THE NIH CATALYST

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Annals of NIH History

Dr. Joseph Goldberger and Pellagra: A Fearsome Disease Tamed

BY GORDON MARGOLIN, OFFICE OF NIH HISTORY

To live in the American South in the early 1900s, you would have had to survive an uncontrolled epidemic known for its fatal consequences. The disease, pellagra, had been a worldwide scourge for about two centuries, with no known treatment. In 1909, pellagra was reported in 26 states and caused the deaths of at least 10 people per day. In 1912, South Carolina reported 30,000 cases with a mortality rate of 40%, making pellagra the second most common cause of death in that state. No one knew what caused pellagra, but the consensus was that it was an infectious disease carried by an unknown organism, possibly in spoiled corn or cornmeal.

Pellagra was known as the illness of "four Ds": diarrhea, dermatitis, dementia, and death. Other signs included sensitivity to sunlight, hair loss, swelling, beefy red tongue, trouble sleeping, weakness, dilated cardiomyopathy (enlarged, weakened heart), nerve damage, and difficulty with balance.

Congress demanded action and asked the surgeon general to investigate the disease. So, in 1914, **Joseph Goldberger**, an epidemiologist employed by the Hygienic Laboratory (forerunner of NIH), was assigned the task of

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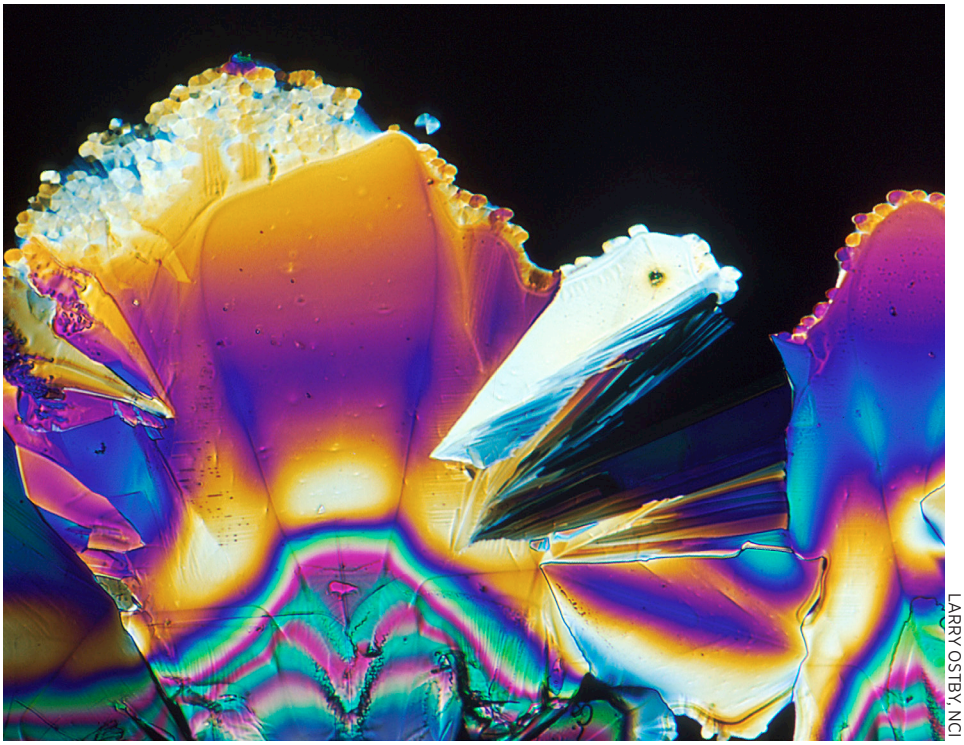
Celebrating NIH Intramural Science

Report from the Single-Day 2019 Research Festival

BY NIH CATALYST WRITERS



LARRY OSTBY, NCI

This dramatic photo of an antiviral drug was the cover image for the 2019 Research Festival brochure and webpage. Shown: Polarized crystals (photographed through a microscope) of the drug 2-3 dideoxyadenosine, also known as ddA, a drug that is closely related to AZT or azidothymidine. The antiviral effect of ddA against HIV was discovered at the National Cancer Institute.

The Research Festival "was very high energy," said **Amy Newman** who along with **John Gallin** co-chaired the 2019 Research Festival held on September 11. "It was all about the celebration." The festival, which in recent years has been a three-day event, was condensed into one day packed full of exciting talks, special exhibits, posters, the Technical Sales Association Vendor Tent Show, a performance by the NIH Director's band, and more.

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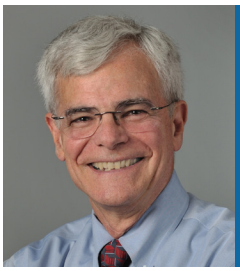


It's Time to Talk

BY MICHAEL GOTTESMAN, DDIR, AND KATHRYN PARTIN, INTRAMURAL RESEARCH INTEGRITY OFFICER

Every year, as summer turns to fall, there is excitement on campus. The Research Festival serves to reconvene the research community after a long, hot summer filled with research and vacations. As our summer trainees go back to school, a new cohort of trainees settle in. The intramural community revels in the process that brings research experience, knowledge, and passion to the next generation of researchers through the intramural training programs. Haven't we all had the experience of overhearing trainee conversations, in the cafeteria or as we walk the halls, about an experiment that finally worked? It brings to mind that our mission at NIH, besides making discoveries, is to prepare the next generation to continue to make important discoveries.

For some of us, the season ushers in excitement about another intramural tradition: our annual ethics case discussions. "Wait, what?" you might ask. No, seriously, this is our 19th year of the concerted ethics-training cases, and for some of us, discussing them is as much fun as training in research methodology. It has become very clear that successful, resilient scientists need formal training in ethical decision-making as well as in the other aspects of the responsible conduct of research (RCR).

RCR training is a formal and informal process through which we impart to our trainees how to determine what is the "right" thing to do when there is an ethical dilemma and, more broadly, a comprehensive understanding of the ethical dimensions of the performance of research. RCR goes beyond the issues of the ethical use of animals in research or of human participants in clinical research. RCR encompasses the processes we use to ensure that the data we collect are accurate and have integrity, and when published are a valid representation of the experiment performed. RCR also includes our mandate to be good citizens in an ethical research community, promoting an environment that is diverse, inclusive, fair, safe, open, and welcoming.

However, sometimes there is a gap between the research environment we believe will be conducive to innovative, productive science and the actual research environment we live in today. Many efforts over the past year at NIH have focused on assessing our research climate, and sadly, we are not where we need to be. Too many employees and trainees experience bullying, harassment, and even sexual harassment. This situation is not acceptable and damages the research enterprise.

We have committed ourselves to improving our research climate. One way we are hoping to tackle this challenge is by using this year's research ethics case studies to delve into the topic in our labs, offices, and clinics. This is a critical opportunity for PIs to take stock of their own role in fostering a welcoming environment.

Many of us heard, when we were being trained, that "if you can't stand the heat get out of the kitchen" or other disparaging comments that made training experiences more akin to fraternity hazing than a professional training experience. It didn't work then, and it doesn't work now. That type of toxicity is lethal to many female researchers and other budding scientists from groups underrepresented in our profession who then leave science prematurely, depriving the world of their brilliance, innovation, and genius.

The ethics cases this year allow a PI to carve out some time to help reset the tone and create an environment that we all can be proud of. It is just as important to help trainees develop their reasoning skills in areas of research ethics as it is to train them how to design a rigorous experiment. The cases were carefully written by PIs who serve on the intramural Committee for Scientific Conduct and Ethics. The cases this year deal with interpersonal relationships that disrupt a research lab and that can have a disproportionately negative impact on trainees.

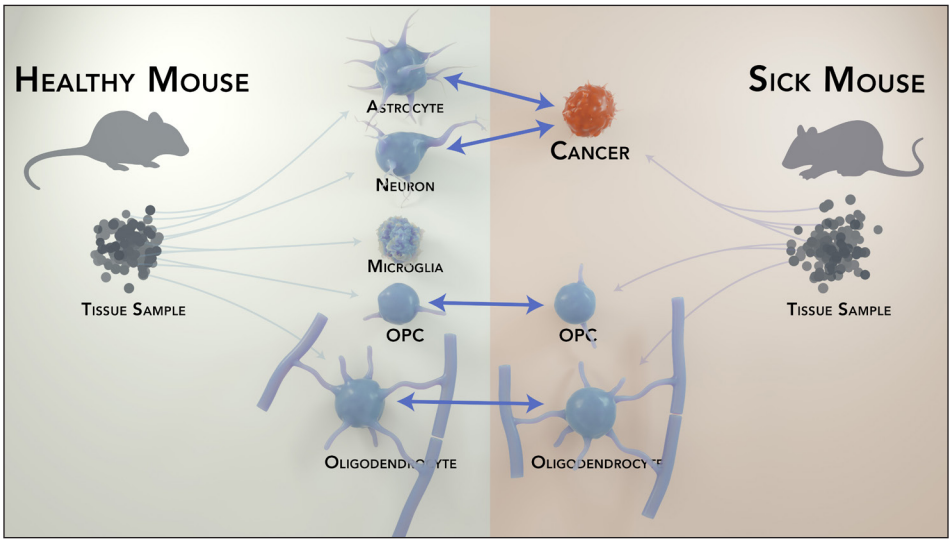
Discussion of the case scenarios will allow PIs to express their own commitment to improving the research climate for all. It is an opportunity to reinforce the intramural policies and procedures, but maybe just as importantly, to learn about the wealth of resources we can turn to when there is a relationship that threatens to disrupt work in the lab. You'll find the cases posted in the Sourcebook at https://oir.nih.gov/sourcebook/ethical-conduct/responsible-conduct-research-training/annual-review-ethics-case-studies.

We hope you take this opportunity to enjoy the excitement that the newest cohort of trainees brings to the intramural program. It is also an opportunity to stand with the NIH leadership in declaring that we are completely committed to necessary change that ensures a positive, productive environment for all researchers in our community. ●

NLM–Made Algorithm Helps NIH Researchers

ScPopCorn Gets to the Kernel of Single-Cell Experimentss

BY TERESA PRZYTYCKA, NCBI



DONALD BLISS, NLM

A new computational method, scPopcorn, allows identification of individual cells by determining which genes are being expressed and can compare them with the same cells types in other animals.

Researchers at the National Library of Medicine's National Center for Biotechnology Information have created a new algorithm called scPopCorn (single-cell subpopulations comparison) to capture the differences among populations of cells from single-cell experiments. The algorithm, developed by my team is available at GitHub (https://github.com/ncbi/scPopCorn) and is described in an article in *Cell Systems* (Y. Wang, J. Honka, and T.M. Przytycka, *Cell Syst* **8**:506–513, 2019).

