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The Merry Band of Stadtmans

BY LAURA STEPHENSON CARTER

Meet 15 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 aims to recruit a diverse group of scientists with interests across the biomedical-research spectrum.

Seven of the Stadtmans focus on cancer research and work in the National Cancer Institute. Two work in the National Heart, Lung, and Blood Institute and both have dual appointments with other institutes. Another hails from the National Institute of Environmental Health Sciences in Research Triangle Park in North Carolina and holds a dual appointment with another institute. The other five Stadtmans each represent a different institute: National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Biomedical Imaging and Bioengineering; National Eye Institute; National Institute on Aging; and the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Get to know them a bit. You'll learn what their research is, what discoveries they've made, how they got interested in science, and even a few secrets. And if you go online, you'll learn even more: https://irp.nih.gov/catalyst/v27i1/the-merry-band-of-stadtmans.

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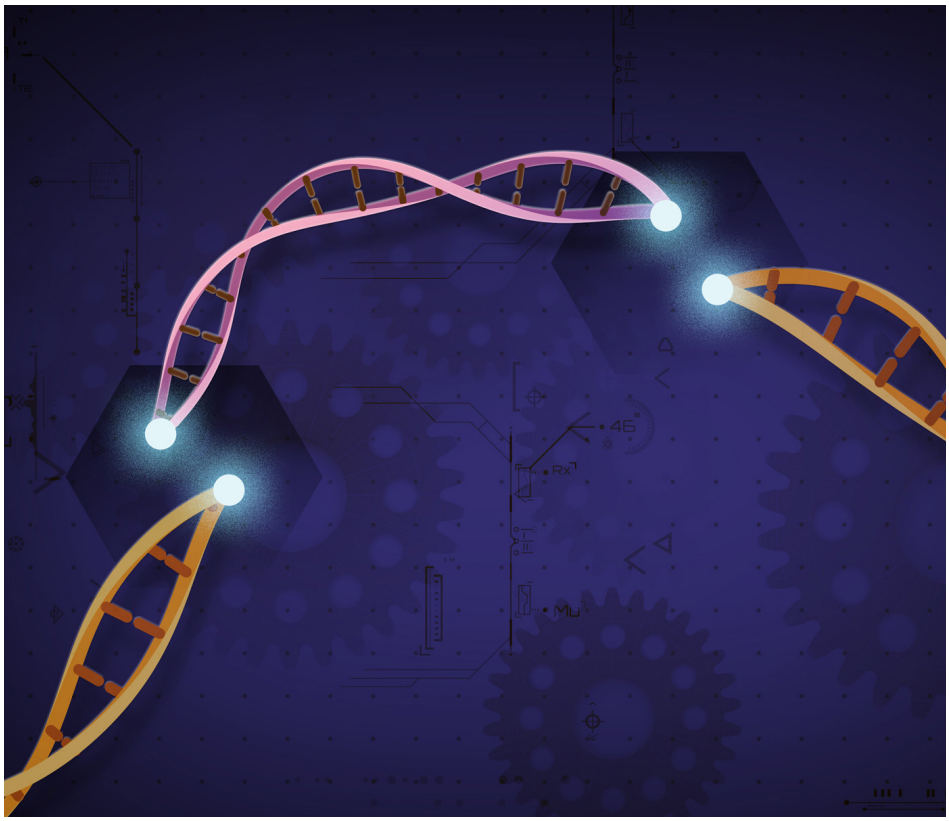
Creating a "Spellchecker" for Genes

BY LISA YUAN, NIDDK



ERNESTO DEL AGUILA III, NHGRI

CRISPR-Cas9 is a customizable tool that lets scientists cut and insert small pieces of DNA at precise areas along a DNA strand. Lothar Hennighausen's team has led the way in describing the extent of unwanted molecular scarring that the CRISPR-Cas9 technique can cause at target sites of mammalian genomes.

Imagine a pair of molecular scissors that could snip and tweak sections of the genetic alphabet. Or tweezers that could pluck one letter and replace it with another. These tools have become a reality in recent years, allowing scientists to correct "misspellings" in the genetic code. And one NIH lab is taking full advantage of this.

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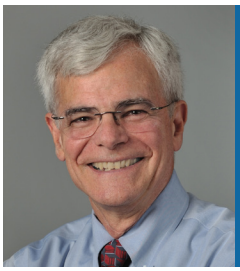


A New Centralized Institutional Review Board

BY MICHAEL GOTTESMAN, DDIR, AND JONATHAN GREEN, OD

As you almost certainly have heard by now, the NIH Intramural Research Program is in the process of centralizing and consolidating the Institutional Review Board (IRB) system. The 12 independent IRBs will be transitioning to one IRB office, and the three different protocol and data-management systems are being consolidated into one. The goal is to improve the consistency of IRB review and the overall efficiency of the IRB system.

This type of IRB reorganization has been deployed successfully at universities around the country not only to enhance human-research protections but also to benefit principal investigators on clinical protocols by ensuring an efficient review process. The IRB reorganization will also ensure that we are compliant with the revised Common Rule (also known as the Federal Policy for the Protection of Human Subjects), which becomes effective on January 21, 2019.

We have brought on two new team members to lead this effort, **Jonathan Green** as the director of the Office of Human Subjects Research Protections (OHSRP) and **Tiffany Gommel** as the director of IRB Operations (IRBO), a new centralized administrative office. Jonathan joins us from Washington University School of Medicine in St. Louis, where he was professor of medicine, pathology, and immunology, associate dean for Human Studies, and executive chair of the university's IRB. Tiffany was executive director of the Research Subjects Review Board Office at the University of Rochester (Rochester, New York).

We are close to completing one step of the centralization process: the migration of protocol information from three different information-technology systems to one central-tracking and data-management system—iRIS, short for integrated-research information system.

The IRBO will handle all protocol submissions for the intramural research program; make exempt and nonhuman subjects determinations; and conduct expedited reviews of minimal-risk research. The office will conduct in-depth pre-reviews before sending protocols to a new, central NIH Intramural IRB committee. During this process, we hope to identify and address any issues that could delay approval. The pre-review will be done by trained professional IRB analysts with consultation from IRB chairs, human-research protection program leadership, and other experts as needed.

The new NIH Intramural IRB—consisting of all current NIH IRB members—will use an innovative "flexible IRB" model and will begin meeting in January 2019. Panels will meet multiple times per week, conducting shorter meetings with fewer agenda items than are on current committee schedules. In this way, once ready, protocols can be scheduled for meetings with less delay.

The revisions to the Common Rule constitute the first substantive changes since its publication in 1991. There are several provisions that will affect all investigators including changes to the informed-consent process, new exemptions, and the elimination of continuing review for some minimal-risk research.

To ensure compliance with the new rule, all new studies slated for initial approval on or after January 21, 2019, will be processed by the IRBO and reviewed by the NIH Intramural IRB. All studies approved before January 21 will remain under the old rule and do not need to comply with any of the revised Common Rule requirements. Amendments and continuing reviews will continue to be handled by the current NIH IRBs. Over the course of the next several months, we will transition each of the committees into the new structure.

We are confident that the new IRB system will be an improvement for everyone. For investigators, there should be greater consistency in IRB review and more efficient turnaround times. For IRB members, meetings will be shorter with fewer agenda items, allowing for greater preparation and participation.

We thank you in advance for your patience and understanding as we undertake this initiative. There will almost certainly be some bumps in the road as we get going, but with your help we will achieve smooth sailing soon. ●

Jonathan Green, M.D., M.B.A., is the director of the Office of Human Subjects Research Protections. For more information, go to irbo.nih.gov.

NIH Distinguished Scholars Program

BY CARL HASHIMOTO, OD

CHIA CHI CHARLIE CHANG

NIH Distinguished Scholars Program participants gathered for an inaugural meeting in the fall. Front row (from left): DSP scholars Joel Vega-Rodriguez, Joana Vidigal, Eric Calvo, Sadhana Jackson, Hugo Tejeda, and Paule Joseph; and Director of Research Workforce Development Roland Owens. Back row (from left): DSP scholar Freddy Escorcia; Deputy Director for Intramural Research Michael Gottesman; senior investigators and mentors Julie Segre, Veronica Alvarez, and John Tisdale; NIH Director Francis Collins; Chief Officer for Scientific Workforce Diversity Hannah Valantine; Senior Advisor for Faculty Development Carl Hashimoto; and DSP scholars Nida Sen, Faustine Williams, Catherine Cukras, and Sherine El-Toukhy (missing DSP scholars: Jennifer Jones and Joseph Rodriguez).

As part of an effort to enhance diversity in the scientific workplace, NIH launched the Distinguished Scholars Program (DSP), which facilitates the hiring and career progression of tenure-track investigators who have demonstrated a commitment to promoting diversity and inclusion in the biomedical-research workforce.

The DSP aims to reduce the barriers to the recruitment and success of principal investigators from underrepresented groups in biomedical research (African-Americans, Hispanics, American Indians, and others; people with disabilities; individuals from disadvantaged backgrounds; and women).

To build a more diverse and inclusive intramural research program, the DSP recruits a cohort of up to 15 tenure-track and some clinical investigators each year. Selection for the program is competitive and recognizes outstanding accomplishments both in scientific research and in promoting diversity and inclusion. The scholars participate as a cohort in activities designed to foster a sense of belonging and to promote research and career success.

They receive mentorship from highly experienced NIH senior investigators; professional leadership training and access to workshops on a variety of management skills and tactics; and informal networking opportunities with NIH leadership such as the NIH director, institute and center (IC) directors, and scientific directors.

In 2018, the DSP recruited 13 scholars for the inaugural cohort: **Eric Calvo** (NIAID), **Catherine Cukras** (NEI), **Sherine El-Toukhy** (NIMHD), **Freddy Escorcia** (NCI), **Sadhana Jackson** (NCI), **Jennifer Jones** (NCI), **Paule Joseph** (NINR), **Joseph Rodriguez** (NIEHS), **H. Nida Sen** (NEI), **Hugo Tejeda** (NIMH), **Joel Vega-Rodriguez** (NIAID), **Joana Vidigal** (NCI), and **Faustine Williams** (NIMHD). Candidates for the DSP are nominated by the NIH ICs that have intramural research programs. Nominations for the 2019 cohort of scholars will be due in March 2019.

