THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

NATIONAL INSTITUTES OF HEALTH • OFFICE OF THE DIRECTOR | VOLUME 24 ISSUE 5 • SEPTEMBER-OCTOBER 2016

Alan Schechter and His Former Postdocs

Where Are They Now?

BY LAURA STEPHENSON CARTER

On July 1, 1965, Alan Schechter drove his light blue VW bug to the NIH for his very first day on the job. The car didn't last long on Maryland's roads, but the driver is showing little sign of wear. "The fact he is still here 50 years later is a testimony to him," **Bob Adelstein** told the crowd that had gathered for a symposium he helped organize to honor Schechter.

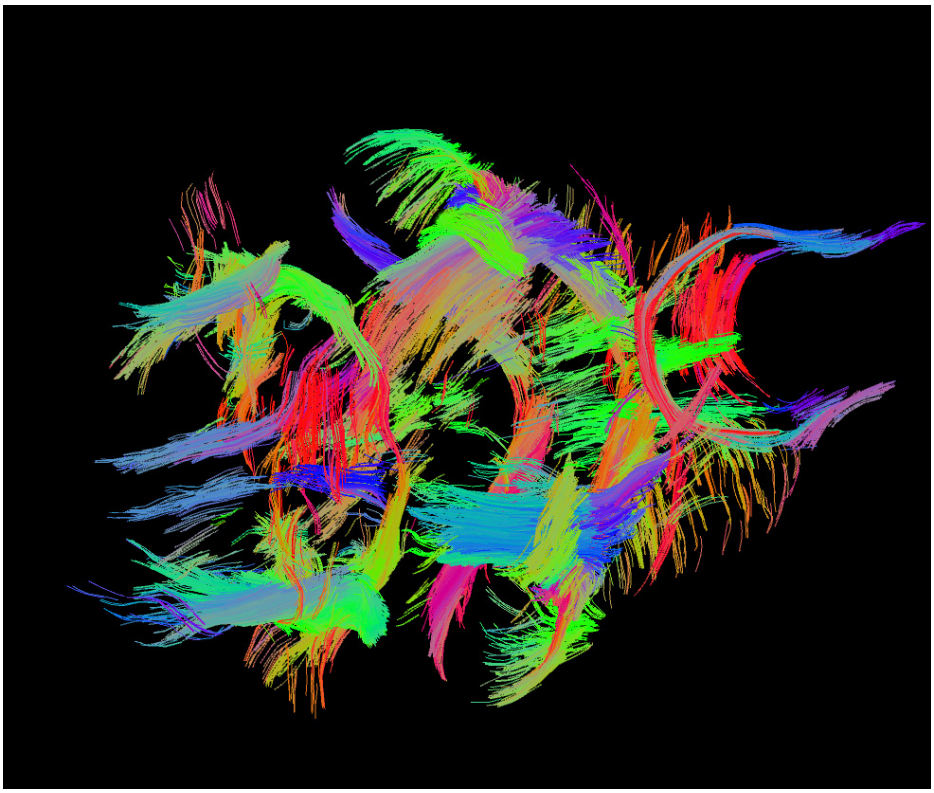
Schechter, who's a senior scientist in and chief of the Molecular Medicine Branch in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), has focused his research on developing treatments for genetic diseases of hemoglobin, including sickle-cell disease. He and his colleagues have contributed to the understanding of the pathophysiology of sickle-cell disease; to pioneering clinical studies that demonstrate the value of hydroxyurea in treating this disease; and, more recently, to the understanding of the role of hemoglobin in the formation and metabolism of the signaling molecule nitric oxide (NO).

Equally as impressive as his research career is his success in training and mentoring dozens of postdocs. He taught his M.D. postdocs to understand basic science and his Ph.D. postdocs to think about how their basic research would apply to health and disease. They've gone on to become distinguished scientists in their own right. Many eagerly attended the symposium, and

CONTINUED ON PAGE 12

Cool Pics

NIH Image Gallery Provides Scientific Photos, Illustrations, and More

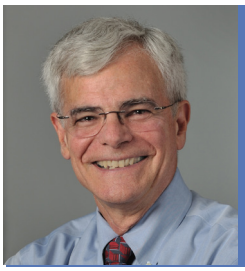


S. SCHWERIN, M. BUDDE, M. SHINDELL, J. MUNASINGHE, S. JULIANO, L.G. COHEN, NINDS

Tracts of white matter in a mouse brain acquired with diffusion tensor imaging. The brain is viewed from below and with the front of the brain to the right. The colors represent different fiber directions. Integrity of the white matter can be studied following brain injury using this visualization method.

Need to improve your image? The NIH sponsors a centralized image service for the dissemination of primarily scientific, biomedical, and disease-related imagery. This portal is provided for use by the science and health community including the press, teachers and other educators, and non-profit organizations that produce health and science information. Visit the NIH Image Gallery at https://www.nih.gov/news-events/images. ●

CONTENTS



Everything You Always Wanted to Know About the Conduct of Research in NIH's Intramural Program

BY MICHAEL GOTTESMAN, DDIR

We all know that the laws, regulations, and guidelines that govern how we do research have become more complex in the past few years. You might very well be confused…or new to the NIH. So, I would like to highlight a new "must-read" work of nonfiction, the *Guidelines and Policies for the Conduct of Research in the Intramural Research Program at the NIH (fifth edition)*. This booklet, available from the intramural Sourcebook is loaded with good stuff, and you need to know about it (http://bit.ly/2bPXrfz).

Thanks to the hard work of the NIH Committee on Scientific Conduct and Ethics, under the leadership of **Melissa Colbert** in the Office of Intramural Research, we have revised and updated this booklet for your reading pleasure and edification. This new user-friendly edition explains in greater detail (than in previous editions) the expectations for the conduct of research in the Intramural Research Program (IRP) and includes all of the guidelines you have grown to know and love plus the policies that inform them.

Having all our rules, regulations, and guidelines together in one document should be a welcome reference. For me, hearing from an NIH scientist that they were unaware of a specific requirement is distressing. I always feel under these circumstances that communication of these requirements has been inadequate in some way. I wanted a new and better enumeration of the *Guidelines and Policies* to be readily available to all intramural staff and NIH leadership so that we will have in one place most of the important requirements of our work. Please check it out and refer to it frequently if questions arise about any aspect of scientific behavior.

This new version includes all of the old guidelines covering mentoring, publication, authorship, and research misconduct, and adds guidelines about peer review, team science, conflicts of interest, research reproducibility, dual-use research, and biospecimen storage. The expectations that we all have about the behavior of scientists in the IRP are spelled out in clear language, with appropriate hypertext links to other websites. New sections outlining policy in the areas of human-subjects research, fetal-tissue research, health and safety, materials management including high-consequence pathogens, animal care and use, and IT security should supplement already existing documents and training that cover these areas. In addition to the scientific expertise and diligence of the NIH Committee on Scientific Conduct and Ethics in assembling these materials, we had help from other subject-matter experts in areas of law, regulation, and policy.

> The new guidelines and policies clearly describe the important requirements for conducting research in the NIH Intramural Research Program.

I would recommend that everyone in the IRP read over these *Guidelines and Policies* at least once and keep the website link or a printed version of the document available for frequent reference. When new staff enter our laboratories and clinics, they should be instructed how to find and read this document, too. Encourage them to ask questions and generate a discussion about any issues that are not clear or require further explanation. Needless to say, with respect to the many requirements incumbent upon NIH-supported research, an ounce of prevention (education) is worth a pound of cure!

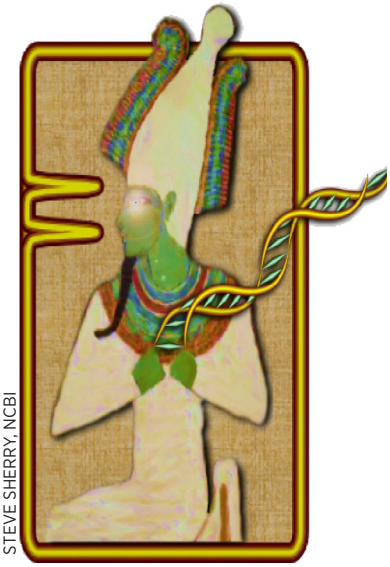
As far as regulation documents go, this really is a wonderful booklet that underscores why the NIH Intramural Research Program has maintained its level of excellence and integrity, respected internationally, for more than 70 years.

Please remember that, as with many of our most important documents, the *Guidelines and Policies for the Conduct of Research in the Intramural Research Program at NIH* is a living document. Rules and policies change over time, and new and better ways to explain these requirements are always possible. Please read this booklet over and send Melissa Colbert (colbertmc@od.nih.gov) and me (GottesmM@mail.nih.gov) your thoughts about how we might improve it. ●

OSIRIS Prolonging Life

Homegrown Forensics

BY KATHRYN MCKAY, NLM



STEVE SHERRY, NCBI

The OSIRIS logo shows the Egyptian god of the dead holding a DNA strand; frame shows STR peaks.

A software tool named after the god of the dead in Egyptian mythology and that began as a way to identify the dead is now, ironically, helping to prolong life.

In the NIH Clinical Center, OSIRIS, or the Open Source Independent Review and Interpretation System, is being used to computationally assess the quality of DNA profile data for transplant patients, saving critical time in determining whether transplants have been successful or have failed.

But OSIRIS didn't begin as a clinical tool.

Rose Out of the Rubble

"OSIRIS started in response to the World Trade Center attacks of September 11, 2001, when the identification of most of the victims required DNA identification," said NCBI staff scientist **George Riley**. "We knew the issues were addressable through software and mathematics."

OSRIS was developed by the National Library of Medicine's National Center for Biotechnology Information (NCBI) in collaboration with state and United States Army forensic laboratories and the National Institutes of Standards and Technology.

When Hurricane Katrina hit New Orleans in 2005, OSIRIS was ready for beta testing and helped to identify some of the people who died.

"Just the gratitude I've seen from some survivors when they've had remains returned convinced me that it is the most privileged event I've had as a scientist," NCBI staff scientist **Steve Sherry** told GCN.com at the time. And that's when it clicked that OSIRIS can help the living.