The most frequently performed analyses of single-cell RNA sequencing (scRNA-seq) datasets include the identification of subpopulations of cells in scRNA-seq experiments and the comparison of such subpopulations across experiments. In multicellular organisms, different cell types execute different transcriptional programs expressing different sets of genes. Current experimental techniques can measure gene expression at single-cell resolution, making it possible to address questions that could not be answered with standard bulk experiments in which the total gene expression from a heterogeneous cell population was measured.

Single-cell transcriptomics opens a window to a better understanding of changes in the functioning of cell populations across different states and conditions including diseases. However, new computational methods are required to effectively gain important insights from these, unfortunately still quite noisy, measurements.

To address this need, my team leveraged several new algorithmic ideas and introduced the computational method scPopCorn. Unlike previous methods that treated the identification of cell types and their comparison across experiments as two separate tasks, scPopCorn identifies subpopulations of cells in individual experiments simultaneously by incorporating these two tasks into one complex optimization problem.

The optimization involves a measure of the homogeneity of a cell population (population consistency), which when combined with a technique much like Google's personalized PageRank approach, guides subpopulation detection. (PageRank is Google's algorithm that ranks web pages in search engine results.)

In addition, a cell-to-cell similarity measure is used to guide the mapping. In the scPopCorn method, the researchers substituted a cell-to-cell expression similarity graph for the network of webpages, and for each cell, estimated its preference (a "vote") for which other cells should be included in the same subpopulation.

This integrative approach helps researchers confidently define both the common and unique cell types across many experiments. Scientists can use this method to understand and map the differences among populations of cells with different disease status and developmental stages and of different sexes and species. In particular, scientists can use the algorithm to identify similar and distinct cell types present in such single-cell experiments.

This new computational method, scPopCorn, not only enabled the design of a highly accurate identification of subpopulations and a mapping approach, but also introduced mathematical concepts that can serve as stepping stones for other tools to interrogate the relationships among single cells. ●

From the Fellows Committee

Applying Your Ph.D. Skills to Careers in Science Policy

BY CRAIG MYRUM, NIA

A 2017 SURVEY OF 5,700 GRADUATE students showed that 52% of respondents were planning on a career in academia. Despite the interest, tenure-track positions are only available for approximately 12.8% of new Ph.D. graduates.

One sector in which a growing number of postdoctoral fellows are seeking, and finding, careers is science policy. For many, a career in science policy can actually be a better-suited, more fulfilling career path. Several transferrable skills acquired in previous training can also be assets in science policy including multitasking, communicating complex science to nonexpert audiences, and managing multiple complicated projects. For trainees interested in exploring this career option and becoming more competitive in a science-policy job search, the NIH intramural research program can help.

Ten years ago, then-postdoc **Kristofor Langlais** (now the Genomics and Health Program lead in the NIH Office of Science Policy) and then–graduate student **Sandra Chapman** (now a program officer at the Office of Naval Research) established the NIH Science Policy Discussion Group (SPDG). The Office of Intramural Training and Education (OITE) serves in an advisory role. Since its beginnings, SPDG has met twice a month from October through June.

For some meetings, members invite guest speakers who are experienced in science policy and can offer a glimpse into the policy world of science. Most meetings consist of small-group discussions in which members discuss topics relevant to their interests in science policy. The group is completely trainee-run and is currently co-chaired by postdoctoral fellows **Mary Weston** (National Institute of Diabetes and Digestive and Kidney Diseases) and **Lynda Truong** (National Heart, Lung, and Blood Institute).

"Beyond the exposure to science policy, SPDG also provides an intellectual outlet for scientists who are curious about the intersection of research and policy," said Weston. "We've had fantastic speakers from a range of fields, and the discussions are useful both to fellows pursuing a career in science policy and to fellows simply interested in learning more about how science can impact policy."

SPDG members also have the opportunity to hone their writing skills by contributing to a public blog, *Science Policy for All*. Writing for the blog is "a chance to explore a policy topic of their choosing," said Truong. Members also have the opportunity to peer-review these essays before they are posted.

Many former SPDG members have gone on to participate in the American Association for the Advancement of Science Science and Technology Policy Fellowship (STPF) and subsequently moved into a wide range of policy jobs in government and industry. In September 2019, a former SPDG member and postdoctoral fellow at the National Institute on Aging, **Calais S. Prince**, began an STPF appointment with the United States Department of Defense.

"The best advice that I can give is to determine whether you are interested in science for policy or policy for science. Once you know your interest, then you can participate in activities that will give you the experience you need for the next step," Prince said. "There are so many lessons I learned from my time as a postdoc. The most important was to take advantage of the resources available through your training office and OITE. I said 'Yes' to as many opportunities as I could without sacrificing lab time or time with my family."

Weston offered similar advice: "The OITE is a wonderful resource for fellows interested in pursuing science policy careers."

OITE's "annual career symposium, which is hosted every May, always features panelists of scientists working in policy," Truong added. "And [OITE] frequently host[s] events for a variety of career paths including science policy. Taking advantage of these events is a good first step to learning more about the realm of science policy and expanding your network to include other scientists interested or working in the policy realm." ●

For more information about the NIH SPDG, visit https://www.training.nih.gov/spdg. OITE emails an application announcement to fellows each August with specific deadlines. In the meantime, check out the resources on the website. For more information, contact Lynda Truong (lynda.truong@nih.gov) or Mary Weston (mary.weston@nih.gov).

Links:

- **The NIH Science Policy Discussion Group:** https://www.training.nih.gov/spdg
- **The American Association for the Advancement of Science Science and Technology Policy Fellowship:** http://www.stpf-aaas.org
- **12th Annual NIH Career Symposium Newsletter (contains summaries of panel discussions):** https://www.training.nih.gov/assets/Career_Symposium_2019_Newsletter.pdf
- **Office of Intramural Training and Education home page:** https://www.training.nih.gov

First NIBIB-Clinical Center Translational Research Fellow

Keeping a Foot in Both Clinical Radiology and Research Arenas

BY RAYMOND MACDOUGALL, NIBIB

DEBBIE ACCAME, CC

Michal Mauda-Havakuk, the first NIBIB–Clinical Center Translational Research Fellow, is an interventional radiologist who splits her time between the clinic and the lab.

A new fellowship program at NIH is making it possible for M.D.-Ph.D. radiologists to devote equal time to clinical care and research: the Clinical Translational Research Fellowship Program sponsored by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the NIH Clinical Center.

The program's first fellow is **Michal Mauda-Havakuk**, who has a Ph.D. in molecular biology and an M.D. from Tel Aviv University (Tel Aviv, Israel). She did a residency in radiology at Tel Aviv Sourasky Medical Center (Tel Aviv) and served as an attending physician before coming to NIH in 2017 to begin a radiology fellowship in interventional oncology. She transitioned to the new fellowship in summer 2018.

"Back in Israel, I looked for a unique fellowship that involved both research and clinical work," Mauda-Havakuk said, adding that there are few such opportunities around the world. She wanted to do more than practice medicine based solely on prescribed clinical guidelines—she also yearned to make research advances that would lead to better treatments for disease. "I felt that interventional oncology—both research and clinical—would be a good fit for me."

Mauda-Havakuk splits her time between the clinic and lab. "Every morning I go to the Interventional Radiology suite to observe procedures," she said. "At around 2:00 p.m., I do research-related work. I feel it's very flexible."

Her current research involves developing an animal model for the study of hepatocellular carcinoma (HCC), a form of liver cancer. Each of the animal models—such as mice, rats, rabbits, and woodchucks—used to study the development and treatment of HCC has limitations, but woodchucks seem to be showing the most promise so far. "Woodchucks develop spontaneous tumors in their livers that resemble human HCC," she explained.

She has several research papers in the works and is a co-author of a review article published in the May 2019 *Journal of Hepatology*, in which she and other NIH authors discuss animal models best suited to test combined immune-locoregional treatments for HCC; how tumor-cell death affects immune responses; the type of immune responses observed in patients treated with different types of locoregional therapies; and how to bridge the gap between interventional radiology and cancer immunology (*J Hepatol* **70:**999–1007, 2019; DOI:10.1016/j.jhep.2019.01.027).

"It is rare to be at this intersection of clinical and preclinical work, where I think M.D.-Ph.D.'s have particular insight we can provide." Mauda-Havakuk said. "We know the gaps, what we need, what patients lack, and the technologies we can promote—and then we go back directly to the lab where we try to find solutions. We know the available tools and can talk and work closely with engineers in our lab, whether software engineers, chemical engineers, or experts in other specialties."

Among the tools that facilitate her research and clinical work are several 3-D printers, advanced-imaging facilities for people and animals, and a 28-color flow-cytometry system, which can analyze physical and chemical characteristics of cells or cell particles as they flow past beams of laser light. "The human resources here are even more amazing," she added. "Everyone I've met and asked for guidance is extremely knowledgeable and friendly—and have inspired me to do anything that I would want to do."

For example, when Mauda-Havakuk learned about thermosensitive liposomes—a type of nanoparticle that can deliver chemotherapy by heating targeted tissue—she was inspired to test the approach in pigs with bladder cancer and proposed that the therapy could be used to treat rectal cancer, too.

For the future, she plans "to maintain a foot in both [clinical and research] camps, pursue new treatments, and be innovative," she said. "Everything that I do here I hope to carry on." ●

The NIBIB Clinical Translational Research Fellowship Program in the Clinical Center's Department of Radiology and Imaging Sciences is accepting applications for one- to two-year fellowship positions. Applicants should hold an M.D. or an M.D.-Ph.D. and have completed training in radiology, nuclear medicine, biomedical engineering, or a related area of imaging sciences. For more information, visit https://www.cc.nih.gov/drd/training/index.html.

Read more online at https://irp.nih.gov/catalyst/v27i6/first-nibib-clinical-center-translational-research-fellow.

Dr. Goldberger and Pellagra

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NATIONAL LIBRARY OF MEDICINE

Joseph Goldberger (1874-1929) identified a nutritional deficiency as the cause of pellagra in the early 1900s. It wasn't until 1937, however, that niacin, also called vitamin B3, was proven to be the specific missing component that caused the disease.

determining the etiology of pellagra and hopefully finding a cure.

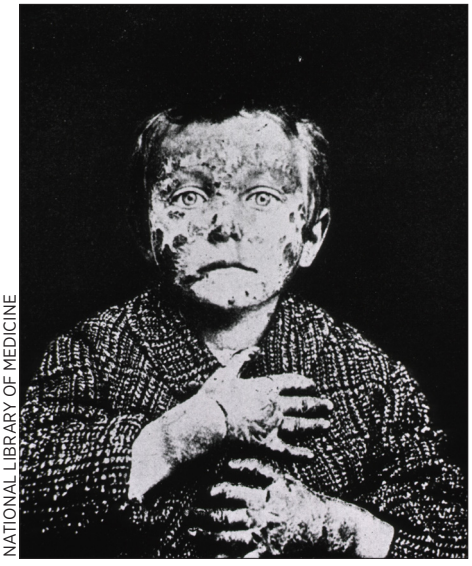
Goldberger learned that institutions such as orphanages and prisons had the highest number of pellagra cases, so he started his investigation there. He quickly challenged the infectious organism theory, noting that none of the caregivers or physicians in contact with children or guards in the prisons ever got ill with pellagra themselves. Also, pellagra was not present in orphans under the age of six or in those over the age of 12. Only those aged seven to 11 were sick.

