientist at the Spanish National Cancer Research Center, I used a CRISPR-Cas9-based screen in mouse embryonic stem cells (ESCs) to explore the existence of genes providing resistance to the inhibition of the DNA-damage-response ataxia telangiectasia and Rad3-related protein (ATR) kinase. (ATR kinase can potentially halt the development of tumors.) I identified *cdc25a* as a gene that when knocked-out conferred full resistance to ATR inhibition. I proposed that the concentration of *cdc25a* would be a great biomarker to predict the selective killing of cancer cells by using ATR inhibitors. (*Mol Cell* **62:**307–313, 2016)

What about you might be surprising?

I play the mandolin; I am addicted to jigsaw puzzles (I even participated at the Spanish National Competition); and I have backpacked in more than 50 countries.

ROXANE TUSSIWAND, PH.D., NIDCR

Research focus: Understanding how transcription factors modulate the differentiation of hematopoietic stem cells into mature immune cells.

What is one of your "greatest hits"?

The activator protein transcription factor B-ATF-3 is required for the development of a subset of dendritic cells (DCs) that are responsible for priming cytotoxic CD8 T cells. We identified an alternative pathway that leads to the expansion of these DCs. This pathway may provide a basis for augmenting therapeutic immune responses. (*Nature* **490:**502–507, 2012; DOI:10.1038/nature11531)

What is the significance of your work?

The ability to modulate immune responses by shaping the environment may open novel therapeutic avenues in the context of autoimmune syndromes, infections, and cancer.

What caused you to choose your career?

When I was eight years old, my little brother was diagnosed with an early pre-B-cell leukemia. I wanted to understand what was happening. From that moment on, I began dedicating myself to shedding light on normal and pathologic biological processes.

Stadtman Investigators

JOANA VIDIGAL, NCI-CCR

ACHIM WERNER, NIDCR

JOANA VIDIGAL, PH.D., NCI-CCR

Research focus: Understanding the roles that noncoding RNAs perform in the cell, how their activity is regulated, and how their dysfunction contributes to human disease.

What is one of your "greatest hits" so far?

My lab described a computational strategy to deal with one of the biggest challenges in using CRISPR gene editing to identify essential noncoding sequences: how to deal with the noise generated by unspecific guide RNAs. By using machine learning we are able to predict how off-targets affect guide-RNA performance in high-throughput screens, and using that information we can estimate the importance of on-target cleavage to cell viability. We are now using this strategy to identify essential sequences in miRNA-mediated phenotypes. (*bioRxiv*, a non-peer-reviewed preprint server, 2019; DOI:10.1101/809970)

What will be the impact of your work?

My laboratory is committed to making our work, and the reagents and tools we develop, publicly available so that other researchers can benefit from it for their own projects. Hopefully, doing so means that the impact of our work will extend beyond our immediate area of research.

ACHIM WERNER, PH.D., NIDCR

Research focus: Studying how stem cells use the post-translational modifier ubiquitin to determine cell-fate choices during human development, in particular those involved in neural crest, craniofacial, and neuronal differentiation.

What are some of your "greatest hits"?

During my graduate studies I discovered a ubiquitin-dependent pathway that regulates actin-based cell-shape changes required for faithful cell-cycle progression (*Nat Cell Biol* **15:**179–188, 2013). During my postdoctoral work, I identified a novel regulatory circuit that controls the function of newly synthesized ribosomes to allow stem cells to adopt a neural-crest cell fate during differentiation (*Nature* **525:**523–527, 2015). Genetic lesions in the substrate of this pathway, treacle protein, result in Treacher Collins syndrome, a genetic disorder characterized by facial deformities.

Would you like to tell us anything else?

I am truly grateful to be part of the Stadtman program. By interacting with other Stadtmans, I was able to better handle the day-to-day challenges of setting up my own lab, establish research collaborations, and, most importantly, quickly make friends.

