

## Opioid Addiction and Chronic Pain

NIH Pain Consortium Symposium Highlights

BY EMILY PETRUS, NINDS, AND LAURA S. CARTER

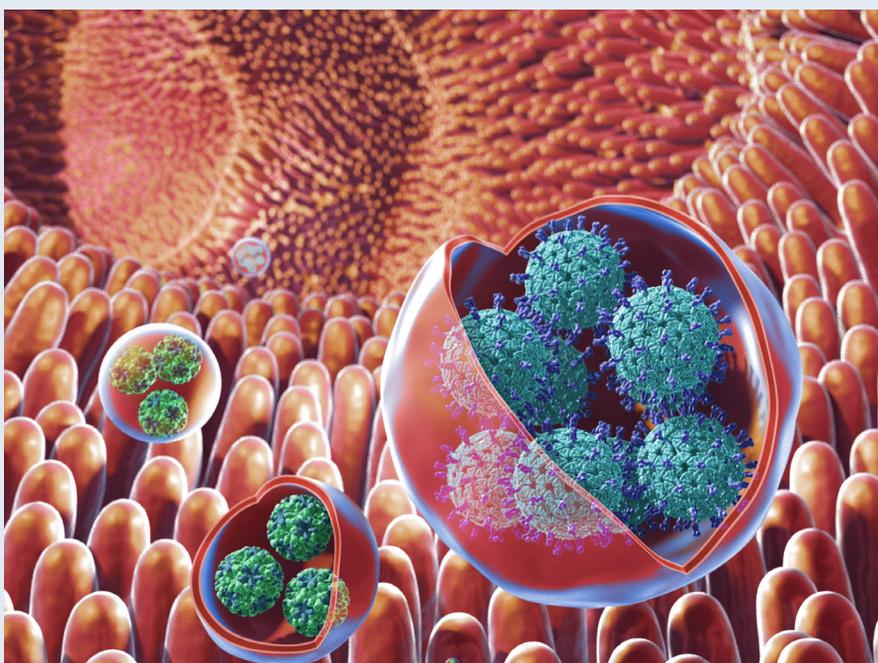
**THE UNITED STATES IS FACING A DOUBLE** crisis: opioid addiction and unrelieved pain. An estimated two million Americans are addicted to opioids; overdose fatality rates rose more than 20 percent in the past two years. Some 25 million Americans suffer from daily chronic pain and lack effective non-opioid treatments to manage that pain.

As part of the effort to address these growing problems, researchers and health-care providers met at the 13th annual NIH Pain Consortium Symposium (held on NIH's Bethesda, Maryland, campus, May 31 and June 1, 2018) to learn about recent advances in pain research, clarify priorities, and discuss opportunities to improve the treatment of pain. The symposium, *From Science to Society—At the Intersection of Chronic Pain Management and the Opioid Crisis*, included presentations, posters, and a fireside chat between NIH Director **Francis Collins** and U.S. Surgeon General **Jerome Adams**.

**Nora Volkow**, director of the National Institute on Drug Abuse (NIDA), opened the symposium by outlining the problems Americans face and the roadmap the NIH has devised to fight this public-health threat. She emphasized that although the overprescription of opioids—which led to misuse of these drugs—may have triggered the opioid crisis, currently the greatest number of overdose deaths are

CONTINUED ON PAGE 10 ►

## Highly Infectious Membrane-Cloaked “Virus Clusters”



MEDICAL ARTS, NIH

Viruses that cause severe stomach illness are transmitted through membrane-cloaked virus clusters rather than through individual virus particles, according to a new NIH study. Shown: illustration of membrane-bound vesicles containing clusters of viruses, including rotavirus (in the large vesicles) and norovirus (in the small vesicles), within the gut.

**NIH RESEARCHERS HAVE FOUND THAT VIRUSES THAT CAUSE SEVERE STOMACH** illness—including the one infamous for widespread outbreaks on cruise ships—get transmitted among humans through membrane-cloaked “virus clusters” that exacerbate the spread and severity of disease. The discovery marks a turning point in the understanding of how these viruses spread and why they are so infectious.

CONTINUED IN “RESEARCH BRIEFS” ON PAGE 8 ►

### CONTENTS

**FEATURES** • [1](#) | Opioid Addiction and Chronic Pain [7](#) | For the Love of Worms: Profile on De'Broski Herbert [12](#) | A Sampling of Intramural Pain Research [14](#) | Profile: Thomas Waldmann  
**DEPARTMENTS** • [2](#) | DDIR: Collaborative Science [3,5](#) | News You Can Use: Eight Ways to Find an Intramural Collaborator; How to Make Your Lab Go Green [4](#) | Training Page: SIGs [6](#) | News Briefs: New Hospice Unit; PHS flag [1, 8](#) | Research Briefs [13](#) | SIG Beat: PAIN SIG [16](#) | Colleagues: Recently Tenured [17, 20](#) | NIH in History: Exhibits; Greenhouse [19](#) | Abbreviations



## Seek and Ye Shall Find: Collaborative Science at the NIH

BY MICHAEL GOTTESMAN, DDIR

**THIS ISSUE OF THE *NIH CATALYST* HAS A** story on finding collaborators at NIH (see facing page). I would warrant that there is no established NIH scientist who has not benefitted from a collaborator who is also part of the intramural program. And a brief survey of intramural publications reveals the enormous extent of collaboration with both intramural and extramural scientific colleagues.

I feel very strongly about the importance of collaboration, not only because of my personal scientific interactions, but also because I have seen time and again difficult problems solved when appropriate collaborators are sought and found.

My own story begins with my long-term collaboration with **Ira Pastan**, co-chief of the National Cancer Institute's (NCI's) Laboratory of Molecular Biology, to study the molecular basis of drug resistance in cancer. We assembled a team of scientists to clone and characterize the energy-dependent ATP-binding cassette subfamily B member 1 (ABCB1) drug efflux pump, also known as P-glycoprotein, and this work led to a deeper understanding of drug pharmacodynamics and drug resistance in cancer. This effort is an example of how a team of scientists was assembled to solve a specific problem.

The cloning of the *ABCB1* gene resulted from a collaboration with extramural researcher Igor Roninson, currently a professor at the College of Pharmacy at the University of South Carolina (Columbia, South Carolina). He had invented a technique for cloning amplified genes from cultured cells whereas we had cell lines in which multidrug-resistant genes were

amplified. The rest, as they say, is history.

As Deputy Director for Intramural Research, I talk to quite a few scientists and attend many seminars at the NIH. I have become something of a vector for ideas and techniques that may be helpful to advance the work of individual scientists. For example, I meet with all of the tenure-track investigators during their first year or two at the NIH. As we talk about their science, I suggest others at NIH who might have a technique or a model system that could advance their science. Not infrequently, these interactions result in new collaborations. These meetings provide a relatively formal structure for suggesting collaborations.

**Howard Gadlin**, former NIH ombudsperson, and **Michelle Bennett**, director of NCI's Center for Research Strategy, developed the "Collaboration Team Science Field Guide," an instruction manual for how to successfully create collaborative teams (<http://bit.ly/2nHQbjw>).

Many interactions with colleagues, however, are informal. There is a legendary observation, attributed to the Nobel Laureate Martin Rodbell, that the slow elevators in the Clinical Center led to many lengthy discussions with colleagues from which great ideas for experiments were derived. So each of us, by attending seminars, the NIH Research Festival, and initiating conversations in the hallways, elevators, and on the pathways of NIH, can contribute to a climate of collaboration with profoundly positive effects on the science here.

My office is always in search of new and better ways to stimulate collaboration. Several years ago we initiated an Innovation

Fund, supported by the NIH scientific directors (SDs), to encourage trans-NIH collaborative research. Although only about 20 percent of the applicants could be funded because of limited resources, many of those who could not be funded told me that the process of creating collaborative proposals led to new ideas for collaborative work that have since born fruit.

The SD's Shared Resources Subcommittee enables the support of several core resources that have resulted in collaborations between individual scientists and core scientific staff. Our new trans-NIH collaborative research exchange website (CREx, at <https://nih.scientist.com>) has lists of most of NIH's core facilities and contact information to encourage trans-NIH collaborative activities.

In addition, there are other resources listed in a previous issue of the *NIH Catalyst* (<http://bit.ly/2BkgKOe>). And finally, the Office of Intramural Research sponsors the NIH Intramural Database, which provides text-searchable listings of all of the research that is going on in the intramural program. So if you need an expert collaborator—or even a cell line, reagent, or technique—just go to <https://intramural.nih.gov> and you can usually find whatever you need.

The major point, of course, is that science is dramatically accelerated when we work with each other and make use of the extensive resources available in the NIH intramural research program. I am sure that many of you have additional stories of how collaborations came about or other ideas about how to stimulate collaborations. Let me know. ●

## Eight Ways to Find an Intramural Collaborator

BY BRANDON LEVY, OIR

**ANNE SUMNER** (NATIONAL INSTITUTE OF Diabetes and Digestive and Kidney Diseases, NIDDK) was puzzled. In 2010, several prominent organizations, including the World Health Organization and the American Diabetes Association, were promoting the hemoglobin A1C blood test (which provides information about average blood glucose over the previous three months) as a valuable new way to diagnose diabetes and pre-diabetes. The approach, however, didn't appear to work for Sumner's African immigrant patients.

Her curiosity about the issue led her to fellow NIDDK investigator **Alan Schechter**, who referred her to **David Sacks**, a senior investigator in the Clinical Center's Department of Laboratory Medicine. Since then, the combination of Sumner's clinical acumen and Sacks' laboratory expertise has produced significant new insights into how to diagnose high blood glucose in individuals of African descent, including the discovery that the A1C test is markedly better at diagnosing the condition in that population if it's combined with either a fasting-glucose test or a test for a sugar-bound blood protein called glycated albumin. The two scientists' collaborative work has been detailed in five journal articles and numerous posters, abstracts, and presentations.

"It's a sort of symbiosis," said Sacks. "Together we come up with papers and ideas that we could never have individually."

Sumner and Sacks are not the only NIH researchers who have found that two heads are better than one. It can seem daunting, though, to find a collaborator. There are many ways, however, that Intramural Research Program (IRP) scientists can identify potential collaborators whose interests and skills complement their own. The following eight methods are a good starting point.

**IRP Website** (<https://irp.nih.gov>): Includes individual pages for all of the IRP's approximately 1,050 principal investigators, complete with contact information, descriptions of their research, and lists of selected publications. The website also handily groups these PI pages into 22 different "Scientific Focus Areas."

**Scientific Interest Groups** (<https://oir.nih.gov/sigs>): IRP investigators, staff, and fellows can participate in more than 90 different Scientific Interest Groups (or "SIGs"), each focusing on a different research topic, method, or model. SIG meetings feature presentations by both intramural and outside researchers and foster discussion about the latest developments in members' fields of interest.