Why was pellagra contained within a specific age group? Goldberger evaluated this strange presentation and asked whether these groups were treated differently. They were—their diets were different. In addition to the basic diet of biscuits, cornmeal mash, grits, molasses, sowbelly, and gravy, the one- through six-year-old orphans had milk, those over 12 were given meat, but the seven- to 11-year-olds weren't fed milk or meat.

With the spread of bacteriology, the theory of infectious disease was becoming accepted by physicians at this time, which perhaps explains why other physicians blamed an infectious organism. But Goldberger thought that perhaps the absence of certain nutrients was responsible for pellagra. He asked that a glass of milk be given daily to the children age seven to 11 to supplement their diets. The result: the rapid cure of existing skin lesions and a major decline in the incidence of this dreaded disease. Goldberger had determined that pellagra was caused by a deficiency of unknown nutrients, rather than by infectious organisms.

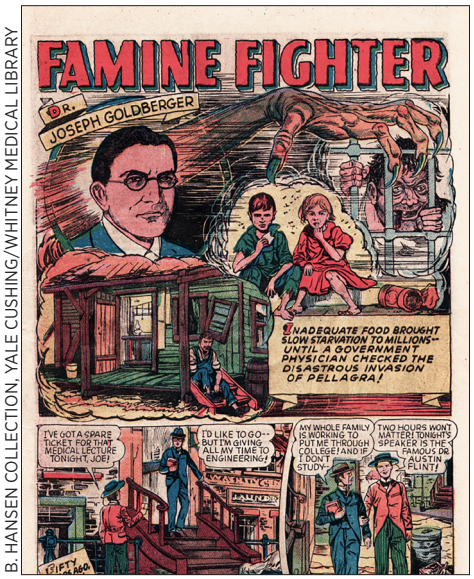
This observation was repeated in a prison where the number of cases of pellagra was high and confirmed by multiple well-designed experiments with healthy individuals, including Goldberger, who could not be "infected" from blood or excreta from ill patients. The prison diet included cornmeal, but no protein and few vegetables.

The medical establishment and, particularly, Southern political leaders rejected Goldberger's identification of nutritional deficiency as the cause of pellagra. He spent the last 15 years of his life trying to isolate the unknown nutrient but never accomplished his goal.



NATIONAL LIBRARY OF MEDICINE

Institutions such as orphanages and prisons had the highest number of pellagra cases because of the poor nutritional value of the food. Shown: a child with dermatitis, one of the symptoms of pellagra.



B. HANSEN COLLECTION, YALE CUSHING/WHITNEY MEDICAL LIBRARY

In 1943 Real Life Comics made Goldberger a subject in its "Real Life Heroes" issue, for his efforts to fight pellagra.

It was not until 1937 that niacin, also called vitamin B3, was proven to be the specific missing component that caused pellagra. Niacin is normally present in meat, meat products, and green vegetables, but not in untreated corn.

Because of Goldberger's persistence, pellagra nearly disappeared, and most Americans don't even realize that a totally preventable nutritional deficiency once caused thousands of deaths. In 1943, however, Real Life Comics made Goldberger a subject in its "Real Life Heroes" issue. You can see part of the comic strip and learn more about Goldberger at a display near the third-floor elevators in Building One. ●

To read more about Goldberger, go to https://history.nih.gov/exhibits/Goldberger/index.html.

National Academy of Medicine

Four NIHers Elected

Of the 100 new members elected to the National Academy of Medicine (NAM), four are from the NIH this year. On October 21, 2019, NAM announced the election of 90 regular members and 10 international members during its annual meeting. Election to the NAM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.

New members are elected by current members through a process that recognizes individuals who have made major contributions to the advancement of the medical sciences, health care, and public health. The newly elected members bring NAM's total membership to more than 2,200 and the number of international members to approximately 180.

Established originally as the Institute of Medicine in 1970 by the National Academy of Sciences, the NAM addresses critical issues in health, science, medicine, and related policy, and inspires positive actions across sectors. NAM works alongside the National Academy of Sciences and National Academy of Engineering to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies of Sciences, Engineering, and Medicine also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding. With their election, NAM members make a commitment to volunteer their service in National Academies activities.

To see a full list of NIHers who are members of the NAM, go to https://irp.nih.gov/about-us/honors/the-national-academy-of-medicine.

The new NIH members are:

Michael Lenardo, M.D. (Chief, Molecular Development of the Immune System Section, Laboratory of Immune System Biology, and Director, Clinical Genomics Program, National Institute of Allergy and Infectious Diseases) "for the discoveries of molecular mechanisms of immunological tolerance, seminal work on programmed cell death, defining new inherited genetic diseases of immunity, and developing targeted therapies that have saved the lives of children suffering from certain of these devastating diseases."

Luigi D. Notarangelo, M.D. (Chief, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases) "for making seminal discoveries in the characterization of the molecular and cellular bases of several forms of primary immune deficiencies, and for his leadership role in the creation of networks of centers that care for patients with these disorders, aiming to improve diagnosis and treatment."

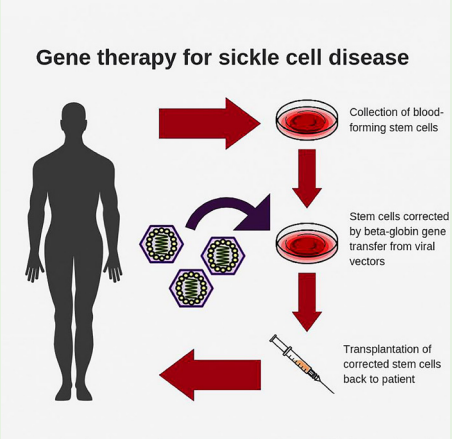
Andre Nussenzweig, Ph.D. (Chief, Laboratory of Genome Integrity, National Cancer Institute) "for making seminal discoveries that speak to how cells maintain their own genome stability, allow chromosome fragility, and license leukemogenesis at the hands of aberrant DNA repair."

Julie A. Segre, Ph.D. (Senior Investigator, Microbial Genomics Section, National Human Genome Research Institute) "for pioneering whole-genome sequencing to track the transmission of fully antibiotic resistant Gram-negative bacterium in the midst of a deadly hospital outbreak." ●

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
DIPHR: Division of Intramural Population Health Research, NICHD
FAES: Foundation for Advanced Education in the Sciences
FARE: Fellows Award for Research Excellence
FelCom: Fellows Committee
FDA: Food and Drug Administration
FNIH: Foundation for the NIH
FNL: Frederick National Laboratory
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCATS: National Center for Advancing Translational Sciences
NCBI: National Center for Biotechnology Information
NCCIH: National Center for Complementary and Integrative Health
NCI: National Cancer Institute
NEI: National Eye Institute
NHGRI: National Human Genome Research Institute
NHLBI: National Heart, Lung, and Blood Institute
NIA: National Institute on Aging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAID: National Institute of Allergy and Infectious Diseases
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB: National Institute of Biomedical Imaging and Bioengineering
NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA: National Institute on Drug Abuse
NIDCD: National Institute on Deafness and Other Communication Disorders
NIDCR: National Institute of Dental and Craniofacial Research
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
OD: Office of the Director
OITE: Office of Intramural Training and Education
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health
OTT: Office of Technology Transfer

Intramural Research Briefs



NHLBI

NHLBI: Diagram shows steps involved in conducting gene therapy for sickle-cell disease.

NHLBI: NEW VIRAL VECTOR FOR IMPROVED GENE THERAPY IN SICKLE-CELL DISEASE

Researchers at NHLBI have developed a new and improved viral vector for use in gene therapy for sickle-cell disease. In advanced lab tests using animal models, the new vector was up to 10 times as efficient at incorporating corrective genes into bone-marrow stem cells as the conventional vectors currently used, and it had a carrying capacity of up to six times as high, the researchers report. The development of the vector could make gene therapy for sickle-cell disease much more effective and pave the way for wider use of it as a curative approach for the painful, life-threatening blood disorder. Sickle-cell disease affects about 100,000 people in the United States and millions worldwide.

The new vector, for which the NIH holds the patent, still needs to undergo clinical testing in humans. Already an estimated 27 people with sickle-cell disease have undergone experimental gene therapy using conventional vectors. (NIH authors: N. Uchida, M.M. Hsieh, L. Raines, J.J. Haro-Mora, S. Demirci, A.C. Bonifacino, A.E. Krouse, M.E. Metzger, R.E. Donahue, and J.F. Tisdale, *Nat Commun* **10:**4479, 2019; DOI:10.1038/s41467-019-12456-3)

NINDS, NICHD: ALS GENE MAY BE A HITCHHIKER'S GUIDE TO THE NEURON

Affecting at least 14,000 Americans, amyotrophic lateral sclerosis (ALS) is a paralyzing and highly fatal neurodegenerative disorder for which there are no effective treatments.

In a new experiment, scientists peered inside neurons and watched the workings of the protein annexin A11, encoded by the *ANXA11* gene, which is linked to a rare form of ALS. Using advanced live-cell microscopy, they found that neurons may normally use the gene to ship internal housekeeping instructions via a newly discovered "hitchhiking" system and that disease-causing mutations may tie up deliveries at the cell's loading docks. The study, published in *Cell*, was led by researchers at NINDS, Howard Hughes Medical Institute Janelia Research Campus (Ashburn, Virginia), and the Cambridge Institute for Medical Research (Cambridge, England).The scientists also found that disease-causing mutations in *ANXA11* prevented hitchhiking, which in turn prevented RNA from being delivered to the far reaches of neurons. These results suggest that there is a link between these seemingly different processes and that understanding this type of hitchhiking in neurons may lead to new treatments for ALS. (NIH authors: M.S. Fernandopulle, L. Hao, R. Patel, M. Nelson, M.A. Gachechiladze, C.A. Stephens, L.R. Forrest, and M.E. Ward, *Cell* **179:**147–164.e20, 2019; DOI:10.1016/j.cell.2019.08.050)

NIAID: HOUSEHOLD BLEACH INACTIVATES CHRONIC WASTING DISEASE PRIONS

A five-minute soak in a 40% solution of household bleach decontaminated stainless steel wires coated with chronic wasting disease (CWD) prions, according to a new study by NIAID scientists at the Rocky Mountain Laboratories in Hamilton, Montana. The scientists used the wires to model knives and saws that hunters and meat processors use when handling deer, elk, and moose—all of which are susceptible to CWD, a brain-damaging and fatal prion disease in members of the deer family. To date, CWD has not been found in people. However, other prion diseases can affect people. Infectious prions are extremely difficult to inactivate, which led the scientists to seek a practical, low-cost CWD decontamination method. Bleach has been proven as a decontaminant against other types of prions but had never been tested against CWD. Notably, the study failed to find an effective method to decontaminate CWD-infected solid tissue. The scientists hope that public-health and wildlife agencies will consider this study when making formal recommendations for decontamination of CWD prions. (NIH authors: K. Williams, A.G. Hughson, B. Chesebro, and B. Race, *PLOS One* **14:**e0223659, 2019; DOI:10.1371/journal.pone.0223659)