Financial support for the DSP comes from a central fund of contributions made by the ICs, which so far have committed support for three cohorts of scholars. Each scholar receives research funding from the DSP for the first four years of their tenure-track appointment; the respective ICs provide any supplemental funding during the first four years and full funding after that. ●

For further information about the DSP and bios of the 2018 NIH Distinguished Scholars, visit https://diversity.nih.gov/programs-partnerships/dsp or contact **Carl Hashimoto**, who leads the DSP, at carl.hashimoto@nih.gov.

NIH Fellows Editorial Board

Influencing Science, One Manuscript at a Time

BY BRANDI CAROFINO AND ERIKA GINSBURG, NCI

BRANDI CAROFINO, NCI

Members of the Fellows Editorial Board (from left): Amelia Parker, Brianna Daley, Manju Bhaskar, Alexis Carter (consulting member), Iain Sawyer, Brandi Carofino, Lukas Bialkowski, Sarah Deasy, Anowarul Amin, Mariana Mandler, Shailesh Advani, Michelle Saré, and Erika Ginsburg (advisor).

The NIH Fellows Editorial Board (FEB) recently celebrated a big milestone: They edited their 1,000th submission. The FEB, founded in 2002, has edited an average of 60 manuscripts a year for the past 16 years.

Companies that offer professional editing services often charge hundreds of dollars to review a scientific manuscript. Luckily, fellows in the NIH intramural research program and the FDA have a better option—the free editing services offered by the FEB. The service is for fellows and by fellows and provides free, fast, and confidential editing for a variety of scientific documents including journal articles, book chapters, and grant proposals. Editors highlight confusing sentences, identify where reorganization is needed, and provide suggestions on how to improve writing skills. The editors do not, however, consider the scientific merit of manuscripts.

All editing is performed by fellows who volunteer to serve as board members. The process of editing helps them hone their editorial, writing, teamwork, and leadership skills. Prior experience is not required, but new editors are extensively trained by more-senior board members on the principle of "See one, do one, teach one."

The FEB is led by Senior Editor **Brandi Carofino** (National Cancer Institute, NCI). Each submission is managed by one of four associate editors, a team that includes **Anowarul Amin** and **Manju Bhaskar** (both from the National Institute of Neurological Disorders and Stroke) and **Iain Sawyer** and **Sarah Deasy** (both from NCI). The rest of the board includes 25 editors—representing nearly all the NIH institutes and centers as well as the FDA—who are postdocs, postbacs, and consulting members.

Each submission is managed by an associate editor, who solicits three or four primary editors from the board to lead the discussion during the weekly FEB meetings, which take place on the Bethesda campus and is videocast to several other NIH locations. The primary editors carefully read and edit a submission and serve as the primary contributors during the meeting.

After an FEB meeting, primary team members each prepare a report for each submission. The reports are then compiled into a single document so that the reviews are comprehensive but not redundant. The process helps newer editors gain experience under the supervision of more practiced editors. The senior editor finalizes the reports; each author receives a letter that summarizes the board's overall impressions and a copyedited PDF version of the document. PDF annotation ensures that authors consider the rationale for the edits as they incorporate them into their final document. Generally, the authors receive reports within 10 business days and may also request an in-person meeting with the editors if desired.

To evaluate and enhance the service provided by the FEB, authors are asked to complete a feedback form for each submission. The FEB frequently receives the highest marks for each query, which includes questions on timeliness, clarity, helpfulness, and likelihood of submitting future manuscripts to the FEB. FEB-edited manuscripts have recently been published in high-impact journals such as *Nature Communications*, *The Proceedings of the National Academy of Science*, *Cancer Cell*, and *The Journal of Biological Chemistry*.

Many members use the FEB as a springboard to begin careers as professional science writers or editors. FEB alumni hold positions at the *Lancet*, the Drug Information Association, Ripple Effect Communications, the Susan G. Komen organization, and several NIH institutes. A recent alumna, **Caeul Lim** (National Institute of Allergy and Infectious Diseases), now an assistant editor at Cell Press in Boston, said that her "experience with the FEB was instrumental in getting the position." ●

The FEB is supported by the NCI Center for Cancer Training's Office of Training and Education. For more information, visit the FEB website at https://ccr.cancer.gov/training/trainee-resources/editorial-board or email NCIeditors@nih.gov.

Breaking Through the Petri Dish Lid

Institutional and Personal Approaches to Enhancing Diversity

BY SUSAN CHACKO, CIT

Mentorship and institutional change were the main themes at the symposium "Breaking through the Petri Dish Lid: Ways for Women and Underrepresented Groups to Advance Their Careers in Science," held on October 5, 2018. The symposium featured three panelists—**Kathryn Zoon**, **Hannah Valantine**, and **Nesrine Taha**—who discussed personal and institutional approaches to changing the existing paradigm.

Debbie Hinton, a PI at the National Institute of Diabetes and Digestive and Kidney Disease, presented some sobering statistics in her welcome address. In the early 1990s, women made up 16.5 percent of senior investigators (PIs) at NIH, and in 2018, the number has barely increased to 24 percent, she said. There has been even less change in the upper leadership positions. During this same period the percent of women getting Ph.D.s in the biosciences increased from 42 percent to 52 percent.

The statistics for individuals from underrepresented groups are even more discouraging. Nationwide, they receive about 12 percent of Ph.D.s but occupy five percent of tenured positions, according to Valantine, NIH's chief officer for scientific workplace diversity.

Zoon, a former scientific director and now scientist emerita at the National Institute of Allergy and Infectious Diseases, stressed the importance of good mentorship—perhaps even having multiple mentors—who can help in handling both scientific and life challenges. She identified several leadership skills for women including networking; having ethics and integrity; being creative and innovative in solving problems; having an awareness of the scientific environment; being flexible; thinking strategically; listening to people and being willing to work as part of a team; learning how to manage conflict; and most of all being resilient. Valantine recommended that aspiring scientists find "sponsors," a step beyond mentors, too.

While individual efforts are part of the picture, Valantine pointed out that these approaches have had limited success. It's now time to fix the institutions. The culture has not changed over time; women and people from underrepresented groups do not have access to an even playing field, and there is no reward system for enhancing diversity in institutions. She has an evidence-based approach to changing this culture: For example, scientific directors are presenting metrics such as resource distribution, salary, and speaking-engagement demographics to the NIH Equity Committee every two years.

Valantine also suggested that there be more rapid turnover of laboratory and branch chiefs at NIH. Although she acknowledged that achieving diversity and equity at the top scientific levels would take time, she was firmly of the belief that within two years, new scientific hires at NIH could be half women. That's because with new methods of hiring that focus on broad, trans-NIH searches with a deeper talent pool (such as the Stadtman search), the percentage of women among new hires has exceeded the percentage of women applicants. Moreover, the proportion of women tenure-track investigators in the NIH intramural research program (IRP) is now 40 percent, a significant increase from even a few years ago. In contrast, the percentage of women in the tenured investigator pool has not increased much over the past 10 years.

Taha, a former pre-doctoral researcher (2013–2014) at the National Eye Institute and now a nanoscale research scientist and entrepreneur, talked about how her four-year career break to raise her family made her realize the challenges facing women who return to the scientific workforce. She founded a nonprofit, the Foundation for American Advancement, to provide specialized training and fellowships for women returning to science, technology, engineering, and mathematics (STEM) workplaces as well as programs for schools.

The panel also recognized that NIH's new anti-harassment policies, which aim to create a culture of civility and respect—will foster a safe working environment at NIH that is friendly to women and underrepresented minorities. The NIH leadership is also looking into ways to influence change at universities, too.

Audience members eagerly asked questions about every aspect of diversity in science. "It's critical to get multiple perspectives at the table and build diverse experiences into policy," said **Valerie Virta**, one of the NIH attendees, who said she had been very inspired by the symposium.

To sum up the conference, Zoon quoted Supreme Court Justice Ruth Bader Ginsburg: "Fight for the things you care about, but do it in a way that will lead others to join you." ●

The event was hosted by the NIH Women Scientists Advisors (WSA) and the Bethesda chapter of the Association for Women in Science (AWIS). To watch a videocast, visit https://videocast.nih.gov/launch.asp?26094. For more information, go to https://www.niehs.nih.gov/careers/research/fellows/alumni-outcomes/index.cfm or contact Tammy Collins (984-287-3651 or tammy.collins@nih.gov).

Office of Patient Recruitment

Extending the Reach of NIH Studies

BY BRANDON LEVY, OIR

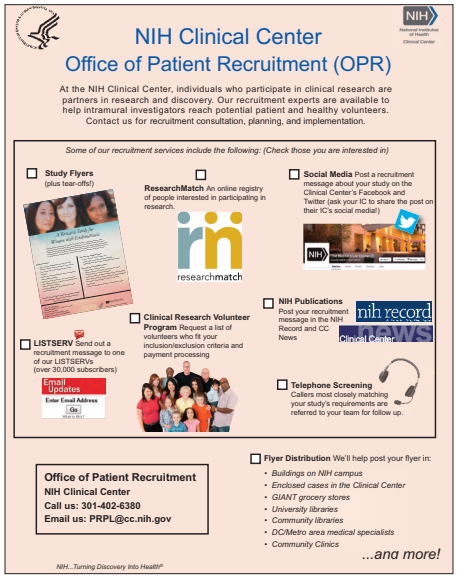
If researchers design a groundbreaking clinical study, and no patients know about it, what's the use?

The scientists may have a supply closet bursting with test tubes and Petri dishes, a set of blank consent forms stacked two feet high, and the latest cutting-edge analytic software loaded onto their desktops. But without any participants, all those test tubes, consent forms, and spreadsheets will remain empty. We are nothing without our patient volunteers.

