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NIH's Early Homes

From N.Y. to D.C. to Bethesda

BY VICTORIA A. HARDEN AND MICHELE LYONS

From its inception, the National Institutes of Health has had responsibilities, scientific knowledge, and ambitions that have increased faster than its real estate. Before moving to its current location in Bethesda, Maryland, in 1938, the NIH and its predecessor, the Hygienic Laboratory, occupied three other sites, each one bigger than the last. One of these sites, on Navy Hill in Washington, D.C., has been added to the National Register of Historic Places.

The United States Public Health Service originated in 1798 as the Marine Hospital Service (MHS), a branch of the Treasury Department that cared for sick and injured U.S. merchant seamen. The Hygienic Laboratory was established in 1887 at the Marine Hospital (in the Stapleton area of Staten Island, New York) just as the germ theory of infectious disease was taking hold.

The MHS hoped that the new field of bacteriology, spurred by the theory's acceptance, would help the MHS clinicians charged with examining newly arrived immigrants—and the crews on the ships that brought them—for cholera and yellow fever. Laboratory Director **Joseph J. Kinyoun** quickly proved the usefulness of the laboratory by demonstrating the presence of the *Vibrio cholera* bacterium among passengers on the steamship Alesia. But the laboratory consisted of one room and one employee—Kinyoun. Supervising Surgeon General John B. Hamilton (who served from

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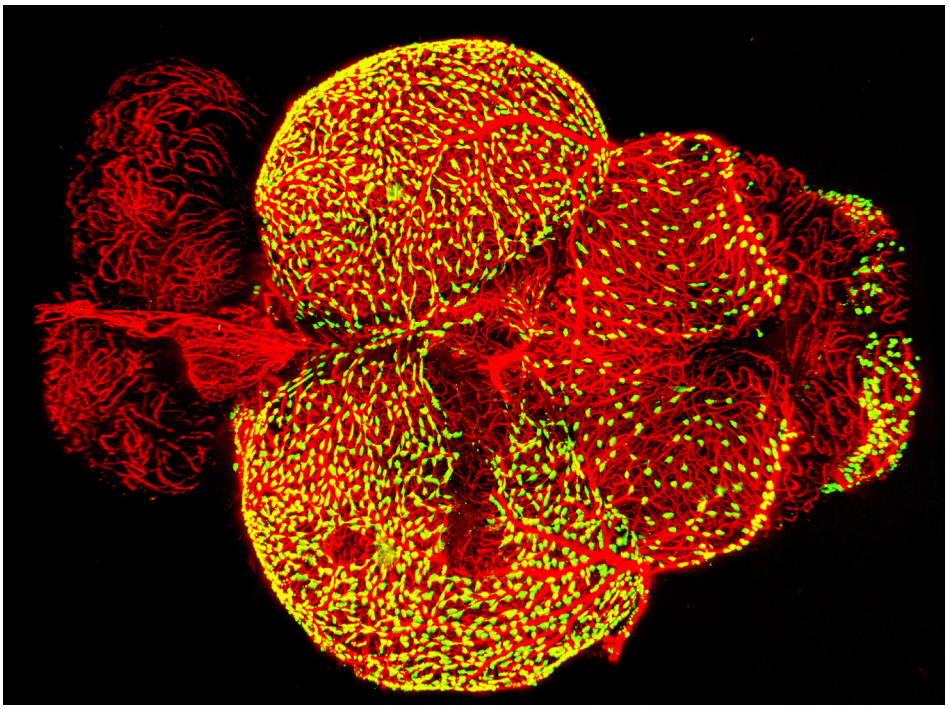
Celebrating the Art of Science

Blood Vessel Cells in a Zebrafish Brain



D. CASTRANOVA, M. VENERO GALANTERNIK, B. WEINSTEIN (NICHD); T. NGUYEN (U OF MD)

Scientists from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) produced this award-winning microscopy image that shows how fluorescent granular perithelial cells (FGPs, in green) are closely associated with blood vessels (red) that surround an adult zebrafish's brain. The investigators recently discovered that FGPs, which are found in both zebrafish and mammals, are related to cells that form the lymphatic system and are thought to play a key role in maintaining the blood–brain barrier and clearing toxic substances from the brain. The image was selected as one of the winners of the 2017 BioArt competition held by the Federation of American Societies for Experimental Biology (FASEB) every year. Read more online at https://irp.nih.gov/catalyst/v26i2/celebrating-the-art-of-science/. ●