NCCIH: STUDY EXPLAINS HOW BRAIN CAN TURN PAIN SIGNALS UP OR DOWN

A new NCCIH study in mice uncovered a previously unknown role that the central amygdala can play in upgrading or downgrading pain signals in the brain's circuitry. "Early research showed that the central amygdala, long known for its role in processing fear, can dial up pain signals. Yet other studies have pointed to the central amygdala's role in suppressing pain or prompting an analgesic response," said **Yarimar Carrasquillo**, senior author of the study, which appeared in *Cell Reports*. "This study unravels what seemed to be a contradiction in early research and reveals a previously hidden 'switch' in the central amygdala that can turn up or turn down pain signals." (NIH authors: T.D. Wilson, S. Valdivia, A. Khan, H.S. Ahn, A.P. Adke, S.M. Gonzalez, Y.K. Sugimura, and Y. Carrasquillo, *Cell Rep* **8:**332-346.e5, 2019; DOI:10.1016/j.celrep.2019.09.011)

Read more briefs and longer versions of these at: https://irp.nih.gov/catalyst/v27i6/research-briefs

High-Performance MRI with Lower Magnetic Field

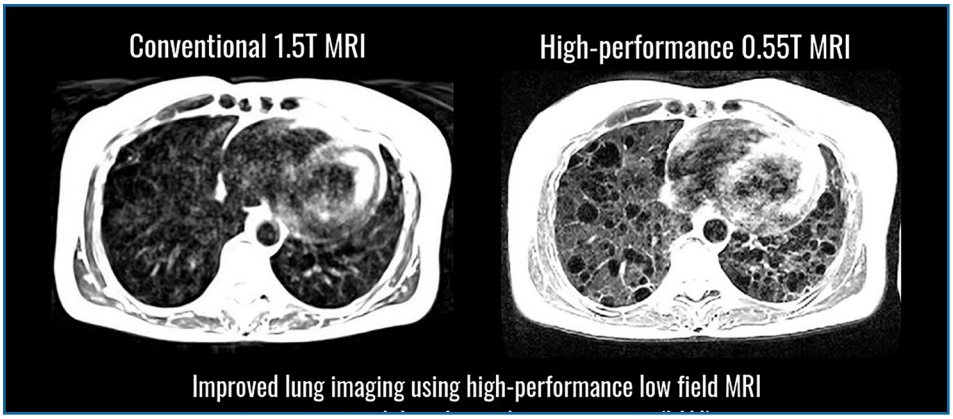
NIH Researchers' Redesigned MRI Holds Promise for Cardiac and Lung Imaging

BY NHLBI NEWS

NIH researchers, along with researchers at Siemens, have developed a high-performance, low-magnetic-field magnetic-resonance imaging (MRI) system that vastly improves the quality of images of the lungs and other internal structures of the human body. The new system is more compatible with interventional devices that could greatly enhance image-guided procedures that diagnose and treat disease, and the system makes medical imaging more affordable and accessible for patients. The low-field MRI system may also be safer for patients with pacemakers or defibrillators, quieter, and easier to maintain and install.

The NIH researchers involved in the study—which appeared on October 1, 2019, in the journal *Radiology*—were from the National Heart, Lung, and Blood Institute, the Clinical Center, and the National Institute of Neurological Disorders and Stroke. The trend in recent years has been to develop MRI systems with higher magnetic-field strengths to produce clearer images of the brain. But, researchers calculated that using those same state-of-the-art systems—at a modified strength—might offer high-quality imaging of the heart and lungs. They found that metal devices such as interventional cardiology tools that were once at risk of heating with the high-field system were now safe for real-time, image-guided procedures such as heart catherization.

The researchers also found that lung imaging improved and that oxygen itself can be observed in tissue and blood much better at a lower magnetic field, providing a unique view of the distribution of this vital molecule in the body.



A.E. CAMPBELL-WASHBURN, ET AL.

Lung cysts and surrounding tissues in a patient with lymphangioleiomyomatosis seen more clearly using high-performance low-field MRI (right) compared to standard MRI (left).

"MRI of the lung is notoriously difficult and has been off limits for years because air causes distortion in MRI images," said NHLBI Staff Scientist **Adrienne Campbell-Washburn**. "A low-field MRI system equipped with contemporary imaging technology allows us to see the lungs very clearly. Plus, we can use inhaled oxygen as a contrast agent. This lets us study the structure and the function of the lungs much better."

The researchers modified a commercial MRI system, Siemens Healthcare's MAGNETOM Aera, which has a magnetic field strength of 1.5 Tesla (T), to operate at 0.55T while keeping the modern hardware and software needed for high-quality images. Researchers first tested the new imaging procedure using objects that mimic human tissues then quickly applied the procedure to healthy volunteers and patients with disease.

When researchers compared their 0.55T images with images obtained at 1.5T, they saw lung cysts and surrounding tissues in patients with lymphangioleiomyomatosis (LAM) more clearly. LAM, which occurs only in young women, is a rare disease characterized by the proliferation of atypical smooth muscle cells throughout the lungs, pulmonary blood vessels, lymphatics, and pleurae.

The researchers also found that inhaled oxygen could increase the brightness of lung tissue more effectively with the lower magnetic-field strength than with the higher field strength. Researchers found similar advantages using low-field MRI during heart catheterization. "We can start thinking about doing more complex procedures under MRI guidance now that we can combine standard devices with good-quality cardiac imaging," said Campbell-Washburn, who noted that the results are also encouraging for imaging of the brain, spine, and abdomen. Imaging the upper airway with this system, she said, may also offer valuable clinical information for both sleep and speech disorders. ●

NIH authors: A.E. Campbell-Washburn, et. al., *Radiology* **293**:No. 2, 2019; DOI:10.1148/radiol.2019190452)

Read more online at https://irp.nih.gov/catalyst/v27i6/high-performance-mri-with-lower-magnetic-field

2019 Research Festival: Plenary Sessions

Plenary I: Celebrating NIH IRP Contributions to Curing Metabolic Diseases

BY AUTUMN HULLINGS, NCI

The labs and clinics of the NIH intramural research program have been at the forefront of the identification and treatment of metabolic diseases. In the first plenary session of the Research Festival, four presenters, including a Nobel laureate, described their groundbreaking research.

The first speaker was **Ferid Murad**, a Nobel and Lasker laureate and alumnus of the National Heart, Lung, and Blood Institute's intramural program (1967–1970). He shared the 1998 Nobel Prize in Physiology or Medicine with Robert F. Furchgott and Louis J. Ignarro and the 1996 Albert Lasker Basic Medical Research Award with Furchgott for their discovery that nitric oxide is a signaling molecule in the cardiovascular system. Their finding that nitric oxide relaxes smooth muscle by elevating intracellular granulocyte-monocyte progenitor (GMP) led to a breakthrough treatment for cardiovascular disease and other common metabolic diseases in the gastrointestinal tract and brain.

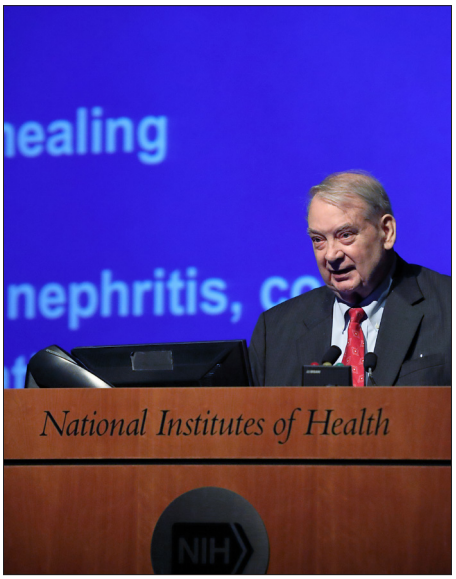
"We proposed that nitric oxide would be an intracellular messenger mediating the effects of various ligands and hormones," said Murad. But this novel concept was not well accepted in the scientific community at first. "We couldn't prove it because the concentrations required to activate [cyclic adenosine monophosphate, or cyclic GMP] were low. [T]here was no technology to measure it or its oxidation products." The use of nitrate vasodilators was not totally new; nitroglycerin had been used for almost 100 years to treat patients with myocardial infarction, but the mechanisms behind how it worked were unknown. It took Murad nearly 10 years to convince the scientific community of the immense potential of nitric oxide as a treatment for metabolic disease.

"Resilience and persistence are really important qualities in scientists who are doing truly innovative work," said Deputy Director for Intramural Research **Michael Gottesman**, who presented Murad with 2019 NIH Distinguished Alumnus Award.

Resilience and persistence are certainly qualities held by the next speaker, **Marston Linehan**, chief of the National Cancer Institute's Urologic Oncology Branch. During his 35 years of research, he showed that kidney cancer is not a single disease, but comes in 17 different types. Each has its own metabolic pathway and reacts differently to various concentrations of iron, oxygen, nutrients, and energy.

By studying the DNA of a large number of patients affected with familial forms of kidney cancer, Linehan and his colleagues discovered the genes for several different types of kidney cancer. They studied patients affected with von Hippel–Lindau (VHL) syndrome, a hereditary condition in which affected individuals are at risk for developing tumors in several organs including the kidneys. The first gene the group discovered was the *VHL* gene, which is not only responsible for VHL syndrome but for the common form of clear-cell renal-cell carcinoma as well. The *VHL* gene also turned out to be a critical link in understanding the body's oxygen-sensing mechanism. The discovery of this gene and its mechanisms of action provided the foundation for the development of targeted approaches to cancer treatment and led to the FDA approval of nine drugs to treat patients with advanced kidney cancer.

Linehan and his colleagues also identified several other kidney-cancer genes that are critical for cellular nutrient and energy sensing. The research has provided a roadmap for the development of novel therapeutic approaches for papillary, chromophobe, and other types of kidney cancer.



CHIA-CHI CHARLIE CHANG

NHLBI alum Ferid Murad, a Nobel and Lasker laureate, talked about his discovery that nitric oxide is a signaling molecule in the cardiovascular system. The discovery led to a breakthrough treatment for cardiovascular disease and other common metabolic diseases.

Next, **Josephine Egan** summarized her group's progress in identifying therapeutic targets for treating type 2 diabetes mellitus, a chronic condition in which the body does not produce enough insulin, a hormone that regulates blood sugar concentrations, and the effects of insulin are diminished.