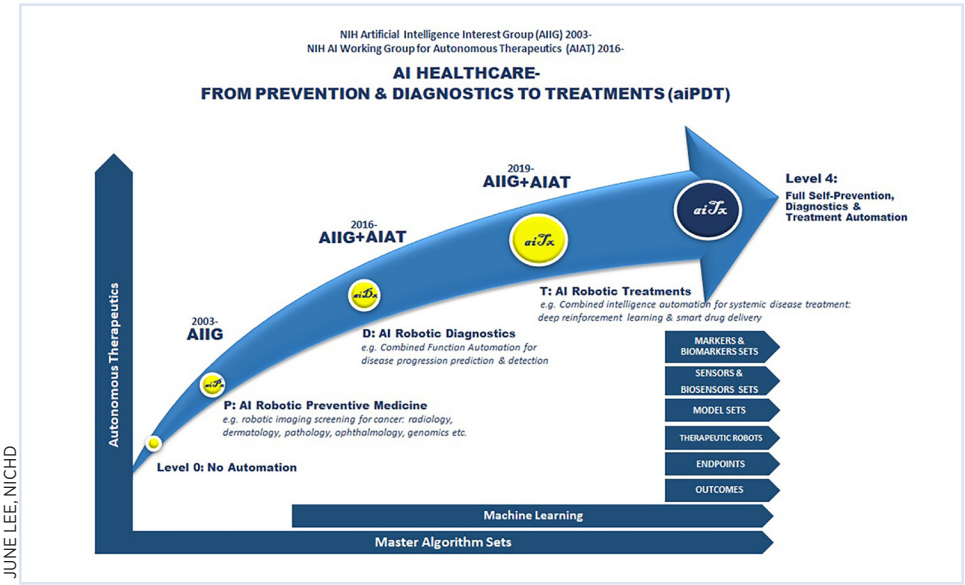
Read longer profiles online at https://irp.nih.gov/catalyst/v28i1/getting-to-know-11-stadtmans.

NEWS FROM AND ABOUT THE SCIENTIFIC INTEREST GROUPS

Artificial Intelligence Health Care

From Prevention and Diagnostics to Treatment

BY SUSAN CHACKO, CIT



JUNE LEE, NICHD

Autonomous vehicles, wearable technology, traffic-aware maps, voice-activated virtual assistants. The opening introductions in a recent artificial-intelligence (AI) workshop mentioned all of these and more, underlining the prevalence of AI in normal life today. In basic biomedical research, AI is being used to interpret neurological images, correlate genetic variants and risk of disease, design and develop drugs, and more. AI's clinical applications include being used to help diagnose disease and determine treatment options for cancer, assist in robotic surgery, and aid in the processing of electronic health records.

Scientists from academia, industry, and the federal government gathered for the workshop "Artificial Intelligence Healthcare–From Prevention and Diagnostics to Treatment" on October 1, 2019. The workshop was organized by NIH Artificial Intelligence Interest Group, the Office of Intramural Research, and the NIH AI Working Group for Autonomous Therapeutics. Following are highlights.

The Defense Advanced Research Projects Agency (DARPA) has been investing in AI since 1960, according to DARPA Deputy Director Peter Highnam. DARPA-funded research is aiming for automated detection of battlefield injuries; healing of blast and burn injuries using bandages that sense and respond to the severity of the wound; and fully automated pipelines to produce small-molecule drugs in hours rather than weeks. Highnam showed a video of a wounded veteran who learned to use brain signals to control his state-of-the-art prosthetic arm that has tactile sensors and can rotate 360 degrees.

Just as exciting was a presentation by Richard Satava (University of Washington Medical Center in Seattle) who discussed the current use of AI-based robotic and image-guided surgery. Soon to come, he said, is minimally invasive and remote surgery. The surgeon guiding the robot becomes more of an information manager, responding to the data provided by live imaging during the surgery. Robot-assisted surgeons could conceivably remove individual cancer cells instead of chunks of tissue, and the patient would recover faster. Satava described even more futuristic implementations of AI such as virtual autopsies based on 3-D reconstruction of skeletal images, and handheld diagnostic and therapeutic surgical devices that could be operated by the patients themselves.

Diana Bianchi, director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), discussed opportunities for AI in maternal and child health. She described an NICHD-funded consumer device that attaches to a smartphone with AI software. The device can analyze saliva and predict ovulation more accurately and easily than current technology. Other NICHD-funded projects include AI analysis of whole-genome sequences from sick newborns for quicker diagnosis and promising AI-based technologies for detecting jaundice in newborns. Research is ongoing to improve electronic fetal monitoring, predict women's risk of maternal morbidity, and study placental function.

More presentations followed including descriptions of intramural projects such as the development of an AI robotic platform that, with little or no human intervention, would diagnose and treat diseases. ●

For a videocast of the workshop, go to https://videocast.nih.gov/launch.asp?28761. For more information about the SIG and its LISTSERV, go to https://oir.nih.gov/sigs/artificial-intelligence-interest-group. You can also contact the chair, June Lee (LeeJun@mail.nih.gov).