Fortunately, the NIH Clinical Center's (CC's) Office of Patient Recruitment is eager to help find participants for intramural studies. In fiscal year 2017, it assisted with recruitment for 229 clinical trials performed at 19 of NIH's institutes and centers. In addition to a staff of knowledgeable recruitment specialists who work with scientists at all stages of the research process, the Office of Patient Recruitment oversees the Clinical Research Volunteer Program, a database of more than 20,000 healthy volunteers interested in participating in NIH research. The registry can be filtered based on demographic criteria such as age and sex, as well as by more specific characteristics such as whether an individual is taking certain medications. The combination of these two resources can greatly reduce the difficulty of finding participants for intramural studies.

Recently, the Office of Patient Recruitment joined forces with the CC's Office of Communications and Media Relations. The technical and creative expertise of the two offices combined means that patient-recruitment services are significantly enhanced.

Using their media savvy and understanding of how biomedical research is done, the office's recruitment specialists work with researchers to create recruitment



approaches tailored to studies' specific target populations. The specialists design flyers, postcards, and other printed materials; create newspaper and radio ads; and draft messages to post on social media and other websites. Although these services are provided for free, investigators do have to pay if they choose to purchase advertising space or request larger printed materials such as banners.

What's more, the recruitment specialists can leverage their knowledge of the Institutional Review Board (IRB) approval process to ensure that recruitment strategies and materials move smoothly through it.

"Some of our specialists have been here a long time [and] can predict how the IRB will react to recruitment materials and whether ... something [should be] phrased or presented a certain way," said **Molly Freimuth**, the media lead in the Clinical Center's Office of Communications and Media Relations.

One of the researchers who is benefitting from the efforts of the Office of Patient Recruitment is **Stephanie Chung**, co-director of the Metabolic Research Program in the National Institute of Diabetes and Digestive and Kidney Diseases. She is conducting a clinical trial with young African-Americans who have type 2 diabetes. Recruiting for the study has been difficult because the condition is rare in young people. And most patients don't understand how biomedical research can benefit them. The recruitment team, in collaboration with specialists from the CC's Office of Communications and Media Relations, initiated a partnership with Children's National Hospital in Washington, D.C. Children's has the largest endocrinology program in the Northeast.

Through the partnership, NIH developed digital, video, and social-media content for Children's to distribute to their physician and patient audiences. A low-cost video about the trial is posted on several websites including YouTube. Chung routinely shows it to her patients to encourage them to join her study. In addition, the NIH recruitment specialists developed a social-media strategy to target those patients directly and designed and mailed flyers to clinicians who work with that population so they can make their patients aware of the trial.

Representatives from these offices "really understood where we were coming from and what we were trying to do," Chung said. "We wanted people to understand why this [study] is important and how it is going to affect them and their families. I think part of the reason the campaign was so successful was that we had a great team." ●

To learn more about the Office of Patient Recruitment and how to submit a request for services, visit http://intranet.cc.nih.gov/recruit/index.html. A recruitment specialist will respond within three business days. If you have any questions, you can also call the office at 301-402-6380.

NIH Library Services

So Much More than Books

BY KATHLEEN MCGLAUGHLIN, OD

Need to know how to develop bibliometrics that will help you evaluate written publications? Want to understand how to use information-systems technology? How about getting assistance with editing your manuscripts or managing your data? The NIH Library, located in Building 10, is at your service. In addition to managing a vast collection of books and journals and helping you with research questions, the NIH Library offers a variety of services to help you acquire and manage the information you need. Here, four of them are highlighted.

Bibliometrics Service

The NIH Library's Bibliometrics Service program provides statistical analysis of written publications produced by scientists, grant programs, and institutions at NIH and around the world. Such analytics can help NIH staff measure the productivity of researchers, detect collaborations, identify research topics, and calculate citation-impact scores. Services include consultations on designing and using bibliometric analyses, customized analyses that will meet specific needs, and training on bibliometrics theory and techniques. In August 2018, the service presented a two-day "Bibliometrics and Research Assessment Symposium," which provided a forum to share expertise, ideas, and best practices in bibliometrics services via a blend of keynote presentations, poster sessions, and training sessions.

Custom Information Solutions Service

The Custom Information Solutions (CIS) service brings together information science and technology to develop online tools and resources that help NIH staff share their research and collaborate more effectively. The CIS team specializes in Drupal, an open-source web-content-management framework, and manages a federally approved cloud-hosting solution for the products they develop. The team uses their expertise in website development, information architecture, and data management to develop innovative information solutions. Examples include an online portfolio of epilepsy research projects, a database of Alzheimer disease preclinical studies, a portfolio of Alzheimer disease grant-funding data, and a collaborative website to share ideas and best practices for designing, constructing, operating, and maintaining buildings.

Among the events the team organizes are the annual NIH-Library-hosted Drupal GovCon event, one of the biggest Drupal conferences on the East Coast. Next year's event is scheduled for July 24–26, 2019.

Editing Service

The NIH Library provides free light and medium editing services for NIH- and Department of Health and Human Services–related work. NIH Library editors will review and suggest revisions to improve your manuscript, slide deck, poster, and more. Additional services include free and confidential plagiarism review using iThenticate; resource suggestions to help get your draft ready for peer review; and consultation and assistance with copyright questions and the PubMed Central submission process.

Training includes special events and classes for new and experienced authors. In October 2018, the Editing Service hosted a two-hour workshop, "Choosing a Quality Journal for Publication," which featured a panel discussion with experts who offered advice on how to identify questionable journals and conferences, work with preprints, enhance the journal article submission process, and understand open-access publishing. The session concluded with an educational presentation, "Identifying Scientifically Sound Journals for Publication."

Data Services

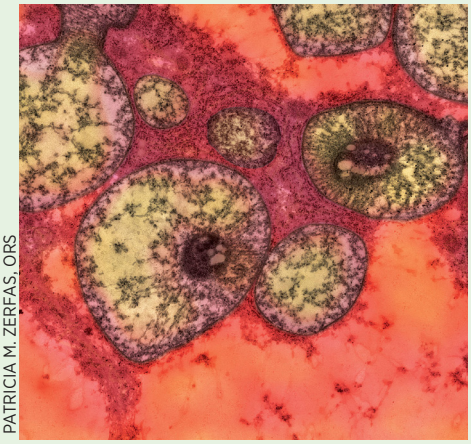
The Data Services team can help you understand how to manage your data from the beginning of your project through the post-project stage of preserving your data so it can be successfully accessed and reused over the long term. Training includes classes on data management, data visualization, data analysis, and the programming language R (used for statistical computing and graphics).

NIH staff are also welcome to use the NIH Library's high-performance data-sciences workstation, which comes complete with a suite of tools for data analysis, processing, and visualization for different types of data. NIH Library staff are available to provide help with the tools.

The Data Services team is also investigating how to support working with electronic lab notebooks (ELNs) at NIH and recently hosted a series of ELN meetings for staff already using ELNs as well as others who are considering them. The information gathered during these sessions will be used to help the NIH Library plan a one-day ELN forum in 2019 to further explore current ELN practices and opportunities at NIH. ●

For more information, go to https://www.nihlibrary.nih.gov/services, call 301-496-1080, or email nihlibrary@nih.gov. To stay up to date on NIH Library classes, events, resources, and services, subscribe to the NIH Library LISTSERV at https://list.nih.gov/cgi-bin/wa.exe?SUBED1=NIHLIB-L&A=1.

Intramural Research Briefs



PATRICIA M. ZERFAS, ORS

NHGRI: The figure is an electron micrograph showing abnormally shaped and structured mitochondria in the liver of a mutant mouse that models methylmalonic acidemia.

NHGRI, NIDDK, NCI, ORS: ELEVATED HORMONE FLAGS LIVER PROBLEMS IN MICE WITH METHYLMALONIC ACIDEMIA

NHGRI researchers led a team that discovered that a hormone, fibroblast growth factor 21 (FGF21), is extremely elevated in mice with liver disease that mimics the same condition in patients with methylmalonic acidemia (MMA). MMA is a genomic disease that impairs a person's ability to break down food proteins and certain fatty acids. The condition affects roughly one in 50,000 children born in the United States and can be detected through newborn screening. Children with MMA suffer from frequent life-threatening metabolic crises when they encounter a minor viral illness or other stressors such as trauma, dietary imbalance, or surgery. They must adhere to a special low-protein diet and take various supplements their entire lives.

Based on the discovery, clinicians treating patients with MMA will be able to measure FGF21 levels to predict how severely patients' livers are affected and when to refer patients for liver transplants. The findings also might shed light on more common disorders such as fatty liver disease, obesity and diabetes by uncovering similarities in how MMA and these disorders affect energy metabolism. (NIH authors: I. Manoli, J.R. Sysol, M.W. Epping, L. Li, C. Wang, J.L. Sloan, A. Pass, J. Gagné, Y.P. Ktena, N.S. Trivedi, P.M. Zerfas, V. Hoffmann, M. Abu-Asab, M.G. Tsokos, D.E. Kleiner, A.G. Elkahloun, J. Schnermann, R.J. Chandler, and C.P. Venditti, *JCI Insight* **3**:e124351, 2018; DOI:10.1172/jci.insight.124351)

NCI: A BACTERIA TOXIN TRIGGERS RUPTURE OF CANCER CELLS LEADING TO THEIR DEATH

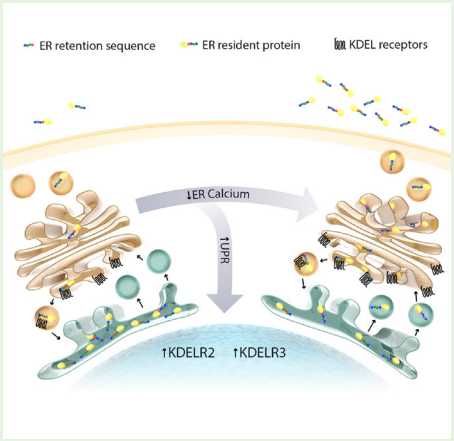
Inflammation serves to kill invading bacteria and viruses. Certain molecules on the surface of the microbes can trigger an inflammatory cascade, and one example of such a molecule is lipopolysaccharide (LPS). Cells can react to LPS by triggering a process called pyroptosis that causes the cell to burst and die. The released cell contents attract blood and lymphatic cells that in turn kill the LPS-producing bacteria.