Egan, who is the clinical director in the National Institute on Aging (NIA) and chief of NIA's Diabetes Section, came to NIH in the early 1990s to study what happens to insulin secretion during aging and what role incretins (hormones that stimulate a decrease in blood glucose concentrations) may play in aging and type 2 diabetes. She found that the incretin glucagon-like peptide–1 (GLP-1), a hormone produced in the small intestine that stimulates insulin secretion and lowers blood sugar concentrations, could be used to treat type 2 diabetes. When GLP-1 is given through a continuous pump infusion for three months, insulin secretion

is normalized.

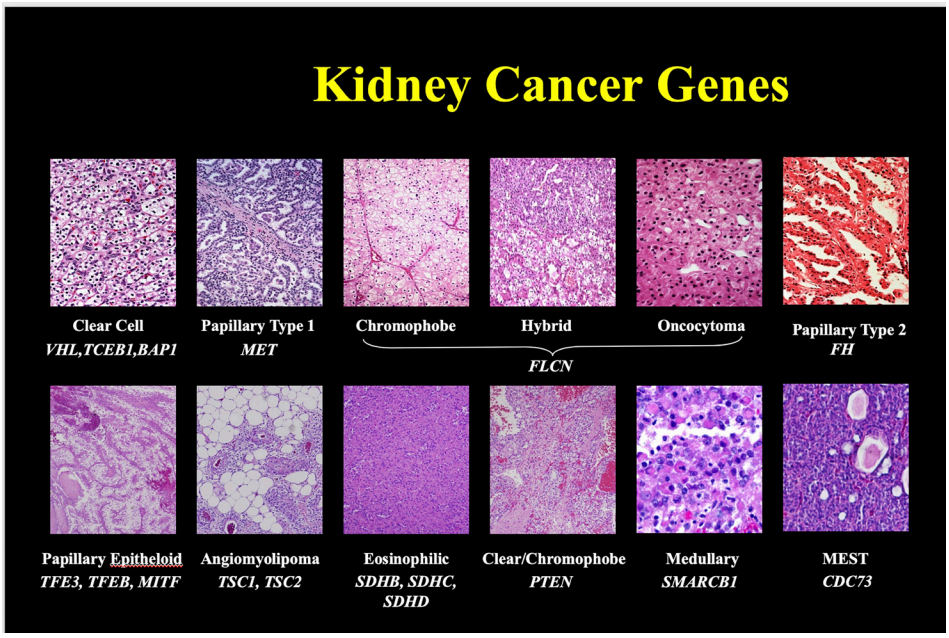
This exciting discovery seemed to offer a promising treatment for people with type 2 diabetes. But there was a problem: GLP-1 is rapidly inactivated, and that's why it needs to be given continuously. Egan's team tested exendin-4, which is produced in the saliva of the Gila monster (*Heloderma suspectum*), a large lizard native to the southwestern United States. Extendin-4 is a potent agonist of the GLP-1 receptor, and it is inactivated more slowly than GLP-1. The team found that bolus injections of exendin-4 restored insulin secretion and maintained lower blood glucose concentrations in diabetic mice. The team later found that the compound increased insulin production and protected the insulin-producing cells (located in the islets of Langerhans regions of the pancreas) against damage in humans. In 2005, exendin-4 received FDA approval as a first-in-class treatment for type 2 diabetes.

The final speaker was **Kevin Hall**, who talked about obesity as a metabolic disease and why it's so hard to maintain a healthy weight. Hall, who is the chief of the Integrative Physiology Section in the National Institute of Diabetes and Digestive and Kidney Diseases, studies nutrition, metabolism, and weight loss in humans. He set out to challenge the common belief that reducing caloric intake by 500 kilocalories per day would result in one pound of weight loss per week.

"As you lose weight, you're fighting an increasing battle with your slowing metabolism and increasing appetite as you lose weight," said Hall. "You're fighting an internal feedback-control system." In fact, for every one kilogram of body weight lost, appetite increases above baseline by about 95 kilocalories per day and your calorie expenditure decreases by about 25 kilocalories per day.

Hall suggested it may be the quality of a diet that makes a difference, not just the number of calories or amount of carbohydrates versus fat ingested. He explained that a new method of categorizing foods, known as NOVA (which is not an acronym), classifies diets based on the proportion of calories derived from ultraprocessed foods (which often contain hydrogenated fats, high-fructose corn syrup, flavoring agents, emulsifiers, and preservatives) versus unprocessed whole foods. After conducting the first clinical trial of ultraprocessed versus unprocessed diets, Hall's group found that, after two weeks, people on a highly processed diet consumed more calories and gained an average of two pounds, whereas people on the unprocessed diet lost about two pounds. Hall is designing a new study in which the ultraprocessed diets are being reformulated.

As the debate rages on about diets, it would it would seem to make sense to avoid, or at least reduce, the consumption of ready-to-eat ultraprocessed foods and instead eat more freshly prepared meals.



During his 35 years of research, Marston Linehan (NCI) showed that kidney cancer is not a single disease but comes in 17 different types. Linehan and his colleagues also discovered genes for several different types of kidney cancer.

Plenary II: Celebrating NIH Efforts to Combat Physical and Emotional Pain

BY JOANNA CROSS, NIMH

Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

The sentiments expressed in the Robert Frost poem "The Road Not Taken" could well describe the choices of the four presenters in their efforts to help patients dealing with physical and emotional pain.

Carlos Zarate (National Institute of Mental Health) decided to stop following the 60-year-old road of using traditional monoamine-based antidepressants that modulate serotonin, dopamine, and noradrenaline. Instead, he explored how ketamine, an anesthetic drug that blocks

2019 Research Festival

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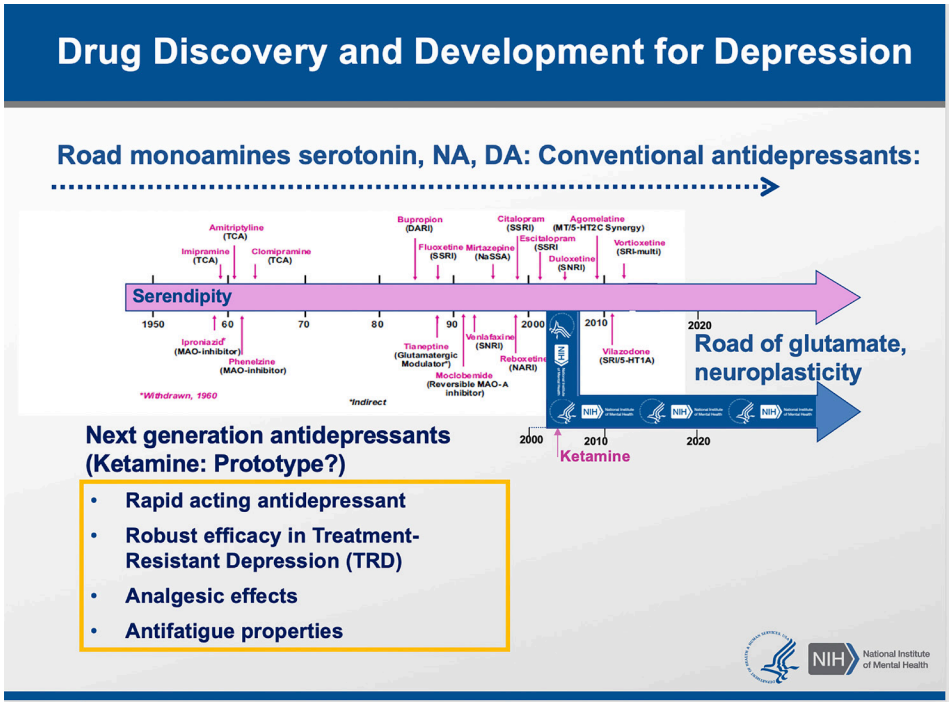


Carlos Zarate (NIMH) took a road less traveled when he veered from the traditional route of using monoamine-based antidepressants, which can take up to six weeks to treat depression. He discovered that the anesthetic drug ketamine was more effective for treatment-resistant depression and worked within hours.

N-methyl-D-aspartate receptors and neuroplasticity, can be used for treatment-resistant depression. Although the traditional drugs require about six weeks to take effect, ketamine works within a single day and sometimes in a couple of hours.

But ketamine can have unpleasant side effects (high blood pressure, nausea and vomiting, hallucinations, and dissociation) and is addictive; therefore, its use is reserved for the severely depressed. Although the physiological and dissociative side effects last for only a few hours, the reduction in depressive symptoms remain for up to a week with a single administration of ketamine.

In collaboration with scientists at the National Center for Advancing Translational Sciences, the National Institute of Aging, and the University of Maryland School of Medicine (Baltimore, Maryland), Zarate and colleagues discovered some of ketamine metabolites rather than ketamine itself might be key to its rapid antidepressant effect. When the breakdown of ketamine was slowed in a mouse model, side effects occurred, and depression symptoms did not improve. If, however, the ketamine metabolite hydroxynorketamine was injected into mice, the depression symptoms improved, and there were no dissociative side effects or evidence of addiction potential. These discoveries are leading the way in finding treatments that are based on molecular mechanisms and have the potential to redefine the field of antidepressant treatment.

Another road less traveled is one exploring the use of placebos to treat pain. **Lauren Atlas** (National Center for Complementary and Integrative Health) is exploring how placebos might be used instead of—or to supplement—opioid treatments. It's known that administering placebos can reduce activity in brain regions collectively known as the "pain matrix." Atlas, who has joint appointments with the National Institute of Mental Health and the National Institute on Drug Abuse, investigated these placebo effects further by using a balanced placebo clinical-trial design. Some patients were told that they were about to receive the drug; others were told they would not. The actual administration of the drug, however, was randomized. The patients were then exposed to pain (from heat or electric shocks in the arm, leg, or hand) while in an functional magnetic resonance imaging scanner, which measures brain activity by detecting differences in blood flow.

Atlas found that 1) there was no change in drug effects on the pain matrix whether the drug administration was hidden or open, and 2) the subjects reported that they felt less pain when they believed they were receiving the drug, regardless of whether they actually did. Interestingly, when the subjects were told they were going to receive the drug, changes were observed in the prefrontal cortex. Additional clinical studies are needed to confirm the findings.