**NIH Intramural Database** (<https://intramural.nih.gov>): Contains a wide array of information about the activities of NIH researchers, including annual reports detailing their current projects and related publications. The database is comprehensive because all research projects that use IRP funds must file annual reports in the NIDB.

**DDIR Web Board** (<http://ddir.nih.gov>): An online bulletin board featuring information about topics of concern including new programs, upcoming events, and recently created SIGs. The site is managed by **Michael Gottesman**, deputy director for intramural research, who also offers his thoughts on recent NIH happenings. (NIH access only).

**NIH Catalyst** (<https://irp.nih.gov/catalyst>): If you're reading this article, you already know about the *NIH Catalyst*, the every-other-month newsletter that covers a wide array of goings-on in the IRP, including news and events, and publishes profiles and stories on new scientific research. The publication, which

made its debut in 1993, was conceived as a forum that both allows scientists at all levels to advise policy development and promotes cross-fertilization of research insights and collaboration across institutes.

**NIH Research Festival** (<https://researchfestival.nih.gov>): If you want to be surrounded by potential collaborators from across NIH, the single best event to attend is the three-day NIH Research Festival, which takes place every year in September.

**Wednesday Afternoon Lecture Series (WALS)** (<https://oir.nih.gov/wals>): The best-known lecture series at the NIH. The talks occur most Wednesdays from September through June and feature prominent researchers in a variety of fields. Each talk is followed by a reception (sponsored by FAES) giving researchers an opportunity to mingle and converse about both the speaker's work and their own.

**Collaborative Research Exchange (CREx)** (<https://nih.scientist.com>): An online research marketplace in which one can identify the capabilities of thousands of external vendors and more than 100 NIH cores and shared resources. It also provides lists of resources, technologies, and expertise offered by NIH labs, branches, and repositories; and contact information to encourage trans-NIH collaborative activities.

Of course, there are many ways of finding collaborators by chance—ranging from informal conversations with fellows and investigators in neighboring labs to interactions with colleagues at national and international meetings. But for those actively seeking collaborators, give one or more of the eight methods described in this article a try. ●

## From the Fellows Committee

### SIGs Facilitate Scientific Dialogue at the NIH

BY CRAIG MYRUM, NIA

**SCIENCE IS CONTINUOUSLY BECOMING** more interdisciplinary and we are expected to obtain and retain both depth and breadth in our respective areas of expertise. One easy way to lessen the challenge is to participate in NIH's Scientific Interest Groups (SIGs), which are assemblies of intramural and extramural scientists with common research interests. There are more than 90 different SIGs, so there's something for every NIH researcher. Separate SIGs cover such topics as methods (flow cytometry or single-cell genomics), animal models (*Drosophila* or yeast), clinical-trials groups, patent law, sex and gender, and virology. SIGs offer many activities including seminars, LISTSERV mailing lists, symposia, poster sessions and lectures, and mentoring and career guidance for junior scientists. SIGs spread the word to members about the latest techniques and research findings and provide a forum for networking.

As new scientific trends arise and vanish, so do specific SIGs. The Neurobiology Interest Group (NBIG) is a prime example. Postdoctoral fellows **Richa Lomash** and **Shireen Sarraf**, both at the National Institute of Neurological Disorders and Stroke (NINDS), recently breathed new life into the group, which had been inactive for several years. NBIG is run by fellows and graduate students from various institutes and centers (ICs); NINDS senior investigator **Katherine Roche** is the group's advisor.

"The whole team has been instrumental in the success of the series," said Lomash. "NBIG was started with an aim to bring together the different aspects of neuroscience research being carried out across campus."

The NBIG typically holds two seminars a month in order to extend speaking opportunities to as many trainees as possible. Given that the NIH is home to a large and diverse group of neuroscientists, the SIG attracts

investigators from at least a dozen ICs. Seminars typically last 40 minutes and are followed by questions and an informal networking session. Even if you're not located on the main campus, you can participate remotely by connecting

through WebEx.

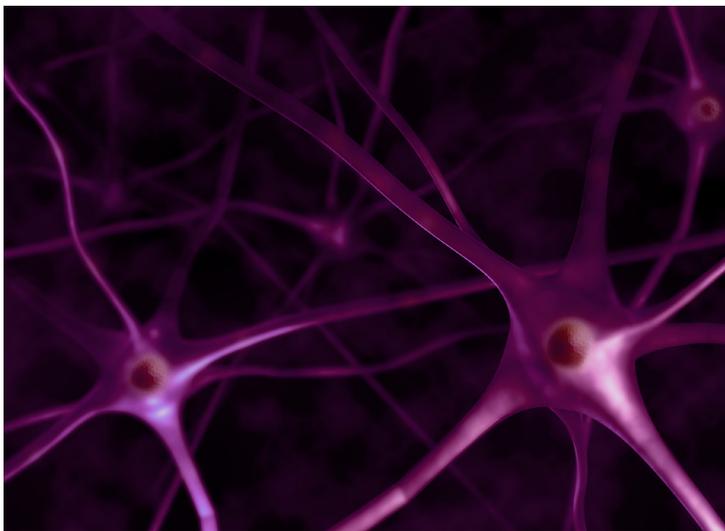
"The main aim of the [NBIG] seminar series is to provide a platform for graduate students and postdocs to share their exciting research stories to a varied audience," said Lomash. And the presenters receive "critical and constructive feedback from on-campus experts."

"We want it to be both a forum for scientific feedback [and] an opportunity to hone our presentation skills before going on the job market," added Sarraf. "We want everyone to attend and hope to promote an environment for open scientific discussion and networking."

Helping to organize the NBIG has been a rewarding and educational experience for Lomash and Sarraf, too. It "has given us [the] experience of organizing and running a committee as well as really understanding everything that goes on in the background of setting up something like this," said Sarraf. "It's been a great learning opportunity in that sense, and we encourage fellows who want to get involved to contact us."

Given the wide variety of SIGs available, there is bound to be one that piques your interest. Check them out at <https://oir.nih.gov/sigs>. ●

For a list of SIGs, scientific LISTSERV newsletters, and intramural organizations, go to <https://oir.nih.gov/sigs>. SIGs form and evolve regularly as new scientific trends arise. Information about group activities or new groups is published in the *NIH Catalyst* at <https://irp.nih.gov/catalyst> under "The SIG Beat" department and on the DDIR Web Board (NIH only) at <http://ddir.nih.gov>. To learn how to set up a new SIG, email [OIRinfo@mail.nih.gov](mailto:OIRinfo@mail.nih.gov).



PATRICIA DZ, THINKSTOCK.COM

The Neurobiology Interest Group (NBIG), one of the more than 90 SIGs on the NIH campus, aims to promote interactions among scientists from different institutes and centers who are studying all aspects of the nervous system. Shown: neurons in the brain.

## How to Make Your Lab Go Green

BY MANJU BHASKAR, NINDS

**THERE'S A LOT OF TALK THESE DAYS** about labs “going green” in an effort to reduce their environmental footprint and promote sustainable laboratory practices. But what does “going green” mean exactly, and how do you go about it?

Some of the basic fundamentals of a green lab include conserving energy and water, reducing waste, and recycling. Proper disposal of chemical, medical, and radioactive waste in safe, environmentally friendly ways plays an additional critical role in supporting sustainability. Even using “green” chemicals should be considered as part of the effort to “go green.”

The good news is that several NIH labs already meet the green-labs criteria. But, until now, there has been no official process for recognizing them. Now labs can be assessed and certified as green under a new initiative sponsored by the Green Labs Program.

The Green Labs Program aims to encourage “going green” in NIH laboratories, to conserve natural resources, and to protect the health of the environment and the people who live in it. Any lab wishing to be certified as a green lab—and receive recognition for participating in safe and sustainable practices—completes an online application that includes a self-assessment tool and submits it for consideration. After the form is submitted, applicants will be notified of results within two weeks. Labs meeting the award criteria will receive a Green Labs certificate. For more information, see the end of this article.

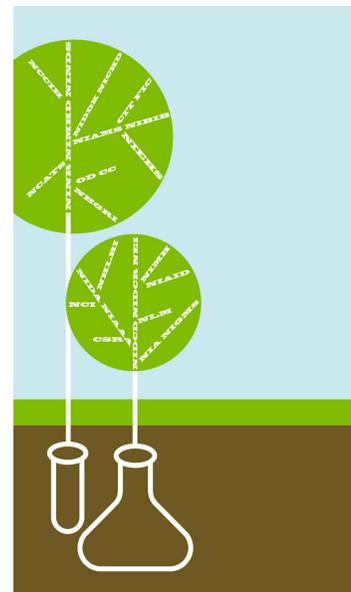
Taking a deeper dive into “going green,” some applications of sustainable environmental practices include using energy-efficient freezers and other lab equipment; replacing wet-chemistry photo processing with digital-imaging techniques; reducing chemical waste and cost by the

minimal usage of radioisotopes, methanol, and X-ray film; and using green products as safer alternatives to certain toxic chemicals. For example, try semidry transfer techniques for Western blot analysis to avoid using methanol, limit waste, and save time and energy. Throughout the campus, there's been increased use of safer substitutes for ethidium bromide. Labs are also trying environmentally friendly DNA-purification and DNA-isolation kits that use significantly less plastic and are in recyclable packaging.

In the electrophoresis realm, the National Institute on Deafness and Other Communication Disorders (NIDCD) is playing a role: The Section on Human Genetics (in the Laboratory of Molecular Genetics) has an E-Gel Agarose Gel Station with a digital imager that uses less power than a large agarose gel-electrophoresis box. The gels come prestained with either ethidium bromide or SYBR Green, and, to increase safety, they are encased in plastic so the stain does not leak out.

Water-filtration systems can be made eco-friendly, too. For instance, NIDCD replaced its bottled laboratory-grade water system with a water-filtration system that undergoes preventative maintenance once a year and constantly monitors water quality to be sure that no plastics leach into and contaminate the water. The Genetics and Metabolism Section (in the Liver Diseases Branch) in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is using another system to provide metal-free water.

Another green technique involves taking lab notes in a way that has a less-harmful effect on the environment. For instance, researchers in NIDDK's Gene Structure and Disease Section (in the Laboratory of Cell and Molecular Biology), use a web-based



electronic notebook that can store, organize, and publish data, maintain multiple backups of data, save paper, and free up lab space that can be used for storing other items.

Other sustainable practices include using refillable pipette-tip racks that reduce plastic waste because the tip box can be used many times. In addition, NIDDK is using small equipment such as small centrifuges and a NanoDrop spectrophotometer to save on power consumption and bench space.