LPS was used in the very early days of medicine to treat cancer, although it has fallen out of favor because it causes severe side effects, such as a hyperinflammatory response (sepsis) that can result in death. It was not known exactly how LPS kills cancer cells.

NCI researchers have now shown that a protein called secretoglobin family 3A member 2 (SCGB3A2), which is produced by the cells that line the lung airways, binds to LPS. Tests on mouse immune cells and lung-cancer cells grown in the laboratory showed that the resulting SCGB3A2-LPS complex can then bind to a cell-surface protein called syndecan 1. This binding enables LPS to enter the cell and trigger pyroptosis and cell death.

Currently available cancer immunotherapy is targeted primarily to the host immune cells whereas the NCI study shows the possibility to directly target cancer cells. However, it remains to be examined whether molecules that trigger pyroptosis, like LPS, could also be used to treat cancers other than those from the lung. Further work is also needed to understand in more detail how SCGB3A2 and LPS work together to cause cancer-cell death. The combination of cancer immunotherapy and stimulation of cancer-cell self-destruction could greatly advance the treatment of cancer patients. (NIH authors: S. Yokoyama, Y. Cail, M. Murata, T. Tomita, M. Yoneda, L. Xu, R.E Cachau, and S. Kimura, *eLife* **7**:e37854, 2018; DOI:10.7554/eLife.37854)

[BY SHIOKO KIMURA, NCI]



SUSANNE BACK

NIDA: This graphic shows an exodus of proteins from the endoplasmic reticulum (ER) in response to the loss of luminal ER calcium. The cell works to maintain the calcium-deprived ER proteome by upregulating KDEL receptors.

NIDA: MAINTAINING THE ER PROTEOME UNDER CALCIUM DEFICIENCY

A new paper published by NIDA scientists describes, for the first time, a novel pathological mechanism that may contribute to a variety of disease states. Within the cells of our body, many of the proteins and lipids are produced by a structure within a cell called the endoplasmic reticulum (ER). The ER also serves as the cell's primary reservoir of calcium. Each of the resident ER proteins is kept in the ER by a tail sequence called an ER-retention sequence. If a protein escapes the ER, its tail is recognized by a receptor called a "KDEL (Lys-Asp-Glu-Leu) receptor" and returned to the ER. This function is critical to the maintenance of a healthy body. The study shows that when the calcium concentration drops in the ER, the cell proteins overwhelm this retrieval mechanism and redistribute to the outside of the cell. As a result, protein functions are lost in the ER, and

unwanted expression occurs outside the cell, which may contribute to a variety of disease pathologies such as diabetes, stroke, Alzheimer disease, cardiac diseases, and substance-use disorders. This greater understanding of the most delicate mechanisms in the body suggests that stabilizing ER calcium or increasing KDEL receptors has therapeutic potential. (NIH authors: K.A. Trychta, S. Back, M.J. Henderson, and B.K. Harvey, *Cell Reports* **25:**1829–1840, 2018)

[BY BRANDON K. HARVEY, NIDA]

NIDDK, NHLBI, NIAMS: T-REG CELLS SUPPORT INTESTINAL WOUND HEALING

A subset of regulatory T cells, called CD161+ Treg cells, accelerated wound healing and may also reduce inflammation in the gut, according to scientists from NIH and the United Kingdom. The study described the biological mechanisms of CD161+ Treg cells in humans, finding them to be a distinct, stable, and highly suppressive population of regulatory T cells. CD161+ Treg cells were also associated with regions of lower inflammation in Crohn disease. These findings suggest that infusion of CD161+ Treg cells may be a valid therapy for inflammatory bowel disease. (NIH authors: Y.-C. Chen, D. Chauss, H.-W. Sun, H.-Y. Shih, C. Kemper, M. Pirooznia, and B. Afzali, *Nat Immunol* **19:**1403–1414, 2018; DOI:10.1038/s41590-018-0230-z)

[BY BEHDAD AFZALI, NIDDK]

NIEHS: MALE MICE GROW OVARIES AFTER SINGLE GENE TWEAK

By turning on the mammalian gene *FOXL2*, NIEHS scientists prompted male mice to grow ovaries. Among vertebrates, there is a wide variation in the signals that trigger sex determination of the gonads. In some types of turtles and alligators, sex is shaped by environmental cues such as temperature or the availability of nutrients. In humans, it is written in the composition of the sex chromosomes. Although there are differences, many of these organisms use the same proteins to guide sexual development, such as sex-determining region Y (SRY) and SRY-related box 9 (SOX9) in the testis and wingless-related integration site (WNT) family member 4 and forkhead box protein L2 (FOXL2) in the ovary.

Male mice were genetically engineered to produce FOXL2 protein in their testes. Their gonads morphed into ovaries, although they retained some molecular and structural features related to their original sex programming. The study suggests that sexual development is flexible and may be able to shift in response to different genetic or environmental factors. The findings could give insight into disorders of sexual development and defects in fertility. (NIH authors: B. Nicol, S.A. Grimm, A. Gruzdev, G.J. Scott, M.K. Ray, and H.H.C. Yao, *Hum Mol Genet* **27:**4273–4287, 2018; DOI:10.1093/hmg/ddy312)

[BY MARLA BROADFOOT, NIEHS]

HUMPHREY YAO, NIEHS

NIEHS: The normal mouse testis, left, produces large amounts of a testis-specific marker called SOX9, shown in green. The normal mouse ovary, middle, produces large amounts of an ovary-specific marker called FOXL2, highlighted in pink. The genetically tweaked mouse testis, right, produces mostly FOXL2, but retains small amounts of SOX9.

NIEHS: SOX17 PROTEIN IS CRITICAL FOR PREGNANCY

Using mouse genomic data, genome editing, and bioinformatics, a team led by NIEHS scientists determined that the protein SOX17 may be critical to a woman's ability to become pregnant. The researchers found that the SOX17 transcription factor works with the progesterone receptor in female mice to regulate the ability of the uterus to support embryo implantation. The scientists hope they can use the information to eventually turn stem cells into healthy uterine-lining cells, which would help some women with infertility or uterine disease. SOX17 regulates both development of the uterus and the genes that support embryo implantation. Removing either the SOX17 binding site, which the team determined to be near the *Ihh* gene, or the entire *SOX17* gene altered communication between uterine epithelial cells and the stroma. As a result, the uterus did not form properly and was unable to support pregnancy.

When SOX17 was present, it worked with the progesterone receptor to control the ability of the uterus to receive an embryo. The team found that mouse SOX17 used the protein Indian hedgehog homolog, which is coded for by the *Ihh* gene, to communicate with and regulate uterine genes. The finding has implications for treatment of infertility and diseases in which patients do not respond well to progesterone therapy—such as endometriosis, endometrial cancer, and some infertility cases. (NIH authors: X. Wang, T. Wang, S.-P. Wu, and F.J. DeMayo, *Nature Comm* **9:**Article number 4421, 2018; DOI:10.1038/s41467-018-06652-w)

[BY ROBIN ARNETTE, NIEHS]

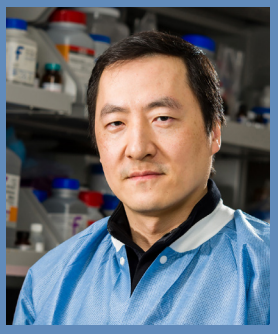
Read more online:
https://irp.nih.gov/catalyst/v27i1/research-briefs

Stadtman Investigators


PEDRO J. BATISTA, NCI-CCR


ISABEL BEERMAN, NIA


JOHN BROGNARD, NCI-CCR


CHENGKAI DAI, NCI-CCR


BRIAN GLANCY, NHLBI and NIAMS

PEDRO J. BATISTA, PH.D., NCI-CCR

Research focus: Understanding in what way RNA post-transcriptional modifications regulate gene expression during development and disease.

What discoveries have you made?

I found that the RNA modification N6-methyladenosine confers flexibility to the transcriptome and modulates the balance between pluripotency and differentiation (*Cell Stem Cell* **15:**707–719, 2014).

What is exciting about your work?

All the new questions that emerge every time we take a step forward on understanding how cells regulate gene expression.

What would surprise most people?

That I have been practicing martial arts since high school.

ISABEL BEERMAN, PH.D., NIA

Research focus: Understanding the mechanisms that underlie age-associated functional decline, with a focus on adult tissue-specific stem cells. Reestablishing the full potential to these aged cells could mitigate many age-associated phenotypes.

What discoveries have you made?

My work has contributed to understanding how aging affects hematopoietic stem cells (*Proc Natl Acad of Sci USA* 107:5465–5470, 2010). We also demonstrated that DNA damage accumulation was tied to the quiescent nature of HSCs. (*Cell Stem Cell* 15:37–50, 2014). These findings suggest a potential for restoring restricted potential of aged HSCs by resetting these nonpermanent modifications on the DNA.

What would surprise most people?

Anyone who has heard my off-key humming would be surprised that I was trained to sing classical music and played the organ for my hometown church. I also proudly maintain my skill at driving a combine, which I learned growing up on a farm.

JOHN BROGNARD, PH.D., NCI-CCR

Research focus: Elucidating cancer-associated kinases in the unexplored human kinome. We hope to identify novel druggable drivers so cancer patients can benefit from targeted therapies.

What discoveries have you made?

I helped define protein kinase B (AKT) as a critical mediator of survival in lung cancer and determined that combining AKT inhibitors with chemotherapy could be beneficial for lung-cancer patients (*Cancer Res* **61:**3986–3987, 2001). I also helped to define the protein kinase C (PKC) family of enzymes as tumor suppressors, overturning the established dogma that PKCs were oncogenes (*Cell* **160:**489–502, 2015; DOI:10.1016/j.cell.2015.01.001).

What would surprise most people?