Multiple Applications

To ensure high-quality interpretation of DNA profiles, OSIRIS analyzes the chromatogram for peaks that correspond to different size pieces of DNA and sorts the information by location and length of short-tandem-repeat (STR) sequences. STR units are especially useful for human identification. For one thing, the number of repeats in STR markers can vary widely among individuals, making it easier to distinguish samples from one another. For another, the number of STRs can be easily amplified so there's more material to analyze.

"Short-tandem-repeat polymerase chain reaction—that's a fancy way of saying you copy DNA over and over again," said Riley. "We can start with a very small amount of DNA...and wind up with a sizable amount."

OSIRIS, which has been approved by the FBI, helps to identify victims, criminals, and missing persons, and determine paternity.

"OSIRIS can help with a lot of weird and awful crimes," says Riley. He should know. He ran forensic DNA labs in Seattle and in Fairfax, Virginia, before joining NCBI in 2010. But for Riley, the most impressive use of OSIRIS happens at NIH in the Clinical Center.

When the Situation Isn't Black or White

OSIRIS plays a valuable role for patients who are undergoing stem-cell transplantation for a variety of conditions including aplastic anemia, sickle-cell anemia, and some types of cancer such as leukemia, pre-leukemia, and malignant lymphomas. At various times after the transplant, the software is used to measure the percentage of donor cells in the patient's tissues, an indication of how well the new stem cells are producing healthy blood cells.

Roger Kurlander, who runs the NIH Clinical Center's molecular hematology lab, uses OSIRIS to monitor patients after allogenic hematopoietic stem-cell transplantation, which is the transfer of immature cells from a donor's bone marrow or blood into another individual.

"OSIRIS has very sophisticated algorithms for accurately measuring changes in chimerism over time," Kurlander said. Chimerism simply refers to an organism that's made up of cells from two or more individuals—a transplant patient has both his own cells and the donor's cells. "Accurate detection of these changes allows clinicians to respond quickly during the early phases of disease recurrence or graft failure," Kurlander continued. "When the situation isn't black and white but gray, the better your tools, the more confident you are at knowing what's going on. OSIRIS helps build that confidence."

"It's not common that you get to work on life and death matters," said Riley. "OSIRIS is used by police, people in the armed services, and doctors. [It] touches people's lives." ●

OSIRIS is a public-domain quality-assurance software package that facilitates the assessment of multiplex short-tandem-repeat (STR) DNA profiles based on laboratory-specific protocols. For more information, go to http://www.ncbi.nlm.nih.gov/projects/SNP/osiris/.

LASKER LESSONS IN LEADERSHIP PROGRAM

Experts Advise Graduate Students Not to Try to Lead Too Soon

BY LAURA STEPHENSON CARTER

"I NEVER INTENDED TO BE RUNNING AN academic hospital and research institute like Sloan Kettering," said Craig Thompson, who has been the president and CEO of Memorial Sloan Kettering Cancer Center in New York since 2010.

Thompson was one of several professionals sharing leadership secrets with NIH graduate students who had gathered on March 31, 2016, for the Lasker Lessons in Leadership Program.

"Don't worry about leadership now. That's not what's important," was Thompson's first piece of advice. Students should, instead, focus their energies on learning, understanding, and excelling at their discipline. "You need to know your discipline, whether it's as a translational scientist or as an M.D.-Ph.D. You need a deep understanding of whatever your lab is working on, develop your own ideas about what you want to study and concentrate on. [But don't] exclude everything else in biology. . .be a generalist in that sense. You can worry about leadership later on."

Thompson received his undergraduate degree from Dartmouth College (Hanover, New Hampshire) and his M.D. from the University of Pennsylvania Medical School (Philadelphia). He then did clinical training in internal medicine at Harvard's Peter Bent Brigham Hospital (Boston) and in medical oncology at the Fred Hutchinson Cancer Research Center, University of Washington (Seattle),. He confessed that he never even held a student-government position while he was in school. As he progressed through his career—treating patients and doing cancer research—he worked as a physician at the National Naval Medical Center (Bethesda, Maryland) and held faculty positions at various institutions, landing at the University of Pennsylvania in 1999 and becoming director of its Abramson Cancer Center in 2006.

He has followed his own advice and concentrated on excelling in his work: His lab pioneered the study of a family of cancer-related genes and how they regulate cell survival; he has made several other significant discoveries that have contributed to the understanding of immune-cell development and cancer mechanisms. Today his lab is studying the molecular-signaling pathways that regulate nutrient uptake and the role these pathways play in the regulation of cell growth and survival.

In recognition of his research in cancer biology, he was elected to the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. In addition to heading up Sloan Kettering, he has held several other important leadership positions, too.

Thompson shared what he has learned about leadership:

- 90 percent of leadership is common sense.
- Leaders have no job description. You have to prove to everyone who works for you that you will roll up your sleeves and do everything it takes to get the job done.
- As you get more and more people who report to you, you want to be second best at everything. You need understand who can do what best, then respect and follow their lead to get the best out of them.
- The best leaders are player-coaches.
- Challenge but don't obstruct—give your staff members the support they need once they've made a decision.
- Collaboration: Medical organizations are horizontal not vertical. Mechanisms to build collaborations are more important than reporting structure.
- You need a fundamental understanding that medicine is [an "art" and] not yet a science; science is the only hope for medicine's future.
- You've got to make your own opportunities.
- Leadership is not about management.

Expert panel

After Thompson's talk, he joined a panel of other experts: **John Niederhuber**, former director of NCI now at Inova Translational Medicine Institute; Marshall Fordyce, a physician, Entrepreneur-in-Residence at a venture-capital firm in California, and member of the Lasker Foundation Board of Directors; and investigator **Christina Annunziata**, an investigator in the National Cancer Institute. Together they fielded questions from the audience. Following are some highlights. (Read more at http://irp.nih.gov/catalyst/v24i5/the-training-page).

How can I be a good apprentice and yet not be fast tracked?

Thompson: What matters is that you learn the discipline, not that you have a tenure-track job at a young age. I turned down a tenure-track job so I could get more training in molecular biology.

Annunziata: You need to know your profession. As you become more senior, you should have more of a leadership role.

Fordyce: Trust yourself. Take your own time to build your skills. If you think you're not ready, don't do it. Don't take a tenure-track job too soon. Fight careerism for yourself so you can work on your skills. Careerism threatens that confidence.

Niederhuber: Common sense applies to your personal life and career. It's about what's going to make you happy and are you going to be able to grow in that job.

CONTINUED ON PAGE 19

JOSHUA A. GORDON

Joshua Gordon Named Director of NIMH

Joshua A. Gordon has been selected to be the new director of the National Institute of Mental Health (NIMH) and will oversee the lead federal agency for research on mental illnesses. He is expected to join NIH in September.

With an annual budget of approximately $1.5 billion, NIMH supports approximately 300 intramural scientists and more than 2,000 research grants and contracts at universities and other institutions across the country and overseas.

Gordon is an associate professor of psychiatry at Columbia University Medical Center, a research psychiatrist at the New York State Psychiatric Institute, and an associate director of the Columbia University/New York State Psychiatric Institute Adult Psychiatry Residency Program.

His research has focused on the analysis of neural activity in mice carrying genetic mutations of relevance to psychiatric disease. His work has direct relevance to schizophrenia, anxiety disorders, and depression, and it has been funded by grants from NIMH and other research organizations. Gordon maintains a general psychiatric practice and cares for people who suffer from the illnesses he studies. At NIH, he will continue his research in a lab that he will establish in the National Institute of Neurological Disorders and Stroke. ●

DIANA W. BIANCHI

Diana Bianchi to Head NICHD

the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) will have a new director come October 31: **Diana W. Bianchi.**

As NICHD director, Bianchi will oversee research on pediatric health and development, maternal health, reproductive health, and intellectual and developmental disabilities. NICHD has an annual budget of approximately $1.3 billion and supports an intramural research program as well as research grants and contracts at universities and other institutions across the country and overseas.

Bianchi is now at the Floating Hospital for Children and Tufts Medical Center in Boston, where she serves as the founding executive director of the Mother Infant Research Institute and vice chair for pediatric research. She is also the Natalie V. Zucker Professor of Pediatrics and professor of Obstetrics and Gynecology at Tufts University School of Medicine and the editor-in-chief of *Prenatal Diagnosis*.

Bianchi is a practicing medical geneticist with special expertise in reproductive genetics. Her research focuses on prenatal genomics with the goal of advancing noninvasive prenatal DNA screening and diagnosis to develop new therapies for genetic disorders that can be administered prenatally. She expects to continue her research at NIH. ●

Clinical Center Changes

John Gallin, who has been the director of the NIH Clinical Center (CC) for 22 years, has accepted the newly created dual position of NIH Associate Director for Clinical Research (ADCR) and Chief Scientific Officer (CSO) for the CC. This new leadership post will report directly to NIH Director **Francis S. Collins** and have extensive interactions with the institutes and centers (ICs) and the Intramural Research Program (IRP).

Gallin will also play a major role in developing a systematic approach to distributing resources within the CC. Among his duties, he will oversee the scientific review process for all clinical protocols conducted within the IRP; help set priorities for clinical research; oversee the independent research programs of CC investigators; oversee the strategic planning process for Intramural Clinical Research; develop strategic partnerships; and oversee clinical-research training. He will continue as CC director until a new CEO is in place.

In other CC news, **Majid Tanas**, who was recruited to NIH from the Oregon Health and Science University (Portland, Oregon), has become the new chief of pharmacy. **Andrew Griffith**, scientific director for the National Institute on Deafness and Other Communications Disorders, is overseeing the NIH Office of Research Support and Compliance (ORSC) until a permanent director is hired; **Valerie Bonham**, who has expertise in human-subjects protections, has been named deputy of this office; and **Bruce Burnett**, an expert in regulatory, quality, and preclinical Good Laboratory Practices support, joined NIH from Duke University (Durham, North Carolina) for a year to help with the ORSC. ●

Read longer versions online at http://irp.nih.gov/catalyst/v24i5/news-briefs.