Read more online at https://irp.nih.gov/catalyst//v28i1/the-sig-beat-artificial-intelligence

New: Matrix Biology SIG

The new Matrix Biology Scientific Interest Group, which grew out of the trans-NIH Matrix Club, focuses on research related to the extracellular matrix (ECM). ECM is not only a scaffold but also the environment that defines cell differentiation, function, and signaling in all tissues and organs. The ECM is also a conduit for many higher-level functions in multicellular organisms. The importance of ECM biology for the mission of many NIH institutes and centers (ICs) was the motivating factor behind monthly trans-NIH Matrix Club meetings, which were jointly hosted for many years by the National Institute of Dental and Craniofacial Research and the National Institute of Child Health and Human Development.

Over the years, Matrix Club meetings provided NIH trainees with opportunities for making presentations to a wider audience, meeting with experts in the field, and finding mentors beyond their labs. Trainees from many ICs have presented at these meetings, some getting useful feedback and advice, some finding new collaborations, and some finding new NIH fellowships after completing training at another NIH IC. The creation of the trans-NIH Matrix Biology Scientific Interest, Group, which replaces the Matrix Club, further enhances these benefits and opens them up to a wider NIH community. Monthly meetings of the new Matrix Biology SIG will be hosted by NIDCR and NICHD.

For more information, go to https://oir.nih.gov/sigs/matrix-biology-interest-group, or contact the co-chairs: **Pamela Robey** (NIDCR) or **Sergey Leikin** (NICHD). To join the LISTSERV, please visit https://list.nih.gov/cgi-bin/wa.exe?A0=MATRIX_BIOL_SIG, then click the "Subscribe or Unsubscribe" link in the right sidebar.

L. ALEXANDER/THINKSTOCK.COM

Renamed: Metabolism SIG

The NIH Metabolism Interest Group (MIG), formerly the Diabetes/Metabolism Scientific Interest Group (run by **Sam Cushman**), hosts a seminar series that promotes the basic, translational, and clinical research in metabolism. The group fosters interactions and collaborations across the entire NIH intramural community. The wide scope of seminar topics reflects the increasing recognition that the study of cellular and whole-body metabolism is relevant for understanding processes as diverse as aging, obesity, oncogenesis, cancer biology, and mitochondrial function. The group plans to meet each month on the second and fourth Mondays, from 3:30 p.m. to 4:30 p.m., in Room 9S-233, Building 10. Each meeting will feature one 60-minute presentation from an intramural or extramural senior scientist or two 30-minute presentations from trainees. To join the MIG LISTSERV email list, go to https://list.nih.gov/cgi-bin/wa.exe?SUBED1=MIG&A=1, and hit the "Subscribe" button. For more information, go to https://oir.nih.gov/sigs/metabolism-interest-group or contact one of the co-chairs, **Aaron M. Cypess** (aaron.cypess@nih.gov) or **Marc Reitman** (marc.reitman@nih.gov).

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

New: Stigma SIG

Stigma plays a fundamental role in the development and perpetuation of health inequities in the context of a range of diseases including cancer, epilepsy, human immunodeficiency virus infection, mental illness, and obesity. Stigmatized individuals may be excluded from receiving effective or quality treatment and care. They may be subject to human-rights abuses that in turn can lead to avoiding health care and having adverse health outcomes. Although research across disciplines finds that drivers of stigma are similar, current research is siloed by disease or population, thus limiting opportunities for research that builds on the progress made across disciplines.

The Stigma SIG is open to intramural and extramural scientists who are interested in cross-cutting, theoretically-driven research that advances measurements of stigma, and in the biological, behavioral and social mechanisms and pathways by which stigma leads to poor health outcomes. Regular activities include monthly meetings, a quarterly seminar, and a range of activities both inside and outside the NIH including major conferences and summits, lectures, webinars, and collaborations with other federal and non-federal entities. The monthly meetings will highlight NIH-supported stigma research (intramural and extramural), scientific priorities and related activities, and will be used to advance collaborative, cross-cutting projects pursued by the SIG.