George Koob (director of the National Institute on Alcohol Abuse and Alcoholism and a researcher in the National Institute of Drug Abuse) described an unexpected path for opioids. Although opioids can relieve pain, if people become dependent on or addicted to the drugs, they can actually become hypersensitive to pain and remain so even two years after withdrawal. Koob invented the word "hyperkatifeia" to

CHIA-CHI CHARLIE CHANG

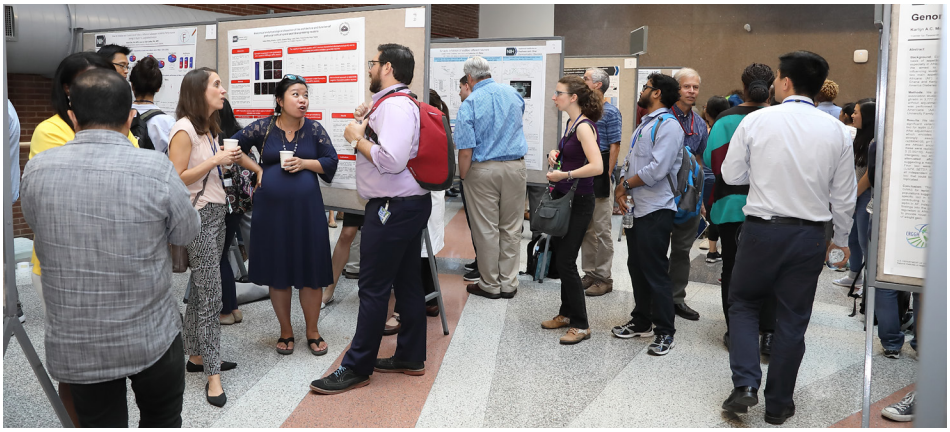
During her presentation, Lauren Atlas (NCCIH, NIMH, and NIDA) described how psychological factors influence responses to pain and opioid analgesics.

describe the increased negative emotional state experienced during withdrawal from addictive drugs. He proposed that hyperkatifeia could be caused by dysregulation of the emotional pain circuit in the brain. There are several neurotransmitters in our brain–some are designed to buffer stress, while others help in "fight or flight" scenarios. During withdrawal, the antistress neurotransmitters are dysregulated, while the stress-inducing neurotransmitters, such as corticotropin-releasing factor (CRF), are activated. This scenario causes a negative feedback cycle and enhances the likelihood of relapsing and taking the addictive drug again. Blocking CRF receptors in animal models reduced both the hypersensitivity to pain and the amount of drug consumed. By understanding the molecular circuitry behind addiction, we may be able to break the negative cycle.

Andrew Mannes (Clinical Center) explored yet another less-traveled road by considering how nonopioid therapy can be used to treat severe cancer pain. He is investigating the use of resiniferatoxin (RTX), which targets the transient receptor potential cation channel subfamily V member 1 (TRPV1) channel, also known as the capsaicin receptor, which provides a sensation of scalding heat and pain. (Capsaicin is the spicy ingredient in chili peppers.)

CHIA-CHI CHARLIE CHANG

Research Festival co-chairs and scientific directors Amy Newman (National Institute on Drug abuse), left, and John Gallin (Clinical Center) were pleased that the one-day festival was so successful. "Enthusiasm was high," said Gallin.



CHIA-CHI CHARLIE CHANG

Research festival goers engaged in lively conversations with poster presenters.

RTX is unique in that it is highly selective for the TRPV1 channel; it is selectively expressed in a subpopulation of neurons (the A-delta fibers); and it causes the channel to be open for a prolonged time. The A-delta fibers transmit pain, and the continual opening of the channel causes an influx of calcium into the cell, resulting in cell death. This action occurs very rapidly, within a few minutes of exposure. Studies in both rats and dogs that were nonresponsive to standard pain medication revealed that RTX was efficient in decreasing the amount of pain. Mannes together with **John Heiss** (National Institute of Neurological Disorders and Stroke) initiated a clinical trial with cancer patients who were suffering from severe pain. One participant in the trial, who was being treated with opioids, reported a decreased pain score from 8.3 to 3.8 after RTX treatment and needed less opioid pain medication. This reduction in pain was seen in several patients in the trial. The drug did have unpleasant side effects such as urinary retention and loss of temperature sensation. Nevertheless, this clinical trial resulted in improvement of life for many participants. Further study could provide hope for patients who do not respond to traditional pain treatments.

More photos and longer articles at:
https://irp.nih.gov/catalyst/v27i6

Plenary III: Celebrating Cutting–Edge Technologies

BY MEGAN ROEGNER, NIDDK

If you asked intramural researchers what their favorite part of working at NIH is, many would tell you it's the availability of cutting-edge technology. Four scientists shared their stories.

The first speaker, **Adam Phillippy**, who's head of the Genome Informatics Section in the National Human Genome Research Institute, talked about a nanopore sequencing technique for completing the human genome. The scientific community reveled at the 2003 announcement that the entire human genome had been sequenced, but it is really only 95% complete given the technology available at the time. Typically, to avoid being overwhelmed, DNA-sequencing machines chop up copies of the 23 pairs of chromosomes (some 3 billion base pairs) into chunks containing a few hundred base pairs. The overlaps are matched up and the chunks assembled into the correct sequence. "But like a jigsaw puzzle, the smaller the pieces, the harder the puzzle is to assemble," said Phillippy, and the more likely there will be gaps in the sequencing.

Phillippy's lab is applying a newer technique, called real-time nanopore sequencing, to solve this problem. By pulling a single strand of DNA through a protein

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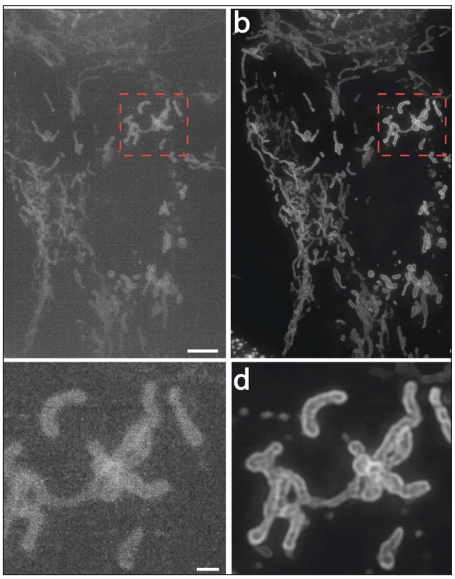


H. SHROFF, ET. AL. (UNPULBLISHED DATA

Hari Shroff (NIBIB) described how his team is applying deep-learning techniques to achieve better fluorescence microscopy. Shown: Mitochondria in live human bone osteosarcoma epithelial cells (U2OS line): (a) imaged on a high-speed structured illumination microscope at low power; (b) Artificial intelligence algorithms were used to greatly restore signal, contrast, and resolution; (c, d) show higher magnification views of red dotted rectangular regions in a and b. NOTE: Scale bars are 5 micrometers in a and b and 1 micrometer in c and d. *(CREDIT: Unpublished data, J. Chen (AIM), Y. Su (NIBIB), H. Shroff (NIBIB, AIM), and colleagues from DRVISION.)*

nanopore (modified from a transporter protein in *Escherichia coli*), the sequencer can produce DNA-sequencing reads up to one million base pairs long. He hopes to produce reads long enough to accurately cover difficult-to-sequence regions of the genome, thus filling in the gaps and truly completing the Human Genome Project. While completing the human genome offers a monumental advantage to human research worldwide, the mere availability of nanopore sequencing provides scientists a new tool to tackle difficult genomic questions across all species.

The second speaker, physician **Elizabeth Kang** (National Institute of Allergy and Infectious Disease, NIAID), shifted the focus from *reading* the genome to *modifying* it. Kang heads up the Hematotherapeutics Unit in NIAID's Laboratory of Clinical Immunology and Microbiology and frequently conducts clinical trials. Her current projects focus on chronic granulomatous disease (CGD), a primary immunodeficiency disease in which patients have defective neutrophils unable to fight off specific infections. These neutrophils also form granulomas, hence the name of the disease, and patients are also prone to autoimmune problems such as inflammatory bowel disease.

The current treatment for all types of CGD is bone-marrow or stem-cell transplantation, but it can be difficult to find a suitable donor and there's a risk of tissue rejection as well as graft-versus-host disease, in which the donor graft attacks the normal tissues of the patient. Gene therapy—using a retroviral vector to insert modified genes into a patient's cells—is being explored, but so far it offers only temporary improvement.

Kang's lab is testing a different type of retrovirus vector called a lentiviral vector, which can enter both dividing and nondividing cells (standard retroviruses can only enter dividing cells). The researchers found that using this vector combined with a white-cell-specific promoter for the NADPH oxidase enzyme resulted in an increased production of the non-mutated protein in both mouse and human cells. Their clinical trials in patients with the X-linked form of CGD are showing that the patients have high nicotinamide adenine dinucleotide phosphate oxidase production that remains relatively high even two years post-treatment. Kang is conducting other studies to determine how to further improve genetic therapies for the X-linked form as well as other types of CGD.

Artificial intelligence was the next topic. Senior Investigator **Hari Shroff** (National Institute of Biomedical Imaging and Bioengineering, NIBIB) described how his team is applying deep-learning techniques to achieve better fluorescence microscopy. Deep learning is a type of machine learning in which computer systems automatically learn from experience, without being explicitly programmed, by analyzing data to look for patterns, determining complex statistical structures that identify specific features, and finding those same features in new data. In deep learning, massive amounts of data and powerful computers train large and complicated artificial neural networks.

Shroff's lab is applying deep learning to improve and augment fluorescent-microscopy images. Normally, taking high-resolution images requires applying a strong laser to a sample; the laser quickly bleaches the sample of its fluorescence. The deep-learning neural network, however, can read lower-level fluorescence taken over a longer time and then produce a high-resolution image by predicting it from the data. Shroff has been using this technology in conjunction with the Trans-NIH Advanced Imaging and Microscopy (AIM) facility,

CHIA-CHI CHARLIE CHANG

The day's festivities ended with a performance by the NIH Director's band, "The Affordable Rock 'n' Roll Act" or "ARRA."

with the eventual goal of disseminating the technology so that NIH researchers can use the microscopes and computer algorithms to make high-resolution and long-term fluorescent images. A computer that thinks more like a human can be an unsettling notion, but there is no denying its usefulness, and Shroff's team has shown its reliability in predicting high-resolution images at very low illumination.

The final speaker, **Hannah Valantine**, is a senior investigator (National Heart, Lung, and Blood Institute) as well as NIH's Chief Officer for Scientific Workforce Diversity. Her research is on finding better ways to predict and diagnose heart-transplant rejection, a common problem in people who've received the organ. Current methods to detect rejection involve painful and invasive biopsies of the donated heart tissue.

Valantine has developed a noninvasive liquid-biopsy method—a simple blood test for cell-free DNA (cfDNA)—as an alternative to the physical biopsy for predicting when a transplanted heart is in danger of being rejected. The liquid-biopsy technique was first developed at Stanford University (Stanford, California) and involved detecting and sequencing fetal-cell-free DNA from a mother's blood for prenatal diagnosis of genetic abnormalities such as Down syndrome. Valantine developed a similar technique to predict organ rejection in heart-transplant patients and found that rapidly increasing concentrations of donor cfDNA predicted rejection.

She also set up the Genomic Research Alliance for Transplantation (GRAfT) among the NIH and multiple hospitals and donation centers across the region. GRAfT studies have shown that these cell-free DNA tests are reliable and reproducible and act as good predictors of long-term outcomes. Valantine hopes the technology will prove a noninvasive and valuable tool for detecting rejection and allowing early treatment for heart-transplant patients. ●

Lightning-Fast Journey into the IRP World

BY EIMEAR HOLTON, NIAID

Punctuated by the silvery chimes of the glockenspiel to keep time, the NIH Research Festival's first ever Data Blitz and Lightning Round launched the audience on a journey into the world of intramural research. In rapid succession, 21 postdoctoral fellows—all winners of the Fellows Award for Research Excellence—took the stage and presented three-minute summaries of their work. The glockenspiel would chime pleasantly to warn presenters when they only had 15 seconds left, but would ring noisily when time was up.