Leslie Ungerleider: Reading Faces

How the Brain Recognizes Faces and Their Expressions of Emotions

BY MANJU BHASKAR, NINDS

Leslie Ungerleider

"Face recognition is a remarkable ability, given the tens of thousands of different faces one can recognize, automatically and effortlessly, sometimes even many years after a single encounter," said National Institute of Mental Health (NIMH) neuroscientist **Leslie Ungerleider**. Her research has helped to identify how different regions of the brain work together to identify faces as well as to read facial expressions of emotion.

The ability to recognize emotions from facial expressions is essential for effective interpersonal interactions. It enables us to judge the intent, mood, and focus of attention of others so we can respond appropriately in social situations. But some people suffer from an inability to recognize faces, and others can't interpret facial expressions. Ungerleider's work is shedding light on how the brain networks operate under both normal and impaired conditions.

An NIH distinguished investigator who came to NIMH in 1975, Ungerleider has long been devoted to establishing the links between neural structure and cognitive function, especially in the visual system. Her early work with macaque monkeys (*Macaca mulatta*) involved mapping the visual cortex and identifying brain functional systems. In the 1980s, she and NIMH colleague **Mortimer Mishkin** formulated the theory of "two cortical visual systems," which proposes that one visual system specializes in object recognition and another in visuospatial perception. Later, the development of imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography made it possible for Ungerleider and others to define brain regions that are important for cognition.

Ungerleider described her current research at an Anita Roberts Lecture that took place on May 10, 2016, in Wilson Hall (Building One). She explained how neuroimaging of the human and nonhuman primate brain has revealed an intricate network of face-selective regions. Core and extended regions each play a role in recognizing specific facial features and interpreting facial expressions.

The core regions are made up of the occipital face area (OFA), which recognizes facial features; the fusiform face area (FFA), which pays attention to size, position, and spatial scale; and the superior temporal sulcus (STS), which tracks movements of the eyes, gaze, lips, and facial expressions. The extended regions include the anterior temporal cortex (ATC), which is responsible for facial identity; the prefrontal cortex (PFC), which maintains a working memory of faces; and the amygdala, which handles emotional processing.

The network is out of whack in people with congenital prosopagnosia (CP), an inherited condition affecting about two percent of the population in which individuals are impaired in their ability to recognize familiar faces. Ungerleider and outside colleagues figured out why: There is reduced functional connectivity between the core and extended face-processing regions, resulting in a functional disconnection of the anterior face region from the OFA and FFA, the posterior face regions that would normally supply it with face information.

Ungerleider is also studying how the amygdala, located in the medial temporal lobe of the brain, controls and modulates human emotions. She and her postdoc **Fadila Hadj-Bouziane**, together with NIMH colleague **Elisabeth A. Murray** (Laboratory of Neuropsychology), discovered that both the amygdala and ventral temporal cortex help people distinguish facial expressions of fear from neutral expressions. This ability is compromised in Urbach-Wiethe disease, a rare genetic disorder in which there is a general thickening of the skin and mucous membranes and, in some cases, a calcification of brain tissue that can lead to bilateral damage to the amygdala and result in epilepsy and neuropsychiatric abnormalities. Studying this disease allows researchers to learn about other diseases, such as autism, that exhibit similar neurological symptoms.

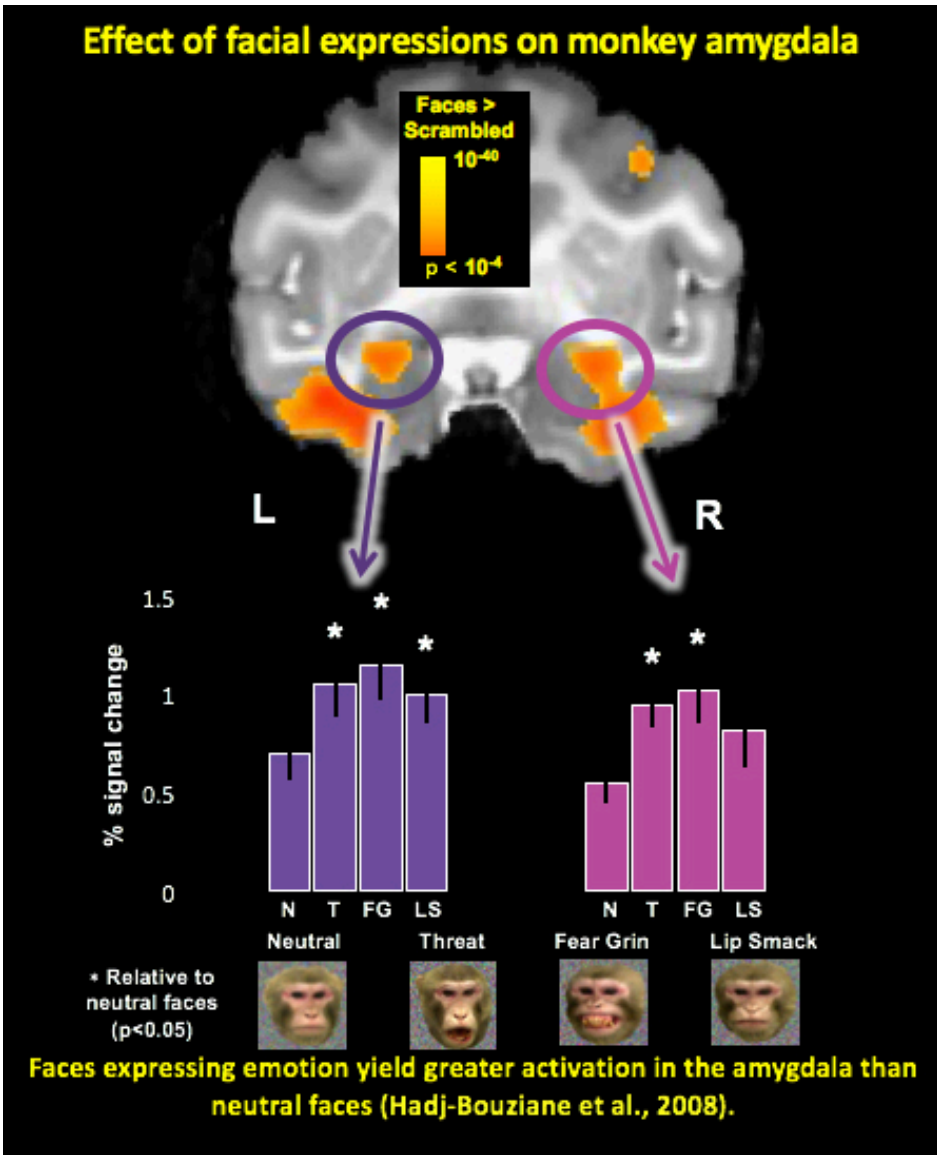
In another study in monkeys, Ungerleider and her postdoc **Ning Liu** are examining how the neurosecretory hormone oxytocin affects how the amygdala modulates emotional facial expressions. The hormone can influence

social behavior such as building trust and has been proposed as a treatment for people with autism because it can increase their social skills.

The researchers found that intranasal administration of oxytocin reduced the ability of the amygdala, the PFC, and the temporal cortical areas to recognize fearful and threatening facial expressions. Ungerleider plans to explore whether this modulation is mediated by oxytocin receptors in the amygdala.

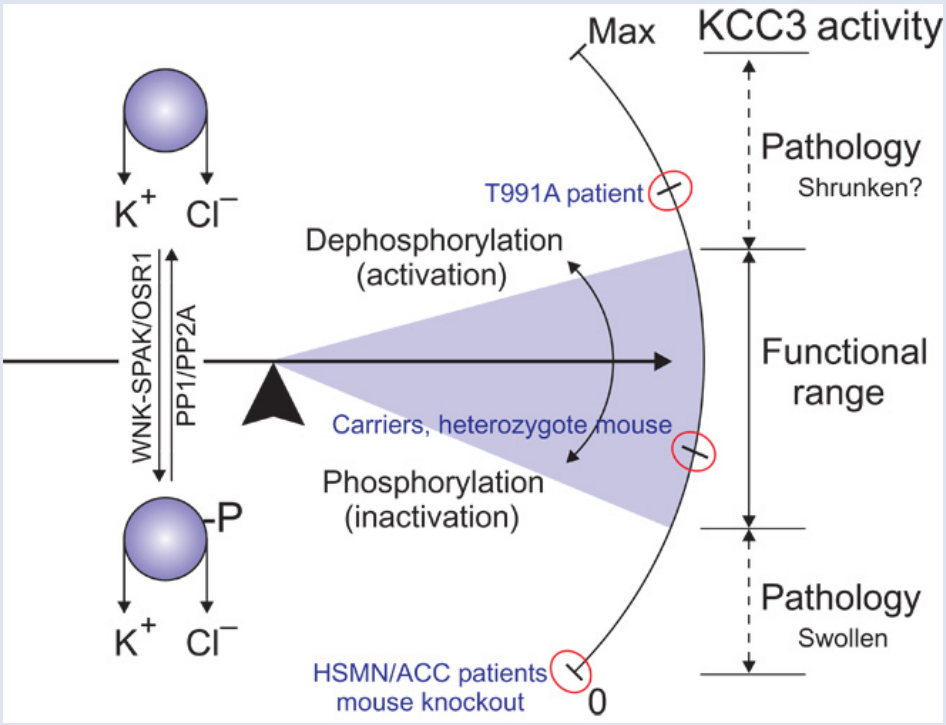
Staff scientist **Shruti Japee** and postbac **Savannah Lokey** in Ungerleider's lab recently worked with Clinical Center patients who have Moebius syndrome (MoS), a rare congenital neurological disorder that affects cranial nerves 6 and 7 and causes facial paralysis. The researchers found that not only did people with MoS lack the ability to show their emotions through their own facial expressions, but they also couldn't detect emotions expressed by others. It therefore appears that the ability to detect emotions in other individuals depends on the feedback one get from one's own facial muscles when expressing emotion.

Ungerleider intends to continue this line of work and is conducting parallel studies in humans and monkeys. In the human studies, she aims to understand how emotion detection is impaired in individuals with MoS: She will use fMRI to scan their brains while they are performing emotion-detection tasks. In the monkey studies, she will combine electrical stimulation with fMRI to map the neural circuits mediating the detection of emotional expression. Her research addresses crucial issues that are relevant to psychiatric disorders, many of which are characterized by impaired social and emotional perception and behavior. ●



This image is a composite of two in the the article: F. Hadj-Bouziane, A.H. Bell, T.A. Knusten, L.G. Ungerleider, and R.B. Tootell, (2008). "Perception of emotional expressions is independent of face selectivity in monkey inferior temporal cortex," *Proceedings of the National Academy of Sciences*, **105:**5591-5596, 2008.