For more information go to https://oir.nih.gov/sigs/stigma-scientific-interest-group or contact **Brenda Curtis** (NIDA) at brenda.curtis@nih.gov or **Gregory Greenwood** (NIMH) at gregory.greenwood@nih.gov. To join the Stigma SIG LISTSERV, please visit https://list.nih.gov/cgi-bin/wa.exe?A0=STIGMASIG, then click the "Subscribe" link in the right sidebar. ●

Pushing the Frontiers of Imaging

CONTINUED FROM PAGE 1

In fact, AIM has been operating for more than three years out of temporary quarters in **Hari Shroff's** lab (in Building 13) at the National Institute of Biomedical Imaging and Bioengineering (NIBIB).

The seeds of the AIM group were planted almost five years ago during a lunchtime conversation among four intramural imaging scientists: Shroff, **Justin Taraska** and **Keir Neuman** (National Heart, Lung, and Blood Institute), and **Dan Larson** (National Cancer Institute). They wanted to push the boundaries of imaging technology to enhance intramural research projects. Wouldn't it be great, they thought, to have a central core facility that could develop cutting-edge microscope technology and new image-processing algorithms?

It took a couple of years for the proposal to be approved and intramural funds secured. Shroff, the managing director of the core facility, has overseen AIM from its inception. Taraska, Neumann, and Larson are on the AIM steering committee along with representatives from other NIH institutes.

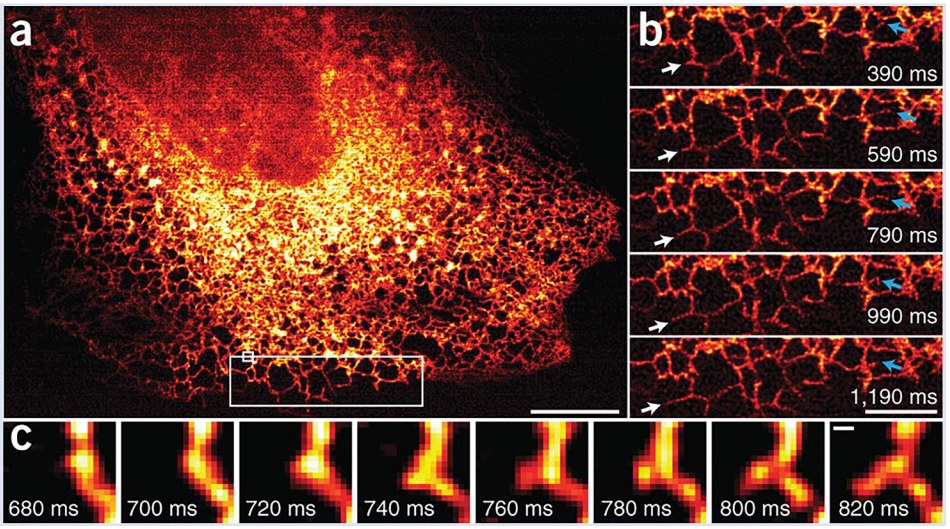
THE AIM MICROSCOPES

AIM will be updating, modifying, and replacing microscopes. Current equipment:

- Dual-view Inverted Selective Plane Illumination Microscope (diSPIM)
- Instant Structured Illumination Microscope (iSIM)/Total Internal-reflection Fluorescence SIM (TIRF-SIM)
- Interferometric Photoactivated Localization Microscope (IPALM)
- High-throughput Single-molecule Imaging Microscope
- Single-molecule TIRF/Inclined-illumination Microscope

COLLABORATIONS

The AIM group did not wait for their facility to be completed before diving into collaborations. Shroff and **Harshad Vishwasrao**, the first hire (in 2016), began to give energetic, exciting seminars around campus that prompted a slew of intramural scientists to contact them about potential collaborative projects. A sampling of these projects is described here.



AIM FACILITY, NIBIB

Images taken by the Instant SIM reveals endoplasmic reticulum (ER) dynamics within human lung fibroblasts. (a) First image in series of 200 time points; (b) Higher-magnification view of the large white rectangle in a. White arrows mark growth of an ER tubule; blue arrows indicate remodeling of an ER tubule; (c) Higher-magnification view of the small white rectangle in a, indicating formation of a new tubule.

IMAGING MOUSE EGGS

Jurrien Dean at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) became one of these collaborators. His lab studies mouse sperm-egg interactions and the postfertilization block to polyspermy. Only one sperm is needed to fertilize an egg; two or more sperm are lethal to the development of an embryo. The egg, however, can protect itself. After fertilization, the egg's peripheral cortical granules (CGs) release ovastacin, an enzyme that modifies the egg's outside layer in a way that prevents additional sperm from binding. **Edgar-John Vogt**, a postdoc in Dean's group, used ovastacin, tagged with a fluorescent probe, to learn more about CG biology. But he and Dean needed super-resolution imaging to properly study the CGs. NIDDK's own confocal microscopes weren't enough. Luckily, Dean had heard Shroff give a presentation and therefore knew about AIM's sophisticated microscopes.