Fellows enthusiastically showcased an exiting repertoire of science and described projects ranging from the development of a wearable robotic knee exoskeleton to artificial-intelligence-powered microscopy for diagnostic screening. They also invited audience members to visit their posters afterwards. Following are highlights of some of the presentations.

Fei Zhao (National Institute of Environmental Health Sciences, NIEHS) startled the audience into laughter when he called his research "sexy." But he went on to give a serious talk entitled "The Remains of the Male: Unexpected Contribution of the Male Tract Mesenchyme to the Female Reproductive Tract," in which he emphasized the critical role of the mesenchyme in sexual-organ differentiation, development, and function. Zhao's presentation was unique because he presented very little data. When asked about this style, he admitted to approaching his mentor, **Humphrey Yao** (NIEHS), for advice and learned that the purpose of the talk was not to wallow in one's data, but to capture the audience's interest and ask questions to make them think, all in the hope of getting a big crowd to your poster.

Karlijn Meeks (National Human Genome Research Institute) summarized her research on a "Genome-wide Association Study [GWAS] on Hormones Involved in Appetite Regulation in Africans." She talked about the importance of studying appetite-regulating hormones leptin and ghrelin to understand rising rates of obesity worldwide. Little research has been done on the genomics of these hormones, and none among continental Africans.

She found novel loci associated with both appetite hormones in African populations. "We found associations of variants that are only found among people with African ancestry, which really highlights the need to include diverse populations in genomics research," Meeks said. "We couldn't have found these results if we were only studying people of European ancestry."

"What happens in the first 48 hours of a viral infection?" is a question that **Emily Speranza** (National Institute of Allergy and Infectious Diseases) hopes to answer one day. In her lightning talk "Single-cell Analysis to Unpack the Complex Immune Responses to Early RNA Virus Infections," she explained how she is analyzing the functional and spatial characteristics of viral infection in vivo and is identifying and differentiating infected, fighting, and immune-response-triggering cells.,

Speranza later admitted that she found it daunting, but beneficial, to condense complex research into such a short talk. It "forced me to think about what are the big goals we are trying to achieve, and what are the general methods we are using." Her strategy for preparing for the Data Blitz included going online to observe the style of three-minute thesis-competition winners. She suggested to anyone contemplating giving a three-minute talk to "Focus on major conclusions, condense background information as much as possible, and allow just one slide for data."

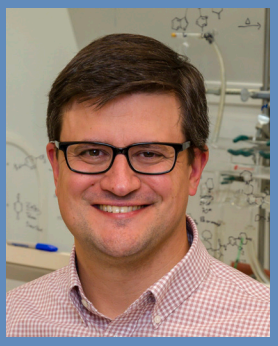
And don't let the glockenspiel unnerve you. ●

Recently Tenured

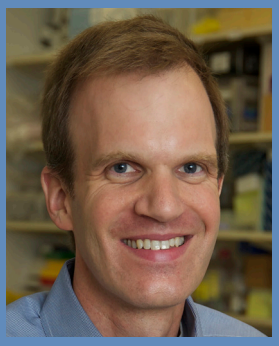
SRIDHAR HANNENHALLI, NCI-CCR

PATRICIA JENSEN, NIEHS

LISA MIRABELLO, NCI-DCEG



JOHN "JAY" SCHNEEKLOTH JR., NCI-CCR



DOUGLAS R. STEWART, NCI-DCEG

SRIDHAR HANNENHALLI, PH.D., NCI-CCR

Senior Investigator, Cancer Data Science Laboratory, Center for Cancer Research, National Cancer Institute

Education: Indian Institute of Technology, Varanasi, India (B.Tech.); University of Central Florida, Orlando, Florida (M.S.); Pennsylvania State University, University Park, Pennsylvania (Ph.D.)

Training: Postdoctoral fellow, Department of Mathematics, University of Southern California (Los Angeles)

Before coming to NIH: Professor, Department of Cell and Molecular Biology, University of Maryland at College Park (College Park, Maryland) and professor, University of Maryland Institute for Advanced Computer Studies (College Park)

Came to NIH: In 2019

Outside interests: Argentine tango; running; playing tennis

Website: https://irp.nih.gov/pi/sridhar-hannenhalli

Research interests: Within the broad field of computational biology, we focus on eukaryotic gene regulation and evolution as it pertains to development and disease including cancer. We develop computational approaches that harness "big" biological data (genomes, epigenomes, transcriptomes, ChIP-seq, chromatin structure, etc.) to answer specific questions pertaining to these domains; a few examples are highlighted below.

We have developed statistical models, which incorporate established transcriptional mechanisms, to link genotype to gene expression as well as to detect single nucleotide polymorphism (SNP)-environment interactions. Such models are crucial in understanding the mechanisms underlying the genotype-phenotype links discovered by large-scale association studies. We are interested in extending these models to identify driver-regulatory mutations in cancer, and to investigate SNP-environment interactions in cancer.

In a collaboration exploring the role of 3-D chromatin structure in transcriptional regulatory mechanisms, we showed that estrogen receptors are pre-bound, in the absence of estrogen signaling, at specific loci in the genome. In the presence of signaling, however, these pre-bound sites mediate additional receptor binding in their relative vicinity. We will continue to investigate the role of chromatin structure in transcriptional regulation.

We have a long-standing interest in understanding context-specific changes in gene function. We developed network-based methods to characterize context-specific function of genes, as well as a data-driven method to identify clinically relevant gene interactions in cancer. Our findings help explain tissue-specific phenotypic manifestation of mutations.

We are also developing methodologies to exploit single-cell omics data to probe a variety of questions in development and in cancer. In a recent collaborative work, we compared the composition of tumor-infiltrating CD4 lymphocyte populations at the tumor and at draining lymph nodes. We discovered a type I interferon-driven signature in type 1–T-cell–like cells, also found in human liver cancer and melanoma, and negatively associated with response to checkpoint therapy.

PATRICIA JENSEN, PH.D., NIEHS

Senior Investigator, Neurobiology Laboratory, and Head, Developmental Neurobiology Group, National Institute of Environmental Health Sciences

Education: Florida Atlantic University, Boca Raton, Florida (B.S. in microbiology); University of Tennessee Health Science Center, Memphis, Tennessee (Ph.D. in anatomy and neurobiology)

Training: Postdoctoral fellow in developmental neurobiology, St. Jude

Children's Research Hospital (Memphis, Tennessee); postdoctoral fellow in genetics, Harvard Medical School (Boston)
Came to NIH: In 2009
Outside interests: Reading; drawing; gardening
Website: https://irp.nih.gov/pi/patricia-jensen

Research interests: My group studies how genetic and environmental challenges during development alter the functions of specific types of neurons later in life. My particular interest is in noradrenergic neurons, which release the flight-or-fight chemical called norepinephrine. Noradrenergic neurons modulate functions as diverse as attention, emotion, appetite, memory, and response to stress. Consistent with this functional diversity, norepinephrine signaling is disrupted in a spectrum of neurodegenerative and neurodevelopmental disorders and after exposure to a number of environmental toxicants. Interestingly, it has been observed that subsets of noradrenergic neurons are differentially susceptible to disease and certain environmental exposures. Given these observations, we suspect that the key to understanding noradrenergic-system dysfunction will not be found by focusing on the system as a whole. Rather, this phenotypic complexity will only be understood by uncovering the developmental and genetic factors that define unique functional subtypes of noradrenergic neurons.

Using genetically engineered mice that we designed, we defined subpopulations of noradrenergic neurons based on differences in embryonic gene expression. This novel molecular framework allowed us to determine where these populations are located in the adult mouse brain, what connections they make with other parts of the nervous system, and their role in stress-related behaviors. We found that some of the neurons behave the opposite of most noradrenergic neurons known to promote the stress response. In the mice, we identified a small subset of noradrenergic neurons that, when activated, decrease anxiety-like behavior and promote an active coping strategy in response to acute stressors.

My group is committed to using cutting-edge strategies to establish a body of knowledge that is already transforming our understanding of the noradrenergic system. Building on our molecular framework of the central noradrenergic system, we can now physically isolate unique subpopulations of noradrenergic neurons for molecular profiling or functionally manipulate them with unprecedented precision. Phenotypes resulting from these manipulations promise further insights into the biological roles of noradrenergic neurons and their differential response to disease and environmental insult.

LISA MIRABELLO, PH.D., NCI-DCEG

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

Education: Cornell University, Ithaca, New York (B.S. in pre-medicine and animal science); New York Medical College, Valhalla, New York (M.S. in experimental pathology); School of Public Health, State University of New York at Albany, New York (Ph.D. in biomedical sciences, molecular population genetics and infectious disease)
Training: Postdoctoral fellow, Clinical Genetics Branch, NCI-DCEG
Came to NIH: In 2007 for training; in 2013 became an Earl Stadtman tenure-track investigator, Genetic Epidemiology Branch, NCI-DCEG
Outside interests: Walking, hiking, and biking outdoors; playing with her son; traveling; gardening; listening to music; raising chickens and saltwater fish and coral
Website: https://irp.nih.gov/pi/lisa-mirabello

Research interests: My research program focuses on genetic susceptibility to pediatric cancer and the genomics of human papillomavirus (HPV) carcinogenicity.

In my pediatric cancer work, I primarily study osteosarcoma, which, although rare, is the most common type of bone cancer in children and teens. I am using epidemiologic studies to examine incidence patterns and identify risk groups for this cancer. I use whole-genome approaches, including large genome-wide association studies (GWAS) and whole-exome sequencing, to comprehensively explore the underlying genetic architecture of osteosarcoma. I have identified both common and rare inherited genetic loci associated with risk and clinical outcomes of osteosarcoma patients. My colleagues and I have completed the first international, multi-institution GWASes of osteosarcoma risk, osteosarcoma metastasis, and survival after osteosarcoma diagnosis. I am continuing to conduct large genomic epidemiologic studies of osteosarcoma and other pediatric cancers, in hopes of finding novel germ-line genetic markers of disease risk and outcomes.

In my HPV work, my group is studying the viral genetic basis of HPV carcinogenicity. HPV infections cause more than half a million cervical cancers a year. We have developed high-throughput HPV whole-genome sequencing methods that now enable large-scale HPV genomic studies. My HPV genomics project has established that viral genetics play a pivotal role in HPV carcinogenesis and provide

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insight into why some infections progress to precancer and cancer and others do not. A primary focus is to evaluate why HPV type 16 (HPV16) is more carcinogenic than closely related types. By studying many thousands of carefully annotated HPV16 genomes from women with benign infections and those with precancer or cancer, I have identified important risk differences related to lineages and specific genetic variants of HPV16. My large viral genomic epidemiology studies are leading to new insights into the uniquely high carcinogenicity of HPV16, important regional carcinogenicity of HPV35, and the interplay of host-viral genetics, and the studies are uncovering important observations concerning HPV natural history.