CONTENTS

The NIH Assembly of Scientists

What We Do and How It Affects You

BY CYNTHIA DUNBAR (NHLBI) AND KATHERINE CALVO (CC)

We appreciate this opportunity to update you on the Assembly of Scientists' (AOS) activities and priorities. As recounted in **Alan Schechter**'s history of the AOS (see facing page), robust engagement among the NIH scientific community, NIH leadership, and the AOS has waxed and waned around specific issues that have influenced scientific productivity and quality of life at the NIH. In 2016, the AOS amplified its role by becoming an advisory body to the Deputy Director for Intramural Research (DDIR).

The AOS's objectives include 1) the advancement of science and the maintenance of the highest standards of scientific research; 2) the maintenance of the highest standards in the translation of scientific discoveries to the care of patients suffering from disease; and 3) providing a forum and a representative voice for AOS members on issues that are critical to their accomplishment of the first two objectives.

Membership in AOS is automatic (unless declined) for all intramural tenured and tenure-track investigators, staff clinicians or scientists, senior scientists or clinicians, assistant clinical investigators, and senior extramural program staff members. The AOS is similar to a faculty senate at an academic institution. The members elect a council of 24 representatives, each serving four-year terms with half the seats up for election every two years. Council membership consists of representatives from at least 12 different institutes or centers and includes at least one tenure-track investigator, staff clinician, and staff scientist. Standing and ad hoc committees address specific areas: clinical research, ethics, information technologies, collaboration and community, promotion and tenure, travel, and workforce (includes equity and diversity).

The council meets monthly, but its work is done by the committees. For example, the AOS Clinical Research Committee has coordinated with NIH's Staff Clinician Committee and NIH leadership to improve career-advancement pathways for staff clinicians with the intent of enhancing the retention and recruitment of outstanding clinicians at the NIH.

Representatives from the AOS council are also ad hoc members of critical NIH bodies such as the Board of Scientific Directors, the Clinical Directors Committee, the Medical Executive Committee, the new NIH Equity Committee, and the Deputy Ethics Councilors Committee. As information flows between AOS members and these policy and implementation groups, NIH senior leaders gain perspective on NIH scientists' and clinicians' concerns. These interactions allow us to work toward improving the overall environment for science on campus.

The AOS yearly "town hall" meeting—held each spring—provides an additional forum for the AOS council and invited NIH leaders to interact with AOS members. Everyone is welcome to attend (but only members can vote). The meetings are announced via e-mail from DDIR **Michael Gottesman**.

Council priorities are informed by the AOS survey, which is circulated every two years. Nearly 800 individuals—approximately 30 percent of the over 2,500 AOS members—completed the fall 2017 survey. (Thank you for participating!) This survey gave the AOS council a snapshot of members' priorities for the future. We have provided relevant portions of the survey data to NIH leadership to highlight critical issues and stimulate them to work with us to solve ongoing problems.

Some pressing concerns included departures of active clinicians from both the institutes and the Clinical Center, increased regulatory burden for clinical research, lack of clear and fulfilling career-development pathways for staff clinicians and staff scientists, and significant barriers to hiring and retention.

The council also continues to focus on harmonizing ethics policies among institutes; clarifying travel policies and procedures; and working with the Center for Information Technology on proposed restrictions on travel with NIH computers and other devices. Recently, AOS Council members have joined an intensive effort to develop procedures for reporting, investigating, and responding to sexual harassment.

We are always eager to hear from AOS members with suggestions, information, and concerns. Please contact us (dunbarc@nhlbi.nih.gov or calvok@cc.nih.gov) anytime. Consider running for the AOS council in elections to be held in November 2018 or join any of our committees. The more input and information we gather from the community, the more effective we can be. ●

For more information visit bit.ly/2BKNuQt.

Brief History of the NIH Assembly of Scientists

A Presence Since the 1950s; Rekindled in 2005

BY ALAN N. SCHECHTER, NIDDK

The NIH Assembly of Scientists (AOS), which was abuzz with activity from the late 1950s through the mid-1970s, sprang back to life in 2005 after the Department of Health and Human Services proposed "interim conflict-of-interest rules" for NIH employees. The new rules, which dramatically altered a policy established in 1995, were triggered by newspaper reports about senior NIH scientists being paid as consultants for pharmaceutical companies. Some NIH scientists had even violated aspects of the 1995 policy. The proposed rules prohibited NIH employees from engaging in any paid or unpaid consulting for companies or for universities, hospitals, and research institutes that received NIH funds.