Anita B. Roberts, who spent 30 years at the National Cancer Institute before her death in 2006, was known for her groundbreaking work on transforming growth factor–beta. The "Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH" honors the research contributions she and other female scientists have made. Leslie Ungerleider, who gave the May 10 lecture, has more than 40 years of research experience in cognitive neuroscience and is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the National Academy of Medicine. To watch a videocast of her Anita Roberts lecture ("Functional Architecture of Face Processing in the Primate Brain"), go to http://videocast.nih.gov/launch.asp?19674.



C.G. BONNEMANN LAB, NINDS

NINDS: A newly discovered genetic mutation in a patient with progressive motor weakness causes neurons to expel too much fluid, leading to shriveled cells that fail to signal properly.

NIAID: PROMISING NEWS FOR A ZIKA VACCINE

The recent Zika virus (ZIKV) outbreak and associated birth defects have been a source of great concern in Central and South America. New research from the NIAID and extramural collaborators brings promising news for the development of a ZIKV vaccine. ZIKV strains are grouped into two genetic lineages: African and Asian (the one associated with the current outbreak). Because the two groups of viruses differ slightly in amino-acid sequence, scientists sought to confirm whether it would be possible to immunize at-risk individuals with a single vaccine. Strain variation has presented problems in the development of a vaccine against the related Dengue virus, which has four serotypes.

The researchers showed, however, that serum antibodies from ZIKV-infected individuals were equally effective at inactivating both the African and the Asian lineages of ZIKV. To further confirm this result, the scientists infected mice with different ZIKV strains and collected serum samples. All of the mouse sera were able to neutralize both African and Asian ZIKV equivalently. These results indicate that the strains of ZIKV, while genetically distinct, have sufficiently similar surface antigens to be considered the same serotype. So an individual immunized against one lineage of ZIKV would be protected from both strains. [NIH authors: K.A. Dowd, C.R. DeMaso, R.S. Pelc, S.D. Speer, A.R.Y. Smith, L. Goo, J.R. Mascola, B.S. Graham, J.E. Ledgerwood, and T.C. Pierson, *Cell Rep* 16:1–7, 2016)

NINDS: NOVEL GENETIC MUTATION LEADS TO LOSS OF MOTOR FUNCTION

A recent NINDS study has identified a novel genetic mutation as the cause of a 10-year-old patient's progressive muscle weakness. The altered gene encodes a protein called potassium chloride cotransporter 3 (KCC3), which helps swollen cells remove excess fluid. Previously described mutations in *SLC12A5*, the gene that codes for KCC3, have been linked to a loss of motor and sensory function and to other brain defects that cause mental retardation and seizures. However, the new mutation the NINDS researchers discovered in their patient affected only motor neurons and did not produce changes in sensory neurons or cause behavioral or developmental abnormalities. Experiments in cells with the novel mutation revealed that it interferes with the protein's "off switch" and causes KCC3 to remain active when it is no longer needed rather than reducing its activity. This continued activity leads to shriveled neurons that fail to signal properly.

Future studies will focus on identifying the precise mechanism that links overactive KCC3 to changes in motor neurons. The research also opens the door to the study of potential treatments using already approved drugs that affect fluid retention in cells by inhibiting KCC3. (NIH authors: D. Bharucha-Goebel, S. Donkervoort, and C.G. Bönnemann, *Sci Signal* 9:ra77, 2016; DOI:10.1126/scisignal.aae0546)

NHGRI, NINDS, NCATS: NEW POTENTIAL TREATMENT FOR PARKINSON AND GAUCHER DISEASES

When the pathologies of rare diseases coincide with those of more common diseases, researchers can apply their findings to a broader slice of the population. NHGRI researchers and their collaborators at NCATS, NINDS, and other institutions identified and tested a molecule that shows promise as a possible treatment for the rare Gaucher disease and the more common Parkinson disease. In some patients, the two diseases share a common gene—*GBA1*—that is mutated in both. The gene codes for the protein glucocerebrosidase, which normally helps cells dispose of certain lipids and other waste.

The scientists created pluripotent stem cells from the skin cells of Gaucher patients with and without Parkinson disease and used the stem cells to grow neurons. The study

BRIEFS PREPARED BY K. CARRERA (NIDDK), A. DIBELLO (NIDDK), B. LEVY (NINDS), E. PETRUS (NINDS), A. THOMAS (NCI)

showed that the neurons from Gaucher patients who also had Parkinson disease had elevated concentrations of alpha-synuclein, the protein that accumulates in the brains of people with Parkinson disease and affects neurons controlling movement.

The researchers then looked for a molecule that would help patients with mutant *GBA1* break down cellular waste. Using high-throughput drug screening, researchers at NCATS Chemical Genomics Center evaluated hundreds of thousands of different molecules and identified a promising molecule, noninhibitory chaperone of glucocerebrosidase 607 (NCGC607), which helps to "chaperone" the mutated protein so that it can still function. In the patients' stem-cell-derived neurons, NCGC607 reversed the lipid accumulation and lowered the amount of alpha-synuclein, suggesting a possible treatment strategy for Parkinson disease. The new molecule will be tested to determine whether it can be developed into a prototype drug to treat patients with Gaucher disease and Parkinson disease. (NIH authors: E. Aflaki, D.K. Borger, N. Moaven, B.K. Stubblefield, S. Patnaik, W. Westbroek, W. Zheng, P. Sullivan, Z.M. Khaliq, G.J. Lopez, D.S. Goldstein, J. Marugan, and E. Sidransky, *J Neurosci* **36**:7441–7452, 2016)

NICHD: HIGH CONCENTRATIONS OF URINARY PARACETAMOL ASSOCIATED WITH DECREASED MALE FERTILITY

A recent NIH investigation suggests that high concentrations of paracetamol (acetaminophen, Tylenol) in male urine may impair fertility. Couples in which the male partner had high concentrations of paracetamol in his urine took longer to achieve pregnancy than couples in which the male had lower concentrations of the compound. Paracetamol is a primary metabolic product of the breakdown of aniline, a chemical used in the production of rubber, pesticides, and coloring agents used in food, cosmetics, and clothing. According to the researchers, the high concentrations of paracetamol in the men's urine were unlikely to result only from taking medications and were more consistent with those seen from environmental exposure to aniline, to paracetamol, or to a combination of the two. (NIH authors: M.M. Smarr, K.L. Grantz, R. Sundaram, J.M. Maisog, and G.M. Buck Louis, *Hum Reprod* DOI:10.1093/humrep/dew172)

NCI, NIDDK: NEW PRINCIPLE IN CHEMOTHERAPY RESISTANCE

A laboratory study by NCI and NIDDK scientists has revealed an unexpected process for acquiring drug resistance that bypasses the need to re-establish DNA-damage repair in breast cancers that have mutant *BRCA1* or *BRCA2* genes. In normal cells, the proteins breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) act as DNA-damage sensors, surveyors, and responders and help perform complex functions that facilitate the repair of damaged DNA.

Cells with a *BRCA1* or *BRCA2* mutation have a reduced ability to repair breaks in DNA, making the cells sensitive to DNA-damaging drugs. However, breast cancers eventually acquire resistance to these drugs. One documented mechanism for developing chemoresistance in such tumors is through the restoration of accurate DNA-repair pathways that mend DNA breaks caused by chemotherapy.

In this study, the researchers linked the protection and stabilization of DNA replication forks (where DNA copying takes place) as a major contributory mechanism to drug resistance in *BRCA1/2*-mutant breast and ovarian cancers. These studies also highlighted the complex ways by which tumor cells can evade chemotherapeutic interventions and acquire drug resistance. According to the researchers, a deeper knowledge of the processes that drive drug resistance in *BRCA1/2*-mutant tumors will lead to novel therapeutic approaches that target tumor-specific vulnerabilities. (NIH authors: A.R. Chaudhuri, E. Callen, X. Ding, J.-E. Lee, N. Wong, S. John, A. Day, A.V. Crespo, K. Ge, S.K. Sharan, and A. Nussenzweig, *Nature* DOI:10.1038/nature18325)

Read more online at http://irp.nih.gov/catalyst/v24i5/research-briefs.

NIAAA, NIDDK, NIMH: NEW MEDICATION SHOWS PROMISE AGAINST LIVER FIBROSIS

Liver fibrosis, a condition for which there is no current treatment, often leads to serious liver disease in people with chronic alcoholism and other common disorders. A new drug developed by scientists at NIAAA, NIDDK, and NIMH, however, limits the progression of liver fibrosis in mice and represents an important step toward an effective treatment for the condition. (NIH authors: R. Cinar, M.R. Iyer, Z. Liu, Z. Cao, T. Jourdan, K. Erdely, G. Godlewski, G. Szanda, J. Liu, J.K. Park, B. Mukhopadhyay, A.Z. Rosenberg, J.-S. Liow, P. Pacher, R.B. Innis, and G. Kunos, *JCI Insight* 1:e87336)

NIDDK: HOW CELL-SIGNALING MOLECULES REGULATE THE MAMMARY GENOME

An NIDDK-led team discovered super enhancers that control genetic networks in milk-producing cells in mammals. These super enhancers are cell-signaling regulatory switches that can activate gene sets more than 1,000-fold. The study demonstrated that super enhancers are established during pregnancy as hormone concentrations rise, culminating in the activation of specific gene sets and the production of milk. The findings provide insights into the regulation of cell-type-specific expression of hormone-sensing genes. (NIH authors: H.Y. Shin, M. Willi, K.H. Yoo, X. Zeng, C. Wang, G. Metser, and L. Hennighausen, *Nat Gen* **48**:904–911, 2016)

NIDDK, NCI: STANDARDIZED GUIDELINES FOR BROWN FAT RESEARCH

An NIDDK-led team issued first-time guidelines for conducting research and reporting on human brown adipose tissue (BAT), or brown fat. Researchers are encouraged to send comments to barcist1.0@gmail.com, which is managed and monitored by the authors. (NIH authors: K.Y. Chen, A.M. Cypess, M.R. Laughlin, C.R. Haft, and F.I. Lin *Cell Metab* **24**:210–222,2016) ●

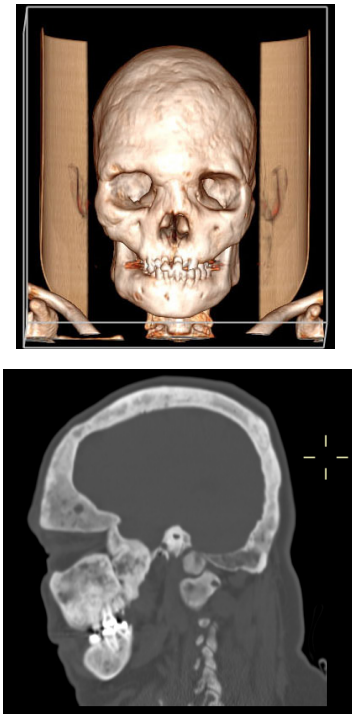
Andrea Burke: Rare Ambition

Finding Treatments for Rare Bone Diseases

BY LAURA STEPHENSON CARTER

The young teenage girl "just wanted to get better and look normal," recalled NIH dental clinical research fellow **Andrea Burke**. The girl's face was asymmetrical, with one eye higher than the other, and the underlying bones were deformed. "It was difficult for her to be around her peers."