AIM's advanced imaging—TIRF, iSIM, and live instant TIRF-SIM—allowed the researchers to see CGs at a single-granule resolution. These images documented for the first time that the myosin IIA protein was involved in transporting CGs to the egg's plasma membrane and actin proteins were cleared to facilitate CG fusion with the membrane. The researchers also demonstrated that a large protein called maternal antigen that embryos require (MATER) helps to anchor the CGs in the cortex of the egg. In the absence of MATER, the CGs are present throughout the egg instead of being near the membrane where they can keep multiple sperm from fertilizing the egg.

IMAGING THE RETINA

At the National Eye Institute, **Anand Swaroop** heard of the AIM group and invited Vishwasrao to give a talk to his lab. Swaroop is trying to understand the molecular and cellular pathways underlying

retinal development, aging, and disease, and developing new treatments for blinding retinal diseases. His lab intends to collaborate with AIM on two or three new projects. One will examine details of the human retina made in a dish from patients' cells. In another project, Swaroop's group is studying the retina in several vertebrate species to determine how rods (responsible for vision at low light levels) and cones (active at high light levels and responsible for color vision) develop, how color vision evolved, and how the cone-rich retinal fovea that provides sharp central vision develops. Swaroop's work has tied the development of rod photoreceptors to the evolution of early mammals from nocturnal creatures to diurnal ones. Discovering how human vision evolved will also advance the study of retinal and macular degeneration.

To further their work, the researchers need histological data from many species at super-high resolution. **Noor White**, a postdoc in Swaroop's lab, has started using the AIM diSPIM, with Vishwasrao's help, to collect images of the retina from birds as part of her research on the evolution of night vision and development of the fovea.

IMAGING OF BACTERIAL SPORE COATS

AIM Co-director of Operations **Jiji Chen**, who specializes in single-molecule imaging techniques, collaborated with Shroff and **Kumaran Ramamurthi's** group at the National Cancer Institute to determine how bacterial spore coats form. The process is a model for understanding the dynamics of structural proteins as they organize in the correct place and time during morphogenesis. In a recent study, the researchers described how the bacterial spore coat, which consists of dozens of proteins, assembles in an orchestrated fashion. Images collected on the AIM single-molecule TIRF microscope showed how these coat proteins recognize and bind to membranes with a specific curvature (*Proc Natl Acad Sci U S A* **116:**21789–21799, 2019; DOI:10.1073/pnas.1907397116).

LENDING TECHNICAL EXPERTISE

AIM researchers are engaged in purely technical collaborations, too, such as one with **Ted Usdin**, the director of the Systems Neuroscience Imaging Resource in the National Institute of Mental Health (NIMH). He wants to image large volumes of brain tissue to examine the connections, distributions, and phenotypes of neurons. His group, and others at NIMH, would like to image the entire brains of mice and rats—and potentially even large primate brains—at high resolution.

NIMH has funded the development of a specialized, cleared-tissue diSPIM—to be housed in and operated by AIM—that can rapidly visualize entire mammalian brains. NIMH investigators are eager to use this instrument because in contrast to other light-sheet instruments there is no theoretical limit to the lateral dimensions of the tissue that can be imaged. The instrument will be able to image material that is up to 50 x 75 millimeters (mm) in length and width and 2 mm thick. A cutting device called a vibratome, mounted onto the microscope stage, will successively remove 1–2 mm of tissue at a time after each section is imaged. An entire brain can be imaged this way. Vishwasrao will be building and maintaining the microscope as well as making design changes when necessary. The microscope is expected to be ready in the next few months. The images will allow NIMH scientists to examine the connections that neurons make among brain regions and identify particular cells involved in these connections.

CHALLENGES

With new technological developments come new challenges. The problem of data processing was noted by both Vishwasrao and Usdin. Although collecting a dataset with the high-powered microscopes can take minutes, processing the data can take weeks. Some of the processing will be done on Biowulf, NIH's biomedical supercomputer, but transferring, storing, processing, and archiving multiterabyte datasets can all be bottlenecks.