The AOS understood the need for rigorous conflict-of-interest rules and "safeguards to ensure that financial interests did not compromise the design of research, the safety and well-being of patients, the collection and interpretation of research data, and the dissemination of research results, as well as funding and contract decisions." (*NIH Catalyst*, February 2005 Special Issue)

But people worried that the new rules seemed harsh and unfair and could seriously impair NIH scientists' professional roles in biomedical research, threaten to restrict academic interactions and "freedom," and impair NIH's ability to recruit and retain scientists. The rules also limited the acceptance of awards, affected aspects of professional travel, prohibited senior employees and their families from owning any stock in drug and biotech companies, and set forth other changes without regard to actual or perceived conflicts of interest.

Through many activities including developing alternative proposals and meeting regularly with the NIH leadership, the AOS successfully fought to make the final rules, issued in August 2005, less "over-reaching." AOS has continued to play an important role in representing the needs of the professional staff since then.

The AOS got its start in 1959 when, after several years of discussion and planning, two institutes—the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness (now the National Institute of Neurological Disorders and Stroke)—created an assembly of scientists "to help develop and promote the professional excellence and scientific achievements of the Institutes." (*NIH Record*, November 10, 1959)

Over the next few years, similar groups were constituted in almost all the institutes, and by 1964, an Inter-Institute Assembly Council of the leadership of each institute's assembly was established and met regularly.

The assemblies—and the Inter-Institute Council—worked with the NIH administration on such issues as overall research directions; policies related to recruitment, tenure, and sabbaticals; and interactions with the press. Other topics included changing policies about the staff's outside activities such as medical practices, for which rules varied from institute to institute. There was also a perceived need for in-house educational opportunities; that interest culminated in the establishment of the Foundation for Advanced Education in the Sciences in 1959 by NIH scientists.

It was, however, the Vietnam War and the divisions within the country, mirrored on a microcosm within the NIH campus, that led to maximum activity of the assemblies of scientists between 1966 and 1974. During that time, these groups sponsored many activities including lectures on campus by such individuals as pediatrician and anti-war activist Dr. Benjamin Spock, and even marches and demonstrations. Large groups of NIH scientists attended assembly meetings to express concern about policies related to various political influences on the NIH leadership. After these heady years, however, some of the assemblies functioned mostly as conduits for extra lines of communication between the institute leaders and their staffs. It was the events of 2005, described above, that resulted in the "reactivation" process, leading to today's very active NIH Assembly of Scientists and its council. ●

More Online:

To see a list of AOS Council members and committees and committe chairs, go to https://irp.nih.gov/catalyst/v26i2/guest-editorial.

From the Fellows Committee

Career Advice from NIH Scientist Serena Dudek

BY CLARISSA JAMES, NIMH

This past November, I took part in the annual Society for Neuroscience (SfN) conference, held in Washington, D.C. Attended by roughly 30,000 scientists, the conference offered nothing short of a neuroscience amusement park. The weekend was jam-packed with hundreds of symposia, workshops, posters, and lectures. My joy at reuniting with old colleagues paralleled only my excitement at the debut of the newest advancements in research.

As a postbac Intramural Research Training Award recipient not presenting any research, I could enjoy the conference at my own pace. I participated in a preconference Vision Workshop hosted by the National Eye Institute. I also attended a press conference on neuroprosthetics, a symposium on object and facial recognition, a press conference presented by several NIH institute directors, a roundtable discussion on neuroimaging biomarkers for mental illness, and poster sessions. My favorite was a talk given by NIH senior investigator **Serena Dudek** (National Institute of Environmental Health Sciences, NIEHS).

Although Dudek's session took place at 8:00 a.m., 40 people gathered to hear about her career journey and the lessons she learned along the way.

In the early 1980s, as an undergraduate at the University of California at Irvine (Irvine, California), Dr. Dudek was a research assistant in the lab of neuroscientist Gary Lynch. This work taught her the value of studying problems at multiple levels. For her Ph.D. in neuroscience at Brown University (Providence, Rhode Island), she worked with Mark Bear on long-term synaptic depression in the hippocampus. There, she learned the lessons of strength and persistence. She emphasized that being strong and persistent is not the same as never giving up.