JOHN "JAY" SCHNEEKLOTH JR., PH.D., NCI-CCR

Senior Investigator, Chemical Biology Laboratory, Center for Cancer Research, National Cancer Institute

Education: Dartmouth College, Hanover, New Hampshire (B.A. in chemistry); Yale University, New Haven, Connecticut (Ph.D. in chemistry)

Training: Postdoctoral fellow, Princeton University (Princeton, New Jersey)

Before coming to NIH: Medicinal chemist, Small Molecule Discovery Center, Yale University

Came to NIH: In 2011

Outside interests: Spending time with his wife and two sons; woodworking; playing baseball; listening to and playing music

Website: https://irp.nih.gov/pi/john-schneekloth

Research interests: My laboratory aims to develop small molecules that target RNA. Recent research has shown that some 85% of the three-billion base pairs in the human genome are transcribed into RNA, but just 3% of these transcripts code for protein sequences. Given that about 15% of proteins are druggable, targeting RNA represents a new opportunity to control noncoding functions of RNA molecules involved in disease or to block the expression of pathogenic proteins that, so far, cannot be targeted pharmacologically.

Our lab has developed a small-molecule microarray high-throughput screening platform that we use to rapidly identify and profile the binding of druglike small molecules to structured RNAs. With the aid of this technology, we are able to gain important insights into which RNA structures are targetable with drugs and the types of chemical compounds that bind to these targets. We have focused our work on targeting nucleic acids that regulate the expression of undruggable oncogenes such as *c-MYC* and K-*RAS*. In addition, we have investigated targeting functional RNAs from pathogenic organisms such as the human immunodeficiency virus. Our research allows us to develop a fundamentally new approach to developing therapeutics by targeting nucleic acids with drug molecules.

DOUGLAS R. STEWART, M.D., NCI-DCEG

Senior Investigator, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute; Attending Physician and Adjunct Investigator, National Human Genome Research Institute

Education: Vassar College, Poughkeepsie, New York (B.A. in chemistry); University of Pennsylvania School of Medicine, Philadelphia (M.D.)

Training: Internship and residency, Department of Internal Medicine, Hospital of the University of Pennsylvania (Philadelphia); clinical fellow, Division of Human Genetics and Molecular Biology, and Division of Biochemical Genetics, The Children's Hospital of Philadelphia (Philadelphia); Research Fellow, Department of Genetics, University of Pennsylvania School of Medicine

Came to NIH: In 2004 as part of NHGRI's Physician Scientist Development Program; in 2010, became an Earl Stadtman tenure-track investigator in NCI-DCEG

Outside interests: Reading; traveling; spending time with his family

Website: https://irp.nih.gov/pi/douglas-stewart

Research interests: As a clinical geneticist, I investigate how genetic variation increases the risk of cancer. To do this, I study genetic data as well as tumors and other medical problems from cancer-prone families. Specifically, I have clinically and genetically studied multiple rare disorders, including neurofibromatosis type 1 (NF1), *DICER1* syndrome, and the RASopathies.

NF1 is characterized by the presence of light-brown patches on the skin; benign growths on the iris; and skeletal abnormalities including scoliosis and bowing of the legs, large head size, learning disabilities, and an increased risk of developing certain benign and malignant tumors. *DICER1* syndrome is a genetic disorder associated with an increased risk for developing benign or malignant tumors in the lungs, kidneys, ovaries, thyroid, and other locations in the body. RASopathies are caused by mutations in genes of the oncogene protein P21 (RAS)–mitogen-activated protein kinases (MAPK) pathway and are characterized by distinct facial features, developmental delays, cardiac

defects, growth delays, neurologic issues, and gastrointestinal difficulties. There is an increased risk for cancer in people with some RASopathies; I am leading a new study focusing on that risk that will be launched soon at the NIH Clinical Center. Ultimately, I seek to develop gene-based approaches to help identify people for screening before they develop cancer.

In my work at NIH, I have evaluated many families at the NIH Clinical Center. Using the data from those visits, I have described novel medical problems of NF1 and the *DICER1* syndrome, developed cancer risk estimates and written clinical-care guidelines. This work helps to identify and manage people with NF1 and the *DICER1* syndrome. In addition, I have worked on finding genes that increase risk for a variety of pediatric cancers, in particular, neuroblastoma and rhabdomyosarcoma.

Looking ahead, there are many opportunities in clinical genetics, especially as the cost of sequencing continues to drop. An important question is how to best work genetic data into everyday care. I am leading a new NCI-funded effort to study exome data (sequencing information on all of the genes) from tens of thousands of people.

We focus on the people with the most worrisome genetic variations in cancer-associated genes and then query their linked medical records. I hope that this new, "genome-first" approach will guide us to people at risk, rather than waiting for a problem (such as cancer) to appear.

ONLINE FEATURE: "NCCIH Researchers Highlighted in Anniversary Symposium": https://irp.nih.gov/catalyst/v27i6/nccih-researchers-highlighted-in-anniversary-symposium

Otolaryngology Surgeon-Scientist Program

From Operating Room to Bench to Bedside

BY LISA YUAN, NIDDK

On any given day, surgeon-scientists might perform surgery, see patients in clinic, or conduct biomedical research. They bring clinical perspectives to the laboratory as they seek to better understand the diseases they treat, and in turn, their lab discoveries help guide and improve patient care. However, the challenges of pursuing a dual career in research and medicine have contributed to a decline in the number of physician-scientists entering the biomedical workforce.

To help address this concern, the National Institute on Deafness and Other Communication Disorders (NIDCD) developed the Otolaryngology Surgeon-Scientist Program (OSSP), a career-development program for junior faculty.

Five surgeons are in the program: **Michael Hoa**, **Clint Allen**, **Wade Chien**, **Nicole Schmitt**, and **Nyall London Jr.**

Michael Hoa, an otolaryngology surgeon-scientist who joined the program in 2013, treats patients with hearing loss and neurotologic diseases at MedStar Georgetown University Hospital (Washington, D.C.), where he co-directs the hospital's cochlear-implant program. When he is not in the clinic or operating room, he spends time in his NIDCD lab, running the Auditory Development and Restoration Program. The lab studies the development and function of adult inner-ear cell types and the mechanisms behind their degeneration.

He recently performed cochlear-implant surgery on a young Clinical Center patient with Niemann-Pick type C1 disease, a rare neurodegenerative disorder caused by the body's inability to metabolize cholesterol and other cellular waste products. The surgery was the first pediatric, bilateral cochlear implantation ever performed at the NIH Clinical Center.

The four others are at Johns Hopkins–Suburban Hospital (Bethesda, Maryland). Like Hoa, they split their time among seeing patients, performing surgery, and overseeing NIDCD intramural research programs.

Allen's Translational Tumor Immunology Program explores how the immune system fights nonmalignant laryngeal papillomatosis and malignant tumors, particularly head-and-neck squamous-cell carcinoma, the most common form of head-and-neck cancer. The lab aims to identify treatments that both kill tumor cells and enhance the body's natural antitumor immune response.

The Integrative Therapeutics Program, run by Schmitt, also focuses on treatments for head-and-neck squamous-cell carcinoma, mainly cisplatin, the most commonly used systemic drug for the disease. Because cisplatin has significant adverse effects, including hearing loss, Schmitt's team is researching alternative agents and strategies to limit the drug's toxicity while optimizing its therapeutic effects.

Chien's Inner Ear Gene Therapy Program investigates gene therapy as a treatment option for hereditary hearing loss and dizziness. The lab was among the first to study whether genome editing could be used to restore hearing and balance in animal models.

London's Sinonasal and Skull Base Tumor Program is focused on how and why malignant tumors develop in the nasal cavity, sinuses, and the base of the skull. The lab seeks to translate these results into better therapies, particularly in a type of malignancy called olfactory neuroblastoma, which researchers think arises from the olfactory epithelium, the area of the nose important for the sense of smell.

The OSSP has been so successful that Johns Hopkins University has reported that it seeks to develop similar collaborations with other institutes across NIH. ●

To find out more about the program and how to apply, go to https://www.nidcd.nih.gov/training/otolaryngology-surgeon-scientist. Read the full article at https://irp.nih.gov/catalyst/v27i6/otolaryngology-surgeon-scientist-program.

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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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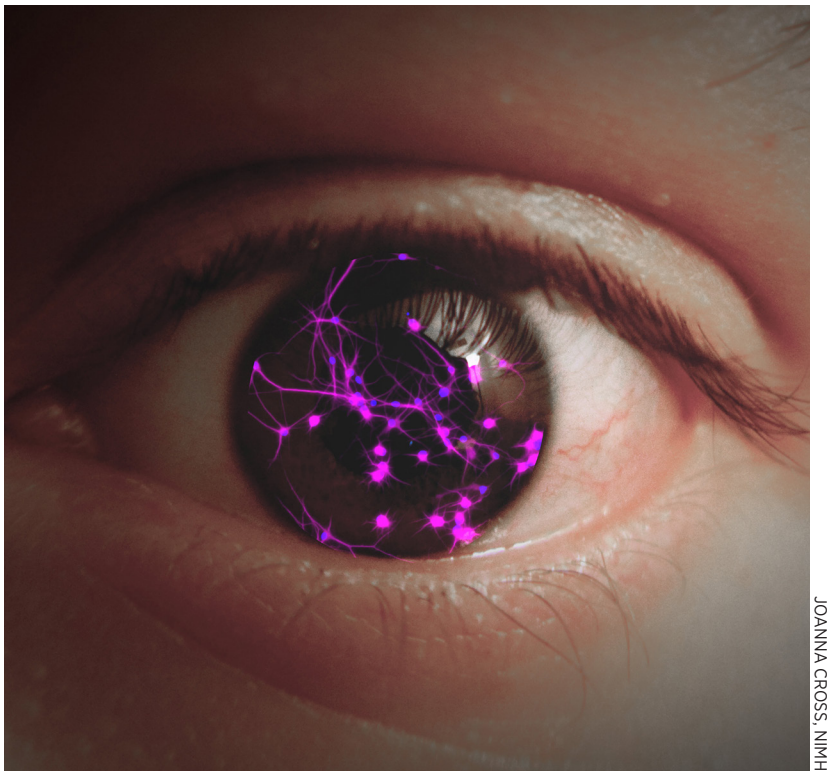
PHOTOGRAPHIC MOMENT

"Eye of the Beholder"

"Our neurons are responsible for how we view the world, and I was intrigued by the possibility of portraying this concept," said **Joanna Cross**, a postdoctoral fellow in the National Institute of Mental Health. "I superimposed an image of cultured neurons onto a macro photograph of an eye to give the feeling that we are looking past the superficial outside and revealing what is truly held within the eye of the beholder."



JOANNA CROSS, NIMH

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