I grew up in a rural area and my dad took me fishing and hunting. However, after living in the United Kingdom for six years and observing the effectiveness of making gun ownership illegal, I am now an advocate for strict gun laws.

CHENGKAI DAI, PH.D., NCI-CCR

Research focus: Using multidisciplinary approaches to interrogate the role of proteomic stability in tumorigenesis and exploiting proteomic instability as an intrinsic vulnerability of cancer for therapy.

What discoveries have you made?

Our group is among the first to discover the unexpected pro-oncogenic role of the proteotoxic stress response and demonstrate that cancer cells are addicted to, or dependent on, this stress response for their growth and survival. (*Cell* **130:**1005–1018, 2007; and *Cell* **160:**729–744, 2015)

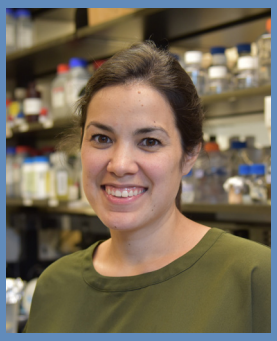
What do you like to do outside of work?

Travel to different places and experience different cultures.

Stadtman Investigators

RAMIRO IGLESIAS-BARTOLOME, NCI-CCR

CHANDRA L. JACKSON, NIEHS AND NIMHD



KATHERINE MCJUNKIN, NIDDK

JAGAN MUPPIDI, NCI-CCR

CARLO PIERPAOLI, NIBIB

BRIAN GLANCY, PH.D., NHLBI AND NIAMS

Research Focus: Determining how mitochondria are optimized within muscle cells to help maintain energy homeostasis during the large change in energy demand caused by muscle contractions. We are also developing and using novel, direct measurements of in vivo mitochondrial function in skeletal muscle under different workloads.

Have you made any discoveries?

We demonstrated that skeletal-muscle mitochondria form a highly connected network resembling that of an electrical power grid and are capable of electrical conduction of the mitochondrial membrane potential throughout the cell (*Nature* **523:**617–620, 2015).

What is exciting about your work?

Finding new ways to look at things. It often involves developing new methods to evaluate research questions we could not answer previously.

RAMIRO IGLESIAS-BARTOLOME, PH.D., NCI-CCR

Research Focus: Elucidating the signaling mechanisms that control and drive tissue-specific stem-cell self-renewal and differentiation and their connections to tumor initiation and growth.

What discoveries have you made?

My group showed that in mice, the deletion of *Gnas* and PKA in the skin induces basal-cell carcinoma, the most common form of cancer in humans.(*Nat Cell Biol* **17:**793–803, 2015). In trying to determine why wounds in the mouth heal faster and with less scarring than wounds on the skin, we found that certain transcription factors were consistently upregulated in the oral wounds but not in skin wounds. The findings suggest that the molecular signature of the oral mucosa could be used to develop therapies for wound healing (*Sci Transl Med* **10:**eaap8798, 2018).

What is exciting about your work?

Its constant dynamic nature. Every day we face new problems to solve and questions to answer. I enjoy continuously learning about new subjects and new techniques, which we must do daily to be at the top of our field.

CHANDRA L. JACKSON, PH.D., NIEHS AND NIMHD

Research focus: Using observational epidemiology and mixed-methods approaches to investigate pathways by which factors in physical and social environments contribute to racial, ethnic, and socioeconomic disparities in sleep health and the subsequent risk of cardiometabolic conditions.

Have you had any significant findings?

We found, in nationally representative studies, that racial and ethnic disparities in sleep health are socially patterned: The most disadvantaged, low-opportunity groups were the most likely to be short sleepers (*Am J Epidemiol* **178:**1442–1451, 2013). We have also found that place may matter more than race, suggesting that environmental factors play a major role in health disparities and should be considered when designing interventions (*Sleep Health* **4:**420–428, 2018).

What is exciting about your work?

It can provide scientific evidence to inform various types of interventions (including policies) designed to improve population health while addressing preventable health disparities. Ultimately, this work has the potential to be translated into action.

KATHERINE MCJUNKIN, PH.D., NIDDK

Research focus: Defining the poorly understood biological functions of microRNAs (miRNAs) in the embryo and the mechanisms of miRNA turnover. We are combining classical *Caenorhabditis elegans*–forward genetics with CRISPR-Cas-9-mediated genome editing, next-generation sequencing, cell biology, and biochemical techniques. Our work has

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Stadtmans

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the potential to uncover regulatory modules that couple miRNA decay to developmental timing.

Have you made any discoveries?

I discovered that embryonically-expressed microRNAs may act as developmental timers, keeping certain genes from turning on too early during development (*Genes Dev* **31**:422–437, 2017).

What is exciting about your work?

Making new scientific discoveries is the best, but since eureka moments happen only rarely, I also enjoy mentoring trainees and seeing their progress in gaining skills and confidence.

JAGAN MUPPIDI, M.D., PH.D., NCI-CCR

Research Focus: Defining how genetic changes in B-cell lymphomas contribute to altered B-cell behavior within the microenvironment and subsequently become malignant. I am trying to define the microenvironmental factors within lymphoid tissue that promote the development of malignancy and also the mechanisms by which lymphomas exit the site where they develop and seed distant sites. I hope that my work may lead to the discovery of new therapeutic targets for B-cell lymphomas.

What discoveries have you made?

I defined a novel tumor-suppressive pathway involving signals mediated by the small G-protein G-alpha-13. My group found that this pathway inhibits the survival of germinal-center B cells and cell migration, and therefore confines germinal-center B cells to a particular location in lymphoid tissue. We proposed that the loss of this pathway in certain kinds of lymphoma might promote the spread of cancer cells to distant sites (*Nature* **516:**254–258, 2014).

What is exciting about your work?

Being able to understand how normal mechanisms of B-cell homeostasis are perturbed in lymphoma and what those perturbations can teach us about the biology of B-cell responses and the pathogenesis of lymphoma.

CARLO PIERPAOLI, M.D., PH.D., NIBIB

Research focus: My group is developing noninvasive biomarkers that can characterize brain anatomy and physiology across the lifespan. We are providing diagnostic and research tools that can use data acquired with imaging techniques, such as magnetic resonance imaging (MRI), to assess neurological disorders.

Have you made any discoveries?

My lab and I pioneered MRI modalities, such as diffusion tensor imaging (DTI), that are now widely used in the neuroscience research community. We performed the first DTI study of the human brain. We proposed biomarkers that are informative of white-matter structure and organization, reversible brain ischemia, stroke, postnatal cortical maturation, and a type of nerve degeneration called Wallerian degeneration (*Neuroimage* **13:**1174–1185, 2001). Recently, we worked on validating diffusion MRI to study brain connectivity (*PNAS* **111:**16574–16579, 2014).

What might surprise most people?

In high school I would bring with me parts of my motorcycle, such as the carburetor, that I would disassemble, under my desk, during the most boring lessons, to discover how they were made.

TIFFANY M. POWELL-WILEY M.D., M.P.H., F.A.H.A., NHLBI AND NIMHD

Research Focus: My group is designing community-based interventions that address cardiovascular health disparities in resource-limited communities in Washington, D.C. We are delineating mechanisms by which the neighborhood environment influences the development of obesity, diabetes, and other markers of cardiometabolic risk; identifying methods for incorporating mobile-health technology into interventions addressing behaviors associated with cardiometabolic health; and identifying and characterizing physiologic pathways influenced by the chronic stress that comes from living in adverse neighborhood conditions.

Have you made any discoveries?

We were one of the first research groups to show that moving to a more socioeconomically deprived neighborhood was associated with a higher risk of obesity over time (compared with staying in the same socioeconomic-level neighborhood or moving to a higher socioeconomic-level one). The environment really must be considered along with individual factors that lead to obesity. It was particularly surprising how robust the effect of neighborhood socioeconomic level as a neighborhood factor appears to be on weight change and obesity (*Am J Prev Med* **49:**72–79, 2015).

What might surprise most people?

My first career choice was to be an airline pilot, but poor vision and my tendency to get motion sickness got in the way.

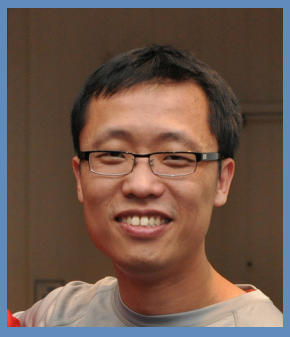
Read longer profiles online at https://irp.nih.gov/catalyst/v27i1/the-merry-band-of-stadtmans/

Stadtman Investigators

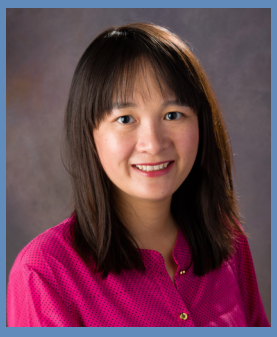
TIFFANY M. POWELL-WILEY
NHLBI AND NIMHD

JOHNNY TAM, NEI

FASIL TEKOLA-AYELE, NICHD



CHUAN WU, NCI-CCR



PING ZHANG, NCI-CCR

JOHNNY TAM, PH.D., NEI

Research Focus: My lab is using advanced optical-imaging techniques to understand the onset and progression of retinal diseases at the cellular level.

Have you made any discoveries?

My lab has pioneered new ways to image cells and structures in the eye by combining technologies such as adaptive optics with other technologies such as autofluorescence of intrinsic molecules, fluorescence microscopy of cells, and angiography of blood vessels.

What is exciting about your work?

To this day, I am still mesmerized by seeing images of cells in the living human eye. Observing life's processes at this level of detail never gets old.

FASIL TEKOLA-AYELE, M.P.H., PH.D., NICHD

Research Focus: Understanding genetic influences and their interactions with past and present-day environmental factors in fetal growth variations/differences and consequent cardiometabolic diseases and health disparities.

What discoveries have you made?