To find out more about what other labs are doing and get tips on how your lab can “go green,” come to the annual Green Labs Fair that is held in conjunction with the NIH Research Festival every year. The fair features exhibits on NIH environmental programs and displays by commercial vendors that provide a wide variety of green laboratory products. ●

For more information including how to apply to the certification program, go to <https://nems.nih.gov/green-teams/Pages/NIH-Green-Labs-Program.aspx> or contact Bani Bhattacharya ([bani.bhattacharya@nih.gov](mailto:bani.bhattacharya@nih.gov)).

## NIH Clinical Center Opens Hospice Unit

BY ZOE SHANCER, NCI



MARLEEN VAN DEN NESTE

The Clinical Center's new hospice unit cared for its first patient six days after its July 10, 2018, opening. Pictured (from left), Chief of Pain and Palliative Care Ann Berger, NIH Director Francis Collins, Clinical Center CEO James Gilman, and Chief Nurse Officer Gwen Wallen.

**“AMAZING EFFORTS THAT GO ON HERE AT** the NIH Clinical Center [help] people for whom medicine basically doesn't have any answers and where the best kind of science is brought to bear, oftentimes for people who are very seriously ill,” said NIH Director **Francis Collins** at the opening of the NIH Clinical Center's (CC's) first hospice unit on July 10, 2018. But not all efforts result in happy outcomes. “We owe it to [our patients] in those circumstances where our best efforts are not succeeding to care for them in a place like this [hospice unit] to provide them with that kind of dignified, loving surrounding while making it possible for them to be with their families in these final moments.”

Six days after the hospice unit opened, it cared for its first patient, a man who had been on a clinical protocol to treat his cancer for several months. His condition had worsened and he was admitted to the intensive care unit (ICU). When it was determined that he could not be stabilized, he was moved to the hospice unit. Eleven hours later, he passed away with his family by his side.

The patient's family “was very pleased that they could have meals together as a family and be with their loved one in a home-like environment,” said **Ann Berger**, chief of the CC's Palliative Care service.

Hospice is a philosophy of care in which terminally ill patients and their families are provided comfort and a place to be together at the

end of life. The NIH hospice unit comprises two suites, each of which has a bedroom and a community room equipped with a kitchen and family sitting area.

About 10,000 new patients a year are treated at the CC, the world's largest hospital devoted exclusively to clinical investigation. Although most people taking part in clinical research have good outcomes, about 50 die each year at the CC. In the past, they have passed away in various units or have gone home or to hospice units elsewhere.

Berger, who was instrumental in developing the hospice unit, believes that the CC is unique in the excellent care it provides when treating patients and says that the NIH can be the best of the best in end-of-life care as well. Compassion and empathy are always important in medical care, but are especially important during the end of life because this period of time will always be remembered by the patient's family, she said.

The 16 nurses who have been trained to work in the new unit have taken an end-of-life course, spent time at Montgomery Hospice (Rockville, Maryland), and then

worked in the CC's palliative-care service, which provides skilled management of symptoms and allays psychosocial, emotional, and spiritual suffering.

“We will be training more nurses on other units so that end-of-life care is improved throughout the [CC],” said Berger.

CC Chief Nurse Officer **Gwen Wallen** explained how important it is to make sure that hospice units are high-touch not high-tech. “Our nursing staff are highly invested in providing this ‘high-touch’ environment for patients at the end-of-life as well as to their families,” she said. “We're going to have to work as interdisciplinary teams to make [the hospice unit] work the way it's supposed to work and so that Ann's team [can] fulfill this high-touch, low-tech area in a clinical-research environment.”

“People come [to the NIH] and hope for a cure for their illness,” said Berger. “That is not always possible, but with excellent end-of-life care we can help both the patient and family heal” psychologically and spiritually. ●

## U.S. Public Health Service Flag at NIH



ERNIE BRANSON, NIH

The U.S. Public Health Service traces its roots to July 16, 1798, when President John Adams signed into law the “Act for the Relief of Sick and Disabled Seaman.” On July 16, 2018, the U.S. Public Health Service flag was raised on the main flagpole outside Building One to commemorate 220 years of protecting, promoting, and advancing the health and safety of our nation. The flag will be at NIH permanently.

## For the Love of Worms

### De'Broski Herbert's WALs Lecture

BY ANNE DAVISON, NICHD

#### GROWING UP IN MISSISSIPPI, DE'BROSKI

Herbert was warned by his great-grandmother never to walk barefoot outside. It wasn't until a parasitology class during his sophomore year at Xavier University of Louisiana (New Orleans) that Herbert understood the phenomena behind his great-grandmother's homespun wisdom: intestinal parasites, specifically hookworms (a type of nematode). Such worms became infamous after they were discovered to cause pernicious anemia and stunted growth among schoolchildren in the southern United States at the turn of the 20th century. They were later targeted for eradication by the Rockefeller Foundation and other programs.

Hookworm larvae live in fecal-contaminated soil and can penetrate the feet of anyone who happens to walk barefoot through the area. The larvae migrate from the skin through blood vessels to the lungs; travel to the trachea, where they are swallowed; make their way to the intestine, where they mature into adult worms; and mate. The females can lay up to 30,000 eggs a day. The eggs leave the body through the feces, and the cycle continues.

It was that sophomore-year parasitology class that hooked Herbert on worms. He then spent two summers at the University of California, San Francisco (UCSF), doing undergraduate research on the blood-infecting parasite *Babesia microti* (which causes malaria-like symptoms), and he became fascinated with biomedical research.

He credits his passion for science to the freedom and novelty of discovery, adopting the motto "If the excitement of a discovery keeps you awake at night, the career possibilities are endless."

Herbert followed his fascination for nematodes (which pose a global health

problem) and immunology to David Abraham's lab at Thomas Jefferson University (Philadelphia) where he got his Ph.D. in immunology in 2000, and then to Frank Brombacher's lab at the University of Cape Town, South Africa, for his postdoctoral training. He went on to hold faculty positions in Ohio and California, and, in 2016, became an associate professor of immunology at the University of Pennsylvania School of Veterinary Medicine (Philadelphia).

Through the study of parasitic worms, his lab has made important contributions toward understanding the mechanisms controlling the development of alternatively activated macrophages and type 2 inflammation in the respiratory and gastrointestinal tracts.

Herbert shared his enthusiasm for nematodes with an NIH audience on June 21, 2018, when he delivered a Wednesday Afternoon Lecture (WALS) entitled "LINGO Proteins: A New Language for the Mucosal Barrier." He told the story of how his lab used a nematode model to discover the LINGO-2 protein. It turns out that a LINGO-2 deficiency in a host results in improved immunity against the nematode *Nippostrongylus brasiliensis*, a natural worm pathogen that infects rats.

The discovery ties into Herbert's recent work on trefoil factors (TFFs), a family of small, abundant, secreted proteins that protect the mucous epithelia in the gastrointestinal tract. TFFs promote tissue repair, for example, in Crohn disease and colitis. Called trefoil factors because of their distinctive three disulfide-bridge loops, these small signaling proteins are produced by goblet cells (secretory cells within the epithelial linings of organs mainly in the intestinal and respiratory tracts) within hours of injury and constitutively reside at epithelium locations where they can influence epithelial



GAYLE JOSEPH, UPENN

De'Broski Herbert, an associate professor of immunology at the University of Pennsylvania School of Veterinary Medicine (Philadelphia), regaled a WALs audience with stories of his research on worms.

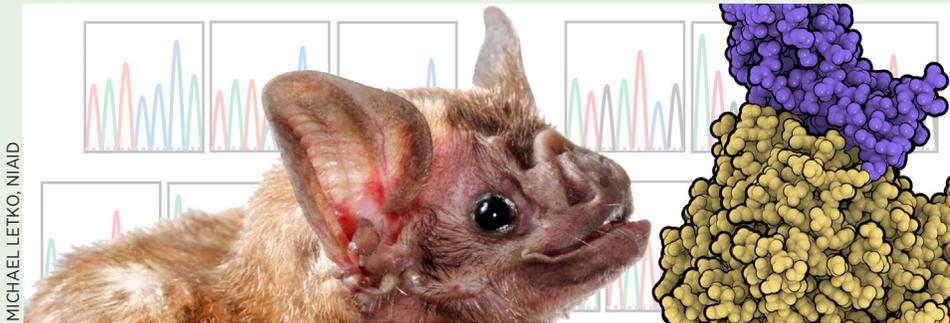
resistance, gastric protection, angiogenesis, and inhibit apoptosis. It was through an interest in trefoils that his lab started to study LINGO-2.

After a worm infection, a deficiency in LINGO-2 enhances the activation of the epidermal-growth-factor receptor, promoting the clearing of gastrointestinal nematode infections and repair of the gastrointestinal tract. Clinical applications include the possibility of making LINGO-2 blockers to increase immunity to nematodes.

Herbert makes a point of having fun with his work. For example, he names his transgenic worm lines after Marvel characters. He has a "Hulk" green fluorescent protein (GFP)-labeled worm line and a "Scarlet Witch" GFP-secreting and red fluorescent protein-expressing worm line. Always enthusiastic about nematodes, Herbert hopes that through spreading his passion there will be "more people in the world who love worms as much as I do!" ●

To watch a videocast of Herbert's WALs lecture, presented on June 21, 2018 (HHS and NIH only), go to <https://videocast.nih.gov/launch.asp?23976>.

## Intramural Research Briefs



MICHAEL LETKO, NIAID

NIAID scientists have figured out how some coronaviruses, which cause severe respiratory disease, evolve to be able to infect new species, including humans. Shown: The vampire bat species used in the study and an illustration representing Middle East respiratory syndrome coronavirus (purple) interacting with host receptor DPP4 (gold).

### NHLBI, NIAID: HIGHLY INFECTIOUS MEMBRANE-CLOAKED “VIRUS CLUSTERS” TRANSMIT VIRUSES AMONG HUMANS

NIH researchers have found that viruses that cause severe stomach illness—including the one infamous for widespread outbreaks on cruise ships—get transmitted among humans through membrane-cloaked “virus clusters” that exacerbate the spread and severity of disease. Previously, it was believed that these viruses only spread through individual virus particles. The discovery of these clusters, the scientists said, marks a turning point in the understanding of how these viruses spread and why they are so infectious. This preliminary work could lead to the development of more effective antiviral agents than existing treatments that mainly target individual particles.

The researchers studied norovirus and rotavirus, hard-to-treat viruses that are the most common causes of gastroenteritis and that afflict millions of people each year. The viruses cause symptoms ranging from diarrhea to abdominal pain and can sometimes result in death, particularly among young children and the elderly. Their highly contagious nature has led to serious outbreaks in crowded spaces, most notably in cruise ships, daycare centers, classrooms, and nursing homes. Fortunately, vaccines against rotavirus are now available and are routinely given to babies in the United States. Rotaviruses and noroviruses are mainly spread by accidentally ingesting tiny particles

of an infected person’s stool such as through contaminated food or liquids.