Luckily, the AIM group is also developing image-analysis software that will speed up processing. A recent addition to the AIM staff is **Jiamin Liu**, who will be using artificial intelligence and deep-learning techniques to enhance image quality by deblurring and denoising them (noisy images are imperfect because of random digital or electronic noise caused by the camera sensor); and to improve image analysis.

HOW AIM IS FUNDED

AIM operates on a partial cost-recovery model where 25% of the costs are covered by the collaborators. Over time, the AIM will be required to recover a larger fraction of its costs.

ONE OF SEVERAL CORE IMAGING FACILITIES

The AIM facility is but one of the several new core imaging facilities at NIH. (See Michael Gottesman's essay on page 2 to find out more).

"The beauty of the NIH is having these pockets of expertise,"said Dean, "when you have the need, you can go and take advantage of it." ●

Read a longer version of this article at https://irp.nih.gov/catalyst/v28i1/pushing-the-frontiers-of-imaging. For more information about AIM, go to https://www.nibib.nih.gov/labs-at-nibib/advanced-imaging-and-microscopy-aim-resource.

IN 2018 (NOT INCLUDED LAST YEAR)

Lewis L. Judd (died on December 16, 2018, at 88) was a nationally known psychiatrist who helped turn the focus of his profession from psychoanalysis to neuroscience. As director of the National Institute of Mental Health (NIMH), from 1988 to 1990, he helped launch a federal research initiative known as the "Decade of the Brain."

Ting-Kai (T.-K.) Li (died on November 18, 2018, at 84) was the director of the National Institute on Alcohol Abuse and Alcoholism from 2002 to 2008. He was a staunch advocate for advancing alcohol research, both clinical and basic science.

IN 2019

Wayne Bardin (died on October 10, 2019, at 85), considered a pioneer in endocrinology, was a researcher at the National Cancer Institute (NCI) from 1964 to 1970. He developed Norplant as well as other contraceptives.

Mary Bochanis (died March 7, 2019, at 94) was one of the longest-serving volunteers at the Children's Inn at NIH (1990-2018).

Stephan D. Brenowitz (died on May 31, 2019, at 51), at the National Institute on Deafness and Other Communication Disorders (2007–2014), investigated the cellular and synaptic mechanisms underlying fusiform cell responses to sounds and how these responses could be influenced by somatosensory stimuli.

Belia "Bel" Ceja (died July 4, 2019, at 94) was a special assistant to three NIH directors (**Robert S. Stone**, **Donald S. Fredrickson**, and **James B. Wyngaarden**) and retired in September 1985 after more than 29 years of federal service.

Philip A. Corfman (died on February 18, 2019, at 92) was the first director of the National Institute of Child Health and Human Development's (NICHD's) Center for Population Research, which was established in 1968. He spent 20 years at NICHD before leaving for the World Health Organization and later, the FDA. At NICHD, he oversaw research programs on contraception and behavioral sciences. He stressed the need for family-planning methods for both men and women.

John Fakunding (died on February 21, 2019, at 73) was the former director of the Heart Research Program in the National Heart, Lung, and Blood Institute. His first NIH position was in the intramural lab of **Kevin Catt** at NICHD. Fakunding retired in 2005.

Nicolaas (Nic) Fourie (died on February 23, 2019, at 38) came to National Institute of Nursing Research as a visiting fellow in 2012. He was a research fellow (2013-2017) and then a special volunteer. He discovered microRNA signatures in digestive and liver disorders.

Michael M. Frank (died on August 1, 2019, at 82) was a past clinical director at the National Institute of Allergy and Infectious Diseases (NIAID) during the early years of the AIDS epidemic. He joined NIH in 1966; he became section chief and ultimately chief of the NIAID Laboratory of Clinical Immunology in 1968 and then the NIAID clinical director in 1977. His work led to the first effective treatment for hereditary angioedema. He left NIH in 1990 to became chairman of the Department of Pediatrics at Duke University (1990–2004).

Fred A. Gill (died on October 12, 2019, at 83) was chief of the Internal Medicine Consultation Service for the NIH Clinical Center from 1998 until retiring in 2016.

Joyce Goldstein (died on August 7, 2019, at 78) conducted groundbreaking research in pharmacogenetics as head of the Human Metabolism Group in the National Institute of Environmental Health Sciences (NIEHS). Her research provided a clearer understanding of how genetic variations can result in adverse reactions to certain drugs. She worked at NIEHS from 1977 to 2015 and retired as an emeritus faculty member.