She was suffering from a rare bone disorder called fibrous dysplasia (FD) in which abnormal fibrous tissue develops in place of normal bone. Burke was an oral and maxillofacial surgery resident at Massachusetts General Hospital in Boston when she saw the girl for the first time in 2012. The patient, who'd been diagnosed with FD at age six, had already had four surgeries to recontour the craniofacial bones, fix the eye socket, remove excess tissue, and even extract teeth so she could smile and eat properly. But the bony tissue kept growing back.



BOTH: ALISON BOYCE, NIDCR

Top: A skull showing evidence of fibrous dysplasia; bottom: X-ray of the same skull.

"The family was desperate," said Burke. How many more surgeries would it take to put a stop to the uncontrollable bone growth?

What little is known about the biology of FD, including that it's caused by mutations in the *GNAS* gene, is based on work done at NIH. FD is usually detected when a patient is young. As the bones develop abnormally, skeletal aberrations become obvious—facial bones may become asymmetric, the spine may curve, and one arm or leg may appear longer than the other. Fibrous dysplastic bones may be painful, and, because they are weaker than normal bones, more likely to break. In FD, normal bone has been replaced by fibrous tissue and varying degrees of abnormal undermineralized, or bonelike, matrix.

Treatment options are limited to using medications to manage pain, performing surgery to repair or strengthen weak or broken bones, or shaving away excess bone. But, often, the fibrous tissue grows back.

It made no sense to Burke that doctors kept removing the fibrous tissue instead of finding a way to stop it from returning. Didn't they want to understand the cellular and molecular underpinnings explaining why the tissue continued to regrow? Burke did. And so began her journey into research on rare bone diseases.

No choice but to operate

Although Burke and her mentor (at Mass General), Leonard Kaban, had no choice but to operate on the teenager to recontour her facial bones yet again, they sent some of the removed tissue to be analyzed by an expert in bone biology and mineral metabolism: NIH endocrinologist **Michael Collins**, chief of the Skeletal Clinical Studies Section at the National Institute for Dental and Craniofacial Research (NIDCR). His research at the NIH Clinical Center with patients from all over the world has helped to define therapies for rare bone diseases.

It turned out that the girl's fibrous tissue had an overexpression of receptor activator of nuclear factor–kappa-B ligand (RANK-ligand), a factor that's in part responsible for increased osteoclastic bone resorption and bone loss in postmenopausal women. Collins had found that a drug called denosumab, used to treat postmenopausal bone loss in women and metastatic bone tumors, stopped the growth of fibrous tissue in two of his patients with aggressive FD. So, with the family's permission, Burke and Kaban started the girl on the drug. It worked. In combination with surgery, the treatment helped her to look more normal and "gave her confidence," Burke said.

After completing her residency in 2013, Burke was determined to conduct research on FD and other rare bone diseases. She didn't want to go directly to a job at a dental school or clinic where she might not have protected time for research. So she came to work as a dental clinical research fellow in the NIDCR with Michael Collins and senior investigator **Pam Robey**.

Burke does see patients at the NIH Clinical Center, but she also has plenty of time for research. In the operating room, she removes bony growths from skulls of patients with FD, who donate the tissue specimens for research. She uses whole-exome sequencing and other molecular methods to analyze and describe genetic variants in the tissue. She would like to one day develop a biobank of samples for future research.

"We believe that many of these rare craniofacial bone diseases exist along the same pathophysiologic spectrum [but] with

different mutations," said Burke. "We want to better characterize them."

Characterizing tissue from rare bone diseases may make it possible for surgeons to better predict treatment responses and thus spare certain patients from having surgeries. Burke envisions a future in which treatments for rare bone diseases are individualized and—along with clinical, radiographic, and histopathologic assessments—based on precise, molecular evaluations of a patient's unique biology. She hopes that one day there will be an alternative to surgery.

"Our group here tries to avoid surgery until patients reach skeletal maturity and/or the lesions stop growing," said Burke. If surgery is done when the patients are too young, "the bone can keep growing back and sometimes you end up chasing your tail. The ultimate goal is to know when surgery is best."

ERNIE BRANSON

Dental clinical research fellow **Andrea Burke** (left) works with clinical research nurse **Padmasree Veeraraghavan** at the NIH Dental Clinic. When Burke is not in the lab or clinic on the NIH campus, you might find her jamming to jazz at a festival in New Orleans, hiking the glaciers in Patagonia, skiing in New Zealand, or scuba diving in Fiji.

Early interest in dentistry

Burke's interest in dentistry had its roots in college when she volunteered at a dental clinic that had two female dentists. She also shadowed her family dentist. Even then, she began to wonder why so little was known about common dental problems such as tooth pain and sensitivity to hot and cold temperatures. Later, after graduating from Barnard College (New York) with a degree in biology, she worked in a research lab at Columbia University College of Dental Medicine (New York). Her first experience at NIH was in 2004, between her first and second years at Harvard School of Dental Medicine (Boston), when she was selected as an NIH Summer Research Student in NIDCR's Functional Genomics Section. There she used microarrays from patients with tooth diseases to identify altered gene-expression profiles in dentin-forming cells.

As her research experience grew, Burke was puzzled that so many fundamental biological questions go unanswered. Her strong need to answer them inspires her desire to pursue research. She hopes to find answers that will lead to improvement in clinical care and patients' quality of life.

Burke and collaborator **Alison Boyce**, a pediatric endocrinologist in NIDCR's Skeletal Clinical Studies Section, along with members of the Fibrous Dysplasia Foundation, are developing a patient registry to collect information that can be aggregated and analyzed. A patient registry, paired with the results of Burke's basic research, will help her reach her goal of providing clinicians with tools for evidence-based treatment planning.

"We're thrilled that Dr. Burke is choosing to focus her career on fibrous dysplasia," said Deanna Portero, the executive director of the Fibrous Dysplasia Foundation. "Brilliant and motivated researchers like her are desperately needed."

Burke is completing her NIDCR fellowship this fall and will be moving on to an academic position at a medical research center (the exact location had not been confirmed before the *NIH Catalyst* went to press). There she will continue her research as well as see patients and teach classes in oral and maxillofacial surgery. She also hopes to stay active with the Collins group and the foundation.

But what gives her the most satisfaction is knowing that she can help people like the young girl she first met at Massachusetts General three years ago. That teenager is now a regular visitor to the NIH Clinical Center and taking part in a natural history clinical trial on FD. Burke is pleased that the girl's condition seems to be under control and that she's gained a lot more confidence in herself. ●

Schechter's Postdocs

CONTINUED FROM PAGE 1

ERNIE BRANSON

ALAN SCHECHTER, M.D.

several were invited to give presentations about their work.

"My background was in physics, so I had to learn a lot," said NIDDK senior investigator **Constance Noguchi**, one of Schechter's former postdocs and co-organizer of the symposium. "He had the patience [to teach me]."

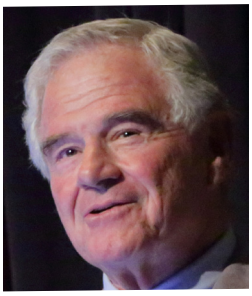
Schechter credits his own mentors—notably Nobel laureate **Christian Anfinsen**—for teaching him how to be a good mentor. After receiving his undergraduate degree from Cornell University (Ithaca, New York) and his M.D. from Columbia University College of Physicians and Surgeons (New York), and then completing a two-year residency in internal medicine at Albert Einstein Medical College hospitals (New York), Schechter came to NIH as a research associate in the Laboratory of Chemical Biology in the National Institute of Arthritis and Metabolic Diseases (NIAMD). There he worked on protein chemistry and protein folding with **Charles Epstein** and Anfinsen (who was a co-recipient of the Nobel Prize in Chemistry in 1972 for his work on protein folding).

"Conducting research in molecular biology is not just work, but it is [Schechter's] passion," said Adelstein, who was also a postdoc in the Anfinsen lab in the 1960s and is now a senior investigator in the National Heart, Lung, and Blood Institute. "In addition to his passion for molecular biology, Alan, fortunately for us, has many other passions," including mentoring and serving the scientific community in many ways. He has served on the board of the Foundation for Advanced Education in the Sciences for many years, chaired the advisory committee for the Office of NIH History and was later acting NIH Historian, and served on and chaired the Council of the NIH Assembly of Scientists.

"Dr. Schechter has had a remarkable career of scientific accomplishment," said NIDDK Scientific Director **Michael Krause**. "Equally important have been his contributions to mentoring and his service to the NIH community in his many roles."