STEVEN R. MCCAW, NIEHS

NIEHS senior investigator Serena Dudek shared career advice with people who attended the annual Society for Neuroscience conference in Washington, D.C., in November 2017.

"You need to know when to change your strategy," she explained. "But if something looks like it might be working—stay strong!"

During her first postdoctoral fellowship in neurobiology at the University of Alabama at Birmingham (Birmingham, Alabama), Dr. Dudek learned not to spread herself too thin. She found that when she was too stressed, she simply couldn't engage in creative problem solving. In 1996, she came to the NIH for a second postdoc and worked with **Richard D. Fields** in the Laboratory of Cellular and Synaptic Neurophysiology (National Institute of Child Health and Human Development). During that time, Dr. Dudek struggled with repeated failures and obstacles in her research. Such difficulties, she said, weigh especially hard on postdocs. But, she reminded the audience, when things are going well, you need to work as hard as you can.

"When you have a good thing going, just collect the data and go for it!" she said. "You never know when things will stop working." She also recommended that, to maintain a healthy state of mind, we should always have a side project that we know will work. We can turn to it when our main project isn't doing so well.

In 2001, Dr. Dudek was appointed a tenure-track investigator in NIEHS. One of the first lessons she learned was that good ideas can emerge anytime, often when you least expect them. For that reason, she recommended never missing departmental seminars.

An even more valuable lesson she shared was that when it comes to mysterious lab problems, sometimes it is something as simple as the quality of the water—you may need to have the water system fixed. Or the problem could be the "black stuff in the rig" (so don't be afraid to use bleach to get rid of it); or the oxygen; or drifting baselines that act as bad manipulators. She opined that women, especially, tend to blame themselves when things go wrong. Unless all other options have been ruled out, she said, do not blame yourself.

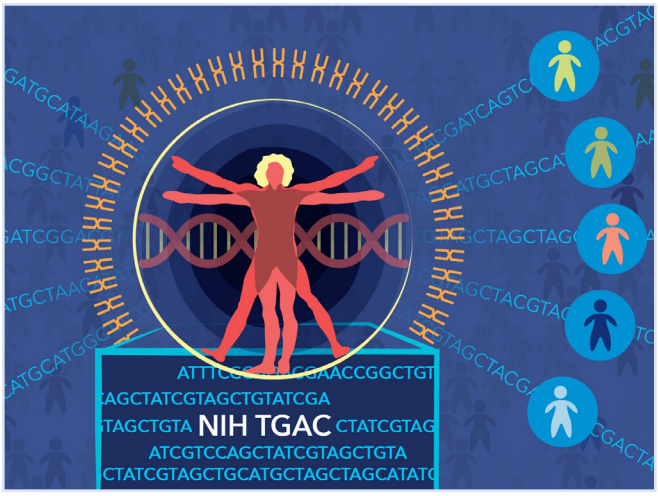
Dr. Dudek also said that there was no substitute for practice and that we must track our own progress. She confessed that although she was an expert now, it took hundreds of repetitions before she could perfect the techniques used to record neural activity in brain slices. If it takes years to become a skillful tennis player, she asked, why would it take less time to master a complicated technical skill?

Hearing Dr. Dudek recount her career journey and the often humorous lessons she learned along the way was such a pleasure. Her zeal for science inspired me as a young trainee, and her sage advice will surely stick with me as I continue my studies. ●

Genotype, Meet Phenotype

The Genomic Ascertainment Cohort is Open for Business

BY LESLEY EARL, NCI



NHGRI

The past decade has seen an explosion in the availability of genome-scale data—including chip genotypes, exome sequences, and even full-genome sequences—from hundreds of thousands of individuals. But even with all these data, it can be challenging for scientists to figure out the exact roles that particular genetic variants play in the development of diseases. Often, the problem is not the research itself, but the difficulty of finding enough people with the variant of interest.

To solve this conundrum, intramural researchers from the National Human Genome Research Institute (NHGRI) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) have joined forces to create a pilot program called The Genomic Ascertainment Cohort (TGAC). The program—guided by **Leslie Biesecker** (NHGRI), **Richard Siegel** (NIAMS), and former NCI Director **John Niederhuber** (now CEO of Inova Translational Medicine Institute, ITMI)—is aggregating genomic data from many existing cohorts into a single, searchable system. The goal is to enable NIH intramural investigators to study the phenotypic consequences of genetic variants.