Philip Gurnev (died in August 2019, at 41) had been a staff scientist in the NICHD Section on Molecular Transport since 2015. He made significant contributions to the field of ion-channel biophysics in the lab of **Sergey Bezrukov**. Gurnev was a postdoctoral trainee and then a research fellow at NICHD (2004–2012).

Kurt Isselbacher (died on July 18, 2019, at 93), the great teacher and practitioner of gastroenterology, spent his entire career in Boston at Harvard Medical School and Massachusetts General Hospital. His connection to NIH dates back to to the 1950s, when he was a clinical associate, and then sabbaticals and later visits. He worked closely with **George Khoury** (NCI) and **Tony Fauci** (NIAID), among others.

William B. (Bill) Jakoby (died in late August 2019 at the age of 90), former chief of the National Institute of Diabetes and Digestive and Kidney Diseases' (NIDDK's) Laboratory of Biochemistry and Metabolism, was a seminal figure in enzymology. He came to NIH in 1955 first at the then–National Institute of Arthritis and Metabolic Diseases. He was chief of NIDDK's Laboratory of Biochemistry and Metabolism (1985–1999). He retired in 1999 and became a scientist emeritus.

Edward Kelty (died on September 27, 2019, at 89) was a psychologist at NIMH from 1968 to 1994.

Andrew Lee (died on April 21, 2019, at 23) was diagnosed with a rare kidney cancer in college. Determined to fight the terminal disease and contribute to research, he participated in seven NIH-led clinical trials. In 2016, he founded a nonprofit and raised more than $400,000 for the Foundation for the NIH to fund kidney-cancer studies at the NIH Clinical Center.

Donald A.B. Lindberg (died on August 16, 2019, at 86) was a pioneer in medical informatics and director of the National Library of Medicine (NLM) from 1984 to 2015. During his tenure, NLM created PubMed, MedlinePlus.

gov, ClinicalTrials.gov, and many other online repositories of scientific information. He helped the NLM grow into the world's largest biomedical library.

Marcelle Morrison-Bogorad (died in September 2019) was a researcher and director of the National Institute on Aging's (NIA's) Division of Neuroscience for 14 years (1997–2011) before retiring in 2011. In the 1970s, she was one of the first researchers to isolate and study the properties of globin messenger RNAs in red blood cells.

Carole Kemm Regan (died on January 7, 2019, at 72) was a former laboratory manager of NCI's Laboratory of Cellular and Molecular Biology. She joined the NCI more than 40 years ago. When she retired in 2017, she was then the longest-serving member of the lab.

John Robbins (died on November 27, 2019, at 86) was a codeveloper of the *Haemophilus influenzae* type b (Hib) vaccine, which spared millions of young children from early death, deafness, and neurological impairment. He was the first clinical director for NICHD (1970-1974); the director of FDA's Division of Bacterial Products (1974–1984), then in Building 29; he returned to NICHD in 1984 and became chief of its Laboratory of Developmental and Molecular Immunity; and retired in 2012.

Saul Rosen (died on February 28, 2019, at 90) whose 35-year career was spent at NIH, was named deputy director of the NIH Clinical Center in 1984, became acting director in 1990, and remained there until his retirement in 1994. He came to NIH in 1958 as a clinical associate in what was then the National Institute of Arthritis and Metabolic Diseases. He was proud of his clinical white coat, which was festooned with patches from different Clinical Center departments.

Leon Sokoloff (died on March 22, 2019, at 99) who was professor emeritus of pathology at the University of New York at Stony Brook spent two decades at the National Institute of Arthritis, Metabolism, and Digestive Diseases. He was chief of the Section on Rheumatic Diseases (1953–1973) and specialized in the pathological investigation of human and experimental arthritis.

Melvin Spann (died on May 7, 2019) was the first African American appointed associate director of NLM (1995–1999). Before his arrival at NLM in 1976, he spent 10 years with the FDA, first as a chemical information specialist and then as chief of FDA's Scientific Information Systems Design Branch.

Nadarajen "Nada" Vydelingum (died on August 28, 2019) was a cell biologist, educator, researcher (in the cancer biomarkers research group, 2012–2016), and health administrator at NCI from 1991 to 2016.

Huber Warner (died on September 12, 2019, at 83), a biochemist and associate director of NIA's Biology of Aging Program, worked at NIA from 1984 to 2004. His research included oxidative stress, molecular mechanisms of apoptosis, functional genomics, and stem cells.