I helped identify a genetic variant in the human leukocyte antigen class II region of chromosome 6 that increases susceptibility to podoconiosis (a tropical lower-leg lymphedema resulting from long-term barefoot exposure to red-clay soil derived from volcanic rock). The study has shed the first insight into the potential role of T-cell-mediated immune response in the pathogenesis of podoconiosis. (*N Engl J Med* **366:**1200–1208, 2012).

What is exciting about your work?

Seeing how some research projects lead to discoveries!

CHUAN WU, M.D., PH.D., NCI-CCR

Research Focus: My group is trying to gain a deeper understanding of how cell-cell interactions, particularly neuron-immune interactions on the mucosal surface, orchestrate immune responses that help cells cope with environmental insults.

What discoveries have you made?

I helped identify an inducible kinase called SGK1 as essential for the development of a pathogenic T-helper 17 cell response. In addition, our recent work—identifying key factors specific for regulatory T cells' function on the mucosal surface—may lead to the development of therapeutic modulation of T-cell responses on mucosal sites in inflammatory bowel disease, asthma, and allergies.

What might surprise most people?

I was not a good student and almost dropped out of medical school. None of my college classmates and teachers back then would have believed that I would become a scientist one day.

PING ZHANG, PH.D., NCI-CCR

Research focus: My laboratory applies a combination of biochemical and structural microscopy and X-ray crystallography approaches to reveal the structural and mechanistic basis of kinases that are closely related to human cancers.

How did you get interested in science?

Fundamental questions such as "why are we here," "how do we fit into the universe," and "what is life" have always intrigued me. Science can help us turn the last question into projects leading to discoveries; and tell us why things are the way they are and how the natural world works—from atoms to galaxies.

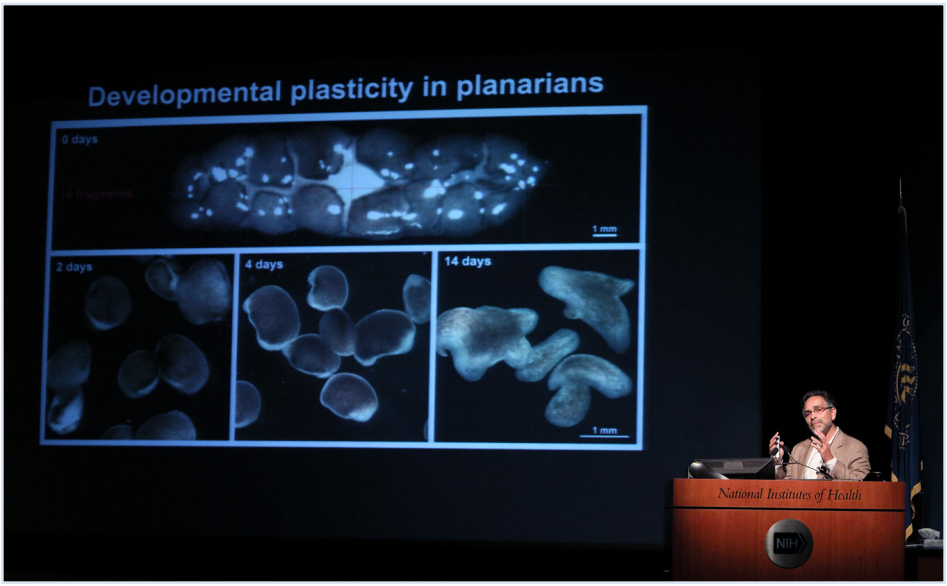
What is exciting about your work?

Helping to understand how things work with the potential for making people's lives better. ●

Finding the Elixir of Life

Alejandro Sánchez Alvarado Studies How Flatworms Regenerate

BY AMRITA MANDAL, NICHD



CHIA-CHI CHARLIE CHANG

Alejandro Sánchez Alvarado, who spoke at a recent Wednesday Afternoon Lecture Series (WALS) lecture, explores the origins of life by focusing on planarian flatworms, simple organisms that are famous for their regenerative ability.

Alejandro Sánchez Alvarado may have found the elixir of life in a simple organism that scientists have mostly ignored: the tiny flatworm planarian *Schmidtea mediterranea*. The worm has an amazing ability to regenerate itself from the smallest bits of its tissue.

"Alejandro has studied and pioneered work in planarians," said National Institute of General Medical Sciences (NIGMS) Director **John Lorsch**, who introduced him at the DeWitt Stetten Lecture on October 10, 2018. "He sequenced the worm's genome and developed a wide variety of approaches to search for the specific cells that allow regeneration to occur from even very small pieces of the animal."

Sánchez Alvarado—a Howard Hughes Medical Institute investigator at the Stowers Institute for Medical Research (Kansas City, Missouri) and recipient of many prestigious awards including being elected to the National Academy of Sciences in 2018—is fascinated by the origins of life.

The Earth is 4.5 billion years old, and the fossil record suggests that multicellular life may have originated 650–700 million years ago. But only those organisms possessing an exoskeleton endured the process of fossilization, he explained; there is no verifiable and uncontroversial fossil record for soft-bodied organisms. He pointed out that microfossils (tiny remains of bacteria, protists, fungi, animals, and plants) recently characterized in western Australia, may indicate that life was trying to establish itself 3.5–4 billion years ago. "Maybe what we've seen in the record [are] multiple attempts for complex life to emerge."

Sánchez Alvarado figured that one way to explore the origins of complex life was to focus on planarian flatworms, simple organisms that are famous for their regenerative ability. (Geneticist Thomas Hunt Morgan became fascinated with this discovery more than 100 years ago.) The most remarkable feature of the asexual form of this planarian is that you can "slice and dice them… in a number of ways and every one of those fragments will go on to generate a complete animal" within two weeks, said Sánchez Alvarado. "That's the equivalent of cutting [off] my little finger and watching [it] regenerate me."

In an attempt to find the source of the regenerative potential of these animals, Sánchez Alvarado's lab combined single-cell RNA sequencing, flow cytometry, genomics, and high-resolution imaging techniques. His lab identified and isolated a subtype of a proliferating cell called a neoblast that is capable of regenerating the whole animal (*Cell* **173:**1593–1608.e20, 2018; DOI:10.1016/j.cell.2018.05.006). These cells express a cell-surface protein-coding gene, *TSPAN1*; single-cell transplantation of a *TSPAN1-positive* cell can completely rescue a lethally irradiated host that no longer has any stem cells. Sánchez Alvarado concluded his talk with a movie that showed for the first time ever a neoblast cell dividing in a Petri dish. He hopes that because it is now possible to culture these cells in vitro, a whole new era for the regeneration field will open up.

Sánchez Alvarado believes we all have a bit of "planaria" hidden in our genomes, according to his website. "You and I are turning over a number of cells equivalent to our body weight every year."

"In addition to his many research accomplishments, Sánchez Alvarado [is] also committed to inspiring the next generation of scientists," said Lorsch. He brings the magic of science to middle-school and high-school students with hands-on classroom activities to study regeneration and stem-cell biology. ●

The annual DeWitt Stetten lecture, part of WALS, was established by NIGMS in 1982 in honor of Stetten, who was the third director of NIGMS. To watch the videocast of Sánchez Alvarado's October 10, 2018, talk, go to https://videocast.nih.gov/launch.asp?26100.

SIG: Adherence Research Network Scientific Interest Group

The Adherence Research Network SIG is a transdisciplinary consortium of NIH institutes and centers (ICs) that provide leadership, vision, and support to strengthen adherence research funded by the NIH.

Poor adherence to prescribed medications and other recommended prevention, screening, treatment, monitoring, and health-behavior regimens is common across many chronic illnesses and patient populations. The continued evidence of nonadherence in many chronic conditions, and insufficient evidence for how to improve adherence, highlights the need for transformative research. A critical public-health need is to build upon the current evidence base to fully understand the conditions that precipitate poor adherence. We also need to develop and implement next-generation interventions to improve adherence and health outcomes.

To advance the field of adherence research, the Adherence Research Network SIG works to evaluate the state of the science and disseminate scientific information and NIH research priorities through conference symposia, meetings, and white papers. The SIG, in collaboration with the Office of Behavioral and Social Science Research, also sponsors R01 and R21 research grants to improve adherence to treatment and prevention regimens.

The Adherence Research Network SIG meets once a month. Regular meetings highlight adherence research that is funded by NIH as well as the scientific priorities and related activities of participating ICs. Meetings are used to advance collaborative projects pursued by the SIG. The SIG also hosts a webinar series to showcase cutting-edge research on adherence measurement and approaches to optimize adherence to treatment and prevention regimens.

To join the LISTSERVE for this SIG, go to https://list.nih.gov/cgi-bin/wa.exe?SUBED1=adherence_network&A=1. For more information, visit https://oir.nih.gov/sigs/adherence-research-network-scientific-interest-group, or email one of the chairs, **Michael Stirratt** (stirrattm@mail.nih.gov) or **Janet de Moor** (janet.demoor@nih.gov). ●

New SIG: Circulating Nucleic Acids/Liquid Biopsy Interest Group

Interest in circulating, cell-free nucleic acids (CNAs) has increased sharply over the past decade with the advent of noninvasive liquid-biopsy techniques that span fields including prenatal testing, toxic exposures, and tumor characterization.

The creation of the CNA SIG was inspired by a workshop—hosted by the National Institute of Environmental Health Sciences in September 2018—that focused on circulating cell-free DNA. Topics discussed included identifying mechanisms of recurrence in prostate cancer; earlier screening of prenatal genomic abnormalities; understanding tissue damage associated with sickle-cell crises; monitoring stress; measuring tissue-specific exposures to environmental toxins in adults and the unborn; guiding treatment of metastatic tumors; and following patients diagnosed with systemic lupus erythematosus. Other key areas of discussion included limitations of detection, the control of error rates in analysis, and interpretation of results with appropriate biological context.

The SIG's goals are to establish standard practices for CNA studies; share and optimize methods CNA experimental design and analysis; and communicate CNA research across institutes. The CNA SIG meets by WebEx monthly for hour-long seminars.