TGAC will include at least 10,000 individuals whose genomes or exomes have been sequenced and who have agreed to be re-contacted for secondary phenotyping studies.

"So many times you have a very specific question; you may have even found a very important variant in the genome," said Siegel. But "you can't study it because you can't dial up the patient who has those specific variants."

"The beauty of [TGAC] is that you have all these data that are attached to able and willing research participants," said Biesecker. "It allows us to be much more efficient with research data."

TGAC is modeled after ClinSeq, an NHGRI clinical study launched by Biesecker in 2007 that was designed to facilitate the use of genomic data for a wide variety of research programs. The ClinSeq cohort includes about 1,500 participants who have consented to being re-contacted for additional clinical trials at the NIH. The genome or exome of each individual in the ClinSeq study was sequenced, and the aggregate data were made available to NIH researchers. Several studies, such as one by **Joshua Milner** (National Institute of Allergy and Infectious Diseases) on hereditary alpha-tryptasemia, have used the ClinSeq resource to identify individuals with particular variants of interest.

However, the ClinSeq cohort is relatively small, which makes finding infrequent alleles challenging. To increase the number and variety of participants—and therefore the likelihood of finding sufficient numbers of important genetic variants—TGAC is partnering with the ITMI to incorporate participants and genomic data from the Inova Longitudinal Childhood Genomic Study cohort. The study, which was established by Niederhuber in 2012, includes more than 8,000 individuals in parent-child trios; all of the children were born at Inova Fairfax Hospital in northern Virginia.

"It's really important to have a local cohort," said Siegel. In addition to the large size of the ITMI cohort, location "is the real spark to working with Inova, because it can be difficult to persuade a person to come a long distance to participate as a healthy volunteer."

To make the genomic data available, Siegel and Biesecker are entering the aggregate data from these cohorts into a software architecture that was originally developed by an international coalition of researchers for the Genome Aggregation Database. This system allows NIH researchers to use a web portal to explore whether specific variants are present in the TGAC participant cohort while preserving the privacy of study subjects.

Although there are many larger anonymized exome, genome, and genotyped datasets available, TGAC's key advantage is its association with the NIH Clinical Center (CC). The CC, the largest clinical-research center in the world, can do much more in-depth phenotyping of patients than can be done at extramural facilities.

"If you couple the genomics with what you can do evaluating patients at the Clinical Center, that's a potential combination nobody else has," said Biesecker.

For example, "you can do a blood study anywhere," said Siegel, "but where are you also going to do functional [magnetic resonance imaging studies] on 100 people?

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Behavioral and Social Sciences Research Festival 2017

Charting New Paths

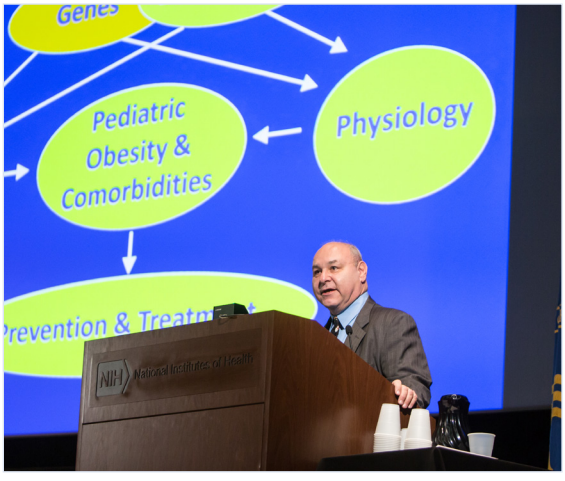
BY SARA HARGRAVE, OBSSR

"These days, we once again see behavioral science at the forefront of health research," said NIH Principal Deputy Director **Lawrence Tabak** during the opening remarks of the NIH Behavioral and Social Sciences Research Festival, held in December 2017. Behavioral and social sciences are "charting new paths in [mobile] health [and] disease monitoring, reducing tobacco use, lowering sudden-infant death, [and] preventing diabetes." Tabak went on to discuss the importance of behavioral and social sciences in combating the crisis of opioid abuse that is gripping our nation. "Without the behavioral and social sciences overlay, pharmaceutical [treatments for opioid abuse] don't matter," Tabak stressed. "If the patient doesn't take advantage of them, if the prescribers don't think through what they are doing, none of this will matter."