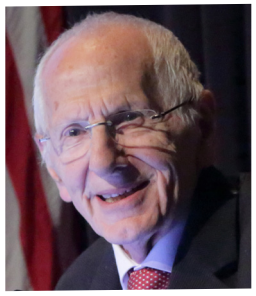
Following is a sampling of the former postdocs and staff (the ones who gave presentations at the symposium)—where they are now, when they trained or worked with Schechter, their research interests, and what they have to say about their mentor. ●

To watch a videocast of the symposium, which was held on June 27, 2016, and titled "Yellow Berets to Gray Hair: Training Physicians for Research Careers," go to https://videocast.nih.gov/launch.asp?19773.

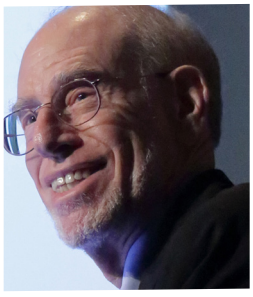


DAVID SACHS, M.D.

GRIFFIN RODGERS, M.D.



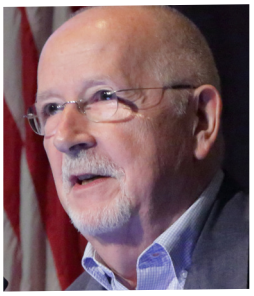
ANDRÉ VAN STEIRTEGHEM, M.D.



JAY BERZOFSKY, M.D., PH.D.

NEAL YOUNG, M.D.

BRUCE FURIE, M.D.



JACQUES ELION, M.D., PH.D.

MARK GLADWIN, M.D.

VLADAN COKIC, M.D., PH.D.

CONSTANCE NOGUCHI, PH.D.

BARBORA PIKNOVA, PH.D.

DAVID H. SACHS, M.D.

Professor Emeritus, Harvard Medical School, Boston; Professor of Surgical Sciences, Columbia University Medical Center, New York; Scientific Director, Transplantation Biology Research Center Laboratories, Center for Transplantation Sciences Massachusetts General Hospital, Boston

Education: Harvard University, Cambridge, Mass. (A.B in chemistry.); University of Paris, Paris [D.E.S. in organic chemistry (M.S. equivalent)]; Harvard Medical School, Boston (M.D.)

NIH: Laboratory of Chemical Biology: Research associate (1970–1972)

Research: Transplantation biology, with an emphasis on understanding and manipulating transplantation immunity and tolerance.

Comment: This was a very important, productive, period for me. Since I had previously done work with nuclear magnetic resonance (NMR) spectroscopy, Alan and I began our studies together by investigating the potential of using NMR to examine protein structure. These experiments were followed by a series of studies, together with Chris Anfinsen, using antibodies to study the conformation of Staphylococcal nuclease. Working with Alan was always a privilege and a pleasure.

GRIFFIN RODGERS, M.D.

Director, NIDDK

Education: Brown University, Providence, R.I. (Sc.B., M.M.Sc., M.D.); Carey Business School, Johns Hopkins University, Baltimore (M.B.A.)

NIH: Laboratory of Chemical Biology: Postdoctoral training (1982–1987); senior staff fellow (1988–1990); senior investigator (1990)

Other positions in NIDDK (1991–present): Chief, Molecular Hematology Section; chief, Molecular and Clinical Hematology Branch; deputy director (2001–2009), acting director (2006–2007), and then director, NIDDK (2007–present)

Research: Sickle-cell anemia; widely recognized for his contributions to the development of the first effective—and now FDA-approved—therapy for sickle-cell anemia, the drug hydroxyurea.

Comment: Alan has taught me quite a bit about not only the science of medicine, but also the "art" of medicine, particularly when it comes to negotiations and subtle diplomacy. His mentorship has been quite useful to me in my frequent trips to Congress to try to educate members and their staff about the mission and goals of our institute.

ANDRÉ VAN STEIRTEGHEM, M.D., PH.D.

Emeritus Professor of Embryology and Reproductive Biology, Vrije Universiteit (the Free University) in Brussels

Education: Vrije Universiteit Brussels (M.D. and Ph.D.)

NIH: Clinical Center: Visiting fellow, Clinical Chemistry Department (1974–1977), Schechter was his prime mentor

Research: One of the leaders in the field of in vitro fertilization (IVF); developed and led the renowned IVF program at the university's medical school since the early 1980s. His program has been responsible for about 20,000 successful pregnancies. (Read more about Van Steirteghem's work in the March-April 2014 issue of the *NIH Catalyst* at http://irp.nih.gov/catalyst/v22i2/alumni-news.)

Comment: The NIH experience was a determining factor in my career. Thanks, Alan, for your mentorship.

ALL PHOTOS ON THESE TWO PAGES WERE TAKEN BY ERNIE BRANSON, EXCEPT FOR THE ONE OF BRUCE FURIE, WHICH HE PROVIDED.

CONTINUED ON PAGE 14

Schechter's Postdocs

CONTINUED FROM PAGE 13

JAY A. BERZOFSKY, M.D., PH.D.

Chief, Vaccine Branch, Center for Cancer Research, National Cancer Institute

Education: Harvard University, Cambridge, Mass., (A.B. in chemistry); Albert Einstein College of Medicine, New York (Ph.D. in molecular biology; M.D.)

NIH: Laboratory of Chemical Biology: Research associate (1974–1976);

National Cancer Institute (1976–present): Has held various leadership positions; became chief of Vaccine Branch in 2004

Research: Antigen processing by major histocompatibility complex molecules; control of T-cell function; NKT cells in immune regulation and tumor immunology; and translation to the design of vaccines for AIDS, cancer, and viruses causing cancer.

Comment: My research with Alan introduced me to immunology and converted me from a protein chemist to an immunologist. I owe a lot to Alan for leading me in a new direction that set the stage for the rest of my career in immunology. He also taught me peptide chemistry, which was a major foundation for much of my future research.

NEAL YOUNG, M.D.

Chief, Hematology Branch, National Heart, Lung, and Blood Institute; Director, Trans-NIH Center for Human Immunology, Autoimmunity, and Inflammation

Education: Harvard University, Cambridge, Mass. (A.B.); Johns Hopkins School of Medicine, Baltimore (M.D.)

NIH: Laboratory of Chemical Biology: Research associate (1973-1975)

Research: Bone-marrow failure. (Read more at http://irp.nih.gov/catalyst/v21i3/neal-young-conquering-aplastic-anemia.)

Comment: Alan taught me, very patiently, to think rigorously and quantitatively—a little bit like a Ph.D. And he has remained a friend and mentor for decades.

BRUCE FURIE, M.D.

Professor of Medicine and Director of the Blood Coagulation and Vascular Biology Training Program, Harvard Medical School, Boston; Chief of Hemostasis-Thrombosis at Beth Israel Deaconess Medical Center, Boston

Education: Princeton University, Princeton, N.J. (A.B.); University of Pennsylvania, Philadelphia (M.D.)

NIH: Laboratory of Chemical Biology: Two years in the mid-1970s

Research: Hemostasis and thrombosis; has made landmark contributions to the understanding of the structure, biochemistry, and function of coagulation and platelet proteins.

Comment: I am very grateful for all the generous support and sage advice that my wonderful mentors, Christian Anfinsen and Alan Schechter, provided along the way. My time in their lab represented two very important years in my life. I was exposed to biophysics and quantitative biology in a world-class laboratory. I was taught not to be afraid of doing novel techniques.

JACQUES ELION, M.D., PH.D,

Professor of Biochemistry and Molecular Biology at Paris Diderot University Medical School, Paris; Former Director, Department of Medical Genetics at Robert Debré Mother and Child University Hospital, Paris; Director of Research, Unit 1134 of the French National Institute of Health and Medical Research (Inserm), Paris; and Guadeloupe, French West Indies

Education: Paris Descartes University Medical School (M.D.); Paris Diderot University (Ph.D.)

NIH: Molecular Medicine Branch: Fogarty Visiting Scientist position (1985–1986)

Research: Pathophysiology of sickle-cell disease and the identification of new therapeutic targets; identified several genetic markers contributing to the clinical variability of the disease.

Comment: Working at NIH with Alan 30 years ago in the late 1980s was a great experience. It has been the privileged occasion to work alongside and get inspiration from many brilliant and sharp-minded individuals among whom stood Alan with his broad and profound view of science in medicine and medicine in science.

MARK T. GLADWIN, M.D.

Jack D. Myers Professor and Chair of Medicine, University of Pittsburgh; Co-director, University of Pittsburgh Medical Center Heart and Vascular Institute; Director, Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute

Education: University of Miami Honors Program in Medical Education, Miami, Fla. (B.S. and M.D.)

NIH: Clinical Center: Critical care fellow (1995–1996); senior research fellow (1998–2000); **Laboratory of Chemical Biology**: Tenure-track investigator (2001–2004); senior investigator (2004–2005); **NHLBI:** Various positions (2005–2008), including director of NHLBI Functional Genomics Core and Chief, Pulmonary and Vascular Medicine Branch

Research: Pulmonary hypertension, nitrite biochemistry and signaling, and pulmonary complications of sickle-cell disease.

Comment: Lessons from Alan Schechter: Think big and appreciate what the big questions are in science; your best work will likely arise from your studies of normal volunteers; appreciate fundamental science; focus on the clinic, answer questions with translational methodologies as much as possible.

VLADAN COKIC, M.D., PH.D.

Professor of Research and and Principal Investigator, Laboratory of Experimental Hematology, Institute for Medical Research, University of Belgrade, Belgrade, Serbia

Education: Belgrade University School of Medicine, Belgrade, Serbia (M.D., M.S., Ph.D.)
NIH: Molecular Medicine Branch: Visiting fellow (1999–2004)
Research: Nitric oxide mediated globin genes induction, erythroid differentiation, pathogenesis of myeloproliferative neoplasms (translational research).
Comment: It was a great pleasure to have the opportunity to do research in Alan's lab, and I'm grateful for his mentorship , confidence, and continued support.

CONSTANCE NOGUCHI, PH.D.

Chief, Molecular Cell Biology Section, Laboratory of Chemical Biology, NIDDK; Dean, Foundation for Advanced Education in the Sciences Graduate School at NIH

Education: University of California, Berkeley (A.B. in mathematics and physics); George Washington University (Ph.D. in physics)
NIH: Laboratory of Chemical Biology: Fellow (1975–1977); staff fellow (1977–1979); other fellow positions (1979–1985); other positions (1985–present)
Research: Identifying progenitor-cell response to erythropoietin and the potential for therapeutic intervention in hematopoietic diseases and beyond.
Comment: Alan would get Ph.D.s to think like M.D.s and about how our research would apply to health and disease. He tried to get M.D.s to think like Ph.D.s in terms of structured mechanisms.