The researchers obtained fecal samples of humans and animals (pigs and mice) and found that the viruses are shed in the stool as virus clusters inside membrane-bound packets. In addition, they found that these virus-containing vesicles were significantly more infectious than the free, unbound viruses within the samples. (NIH authors: M. Santiana, S. Ghosh, B.A. Ho, V. Rajasekaran, W.-L. Du, Y. Mutsafi, D.A. De Jesús-Díaz, S.V. Sosnovtsev, E.A. Levenson, C. Bleck, K.Y. Green, and N. Altan-Bonnet, *Cell Host Microbe* 24:208–220E8, 2018; DOI:10.1016/j.chom.2018.07.006)

### NIAID (HAMILTON, MONTANA): HOW MERS CORONAVIRUS EVOLVES TO INFECT DIFFERENT SPECIES

In the past 15 years, two outbreaks of severe respiratory disease have been caused by coronaviruses that originated in bats and were passed to humans through other animals. Scientists don’t yet understand the genetic mechanisms underlying cross-species adaptation. New NIAID research shows how Middle East respiratory syndrome coronavirus (MERS-CoV) can adapt to infect cells of a new species, which suggests that other coronaviruses might be able to do the same.

In 2003, severe acute respiratory syndrome coronavirus (SARS-CoV) spread from civets to infect more than 8,000 people, leading to

a yearlong global public-health emergency. MERS-CoV, first identified in 2012, jumps from dromedary camels (*Camelus dromedarius*) to people, resulting in periodic outbreaks with a roughly 35 percent fatality rate.

To evaluate how MERS-CoV evolves to infect host cells, the scientists tested 16 bat species and found that the virus could not efficiently enter cells with receptors from the common vampire bat, *Desmodus rotundus*. The researchers then grew virus on cells that had vampire bat receptors and observed the virus evolving to better infect the cells. After a few generations, the virus had completely adapted to the vampire bat receptor. MERS-CoV and SARS-CoV use the same general approach to enter the cells of new species. Understanding how viruses evolve to infect new species may be important for developing new vaccines. (NIH authors: M. Letko, K. Miazgowiec, R. McMinn, S.N. Seifert, A. Carmody, N. van Doremalen, and V. Munster, *Cell Rep* 24:1730–1737, 2018; DOI:10.1016/j.celrep.2018.07.045)

### NIAMS AND NIDCR: WHY WOUNDS HEAL QUICKER IN THE MOUTH THAN ON SKIN

Oral wounds heal more rapidly and with little scarring than wounds on the skin. Researchers from NIAMS and NIDCR identified the physiological and molecular determinants for this repair paradigm. They took biopsies from the cheeks and arms of 30 people and then took biopsies again two or five days later. The scientists determined that wound-activated transcriptional networks are present at the basal state in the oral mucosa, priming the epithelium for wound repair. The researchers found that activating the gene regulators in mouse skin cells improved skin healing. The findings could have widespread implications for the wound-healing field. (NIH authors: R. Iglesias-Bartolome, A. Uchiyama, A.A. Molinolo, L. Abusleme, S.R. Brooks, J.L. Callejas-Valera, D. Edwards, C. Doci, N.M. Moutsopoulos, J.S. Gutkind, M.I. Morasso, *Sci Transl Med* 10:eaap8798; DOI:10.1126/scitranslmed.aap8798)



### **NIDDK, CC: A DRUG TO TREAT OVERACTIVE BLADDER HAS OTHER METABOLIC EFFECTS**

An NIDDK study showed that a class of medications, beta-3 adrenergic receptor (ADRB3) agonists, may have multiple physiological effects on human metabolic functioning. The researchers found that the ADRB3 agonist mirabegron, an FDA-approved drug to treat only overactive bladder, increased brown-fat metabolic activity, white-fat lipolysis, and resting-energy expenditure in 12 healthy men. (Only men were recruited for this study because the 200 mg dose used might have caused heart rhythm problems in women; another study is underway to test a 100 mg dose in women.) Mirabegron also affected gallbladder size and bile-acid metabolism, two functions previously unreported in studies of the drug in either rodents or humans. All these effects were substantial only at a dosage higher than that approved to treat overactive bladder, which may explain why many of the physiological responses to ADRB3 agonists in humans have not yet been reported. (NIH authors: A.S. Baskin, J.D. Linderman, R.J. Brychta, S. McGehee, E. Anflück-Chames, C. Cero, J.W. Johnson, A.E. O'Mara, L.A. Fletcher, B.P. Leitner, C.J. Duckworth, S. Huang, H. Cai, H.M. Garraffo, C.M. Millo, W. Dieckmann, P.J. Walter, P. Herscovitch, K.Y. Chen, and A.M. Cypess, *Diabetes Jul*;db180462, 2018; DOI:10.2337/db18-0462)

[BY LISA YUAN, NIDDK]

### **NCI: PREDICTOR FOR IMMUNOTHERAPY RESPONSE IN MELANOMA**

In a new study, NCI researchers and colleagues at three universities developed a gene-expression predictor that can indicate whether melanoma in a specific patient is likely to respond to treatment with immune checkpoint inhibitors, a novel type of immunotherapy. They analyzed neuroblastoma, a type of cancer that frequently undergoes spontaneous regression in young children, and were able to define gene-expression features that

separated patients with nonregressing disease from those with regressing disease. The researchers computed an immuno-predictive score (IMPRES) for each patient sample. The higher the IMPRES score for a sample, the more likely the sample was to undergo spontaneous regression. To see whether IMPRES could be used to predict melanoma patients' responses to checkpoint inhibitors, the authors analyzed 297 samples from several studies. They found that the predictor could identify nearly all patients who responded to the inhibitors and more than half of those who did not. According to the researchers, the results need to be carefully evaluated in additional patient datasets. (NIH authors: N. Auslander, J.S. Lee, S. Madan, and E. Ruppin, *Nat Med*; DOI:10.1038/s41591-018-0157-9)

### **NIDCD: THAT STINKS! ONE IN 15 AMERICANS SMELL ODORS THAT AREN'T THERE**

One in 15 Americans over the age of 40 experiences phantom odors, according to a new study led by researchers from NIDCD. Problems with the sense of smell can have an impact on appetite, food preferences, and the ability to smell danger signals such as fire, gas leaks, and spoiled food. The team used data from 7,417 participants over 40 years of age from CDC's 2011–2014 National Health and Nutrition Examination Survey (NHANES). (NIH author: K.E. Bainbridge, *JAMA Otolaryngol Head Neck Surg*; DOI:10.1001/jamaoto.2018.1446)

### **NICHD, NCI: DIAGNOSING GESTATIONAL DIABETES RISK IN FIRST TRIMESTER**

Pregnant women are typically screened for gestational diabetes between 24 and 28 weeks of pregnancy, but a new study by NIH researchers suggests that a blood test at 10 weeks may diagnose the condition sooner. The researchers evaluated whether the hemoglobin A1c (HbA1c) test (also called the A1C test), commonly used to diagnose type 2 diabetes, could identify signs of gestational diabetes in

the first trimester of pregnancy. Using data from the NICHD Fetal Growth Study, a large observational study that recruited more than 2,000 low-risk pregnant women between 2009 and 2013, the researchers compared HbA1c test results from 107 women who later developed gestational diabetes with results from 214 women who did not. Women who went on to develop gestational diabetes had higher HbA1c measurements (an average of 5.3 percent) than those without gestational diabetes (an average HbA1c of 5.1 percent). Each 0.1 percent increase above 5.1 percent in early pregnancy was associated with a 22 percent higher risk for gestational diabetes. Further studies are needed to confirm the findings and to determine whether lowering HbA1c with lifestyle changes—such as exercise and healthy diet—either in early pregnancy or before pregnancy, could reduce the risk for the condition. (NIH authors: S.N. Hinkle, S. Rawal, P.S. Albert, and C. Zhang, *Sci Rep* 8:12249, 2018; DOI:10.1038/s41598-018-30833-8)

### **NIDCD: NOVEL DRUG THERAPY PARTIALLY RESTORES HEARING IN MICE**

A small-molecule drug is one of the first to preserve hearing in a house mouse (*Mus musculus*) model of an inherited form of progressive human deafness, reported investigators from NIDCD and the University of Iowa (Iowa City, Iowa). The study sheds light on the molecular mechanism that underlies an inherited form of deafness called DFNA27 and suggests a new treatment strategy. (NIH authors: M.C. Kelly, A.U. Rehman, E.T. Boger, R.J. Morell, M.W. Kelley, and T.B. Friedman, *Cell* 174:536–548, 2018; DOI:https://doi.org/10.1016/j.cell.2018.06.004)

Read longer versions of these research briefs and other briefs online at <https://irp.nih.gov/catalyst/v26i5/research-briefs>.

## Pain

CONTINUED FROM PAGE 1

NIH HEAL INITIATIVE

HEAL Initiative

- [Addiction Treatments](#)
- [Pain Management](#)
- [Public-Private Partnership](#)
- [Research Plan](#)
- [Funding](#)
- [Events](#)



NIH research program to explore the transition from acute to chronic pain



NIH outlines research plan to address the opioid epidemic

At the Pain Consortium Symposium, NIDA Director Nora Volkow described how the trans-NIH Helping End Addiction Long-term (HEAL) Initiative will support research to provide new strategies for the prevention and treatment of opioid misuse and addiction; understand the biological underpinnings of chronic pain; develop new drugs to treat pain; and find evidence-based ways to integrate nonpharmaceutical pain-management techniques. Website: <https://www.nih.gov/heal-initiative>.

from heroin and fentanyl, black-market alternatives for prescription opioids. The high rates of patients suffering from chronic pain combined with the potency and addictiveness of opioids mean there must be a coordinated effort between basic and clinical researchers to address the crisis. Researchers are tasked with finding nonaddictive pain relievers, characterizing the transition from acute to chronic pain, and developing biomarkers for pain.

Volkow described the April 2018 launch of the NIH Helping End Addiction Long-term (HEAL) Initiative, an aggressive trans-agency effort to speed scientific solutions to stem the opioid public-health crisis. Thanks to a Congressional appropriation of \$500 million in fiscal year 2018, NIH nearly doubled its funding for opioid-related and pain research from almost \$600 million to \$1.1 billion. The HEAL initiative will support research to provide new strategies for the prevention and treatment of opioid misuse and addiction; understand the biological underpinnings of chronic pain; develop new drugs to treat pain; and find evidence-based ways to integrate nonpharmaceutical pain-management techniques. NIH will also work with partners from the biopharmaceutical industry to develop a data-sharing

collaborative; find new biomarkers for pain; and develop a clinical-trials network to test new pain therapies.

The symposium's keynote address featured Judith Paice (a research professor of medicine and director of the Cancer Pain Program at Northwestern University, Evanston, Illinois), who highlighted the unintended consequences of restricting prescription opioids for people suffering from chronic pain.