After Tabak's remarks, NIH Associate Director for Behavioral and Social Sciences Research **William Riley** discussed the state of the behavioral and social sciences at NIH in fiscal year 2017 (FY17), noting a steady increase in funding from FY15 to FY17 with nearly every institute supporting behavioral and social science research. Riley then addressed OBSSR's co-funding initiative—approximately $20 million annually—which supports meritorious intramural and extramural research from all NIH institutes and centers. In 2017, OBSSR funded 123 grants.

> Without the behavioral and social sciences overlay...none of this will matter."

For the first time, this year's Research Festival highlighted some intramural research. **Jack Yanovski,** chief of NICHD's Section on Growth and Obesity, presented "Depression and Insulin Resistance in Adolescent Girls—an Intramural NIH Bench-to-Bedside Investigation," in which he presented several studies that investigated the link between depression and insulin resistance in adolescent girls at risk for developing both type 2 diabetes and depression. Using their 15-year prospective, longitudinal study, Yanovski's lab found that early symptoms of depression predicted greater insulin resistance at follow-up visits. He also found that successful treatment of depression with cognitive-behavioral therapy led to a significant reduction in insulin concentrations. Ongoing studies are assessing the mechanisms that underlie depression-induced insulin resistance in adolescent women. (*Depress Anxiety* **34:**866–876, 2017; DOI:10.1002/da.22617)



CHIA-CHI CHARLIE CHANG

Jack Yanovski, chief of NICHD's Section on Growth and Obesity, presented several studies that investigated the link between depression and insulin resistance in adolescent girls at risk for developing both type 2 diabetes and depression.

Another new feature of the 2017 Research Festival was the NIH Institute Perspective, provided this year by **Eliseo Pérez-Stable**, director of the National Institute on Minority Health Disparities (NIMHD). One of the NIMHD-supported research projects is the first U.S. national study that assessed the impact of direct-mail marketing on smoking behaviors. The study, conducted by NIMHD Earl Stadtman Investigator **Kelvin Choi** (in collaboration with researchers at two universities), found that tobacco company marketing strategies—specifically, distribution of direct-mail coupons—were disproportionately targeting low-income individuals with limited educations. The strategies were associated with recruiting new smokers and the continuation of smoking among current smokers. (*Nicotine Tob Res* ntx141; DOI:10.1093/ntr/ntx141)

The festival also featured three panel discussions. The first panel described findings from studies of behavioral interventions: the use of mindfulness techniques to improve memory and prevent dementia among elderly individuals; how small econimic incentives, including participation in a low-stakes lottery or a competition with peers, could improve adherence to anti-retroviral medication among Ugandans with HIV; and how individual and community-based interventions helped prevent alcohol abuse in white and Native American teens.

The second panel emphasized behavioral neuroscience research. One study found that nicotine intake was reduced by glucagon-like

peptide-1, a hormone known to decrease blood sugar. Another involved using operant conditioning to examine cocaine-induced changes in decision-making among adolescents; the findings suggest that the receptor for brain-derived neurotrophic factor, tropomyosin receptor kinase B, may be a useful therapeutic target.

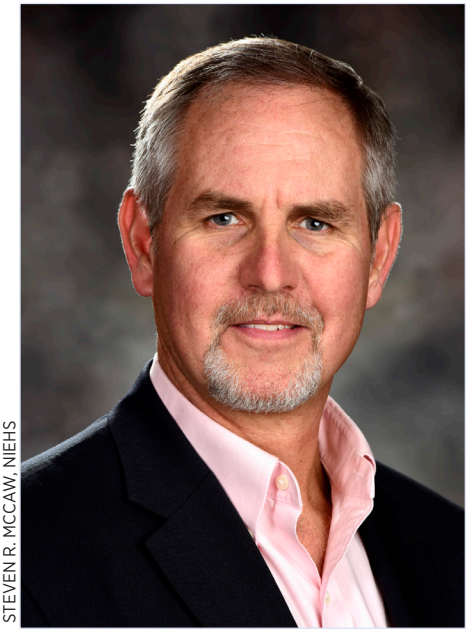
The final panel on "Social Factors and Health" featured discussions on the opioid crisis, social stress on people as they age, and how health disparities are a problem of child development. Intramural researcher **Stephen Gilman** (NICHD) described his investigations into whether social and economic hardship disrupts maternal immune activity during pregnancy and, if so, whether there are implications for offspring neurodevelopment. He assessed biological samples and socioeconomic, psychological, and developmental data gathered from nearly 1,500 women—and their children—enrolled in the New England Family Study cohorts of the Collaborative Perinatal Project. He found that greater maternal socioeconomic disadvantage was tied to higher rates of neurodevelopmental abnormalities in their offspring. The findings suggest these abnormalities were mediated by activation of the immune system during pregnancy (*Proc Natl Acad Sci U S A* **114:**6728–6733, 2017; DOI:10.1073/pnas.1617698114) ●