BARBORA PIKNOVA, PH.D.

Staff Scientist, Laboratory of Chemical Biology, NIDDK

Education: Comenius University, Bratislava, Slovakia (M.S. equivalent; Ph.D.)
NIH: Laboratory of Chemical Biology: Contractor staff scientist (2005–2010); staff scientist (2010–present)
Research: Basic mechanisms influencing microcirculation during functional hyperemia; the use of dietary intervention to modulate skeletal-muscle blood flow in aging, during exercise, and in neuromuscular diseases.
Comment: When I came to NIH, I was a biophysicist with no experience in physiology. Dr. Schechter showed me how to ask (and answer) physiology questions in physical-chemistry language. That was a big step for me and I'm thankful that he took me under his wing. ●

Laboratory of Chemical Biology (early 1980s): Two of the former postdocs presented at the symposium on March 31. Seated: Alan Schechter, chief (third from left) and Constance Noguchi (far right). Standing: Griffin Rodgers (third from right).

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CDC: Centers for Disease Control and Prevention
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
FAES: Foundation for Advanced Education in the Sciences
FARE: Fellows Award for Research Excellence
FelCom: Fellows Committee
FDA: Food and Drug Administration
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

Recently Tenured


CHARLES W. BRADBERRY, NIDA


JENNIFER C. LEE, NHLBI


MATTHIAS P. MACHNER, NICHD


HELEN C. SU, NIAID


CARMEN WILLIAMS, NIEHS

CHARLES W. BRADBERRY, PH.D., NIDA

Senior Investigator, Preclinical Pharmacology Section, National Institute on Drug Abuse

Education: University of Kansas, Lawrence, Kan., (B.S. in chemistry; Ph.D. in biochemistry)

Training: Postdoctoral training in psychiatry, Yale School of Medicine (New Haven, Conn.)

Before coming to NIH: Professor of psychiatry, University of Pittsburgh School of Medicine (Pittsburgh); research career scientist, Veterans Affairs Pittsburgh Healthcare System (Pittsburgh)

Came to NIH: In 2016

Selected professional activities: Participating in the American College of Neuropsychopharmacology and European Behavioral Pharmacology Society; engaging in collaborative exploratory neuroscience; mentoring

Outside interests: Spending time with family; traveling; enjoying real food; exercising; playing billiards

Research interests: I am studying the neurobiology of addiction to drugs and alcohol in hopes that what I learn will help in the development of effective treatments. I am using nonhuman primates to study the addictive and rewarding properties of drugs of abuse and how drug use alters cognitive performance.

Before now, most of my work focused on cocaine. Using chronic self-administration models in rhesus macaques (*Macaca mulatta*), we demonstrated patterns of cognitive deficits result from chronic use that are similar to impairments associated with selective lesions in the orbitofrontal cortex. We also conducted longitudinal structural magnetic resonance (MR) imaging in the same animals. We are analyzing the MR data, as well as postmortem tissues, to determine whether cocaine has regionally selective effects and what the underlying substrates might be. We have also used electrophysiological approaches to study how multiunit activity across multiple brain regions mediates the ability of drug-associated cues to engage cognitive resources. We will continue to expand that work and study the encoding of choice between drug and nondrug rewards.

A major part of my work has been collaborating with colleagues who conduct positron emission topography (PET) imaging. We used trace analytical techniques to measure drug-induced release of extracellular dopamine in the cortex during PET imaging. Our findings validated the PET approaches for measuring extracellular cortical dopamine dynamics in humans. In another important collaboration with PET imagers, we demonstrated that chronic cocaine use causes a striking decrease in the number of neuronal vesicles from which dopamine is released.

In the NIDA intramural program, I will be expanding my work to include nicotine and tetrahydrocannabinol (the active agent in marijuana). In collaboration with MR and PET colleagues at NIH, we will use multimodal imaging approaches to continue to develop novel "systems" neuroscience approaches for studying how these widely used substances influence behavior, cognition, and the underlying brain mechanisms.

JENNIFER C. LEE, PH.D., NHLBI

Senior Investigator, Laboratory of Protein Conformation and Dynamics, National Heart, Lung, and Blood Institute

Education: University of California at Berkeley, Berkeley, Calif. (B.S. in chemistry and a B.A. in economics); California Institute of Technology, Pasadena, Calif. (Ph.D. in chemistry)

Training: One-year postdoctoral stint at the Keck School of Medicine of University of Southern California (Los Angeles); Beckman Senior Research Fellow at the Beckman Institute Laser Resource Center at the California Institute of Technology

Came to NIH: In 2006

Selected professional activities: Editorial board member of the *Journal of Biological Chemistry*; member of the American Chemical Society

Outside interests: Keeping up with her two boys (ages two and five); traveling; and experiencing the world

Website: http://irp.nih.gov/pi/jennifer-lee

Research interests: My laboratory conducts biochemical and biophysical studies of protein conformation and interactions. We

are trying to understand the mechanisms of amyloid formation and how cellular interactions of amyloids contribute to disease. Aggregation of proteins into amyloid structures is a hallmark of Alzheimer, Parkinson, and Huntington diseases. However, amyloid fibrils can also serve essential biological roles in organisms ranging from bacteria to humans. It remains a mystery whether pathological consequences are due to the structural features of amyloids or to the loss of specific cellular functions.

To understand the differences between functional and pathological amyloids, I am investigating the mechanisms of amyloid formation for two human proteins: alpha-synuclein, which is localized to nerve terminals and associated with Parkinson disease; and premelanosome protein 17, which serves as a template for melanin deposition in the skin and eyes. I am characterizing how individual residues affect protein-protein interaction during the amyloid-assembly process. I am trying to determine the role of membranes in the aggregation process of alpha-synuclein.

I am using many biophysical techniques including time-resolved fluorescence anisotropy measurements to probe local conformational changes, circular dichroism and Raman spectroscopy to determine protein secondary structure, and transmission electron microscopy to visualize filament morphology. I am also pioneering the use of neutron reflectometry to investigate protein-membrane interactions. Recently, I have been studying the interaction between alpha-synuclein and glucocerebrosidase, the enzyme deficient in Gaucher disease, to explain why mutations in GBA, the gene encoding glucocerebrosidase, is a risk factor for Parkinsonism.

MATTHIAS P. MACHNER, PH.D., NICHD

Senior Investigator; Head, Section on Microbial Pathogenesis, Division of Molecular and Cellular Biology, National Institute of Child Health and Human Development

Education: University of Osnabrück, Osnabrück, Germany (M.S. in biology); Technical University of Braunschweig, Braunschweig, Germany (Ph.D. in natural sciences)

Training: Postdoctoral Howard Hughes Medical Institute fellow at Tufts University School of Medicine (Boston)

Came to NIH: In 2008

Selected professional activities: Symposium organizer and chair for the American Society for Microbiology meeting (2015, 2012) and the American Society for Cell Biology meeting (2014); topic editor for *Frontiers in Cellular and Infection Microbiology*

Outside interests: Being outdoors; taking long walks with the dog; listening to music (anything from Hawaiian to classical music); spending quality time with friends and family

Website: http://irp.nih.gov/pi/matthias-machner

Research interests: Our main research goal is to obtain a detailed understanding of the molecular mechanisms by which pathogenic bacteria can manipulate host cells during infection.

We use as a model organism the bacterium *Legionella pneumophila*, which is commonly found within freshwater reservoirs as a natural parasite of ameba. When inhaled by humans, *L. pneumophila* can cause a potentially fatal pneumonia known as Legionnaires' disease. Contrary to what its name may imply, Legionnaires' disease occurs in individuals of all ages including children who receive respiratory therapy, newborns who recently underwent surgery or underwater birth, and children who are immune-compromised.

When a person inhales contaminated water droplets, *L. pneumophila* enters the lungs and is phagocytosed (taken up) by specialized immune cells called alveolar macrophages. Instead of being degraded by these cells, the pathogen establishes a protective membrane compartment around itself, the Legionella-containing vacuole (LCV). Within this protective chamber, *L. pneumophila* can replicate in high numbers before it kills the host cell and infects neighboring cells.

Intracellular survival of *L. pneumophila* depends on the activity of close to 300 proteins, or effectors, that the bacterium injects into the host cell, where they create conditions favorable for infection. *L. pneumophila* mutants that are defective in effector-protein delivery fail to escape endolysosomal degradation, underscoring the key role of microbial effectors for bacterial virulence.

Our goal is to obtain a detailed mechanistic insight into the regulation and function of *L. pneumophila* effectors by investigating host-pathogen interactions at the molecular, cellular, and structural levels. Deciphering the virulence program of this dangerous pathogen will set the stage for the development of novel therapeutics aimed at treating or preventing Legionnaires' disease and related illnesses.

HELEN C. SU, M.D., PH.D., NIAID

Senior Investigator; Chief, Human Immunological Diseases Section, Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases

Education: Brown University, Providence, R.I. (A.B. in biochemistry, M.D., and Ph.D. in pathobiology)

Training: Residency in pediatrics at St. Louis Children's Hospital, Washington University (St. Louis); clinical fellowship and research fellowship in allergy and immunology at NIAID

Came to NIH: In 2001 for training; became tenure-track investigator in 2007

Selected professional activities: Adjunct faculty member in the NIH–University of

CONTINUED ON PAGE 18

Recently Tenured

CONTINUED FROM PAGE 17

Pennsylvania Immunology Graduate Partnership Program

Outside interests: Reading; listening to music and playing the piano; hiking; sleeping!

Website: http://irp.nih.gov/pi/helen-su

Research interests: My laboratory carries out research to elucidate novel molecular mechanisms that regulate the human immune system. In particular, we study lymphocytes and how their derangements cause susceptibility to viral and other infections. We use state-of-the-art genomic approaches to study patients who have rare and poorly characterized inherited immunodeficiencies. By carefully investigating these "experiments of nature," we can draw inferences about molecular functions based on patient phenotype. Cell-mediated immunity is crucial in protecting against viral infections. We have observed that these patients usually have partial T-cell or combined immunodeficiencies, which are often accompanied by autoimmunity or lymphoproliferation.