Limits on these prescriptions may cause patients to undermedicate; health-care providers to deny opioid-prescription authorizations for fear of being held responsible for opioid misuse; [and] physicians [to be] limited in their ability to treat chronic pain including for “people with cancer [who] can live for a very long time [with] pain,” said Paice. “We need to improve access.”

Paice pointed out that finding effective ways to control pain and deal with the opioid epidemic must consider the roles of economic despair, mental illness, and social isolation in the spread of the opioid epidemic. She also stressed the importance of integrating evidence-based guidelines with treatment plans for dealing with both chronic pain and substance-use disorders.

### Symposium highlights

Other presentations at the symposium focused on pain management from a variety of perspectives including interactions between pain and reward circuitry in opioid action, demographic disparities in pain management, a patient's perspective on the intersection of chronic pain and opioid restrictions, and non-opioid neurotechnologies developed under the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. Following are highlights from talks by an intramural investigator and two NIH alums.

**Michaela Prochazkova**, a postdoc in **Ashok Kulkarni's** lab (National Institute of Dental and Craniofacial Research, NIDCR), is exploring ways to relieve orofacial pain by blocking cyclin-dependent kinase 5 (Cdk5) activity in mouse models. Cdk5 plays an important role in pain signaling, but commercially available Cdk5 inhibitors lack specificity and might cause unwanted side effects. Prochazkova described how she and other lab members collaborated with **Harish Pant** (National Institute of Neurological Disorders and Stroke, NINDS) and found that the neuroprotective agent TFP5, a peptide inhibitor of aberrant and hyperactive Cdk5, was effective in relieving orofacial pain. (TFP5, developed by Pant's lab, is typically used to provide neuroprotective effects in animal models of neurodegenerative disorders.)

NIH alum **Jose Moron-Concepcion**, an associate professor of anesthesiology and neuroscience at Washington University (St. Louis, Missouri), is determined to understand the mechanisms underlying opioid addiction and pain. From 1999 to 2001, he was a postdoc in the lab of the late **Toni Shippenberg** (NIDA), a pioneer in the field of opioid pharmacology. In his symposium presentation, “Opioid-induced Plasticity and the Intersection with Pain,”

Moron-Concepcion described his research showing how the relationship between pain and motivation plays a role in governing opioid self-administration in rodents. He also talked about monitoring neural activity in mice as they navigated virtual reality environments that link cues with the presence or absence of opioids. Initial results show increased firing in the hippocampal region CA1 when the mice enter an environment with stripe patterns previously associated with the drug, suggesting that these memory-associated circuits might play a role in the creation of cues that trigger drug-seeking and relapse.

NIH has shaped the careers of other pain experts who appeared at the symposium including the president of the American Pain Society (APS), **William Maixner**, who gave an update of the organization's priorities and activities. Maixner was a research fellow in NIDCR in the 1980s and is now a professor of anesthesiology and co-director of the Center for Translational Pain Medicine at

Duke University (Durham, North Carolina). He considers chronic pain to be a “hidden epidemic” and voiced his appreciation for how the NIH HEAL Initiative provides new opportunities for APS to partner with the U.S. Department of Health and Human Services to reverse the opioid epidemic. The APS concentrates on research, education, patient management, and advocacy. One of its priorities is to disseminate new knowledge generated by pain research, primarily through publishing the *Journal of Pain* and by hosting the APS annual meeting.

### Fireside Chat with the Surgeon General

The symposium also featured a conversation between U.S. Surgeon General Jerome Adams and NIH Director Francis Collins. They discussed the opioid epidemic, chronic pain, and how disparities in access to health care exacerbate these problems. Adams stressed the need for reducing the stigma surrounding mental-health illnesses and addiction. He is pushing for naloxone, a

medication that rapidly reverses opioid overdose, to be sold over-the-counter in pharmacies. He urged everyone to carry naloxone to help fight the opioid epidemic right now.

“We can't save someone if they're not alive,” said Adams. “We need naloxone to be as ubiquitous as CPR or defibrillators.”

Adams also hopes to tackle disparities in health-care access, particularly in rural America. “Any problem in urban areas is 10 times worse in rural areas because of stigma and [lack of] access” to health-care services.

He encouraged the audience to seize the opportunities that media coverage of the opioid crisis brings to the field of pain research. He warned against an overly mechanistic view of pain with too narrow a focus on new drug treatments. Instead, he encouraged a view that accounts for the biological, emotional, and spiritual components of pain and offers a broad range of interventions. To ensure that these interventions become widely available, value-based payment models would be beneficial.

“We need the most rigorous visionary basic science to teach us critical things we don't know about mechanisms and molecules and learn about a condition to be able to intervene effectively,” said Adams. The challenge is “how do you rapidly translate what have you learned in that basic-science arena into something that's going to help somebody?” ●

The NIH Pain Consortium aims to enhance pain research and promote collaboration among researchers across NIH institutes and centers that have programs and activities addressing pain. For links to the meeting summary and webcast for the symposium (May 31 and June 1, 2018), go to [https://painconsortium.nih.gov/Meetings\\_Events/Annual\\_Symposium/2018-NIH-Pain-Consortium-Symposium](https://painconsortium.nih.gov/Meetings_Events/Annual_Symposium/2018-NIH-Pain-Consortium-Symposium).



ANDREW PROPP, OD

NIH Director Francis Collins (left) and U.S. Surgeon General Jerome Adams discuss the opioid crisis and chronic pain at the NIH Pain Consortium Symposium held on May 31 and June 1, 2018.

READ ABOUT SOME INTRAMURAL PAIN RESEARCH ON PAGE 12

## Pain

CONTINUED FROM PAGE 11

## A Sampling of Intramural Pain Research

BY EMILY PETRUS, NINDS

**MOST OF THE NIH INSTITUTES AND** centers (ICs) are supporting or doing pain research. Following is a sampling being done at four ICs: National Center for Complementary and Integrative Health (NCCIH); National Institute of Neurological Disorders and Stroke (NINDS); National Institute on Drug Abuse (NIDA); and National Institute on Nursing Research (NINR).

**NCCIH and NINDS:** NCCIH Stadtman Investigator **Alexander Chesler** is trying to get a better understanding of the genetic and cellular mechanisms that underlie the somatosensory system, which is involved in the perception of touch, pressure, pain, and other sensations. As part of his research, he is investigating how mutations in the *PIEZO2* gene affect the mechanosensation part of the somatosensory system. Unbeknownst to Chesler, NINDS investigator **Carsten Bönnemann**, who studies the genetic basis for neuromuscular disorders in children, was also interested in the *PIEZO2* gene. Bönnemann had discovered that two of his female patients with a rare neurological disorder—which caused several problems including the loss of the sensations of body position and touch—had mutations in the *PIEZO2* gene. Bönnemann happened to be at a faculty meeting at which Chesler presented confocal microscopy images of *Piezo2* staining in mice.

Bönnemann realized there was an opportunity for collaboration once he saw that Chesler was studying the exact



GEORGE RUDY, THINKSTOCK.COM

Catherine Bushnell (NCCIH), whose expertise is on the brain's role in perceiving, modifying, and managing pain, has found that alternative methods of managing chronic pain such as exercise, meditation, and yoga increase tolerance to pain. Pictured: Two people practicing yoga.

same gene that was mutated in his patients (and later in other patients). As the two investigators began collaborating, Chesler extended his work from mice with *Piezo2* mutations to humans.

“It’s all serendipity. I went from [being] a mouse geneticist to working with people,” said Chesler. “It changed my outlook on the role of human genomics and psychophysics,” a branch of psychology that deals with the relationships between physical stimuli and mental phenomena.

Chesler and Bönnemann have moved back and forth between patients and animal models to describe the molecular mechanisms underlying the patients’ phenotype. In addition, Chesler’s lab is now looking into the role of *PIEZO2* in mechanical-pain sensation, a type of pain that is poorly understood.

Chesler and Bönnemann invited NCCIH Scientific Director **Catherine Bushnell** to join the collaboration to provide quantitative sensory testing and brain imaging of the patients. Bushnell’s expertise is on the brain’s role in perceiving, modifying, and managing pain. She, Chesler, and Bönnemann’s

team are also studying other patients who have abnormal responses to pain. A recent patient, identified by **Diana Bharucha-Goebel** of NINDS and the Children’s National Health System, has them all intrigued: a teenager who can’t feel pain, but his body responds as if he does. However, his primary and secondary somatosensory cortex, the parts responsible for registering that sensation, are not activated.

“It’s a great opportunity to coordinate between clinical and basic” research, said Bushnell. “We get to translate back to animal studies and take it back to the mechanisms. The rare patients’ abnormalities help us understand normal pain processing and the mechanism of the conscious experience of pain.”

Bushnell’s group is also studying alternative methods of managing chronic pain. “Lifestyle changes can alter your pain better than pharmacology,” she said. For example, rats recover faster from an injury and can tolerate pain better if they hit the “rat gym” five times a week. In addition, Bushnell’s lab has shown that meditation and yoga increase tolerance to pain. Her group also



recently demonstrated that chronic pain reduces the number of opioid receptors in the brain's pain-processing areas. This reduction in receptors may reduce the effectiveness of opioids in treating chronic pain.

Even so, opioids are often prescribed before other treatments are considered. Although the science is sound, insurance companies and medical providers haven't caught up: Pain medications, such as opioids, are easier for doctors to prescribe and are more likely to be covered by insurance than are alternative treatments such as yoga classes.

**NIDA:** **Amy Newman** led a group that discovered antagonist compounds that target the brain's dopamine D3 receptors (D3R), which have been implicated in reward and addiction. In animal models, the compounds reduce oxycodone self-administration, naloxone-precipitated withdrawal, and reinstatement of drug-seeking behaviors without affecting analgesia. The findings suggest that a selective D3R blockade may reduce the development of opioid dependence without diminishing the effectiveness of prescription pain killers. In addition, the lead molecules identified may offer a potential treatment for opioid-use disorders. This NIH technology has been licensed by pharmaceutical-industry partners to further develop these promising molecules for the prevention and treatment of opioid misuse and addiction.

**NINR:** Because pain is a difficult condition to characterize, finding a standardized way to classify pain intensity is a clinical goal outlined by the HEAL initiative. **Wendy Henderson's** group, in NINR's Biobehavioral Branch, developed the Gastrointestinal Pain Pointer (GIPP), a new computerized tool for assessing

the location and severity of abdominal pain. The tool combines subjective scores with objective measures such as heartrate and can be used to detect subclinical gastrointestinal issues, such as inflammation, which often underlies chronic pain. This scoring method can be translated to clinical facilities and provide benefits to patients and researchers studying chronic GI pain.