To join the LISTSERV go to https://list.nih.gov/cgi-bin/wa.exe?A0=NIH-CNA-SIG. For more information, contact the chair, **Adam Sowalsky** (adam.sowalsky@nih.gov), or visit the CNA SIG website at https://oir.nih.gov/sigs/circulating-nucleic-acidsliquid-biopsy-interest-group. ●

L. ALEXANDER/THINKSTOCK.COM

Scientific Interest Groups

NIH Scientific Interest Groups (SIGs) are assemblies of scientists with common research interests. These groups engage with their members via a LISTSERV; sponsor symposia, poster sessions and lectures; offer mentoring and career guidance for junior scientists; help researchers share the latest techniques and information; act as informal advisors to the Deputy Director for Intramural Research (DDIR); provide advice for the annual NIH Research Festival; and serve as hosts for the Wednesday Afternoon Lecture Series. Most of these groups welcome interested non-NIH scientists. To learn more and see a list of the SIGS, go to https://oir.nih.gov/sigs. ●

Spellchecker for Genes

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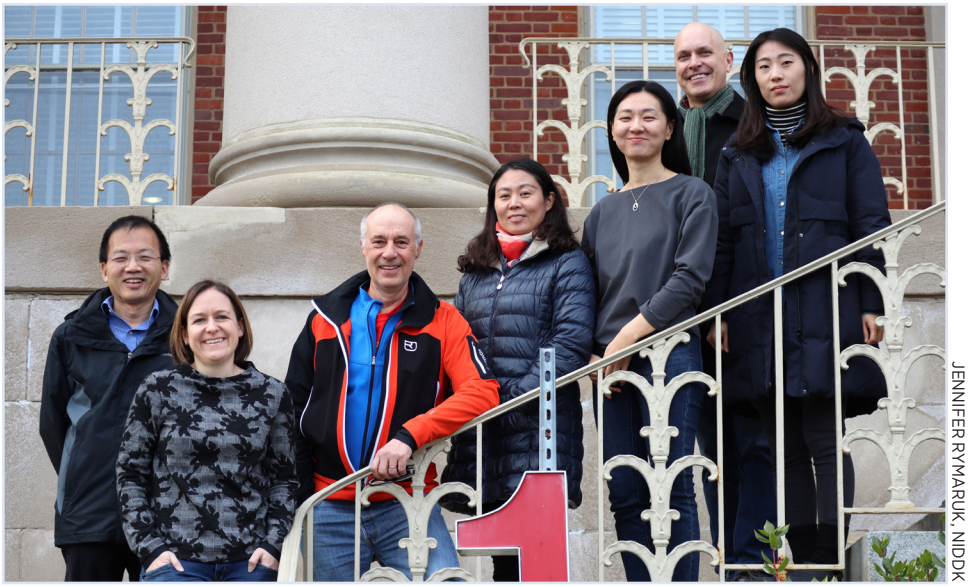
"Gene-editing technologies have taken center stage in biomedical research, with boundless impact on translational medicine," said **Lothar Hennighausen**, chief of the Laboratory of Genetics and Physiology in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

CRISPR, which stands for "Clustered, Regularly Interspaced, Short Palindromic Repeat," together with CRISPR-associated 9 (CAS9), has emerged as one of the most promising gene-editing tools to study disease. Known for its efficiency and ease of use, the CRISPR-CAS9 (hereafter CRISPR) gene-editing method works by making cuts at targeted sites on a genome, altering an organism's DNA.

Hennighausen's lab has embraced this budding technology and examined the mouse genome (*Nucleic Acids Res* **44:**1052–1063, 2016; DOI:10.1093/nar/gkv999). In collaboration with **Chengyu Liu**—the director of National Heart, Lung, and Blood Institute's Transgenic Core facility—the team went on to make key discoveries in gene editing. In 2017, they led the way in describing the extent of unwanted molecular scarring that the CRISPR technique can cause at target sites of mammalian genomes. By mutating 17 genomic sites and analyzing over 600 mice, the researchers discovered large, unintended DNA deletions and insertions associated with the CRISPR method (*Nat Commun* **8:**Article number 15464, 2017). Other scientists have since published similar findings on the random insertions and deletions that the technique can cause.

But what about the CRISPR method's effects outside the sites targeted for mutations? In October 2018, with support from the Deputy Director for Intramural Research Innovation Awards program, Hennighausen's team published a paper on the frequency of new mutations in CRISPR-method-edited mammalian genomes. Using whole-genome sequencing, which reveals an organism's complete DNA makeup, the researchers concluded that CRISPR did not cause unexpected off-target damage throughout the genome (*Nat Methods* **15:**756–758, 2018; DOI:10.1038/s41592-018-0148-2).



JENNIFER RYMARUK, NIDDK

Lothar Hennighausen's team has made key discoveries in gene editing. Some of the team members gathered recently for a group photo on the steps of Building One. From left: Chengyu Liu, Michaela Willi, Hennighausen, Xianke Zeng, Hye Kyung (HK) Lee, Harold Smith (director of the NIDDK Genomics Core), and Sojung Kim.

"This finding was important, as research must address the safety aspects of CRISPR and other new technologies," said lead author **Michaela Willi**, a postdoctoral researcher in Hennighausen's lab.

More recently, Hennighausen's team used deaminase-base editing, a newer form of gene editing, to introduce mutations in the mouse genome. Most known human diseases are caused by mutations in just one of the four letters, or bases, that make up DNA. Base editors can correct these mutations by converting one base pair into another. Unlike conventional CRISPR technology, base editing does not cut through the DNA, reducing the chance for unwanted errors.

"The exceptional precision of base editors brings fresh air into the genome-engineering toolbox and allows us to avoid problems encountered with conventional CRISPR" techniques, said Hennighausen.

With researchers from the NHLBI, the Broad Institute, and Harvard University, Hennighausen's team explored the fidelity, or accuracy and reliability, of deaminase-base editing in the mouse genome. The study, published in November 2018, found that the two classes of base editors—cytosine base editors (CBE) and adenine base editors (ABE)—had different fidelities. ABEs were more accurate and caused no unintended errors (*Nat Commun* **9:**Article number 4804, 2018; DOI:10.1038/s41467-018-07322-7).

Hennighausen's team also applied base editing to linked mutations—two or more mutations at different sites in the same chromosome. Generating linked mutations through gene editing could correct certain genetic diseases. The team's recently published research showed that CBEs can accurately introduce linked mutations into mouse embryos without causing unwanted deletions at target sites (*Sci Rep*, 2018;

DOI:10.1038/s41598-018-33533-5).

"Base editing can correct about 60 percent of known disease-causing mutations," said **Hye Kyung Lee**, another postdoctoral researcher in Hennighausen's lab and a lead author on both base-editing papers. "A thorough understanding of its fidelity is thus critical when considering this technology for human gene therapy."

Other NIDDK scientists are also applying gene editing to the study of human disease. For example, **Andy Golden** in NIDDK's Laboratory of Biochemistry and Genetics uses the CRISPR method to generate mutations in a worm species that shares many genes with humans. By studying how these mutations disrupt gene functioning, the scientists hope to identify potential targets for therapy.

In addition, NIDDK's Genetics of Development and Disease Branch, led by **Richard Proia**, together with NIDDK staff scientist **Maria Laura Allende** and **Cynthia Tifft** of the National Human Genome Research Institute's Medical Genetics Branch, used gene editing in their recent publication on Sandhoff disease, a deadly childhood genetic disorder. Using the CRISPR method, the researchers created healthy stem cells to form cerebral organoids, miniature organs that mimic the brain, and compared them with Sandhoff-affected organoids, gaining new insights into the disease's progression (*J Lipid Res* **59:**550–563, 2018; DOI:10.1194/jlr.M081323).

The Proia and Tifft labs are using the CRISPR method and base editing in several current projects, such as correcting point mutations in cells from patients with late-onset Tay-Sachs disease, a neurodegenerative disorder that affects people in their 20s and 30s.

But as much promise as these gene-editing tools hold for preventing and treating disease, there are ethical issues to be considered, too. Recently, a Chinese scientist reported that he used CRISPR editing on human embryos to disable a particular gene. Scientists worldwide expressed their outrage over the scientist's willingness to flout international ethics norms. In a November 28, 2018, statement, NIH Director **Francis S. Collins** called for the "development of binding international consensus on setting limits for this kind of research," without which, the world could see a flood of "ill-considered and unethical projects."

Applying gene-editing technologies to human health requires a full understanding of their mechanisms and potential negative consequences as well as thoughtful discussion and consideration of ethical implications. While there is still a long way to go, when used responsibly, the CRISPR method and base-editing tools could pave a key pathway to benefit public health. ●

Take the NIH Workplace Climate and Harassment Survey

As part of the NIH Anti-Harassment Program, a Workplace Climate and Harassment Survey will be administered, in early 2019, to NIH staff, trainees, and contractors at all levels of employment. The survey is voluntary, confidential, and anonymous. Results will help to assess the workplace climate at all NIH facilities and identify elements of NIH's organizational climate associated with harassment. Whether your experience has been positive or negative, we want to hear from you. For more information, visit https://diversity.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

IN 2017 (NOT INCLUDED LAST YEAR)

Novera Herbert Spector (died on November 15, 2017, at 98) worked in NINDS's Division of Fundamental Neurosciences from 1978 to 1995 and is credited with coining the word "neuroimmunomodulation."

IN 2018

Alfred W. Alberts (died on June 16, 2018, at 87) discovered a chemical compound that led to the cholesterol-lowering drug lovastatin in the late 1970s when he was working for Merck. He worked as a lab technician at NIH (1959–1966) for biochemist **P. Roy Vagelos**.

Valery Bliskovsky (died on November 13, 2018, at 55) was a staff scientist in the Genomics Core of NCI's Center for Cancer Research. He began his NIH career in 1994 as a visiting fellow in NCI and, in 2012, he helped initiate next-generation sequencing operations.

Monique Dubois-Dalcq (died on October 9, 2018, at age 79) was chief of NINDS's Laboratory of Viral and Molecular Pathogenesis. She joined NIH in 1972 as postdoctoral fellow, held many positions in NINDS, and retired in 1994.