Through a broad program that integrates the patients' clinical evaluations; assessments of their leukocyte function; and genetic and biochemical analyses, including use of new technologies such as whole-genome analysis and two-photon excitation microscopy, we gain profound insights into the molecular and cellular bases of immunity against viruses. In some instances, parallel insights can be gained from experimental animals. In other instances, we learned unique lessons from investigating the human disease. Therefore, my approach as both a clinical and a basic-science researcher is to combine the powerful clinical-investigatory resources of the NIH Clinical Center with the extensive basic-science capability within NIAID's Division of Intramural Research to define new clinical entities and their molecular pathogenesis. By using the latest molecular, genomic, and cellular technologies to elucidate the fundamental mechanisms that normally regulate human lymphocytes for host defense, we also aim to improve the diagnosis and treatment for these and related immunological conditions.

CARMEN WILLIAMS, M.D., PH.D., NIEHS

Senior Investigator, Reproductive Medicine Group, Reproductive and Developmental Biology Laboratory, National Institute of Environmental Health Sciences

Education: Duke University, Durham, N.C. (B.S.E in electrical engineering; M.D.); University of Pennsylvania, Philadelphia (Ph.D. in molecular and cell biology)

Training: Residency in obstetrics and gynecology at Pennsylvania Hospital (Philadelphia); fellowship in reproductive endocrinology and infertility at the University of Pennsylvania; postdoctoral fellowship at the University of Pennsylvania

Before coming to NIH: Assistant professor, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Pennsylvania

Came to NIH: In 2007

Selected professional activities: Editor of *Molecular Reproduction and Development*; serving on various committees of the Society for the Study of Reproduction; section director, "Frontiers in Reproduction" course, Woods Hole, Mass.

Outside Interests: Reading science-fiction novels; power walking

Website: http://irp.nih.gov/pi/carmen-williams

Research Interests: We study mammalian reproductive biology with a focus on fertilization and embryo development. My group prioritizes questions that are directly relevant to human reproduction and how the environment influences fertilization and embryo development.

We are trying to understand the mechanisms that underlie the effects of environmental chemical exposures on early reproduction. Phytoestrogens, found in plants, occur naturally and act like estrogen. Phytoestrogens are readily available in the diet, and many other estrogenic chemicals are released into the environment. Depending on the dose and timing of exposure, these chemicals may have both beneficial and detrimental effects on health. We use a mouse model to study the effects of estrogenic chemicals on female reproductive health including how this exposure may lead to defects in the reproductive tract that can affect fertilization and embryo development.

We are also investigating the role that calcium plays in the preimplantation embryo. The transition of a fertilized egg into a developing embryo, known as "egg activation," is initiated by repetitive cycles, or oscillations, of intracellular calcium. These oscillations begin after sperm-egg plasma-membrane fusion, when the sperm releases the enzyme phospholipase C zeta into the egg's cytoplasm. Continuation of these oscillations requires calcium entry into the egg to replenish calcium stores. We are studying the calcium channels that support this entry. We hypothesize that inadequate calcium entry, which can lead to abnormal calcium oscillatory patterns during fertilization, could explain one of several causes of human infertility. These possibilities include failed fertilization, poor preimplantation embryo development, and miscarriage. ●

If you could rewind, what would you tell your younger self?

Thompson: You need to be more fearless. The hardest part of medicine is learning the language of medicine and the hardest part of science is its rapidly evolving nomenclature. If you don't understand a word, ask what it means.

Annunziata: Have an open mind and listen to where the data are taking you—where you're going next in your career and life.

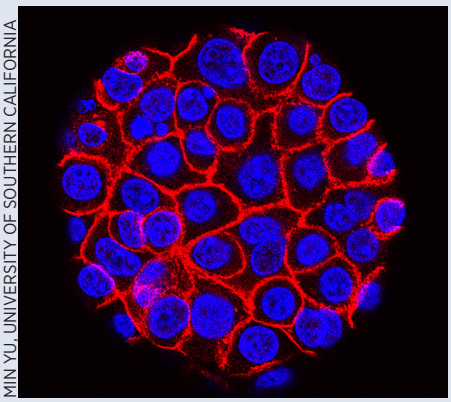
Niederhuber: Don't be in a rush to take on leadership responsibilities. People will pick you to take on leadership jobs—when you are in your 40s. People will throw enticing things your way—chairmanships, etc. I had a mentor who reminded me of what I was going to lose if I took on leadership responsibilities too early.

Fordyce: Trust yourself. I wish I had trusted myself earlier. Challenge yourself and stay open. Don't wait until you've arrived or have your degree. ●

The Lasker Lessons in Leadership represents a collaboration among the Albert and Mary Lasker Foundation, the International Biomedical Research Alliance, and the Global Doctoral Partnerships, which includes the NIH Oxford-Cambridge Scholars Program, the M.D.-Ph.D. Partnership Training Program, and the Wellcome Trust. The Lasker Lessons in Leadership is intended to help the next generation of physicians and scientists develop the leadership skills necessary to advance scientific discovery. The curriculum spans four years and consists of two courses per year in the areas of communication; leadership in medicine and public health; entrepreneurship; international medicine and global health and policy; industry; leadership career path; and publishing. For information about all the NIH graduate partnership programs, go to https://www.training.nih.gov/programs/gpp/partnerships. To see the videocast of the March 31 event ("Lasker Lessons in Leadership: Leadership in Medicine/Public Health"), go to https://videocast.nih.gov/launch.asp?19586.

THE SIG BEAT

NEWS FROM AND ABOUT THE SCIENTIFIC INTEREST GROUPS



MIN YU, UNIVERSITY OF SOUTHERN CALIFORNIA

Pancreatic cancer cells growing as a sphere encased in membranes.

PANCREATIC CANCER

Pancreatic cancer is one of the most lethal malignancies and is the fourth leading cause of death due to cancer in the United States. There is no reliable biomarker for early detection, and the available treatments are ineffective in advanced stages of this disease. Improving the outcome for pancreatic-cancer patients requires understanding pancreatic-tumor biology better; delineating the molecular subgroups and subgroup-specific therapeutic targets in order to enable precision treatment strategies; and identifying reliable biomarkers for early detection.

Achieving these goals can be maximized through regular interactions among intramural scientists. The Pancreatic Cancer Scientific Interest Group is made up of basic researchers and clinicians who are working on various aspects of pancreatic cancer. The SIG promotes the exchange of scientific information and interactions among members of the group through monthly meetings. It also organizes a pancreatic-cancer symposium and invites extramural scientists who are world leaders in the field and whose participation maximizes the exchange of latest information and fosters collaborations.

A steering committee of NIH scientists from basic, epidemiological, and clinical disciplines runs this SIG. More information and how to join it can be found at https://ccrod.cancer.gov/confluence/display/PCIG/Home. To join the LISTSERV, e-mail **S. Perwez Hussain** at (hussainp@mail.nih.gov). For information on the Pancreatic Cancer Symposium, September 8–9, 2016, go to https://ncifrederick.cancer.gov/events/PancreaticCancer2016/default.asp.

SPECIAL POPULATIONS RESEARCH FORUM

The Special Populations Research Forum (SPRF) was developed in 1998 by **J. Taylor Harden**, the former Director of the National Institute on Aging's (NIA's) Office of Special Populations, as a means for NIH staff to share best practices and lessons learned in diversity training and the recruitment and retention of underrepresented populations into biomedical research.

The SPRF seeks to build and foster a community of intramural and extramural NIH staff who share an interest and have expertise in diversity issues. SPRF supports NIH staff who create, innovate, and implement NIH scientific and training programs that are designed to diversify the nation's research enterprise. The group provides a trans-NIH forum for sharing and examining programs, initiatives, and strategies that enhance and accelerate the development of the research careers of individuals from diverse populations. The SPRF encourages the career and professional development of its members through peer mentoring and mutual support; serves as a resource to the NIH's diversity and workforce development communities; and recommends topics and speakers for a range of events including the NIH Research Festival and Wednesday Afternoon Lecture Series. SPRF is open to all NIH and HHS staff with an interest in enhancing the diversity of the nation's research enterprise. To join the LISTSERV, go to https://list.nih.gov/cgi-bin/wa.exe?SUBED1=sprf-special-populations-res&A=1. For more information, contact **Carl V. Hill**, director of NIA's Office of Special Populations, at hillcv@mail.nih.gov. ●

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Permit No. G-802
Publication No. 16-6250

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CATALYTIC REACTIONS?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation or confession that scientists might appreciate and that would be fit to print in the space to the right, why not send it via e-mail: catalyst@nih.gov; fax: 301-402-4303; or mail: *The NIH Catalyst*, Building 1, Room 333.

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

READ ANNOUNCEMENTS AS WELL AS LONGER VERSIONS OF THESE ARTICLES ONLINE (IN COLOR) AT http://irp.nih.gov/catalyst/v24i5

FROM THE ANNALS OF NIH HISTORY

It Came From Beneath the Dental Chair

BY ALANNA NATANSON, OFFICE OF NIH HISTORY

If someone thought a visit to the dentist was torture, one glance at this corkscrew-like wisdom-tooth extractor would likely confirm those fears. But this Standard Exolever, more generically called an "elevator," is much less threatening than it looks.

NIH STETTEN MUSEUM, OFFICE OF NIH HISTORY

It was designed in the early 1900s by George B. Winter (1878–1939), who believed that the elevator was less scary to patients than dental forceps. Modern dental elevators (inset) don't look like corkscrews and the blades come in various sizes sizes and shapes. The Exolever pictured here belonged to **H. Trendley Dean**, the first director of the National Institute of Dental Research (now the National Institute of Dental and Craniofacial Research, NIDCR). Dean was the Public Health Service's first dental researcher even before there was an NIDCR. He studied the effect of fluoride on teeth and dental cavities and was the founding director of NIDCR from 1948 to 1953.

The Office of NIH History and Stetten Museum is preparing an exhibit on NIDCR's history that will feature Dean's toolkit and other historical items. The permanent exhibit will be installed in winter 2017, on the fifth floor of Building 30, where the NIDCR labs are located. ●

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH.

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