**Wish list.** Funding an intramural NIH center for pain is at the top of the wish list for Bushnell, Chesler, and others. Chesler emphasized the benefits of having an effective, centralized place where resources and expertise could be shared.

"Pain has been an orphan for decades," said Bushnell. "It wasn't a disease. It didn't kill you. But now with the [opioid] epidemic it turns out that it does." ●

#### FIND OTHER PAIN RESEARCHERS AT NIH:

**Scientific Interest Groups:** See the PAIN Scientific Interest Group in the adjacent column. For a list of all SIGs, go to <https://oir.nih.gov/sigs>.

**Intramural Research Program (IRP) Website:** Includes individual pages for all of the IRP's approximately 1,050 principal investigators. You can search for "pain" on the principal investigators page (<https://irp.nih.gov/our-research/principal-investigators>) or on the main IRP page (<https://irp.nih.gov>).

**NIH Intramural Database (NIDB):** The NIDB contains a wide array of information about the activities of NIH researchers including annual reports and related publications. Select a year and an IC (or "All ICs") and enter a search term to get a list of related researchers and their projects. The NIDB website is <https://intramural.nih.gov/>.

## PAIN Scientific Interest Group

**THE PAIN SCIENTIFIC INTEREST** Group (PAIN SIG) is comprised of investigators from a number of different NIH institutes and centers that are interested in the neurobiological mechanisms underlying pain. The group includes students, postdocs, postbacs, staff, investigators, and clinicians. Research areas of interest span from molecular and cellular studies in model systems to clinical studies in both healthy individuals and pain patients. The SIG's goal is to provide a forum where researchers from different backgrounds can openly exchange their ideas and perspectives as well as discuss the latest technical approaches for the study of pain.

The PAIN SIG hosts monthly seminars presented by pain research leaders across the country as well as an annual mini-symposium that showcases cutting-edge intramural pain research. Every month, all PAIN SIG trainees are also invited to join the speaker for lunch on the day of the seminar. See <https://nccih.nih.gov/research/intramural/sig/painSIG>.

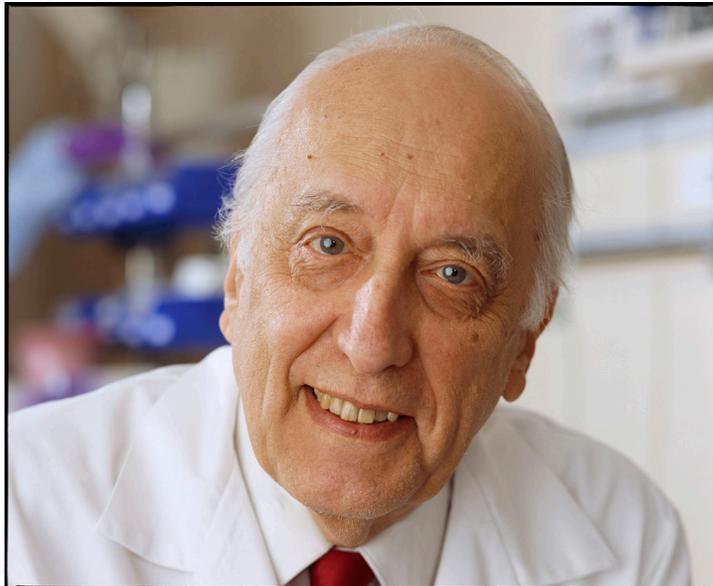
To join the PAIN Scientific Interest Group mailing list, visit the PAIN Scientific Interest Group LISTSERV home page (<https://list.nih.gov/cgi-bin/wa.exe?A0=PAINGROUP-L>), then click the "Subscribe or Unsubscribe" link in the right sidebar.

For additional information about the PAIN SIG or the events it sponsors, contact one of the moderators: **Lauren Atlas** ([lauren.atlas@nih.gov](mailto:lauren.atlas@nih.gov)), **Yarimar Carrasquillo** ([yarimar.carrasquillo@nih.gov](mailto:yarimar.carrasquillo@nih.gov)), **Alex Chesler** ([alexander.chesler@nih.gov](mailto:alexander.chesler@nih.gov)), or **Mark Hoon** ([mhoon@dir.nidcr.nih.gov](mailto:mhoon@dir.nidcr.nih.gov)). ●

## Thomas Waldmann, M.D.

### Making Discoveries in Immunology

BY CLAIRE E. MCCARTHY, NCI



NCI

NIH Distinguished Investigator Thomas A. Waldmann, M.D.

**WHO WOULD HAVE THOUGHT THAT A** mere \$50 grant could launch a career in medical research? But that's exactly what happened in 1954 when Harvard Medical School (Boston) gave a \$50 grant to two medical students—**Thomas Waldmann** and **Sherman Weissman**—to study erythropoietin (a hormone that stimulates the production of red blood cells) in rabbits. After their medical residencies—Waldmann at Massachusetts General Hospital (Boston) and Weissman at Boston City Hospital (Boston)—both went on to be clinical associates at the National Cancer Institute (NCI). And both have gone on to have distinguished research careers—Waldmann at NCI and Weissman at Yale (New Haven, Connecticut).

Waldmann's fascination with immunology emerged during his internal medicine residency when he did a rotation in Mass General's polio ward, which had 300 patients, 70 of whom could only breathe while encased in giant mechanical respirators called iron lungs. "That was the last polio epidemic in our country," he said. Jonas Salk

had developed the polio vaccine and by 1956 it had become widely available. "I was truly impressed with how effective a vaccine could be for preventing a very serious, acute, infectious disease."

#### Coming to NIH.

Waldmann applied to NIH for a research position in lieu of serving two years in the mili-

tary. In the 1950s, between the Korean and Vietnam wars, the general military draft and the doctor draft were in effect. The doctor draft channeled physicians into two-year obligatory service in the Army, Navy, Air Force, or U.S. Public Health Service (which included NIH clinical associate positions). In 1956, Waldmann came to NIH as one of the "Yellow Berets" to learn science as a clinical associate in the NCI's Metabolism Branch. (The term "Yellow Beret" came about because those who came to NIH to avoid the draft were initially perceived as cowards. Later, however, most considered "Yellow Beret" to be a badge of pride.)

"I intended to be here for two years—that was 62 years ago," said Waldmann. "My education has been in the corridors of the NIH [because] of the proximity of the Clinical Center to research labs and the ability to have patient-oriented clinical research." The NIH Clinical Center had just opened in 1953.

As a trainee in NCI, Waldman began studying how the body metabolizes proteins, including immunoglobulins, in

the blood. By 1959, he had become a senior investigator, and his research had expanded to include work with patients with primary immunodeficiency diseases and disorders of lymphatic channels. In the 1950s and 1960s, scientists had only a primitive understanding of the immune system. "There was no knowledge of B and T cells, retroviruses were not defined, receptors were unknown, etc.," he recalled.

At that time, scientists didn't yet have the ability to use knockout or transgenic animals, so Waldmann and his colleagues studied patients with genetic immunodeficiency diseases to understand the immune system.

**Discovery.** In one project, Waldmann and his colleagues discovered that some patients who had unusually low concentrations of immunoglobulin in their blood were losing the protein through enlarged lymph vessels that supplied the lining of the small intestine. In 1961, he published a paper in *Gastroenterology* describing the discovery of this disease, which he called primary intestinal lymphangiectasia.

People with the disease were prone to infections, had severe abdominal discomfort, and were not likely to live to adulthood. In 1967, Waldmann and his colleagues published a comprehensive report in the *Journal of Clinical Investigation*. Later, the National Organization of Rare Diseases named the disease "Waldmann Disease."

The genetic cause for this gastrointestinal disease was discovered in 2017 by someone Waldmann had recruited to NIH in 1989: **Michael Lenardo**, who's now chief of the Molecular Development of the Immune System Section at the National Institute of Allergy and Infectious Diseases. Lenardo and his colleagues had encountered children in Turkey who had a similar disease and determined that it could be attributed

to defects in the *CD55* gene. The defect prevented the production of the cell-surface protein complement decay-accelerating factor (which is produced by *CD55*), which regulates proteins that help immune mediators clear pathogens from the body.

**Serendipitous finding.** In 1981, there was a serendipitous finding in Waldmann's laboratory by the late **Takashi Uchiyama**. Uchiyama was trying to make antibodies that would bind to the marker CD4 (extracellular cluster of differentiation-4), which is expressed by a specific helper T cell. However, the antibody he made targeted what turned out to be the receptor for interleukin-2 (IL-2), a cytokine involved in the activation of T cells.

This discovery was important because it showed that the IL-2 receptor was expressed on abnormal T cells—in patients with leukemia, graft-versus-host disease, and autoimmune conditions—but not on most T cells of healthy individuals. In 1997, after years of research and clinical trials, the FDA approved the IL-2 receptor as a treatment to prevent transplant rejection. Later IL-2 and similar IL-2 receptor antibodies were approved as therapies for immune-related disorders, cancer, and multiple sclerosis.

**IL-15 plays a role.** While Waldmann was studying IL-2 and its receptor, he co-discovered a new cytokine, IL-15. “We showed that IL-15 played an enormous role in the maintenance and development of natural killer [NK] cells and memory CD8 T cells,” he said. Intravenous infusions of IL-15 in cancer patients, “showed a 30-fold increase in the number of NK cells and a 350-fold increase an NK-cell subset.”

Further, Waldmann showed that using a combination therapy of IL-15 and tumor-specific antibodies was an effective cancer treatment in mouse models. In clinical trials, this combination treatment has shown encouraging results in cancer patients.

Waldmann hypothesized that IL-15 could also improve the effectiveness of an immunotherapy called checkpoint blockade. The immune system produces molecules that keep immune responses in “check” to prevent uncontrolled inflammation and damage. Some cancer cells have figured out a way to exploit these checkpoints to avoid being attacked by the immune system.

Treating a patient with checkpoint-blockade therapy is like “removing the brakes of the immune system that were preventing immune cells from responding to a cancer,” Waldmann said. “IL-15 treatment would be an accelerator to enhance the CD8 T-cell response to cancer cells. So, combining these treatments would significantly enhance tumor immunity.” His hypothesis was proven correct. Now this combination therapy is being investigated in clinical trials.

**New investigations.** Waldmann's ongoing translational research builds on his previous studies of IL-2 and IL-15 receptor signaling. Now, he is investigating downstream mediators of the IL-2 and IL-15 pathways. He is studying the role of the JAK-STAT (Janus kinase–signal transducer and activation of transcription protein) signaling pathway in cancers and immune disorders. Disruptions in JAK-STAT interactions contribute to increased cell division, cell survival, and tumor formation.

Waldmann is testing the effectiveness of JAK-STAT inhibitors as cancer treatments in experimental models. He wants to watch as this research at the NIH grows, matures, and eventually produces clinical therapies.