Stanley Falkow (died on May 5, 2018, at 84), a professor emeritus at Stanford University School of Medicine (Stanford, California), is considered the father of bacterial pathogenicity. He spent summers at NIAID's Rocky Mountain Laboratories in Hamilton, Montana and received many awards including the Lasker in 2008.

Elizabeth Fee (died on October 17, 2018, at 72) was the chief of NLM's History of Medicine Division (1995–2011) and then NLM senior historian. She retired in 2018 to become an independent researcher, continuing her world-renowned scholarly research in the history of medicine and public health.

James R. Ganaway (died on October 4, 2018, at 91), who retired after 33 years of federal service in 1984, was NIH's principal expert on naturally occurring infectious diseases of laboratory animals. His NIH career began in 1961 when he became a chief in the Veterinary Resources Branch, Division of Research Services.

Cornelis P.J. (Neil) Glaudemans (died on February 1, 2018, at 85), whose work led to a single-shot shigella vaccine, retired from NIH in 1998 after having spent more than 30 years in NIDDK, where he was chief of its Laboratory of Chemistry.

Alexander Gorbach (died on May 11, 2018, at 69) was an NIBIB staff scientist and chief of the infrared imaging and thermometry unit. His innovative research included techniques for monitoring tissue perfusion, oxygen content, and temperature as well as wireless electronic sensors and applications of mobile-phone technology. He joined NIH in 1989 as a visiting research fellow and guest researcher at NIDDK.

Margaret Heckler (died on August 6, 2018, at 87) was a former Secretary of Health and Human Services (1983–1985). Before her time at HHS, she served eight terms in the U.S. House of Representatives, representing the former 10th congressional district in southeastern Massachusetts. She served as U.S. Ambassador to Ireland from 1985 to 1989.

James F. Holland (died on March 22, 2018, at 92) was a renowned cancer expert and considered a founding father of cancer chemotherapy. He helped pioneer a lifesaving drug treatment for pediatric leukemia patients. In 1972, he shared a Lasker Award for his work. He was the father of **Steven Holland**, current NIAID scientific director, and the father-in-law of **Maryland Pao**, current NIMH clinical director.

Stephen I. Katz (died on December 20, 2018, at 77), the director of NIAMS since 1995, joined NIH in 1974 as a senior investigator in NCI's Dermatology Branch initiating a highly productive research program in the immunology of skin diseases. His work both as director of NIAMS and as an eminent scientist in NCI embodied integrity, excellence, and teamwork. A committed mentor, he trained a large number of outstanding immunodermatologists who went on to lead high-quality, independent research programs in the United States, Japan, Korea, and Europe.

Theodor Kolobow (died on March 24, 2018, at 87) was a PI in NHLBI who made important contributions to the field of cardiovascular and pulmonary research including advancements in the development of artificial organs, and the pathophysiology of acute lung injury. In 1962, he joined NHLBI and later served as Section Chief of Pulmonary and Cardiac Assist Devices.

Charles E. Land (died on January 25, 2018, at 87) was an internationally acclaimed statistical expert on radiation-risk assessment. He spent 34 years at NIH and retired in August 2009 from his position as principal investigator in NCI's Radiation Epidemiology Branch. He and colleagues clarified the pattern of breast-cancer risk associated with radiation exposure. These studies served as the prototype for epidemiologic studies of other radiogenic cancers.

Roger B. Mack (died on April 13, 2018, at 76) worked in the Clinical Center for 34 years, first in the inhalation-therapy section of the anesthesiology department; later as chief of respiratory therapy; and, in the 1980s, he became an administrator. He retired in 2000.

Bonnie Mathieson (died on January 8, 2018, at 72) retired in December 2017 after a 43-year career at NIH. She started in 1975 as an NCI investigator and made seminal contributions to the field of basic T-cell immunology. She later became a program officer in the Vaccine Branch of NIAID's Division of AIDS; she most recently served as a health-scientist administrator in the NIH Office of AIDS Research.

Henry Metzger (died on November 20, 2018, at 86) was inducted into the Public Health Service in 1959, serving at the NIH. He spent almost his entire career at NIH pursuing basic research in molecular aspects of the immune system and

in administration. He served for 10 years as the first scientific director of the newly created NIAMS. After he retired and became scientist emeritus in 2002, he remained as active as an advisor to the NIH Board of Scientific Directors; a liaison to the National Academy of Sciences on "dual use research of concern"; with FAES for more than 40 years; and was a longstanding member of the *NIH Catalyst* editorial board and the Office of NIH History advisory committee.

Jun-mo Nam (died on January 4, 2018, at 85), an NCI biostatistician, retired after a 43-year career, but was a special volunteer until mid-2017. He published on efficient statistical inference, optimal study design, sample-size calculations, and statistical genetics.

Vera Marie Nikodem (died on May 17, 2018, at 78) was a molecular biologist at NIH from 1978 to 2008, and served as a section chief at NIDDK. She worked extensively on the mechanism of action of thyroid hormone as well as on various signaling pathways.

Sang-A Park (died on January 22, 2018, at 27), a native of South Korea, came to NIH in 2016 as a visiting postdoctoral fellow in NIDCR's mucosal immunology section. She studied transforming growth factor–beta signaling in breast-cancer stem cells post-chemotherapy.

Alan S. Rabson (died on July 4, 2018, at 92) came to the NIH in 1955 as a resident in pathologic anatomy in the NIH Clinical Center, and joined NCI a year later to pursue research in cancer-causing viruses. He held several leadership positions including as acting NCI director. His wife was the late **Ruth L. Kirschstein.** (See article on this page.)

Wilfred Rall (died on April 1, 2018, at 95), a pioneer in computational neuroscience, spent most of his career at the NIH until his retirement in 1994. His work in establishing the integrative functions of neuronal dendrites provided a foundation for neurobiology in general and computational neuroscience.

Geoffrey Spencer (died on October 27, 2018, at 46) was an accomplished and colorful NIH communications professional. He began his NIH career in 1999 at NHGRI, where he was the primary media-relations contact for the institute and its then-director, **Francis Collins**. Spencer was later the associate director of communications for the Division of Extramural Research; he joined NCATS communications in 2012.

Judith Vaitukaitis (died on October 19, 2018, at 78), a reproductive neuroendocrinologist, came to in NCI in 1970 as a postdoctoral researcher, studying human chorionic gonadotropin (hCG). As a senior investigator in NICHD, she and colleagues published a landmark paper in 1972 that described an assay for measuring elevated hCG levels. The assay became the basis for the first home pregnancy tests in 1978. She retired in 2005.

Martha Vaughan (died on September 10, 2018, at 92) was a scientist emerita in NHLBI's Laboratory of Metabolic Regulation and former chief of its Laboratory of Cellular Metabolism. She came to NIH in 1952 and conducted some of the earliest work on insulin signaling, which ultimately helped reveal the insulin receptor. Her husband was **Jack Orloff**, who was the scientific director in NHLBI from 1974 to 1988.

Elliot Vesell (died on July 23, 2018, at 84) served as a clinical associate at NIAMS (1963–1965) and was head of the section on pharmacogenetics at the NHLBI (1965–1968). In 1968, he became the founding chair of pharmacology at the Penn State Health Milton S. Hershey Medical Center (Hershey, Pennsylvania).

Alfred Yergey (died on May 27, 2018, at 76) was a scientist emeritus in NICHD and former head of the the Biomedical Mass Spectrometry Core. He contributed to the protein characterization in Niemann-Pick disease–type C and identified a key step in the Legionnaires' disease infection process. After working at NIH (1977–2012), he stayed active with his research. ●

Farewell to America's Cancer Doctor

Alan Rabson (1926–2018)

BY MICHELE LYONS, OD

When Katie Couric told her boss that her husband had been diagnosed with stage 4 colon cancer, the first thing he said was, "Call Al Rabson." Couric, a television journalist, related this story at the celebration of **Alan Rabson**'s life on October 30th. Rabson died at the age of 92 on July 4, 2018. Guests gathered to share laughter and some tears while remembering "America's cancer doctor," as he was called by **Norman Sharpless**, director of the National Cancer Institute (NCI). Rabson spoke to anyone who contacted him about a cancer diagnosis for a loved one or themselves. The day's speakers, including his co-workers, had all experienced the benefit of Rabson's knowledge and compassion.

Al Rabson's research as an NCI pathologist in the NIH Clinical Center focused mainly on the role of viruses in the development of cancer. From 1975 to 1995, Rabson was director of the forerunner of the NCI Division of Cancer Biology, which transitioned under him from only conducting intramural research to also managing the funding of extramural research and cancer centers at institutions across the country. In this job, Rabson made dozens of contacts with physicians and researchers. He became deputy director of NCI in 1995 and served in that capacity until his retirement in 2015. ●

To watch a videocast of the "Recognizing Dr. Al Rabson" celebration, go to https://videocast.nih.gov/launch.asp?26156. To read a 1997 oral history interview with Alan Rabson, go to https://history.nih.gov/archives/downloads/rabsontranscript.pdf.

Read more online:
Obits: https://irp.nih.gov/catalyst/v27i1/obituaries-2018
Rabson story: https://irp.nih.gov/catalyst/v27i1/farewell-to-america-s-cancer-doctor

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

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NIH IN HISTORY

Celebrating Nobel Laureate Christian B. Anfinsen

BY HUSSAIN ATHER, NICHD, AND ALAN N.SCHECHTER, NIDDK

He won a Nobel Prize in chemistry in 1972, and his work still influences research being done today. He was a beloved mentor to dozens of scientists at the NIH. And he worked tirelessly to promote human rights for scientists around the world.

Christian Anfinsen's research "continues to underlie new work in biochemistry," said **Alan Schechter** (chief of NIDDK's Molecular Medicine Branch) at a symposium he organized on October 15, 2018, to commemorate his mentor and former colleague, who died in 1995. Anfinsen is also featured in an NIH exhibit that opened earlier this year in the central first-floor corridor of Building 10. ●

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Read the whole article at https://irp.nih.gov/catalyst/v27i1/nih-in-history-christian-b-anfinsen

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