Elizabeth Weisburger (died on February 12, 2019, at 94) was a former assistant director for chemical carcinogenesis in NCI's Division of Cancer Etiology. She made seminal contributions to the understanding of carcinogenesis. She came to the NIH as a postdoc in NCI in 1949, joined by her husband at that time, John. The two worked closely together until John's departure from NCI in 1972. Elizabeth remained at NIH until her retirement in 1988.

Bernhard Witkop (died on November 22, 2019, at age 93) was a renowned organic chemist who worked at NIH for more than 40 years including as head of the NIDDK Laboratory of Chemistry for 30 years. He, **John Daly**, and others discovered the "NIH shift," a term describing the movement of hydrogen, deuterium, or tritium to adjacent carbons on aromatic rings during oxidation, a process key in developing many therapies. Witkop also helped to develop a method that was later used in the production of human insulin. He was appointed an NIH institute scholar in 1987 and a scholar emeritus in 1993. He also helped pioneer the NIH Visiting Fellow Program.

James B. Wyngaarden (died on June 14, 2019, at 94), an internationally recognized authority on the regulation of purine biosynthesis and the genetics of gout, was NIH director from April 1982 through July 1989. Before his NIH appointment, he had been professor and chairman of the department of medicine at Duke University School of Medicine (1967–1982). Among the major challenges during his tenure as NIH director were the nation's biomedical-research response to the HIV and AIDS epidemic and the emergence of recombinant DNA and other ethically charged biotechnologies. He also initiated NIH's leadership role in the international Human Genome Project. He was instrumental in setting up the Children's Inn at NIH and was a strong advocate for the importance of physician–scientists in biomedical research.

Yoshi Yamada (died December 16, 2019, at 76) was a senior scientist in the Laboratory of Cell and Developmental Biology in the National Institute of Dental and Craniofacial Research (NIDCR). In 1978, he joined NCI to study gene evolution and regulation of collagen genes. In 1983, he joined NIDCR, where he studied the functions of basement membrane components, cartilage matrices, and other extracellular matrices during development and diseases. In 2011, he and others at NIH received an award from the Japanese Embassy in recognition of NIH's support of the Japanese research community after the March 2011 earthquake and tsunami disasters. ●

Read more online:
Obits: https://irp.nih.gov/catalyst/v28i1/obituaries-2019

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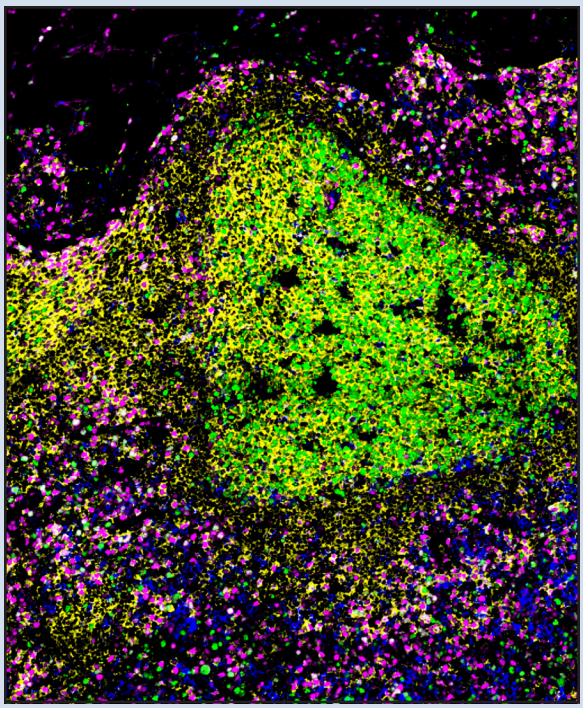
SCIENTIFIC MOMENT

Lymph Node of Person with Untreated HIV

A microscopic image of a biopsied lymph node of a person with untreated HIV, showing large germinal centers containing abnormal proliferating B cells (bright green triangle-shaped area) and an accumulation of cells expressing the transcription factor T-bet (magenta) in the surrounding areas.



CREDIT: NIAID

NIH researchers found that in the setting of HIV-associated chronic immune activation, failure of HIV-specific B cells to enter or remain in the germinal centers may help explain the rarity of high-affinity protective antibodies. A better understanding of this process and the lymph node architecture where these antibodies develop will provide further insight into adaptive immunity in chronic infectious diseases and how responses to pathogens may be improved by therapeutic intervention. (*Sci Transl Med* **11:**eaax0904, 2019)

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