Yet, along with looking forward, Waldmann reflected back on studies that helped immunology advance. “Science builds on what goes on in the past,” he said. “Certainly, the field of immunology has changed [thanks to the] science of the past and the huge number of people that contributed to the field.” ●

**MORE ABOUT THOMAS A. WALDMANN, M.D.**  
*Co-Chief of the Lymphoid Malignancies Branch, NIH Distinguished Investigator, Head of the Cytokine Immunology and Immunotherapy Section, National Cancer Institute (NCI)*

**Website:** <https://irp.nih.gov/pi/thomas-waldmann>

**Born:** New York City

**Grew up:** In New York and Washington, D.C.

**Research interests:** Understanding how the dysregulation of the human immune response leads to autoimmune disorders, immunodeficiency, and malignant diseases  
**Education:** University of Chicago, Chicago (A.B. in philosophy) and Harvard Medical School, Boston (M.D.)

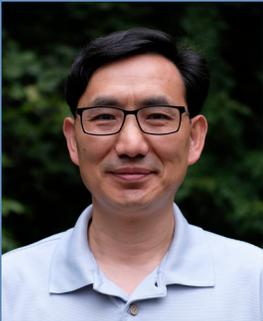
**Training:** Residency in internal medicine at Massachusetts General Hospital (Boston)

**Came to NIH:** In 1956, as a clinical associate; appointed senior investigator in 1959; head of NCI's Immunophysiology Section 1968–1973; in 1971, became chief of the Lymphoid Malignancies Branch; became an NIH Distinguished Investigator in 2007

**Outside interests:** Photography

**Little known fact:** When I was in medical school in the 1950s, it was the era of investigations by Senator Joseph McCarthy and the House Un-American Activities Committee (HUAC). The HUAC came to Harvard to search for communists in academia. In rebellion, someone at Vanderbilt Hall (the dormitory for medical students) painted all the toilet seats red. I woke in the night and went to the bathroom and ticked my tennis shoe in the red paint. The next thing I knew, I was in the dean's office and the people were saying, “Thomas Waldmann, we hold you morally and financially responsible for this reprehensible act.” However, I was too much of a [nose-to-the grindstone sort of person] to be punished, and so I was exonerated. Although I didn't get in trouble, my friend Sherman Weissman [who later came to NIH as a clinical associate] put a red jelly bean in my mailbox every day during that period.

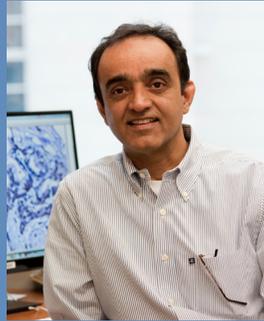
## Recently Tenured



ZHEN CHEN, NICHD



JESSICA GILL, NINR



PERWEZ HUSSAIN, NCI-CCR



ELISEO J. PÉREZ-STABLE, NHLBI



YOUSUKE TAKAHAMA, NCI-CCR

### ZHEN CHEN, PH.D., NICHD

*Senior Investigator, Biostatistics and Bioinformatics Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development*

**Education:** People's University of China, Beijing, China (B.A. in economics); University of Connecticut, Storrs, Connecticut (M.S. in economics; Ph.D. in statistics)

**Training:** Research fellow, Biostatistics Branch, National Institute of Environmental Health Sciences (2001-2003)

**Before coming to NIH:** Assistant professor, Department of Biostatistics and Epidemiology, University of Pennsylvania (Philadelphia; 2003-2008)

**Came to NIH:** In 2001-2003 for training; returned in as a staff scientist in NICHD; became an investigator in 2009

**Selected professional activities:** Associate editor, *Statistics in Biosciences*; Regional Advisory Board, International Biometrics Society's Eastern North American Region; board of directors, International Chinese Statistical Association

**Outside interests:** Photography; playing badminton

**Website:** <https://irp.nih.gov/pi/zhen-chen>

**Research interests:** I am developing statistical methods that will help researchers analyze and interpret data from

epidemiological studies related to maternal and child health. I have focused on Bayesian statistical methods and their applications in analyzing diagnostic accuracy data and modeling chemical mixtures.

In my diagnostic accuracy work, I designed and led the NICHD Physician Reliability Study (PRS), a methodological-clinical study that was built from another larger epidemiological study on endometriosis. My team's goal was to develop statistical methods that could be used to empirically estimate the accuracy of endometriosis diagnosis. This work is important because we don't know what causes endometriosis or what the practitioner-related factors are that influence how accurately it is diagnosed.

For the PRS, we invited gynecologists with different levels of expertise to render gynecologic diagnoses based on clinical information ranging from symptomology to operative reports, imaging data, and histologic findings. We found that the more clinical information we provided to the physicians, the more likely they were to make an accurate diagnosis of endometriosis. Moreover, their diagnostic precision was not significantly associated with their level of experience.

Statistical approaches for modeling chemical mixtures is an exciting and emerging field, especially when exposures to environmental pollutants are measured and

analyzed in relation to health outcomes. In one project, my team developed and applied a statistical approach, called latent-class modeling, to a study of polychlorinated biphenyls (PCBs) and endometriosis. Our analysis revealed that there was a significant association between specific PCB compounds and incident endometriosis.

In the future, I plan to continue developing statistical approaches and will incorporate receiver operating characteristic curve analysis, which is used to assess the performance of diagnostic tests. This work will have applications in a broad range of studies including NICHD's Fetal Growth Studies, in which one research question is whether doing fetal ultrasounds closer to delivery is better than early screening scans at predicting a newborn's size at birth. I also plan to develop and use other statistical methodologies, such as causal-mediation analysis, that will help researchers understand and delineate biological pathways by which treatments or exposures affect health outcomes.

If you have been recently tenured, the *NIH Catalyst* will be contacting you soon about including you on these pages. It's a great way for your colleagues to get to know about you and your work.

**JESSICA GILL, C.R.N.P., PH.D., NINR**

*Senior Investigator, Tissue Injury Branch, Brain Injury Unit, and Deputy Scientific Director, National Institute of Nursing Research*

**Education:** Linfield College, McMinnville, Oregon (B.S. in nursing; minor in biology); Oregon Health and Sciences University, Portland, Oregon (M.S. in psychiatric nursing); Johns Hopkins University School of Nursing, Baltimore (Ph.D.)

**Training:** Postdoctoral fellowship, National Institute of Mental Health (2007–2009); assistant clinical investigator, NINR (2009–2010)

**Before returning to NIH:** Assistant professor in nursing, George Mason University (Fairfax, Virginia) and Krasnow Institute for Advanced Studies (Fairfax, Virginia)

**Came to NIH:** In 2007–2010 for training; returned in 2012 as a Lasker Clinical Research Scholar and tenure-track investigator, NINR

**Selected professional activities:** Elected to serve on the National Academies Committee on Disability Assessment for traumatic brain injuries within the U.S. Department of Veterans Affairs; co-director of biomarker cores for the Center for Neuroscience and Regenerative Medicine, and National Collegiate Athletic Association consortium; editorial board member for *Journal of Head Trauma and Rehabilitative Medicine*, *Journal of Neurotrauma*, and *Brain Injury*

**Outside interests:** Traveling; spending time with her children

**Website:** <https://irp.nih.gov/pi/jessica-gill>

**Research interests:** I am interested in traumatic brain injury (TBI) in military personnel and civilians as well as in athletes with concussions. My lab is undertaking studies to determine the mechanisms underlying the neurological symptoms and deficits of these injuries. We are using leading-edge technology to identify and link -omic biomarkers to neuronal damage through brain-imaging methods that are

unique to the NIH. I am developing methods for identifying brain-injured patients who are at risk for a poor recovery.

In a 2017 study, colleagues and I showed that measuring concentrations of a protein called tau in the blood could potentially provide an unbiased tool to help prevent athletes from returning to action too soon and risking further neurological injury. Tau is also connected to the development of Alzheimer and Parkinson diseases and is a marker of neuronal injury after severe TBIs. Recently, we reported that we have identified tau and other proteins in the blood within 48 hours of a TBI. We also found that we are able to use advanced imaging to identify patients with neuronal injuries.

My interest in research began when I was a undergraduate. I volunteered with women and children whose lives were negatively affected by violence. I observed that this extreme stress resulted in differing outcomes, with some women being substantially impaired, whereas others were able to recover. I went on to pursue a graduate degree in psychiatric nursing, which included clinical training in the post-traumatic stress disorder (PTSD) program at the U.S. Department of Veterans Affairs. Research questions about trauma and resiliency were amplified during my work with Vietnam veterans who remained affected by their combat service decades after returning home. Based on these experiences, I decided to pursue a doctorate in nursing. My dissertation research demonstrated the presence of high rates of PTSD in urban health-care-seeking women and that a PTSD diagnosis was associated with perceived health declines as well as with higher concentrations of inflammatory markers and a dysregulation of endocrine functioning.

My discoveries are providing the foundation for early interventions to prevent the often-irreversible symptoms resulting from post-TBI neurological damage.

CONTINUED ON PAGE 18 ►



## History Exhibits

### A NEW SET OF DRAWINGS BY SANTIAGO RAMÓN Y CAJAL

Newly arrived is the latest set of seven neuroanatomy drawings by Santiago Ramón y Cajal on rotation on the first floor of the Porter Neuroscience Center (Building 35). The drawings date back to the turn of the last century when Santiago Ramón y Cajal shared the Nobel Prize (1906) with Camillo Golgi for their work on the structure of the nervous system. We thank our partners at the Cajal Institute in Madrid, Spain for making this exhibit possible. You can see the original drawings, or touch 3-D prints of enlarged drawing details for the next year.

### CELEBRATING THE LIVES OF MICHAEL POTTER AND CHRISTIAN ANFINSEN

The twin exhibits—titled “Curiosity and Collaboration: The Work of **Michael Potter**” and “**Christian Boehmer Anfinsen: Protein Folding and the Nobel Prize**”—are positioned in the long, first-floor corridor of Building 10, just “north” of the FAES bookstore.

Potter, who died in 2013, was an ingenious and generous researcher whose 50-year career at NCI was distinguished by amazing discoveries and superb mentoring. His 1984 Albert Lasker Award for Basic Medical Research was for his “elegant studies of plasma cell tumors, leading to the development of monoclonal antibodies and enlarging our knowledge of carcinogenesis and the immune system.”

Like Potter, Anfinsen had a long and productive career at the NIH. Anfinsen shared half of the 1972 Nobel Prize in chemistry for “work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation.” ●

Find out about other historical exhibits at <https://history.nih.gov/museum/onsite.html>



## Recently Tenured

CONTINUED FROM PAGE 17

### PERWEZ HUSSAIN, PH.D., NCI-CCR

*Senior Investigator, Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute*

**Education:** Magadh University (now Patliputra University), Patna, India (B.S. in zoology); Patna University, Patna, India (M.S. in zoology); Jawaharlal Nehru University, New Delhi, India (Ph.D. in cancer biology)

**Training:** Postdoctoral fellow, Swiss Institute for Experimental Cancer Research (Lausanne, Switzerland); visiting fellow (1994–1996) and research fellow (1999–2000), Laboratory of Human Carcinogenesis, Division of Cancer Etiology, NCI

**Came to NIH:** In 1994 for training; in 2000 became staff scientist in NCI (2000–2009); in 2009 became tenure-track investigator

**Selected professional activities:** Chairman, Pancreatic Cancer Interest Group, NIH; editorial board member for *Carcinogenesis*, *Cancer Molecular Medicine*, *International Journal of Cancer*, and *Journal of Pancreatic Cancer*

**Outside interests:** Gardening; exploring mountains

**Website:** <https://irp.nih.gov/pi/s-perwez-hussain>

**Research interests:** My research focuses on pancreatic cancer. My lab is using an integrative-biology translation-research approach to investigate the molecular pathogenesis of pancreatic cancer. Pancreatic cancer is one of the most lethal malignancies with a median survival of six months and a five-year survival of eight percent. The dismal prognosis is due to the lack of an effective therapy and reliable biomarkers for early diagnosis. Understanding pancreatic tumor biology is essential if we are to develop strategies for prevention, diagnosis, and effective therapeutic intervention.

We are particularly interested in the role that inflammatory mediators play in the underlying mechanisms of tumor

progression and therapeutic resistance. We are analyzing clinical samples to evaluate how genetic and metabolic markers are associated with disease aggressiveness. We are also using pancreatic cancer cells, genetically engineered mouse models of pancreatic cancer, and patient-derived xenografts to investigate how the disease progresses.

The aim of our research is to understand pancreatic tumor biology and identify critical pathways associated with tumor progression and disease aggressiveness that can be targeted for therapeutic intervention.

In one of our current projects, we are investigating the role of a proinflammatory cytokine—macrophage migration inhibitory factor (MIF)—and nitric oxide in tumor biology. These are two interconnected mediators of immune and inflammatory responses that are produced by both tumor epithelial cells and inflammatory cells. We have recently shown that increased expression of MIF in tumors is significantly associated with poor outcomes in pancreatic cancer, induced epithelial-to-mesenchymal transition, and enhanced tumor growth and metastasis. We are exploring whether MIF and other inflammatory mediators are candidate therapeutic targets in pancreatic cancer.

In another project, we are using genomics, transcriptomics, and metabolomics to molecularly profile pancreatic cancer. The highly heterogeneous characteristics of pancreatic tumors underscores the significance of doing comprehensive and integrative molecular profiling in a larger cohort of tumors. We need to understand how several molecular events are intertwined as a network leading to the disease's aggressiveness and poor outcome. The delineation of subtype-specific biology and critical pathways associated with disease outcome may identify subtype-specific candidate targets for therapeutic intervention.

### ELISEO J. PÉREZ-STABLE, M.D., NHLBI

*Senior Investigator, National Heart, Lung, and Blood Institute; Director, National Institute on Minority Health and Health Disparities*

**Education:** University of Miami, Coral Gables, Florida (B.A. in chemistry); University of Miami School of Medicine, Miami (M.D.)

**Training:** Residency in primary care internal medicine, and research fellowship in general internal medicine, University of California at San Francisco (San Francisco)

**Before coming to NIH:** Professor of medicine, chief of the Division of General Internal Medicine, director of the Center for Aging in Diverse Communities, and attending physician, Moffitt-Long Hospital, UCSF

**Came to NIH:** In September 2015

**Selected professional activities:** Elected to the American Society for Clinical Investigation (1996); elected to the National Academy of Medicine, formerly the Institute of Medicine (2001)

**Outside interests:** Loves movies, theater, music, arts, and visiting nature. Cats have had a special place in his life, too.

**Website:** <https://www.nimhd.nih.gov/about/directors-corner/about.html>

**Research interests:** My research began in Latino health and focused on tobacco use. I aimed to improve the health of racial and ethnic minorities and underserved populations through patient care, education, and discovery. Advancing patient-centered care will require a stronger foundation in primary care and improved cross-cultural communication skills among clinicians, as well as greater diversity in the biomedical research workforce.

I spent more than 30 years leading research on smoking cessation and tobacco control in Latino populations in the United States and Latin America. My collaborations with researchers and public-health



advocates in Argentina helped put tobacco use on the country's public-health agenda, raised awareness of tobacco use as a critical health problem, built capacity for tobacco-control policy, and created opportunities for prevention and treatment measures through physician education and smoking-cessation programs.

As a co-principal investigator of the NCI-funded *Redes en Acción* National Latino Cancer Control Research and Education Network, I spearheaded the development of a research agenda on cancer control for Latinos in the United States. I have also led research on aging among minorities.

My research will continue to focus on: 1) tobacco-use behavior as it relates to other substance use, unhealthy behaviors, chronic stress, and mental health among Latinos of different national origins; 2) differential risk of lung cancer among racial and ethnic minorities as reflected in biomarkers of nicotine and tobacco-specific carcinogens; and 3) communication factors—including language fluency, health literacy, numeracy, cultural factors, and unconscious bias—as they affect clinicians and minority populations within the NIH Clinical Center.

---

**YOUSUKE TAKAHAMA, PH.D., NCI-CCR**

*Senior Investigator, Thymus Biology Section, Experimental Immunology Branch, Center for Cancer Research, National Cancer Institute*

**Education:** School of Science, Tokyo Institute of Technology, Tokyo (B.Sc. in biological chemistry); Graduate School of Medicine, Osaka University, Osaka, Japan (M.Sc. and Ph.D. in immunology)

**Training:** Research fellow, Osaka University Medical School (Osaka, Japan; 1988–1989); visiting fellow and visiting associate, Experimental Immunology Branch, NCI (1989–1993)

**Before returning to NIH:** Director, Institute of Advanced Medical Sciences, and Professor

of Experimental Immunology, University of Tokushima (Tokushima, Japan)

**Came to NIH:** In 1989–1993 for training; returned in 2018

**Selected professional activities:** Founding organizer, *Global Thymus Network*; editorial board, *European Journal of Immunology*; member, Science Council of Japan

**Outside interests:** Playing the shamisen (a three-string lute) for classical nagauta music; playing bass guitar for jazz-rock music

**Website:** <https://irp.nih.gov/pi/yousuke-takahama>

**Research interests:** My main interests are the development and function of the thymus and thymic epithelial cells, especially with regard to the repertoire selection of T lymphocytes. In my lab, we are trying to understand the molecular mechanisms that build functionally competent thymus microenvironments that support the production and selection of T cells, govern thymic selection to establish a functional repertoire of mature T cells, and position developing T cells to localize within the thymus microenvironments for T-cell repertoire formation.

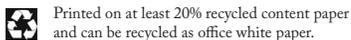
The questions we'd like to address include determining how diverse microenvironments are formed in the thymus; figuring out how the thymic microenvironment contributes to the establishment of self-tolerance in T cells; studying the mechanisms of how developing T cells localize multiple thymic microenvironments for T-cell repertoire formation; and understanding how positive selection in the thymic microenvironment fine-tunes antigen responsiveness in T cells.

A better understanding of the molecular machinery that is essential for establishing thymic microenvironments and governing the selection of T cells should help us control immune diseases such as autoimmunity and allergy as well as overcome cancer and various clinical situations such as post-chemotherapy immune-cell reconstitution.

## 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  
**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  
**NIHES:** National Institute of Environmental Health Sciences  
**NIHGS:** 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

Official Business  
Penalty for Private Use \$300



## CATALYTIC REACTIONS?

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

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

**READ MORE ARTICLES, AND EXPANDED VERSIONS OF THE ONES IN THIS ISSUE, ONLINE AT <https://irp.nih.gov/catalyst/v26i5>**

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

Address correspondence to:  
Building 1, Room 333, NIH  
Bethesda, MD 20892  
Ph: 301-402-1449  
Fax: 301-402-4303  
e-mail: [catalyst@nih.gov](mailto:catalyst@nih.gov)

*The NIH Catalyst* online:  
<https://irp.nih.gov/catalyst>

## NIH IN HISTORY



### Greenhouse at NIH?

**OPENED IN 1959**, Building 32A was a greenhouse used by the National Institute of Mental Health (NIMH) to investigate the biochemistry of medicinal plants. The late **S. Harvey Mudd**, chief of NIMH’s Section on Alkaloid Biosynthesis and Plant Metabolism, used the greenhouse to study how plants synthesize methionine. Methionine is an essential amino acid for humans and is found in meat, fish, and dairy products, as well as in some plants such as nuts, soy, and beans. A deficiency in methionine can lead to inflammation of the liver, anemia, and graying hair. Mudd also did research that led to the practice of putting folic acid into the flour supply to help prevent birth defects. The greenhouse was taken down in the early 1990s. ●



OFFICE OF NIH HISTORY

**PUBLISHER**  
MICHAEL GOTTESMAN  
Deputy Director for Intramural Research, OD

**EDITORS**  
JOHN I. GALLIN  
Associate Director for Clinical Research  
Chief Scientific Officer, CC  
PAUL H. PLOTZ  
Scientist Emeritus, NIAMS

**EDITOR-IN-CHIEF**  
LAURA STEPHENSON CARTER

**WRITER-EDITOR**  
CHRISTOPHER WANJEK  
Director of Communications, OIR

**COPY EDITOR**  
SHAUNA ROBERTS

**CONTRIBUTING WRITERS**  
MANJU BHASKAR  
ANNE DAVISON  
BRANDON LEVY  
CLAIRE E. MCCARTHY  
CRAIG MYRUM  
EMILY PETRUS  
ZOE SHANCER  
LISA YUAN

**PHOTOGRAPHERS/ILLUSTRATORS**  
ERNIE BRANSON, PATRICIA DZ,  
GAYLE JOSEPH, MICHAEL LETKO  
MEDICAL ARTS  
OFFICE OF NIH HISTORY  
ANDREW PROPP, GEORGE RUDY  
MARLEEN VAN DEN NESTE

**EDITORIAL ADVISORY BOARD**  
CHRISTINA ANNUNZIATA, NCI  
DAN APPELLA, NIDDK  
TREVOR ARCHER, NIEHS  
MICHAEL ESPEY, NCI  
AUDRAY HARRIS, NIAID  
SUSAN LEITMAN, CC  
BERNARD MOSS, NIAID  
HYUN PARK, NCI  
EMILY PETRUS, NINDS (FELLOW)  
JULIE SEGRE, NHGRI  
ANDY SINGLETON, NIA  
GISELA STORZ, NICHD  
RONALD SUMMERS, CC  
RICHARD WYATT, OIR  
WEI YANG, NIDDK