To watch a videocast of the festival, held on December 8, 2017, go to https://videocast.nih.gov/launch.asp?23630.

Read the full article at https://irp.nih.gov/catalyst/v26i2/behavioral-and-social-sciences-research-festival-2017

Brian Berridge Tapped to Manage National Toxicology Program

BY VIRGINIA GUIDRY, NIEHS



STEVEN R. MCCAW, NIEHS

"NTP's mission is not just environmental; it includes pharmaceuticals," said Brian Berridge, the new head of NIEHS's National Toxicology Program. "Part of what I'm interested in is how to leverage this full breadth of resources for toxicology."

The National Toxicology Program (NTP), a federal interagency program housed at the National Institute of Environmental Health Sciences (NIEHS), welcomed **Brian Berridge** as its new associate director on January 7, 2018. Berridge, formerly of GlaxoSmithKline (GSK), will oversee day-to-day operations as NTP coordinates toxicology research and testing across nine federal agencies, including the NIH, the U.S. Food and Drug Administration, and the Centers for Disease Control and Prevention.

He hopes to further NTP's integration of cutting-edge toxicology methods, including animal studies, cell-based toxicity testing, and data-intensive computer modeling. He will also have his own lab for studying cardiovascular toxicology.

Berridge, who will also be serving as an NIEHS scientific director, replaced **John Bucher**, who was an associate director of the NTP from 2007 until now and plans to continue as a senior scientist.

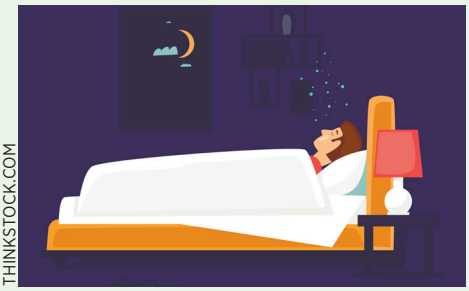
As the former director of Worldwide Animal Research Strategy at GSK, Berridge led efforts to improve animal and non-animal methods for testing pharmaceuticals. He headed a cross-pharma collaboration on tissue-chip technology with the National Center for Advancing Translational Sciences and has contributed expertise to the federal Scientific Advisory Committee on Alternative Toxicological Methods since 2015.

"Traditionally, toxicologists sit in one camp or the other [animal or non-animal], while I've been bridging those two," Berridge said. "NTP squarely bridges those two, which is why this role is really interesting to me."

Berridge began his career in pathology while on active duty in the U.S. Air Force. He completed his undergraduate studies at the University of Arkansas (Fayetteville, Arkansas). He holds a Doctor of Veterinary Medicine degree from Oklahoma State University (Stillwater, Oklahoma) and completed his Ph.D. and residency in pathology in the Department of Veterinary Pathobiology at Texas A&M University (College Station, Texas). As a postdoc, Berridge studied human cardiovascular devices and diseases in animals to inform treatment of human cardiovascular disease at the Texas Heart Institute in Houston. ●

To read the full version of this article, go to https://irp.nih.gov/catalyst/v26i2/news-briefs

Intramural Research Briefs



THINKSTOCK.COM

NHLBI, NHGRI: RESEARCHERS EXPLORE COMPLEX GENETIC NETWORK BEHIND SLEEP DURATION

NIH scientists identified differences in a group of genes that might help explain why some people need a lot more sleep—and others less—than most. The researchers used fruit fly (*Drosophila melanogaster*) populations bred to model natural variations in human sleep patterns. The study provides new clues to how genes for sleep duration are linked to a wide variety of biological processes. A better understanding of these processes could lead to new ways to treat sleep disorders such as insomnia and narcolepsy. (NIH authors: S.T. Harbison, Y.L. Serrano Negron, N.F. Hansen, and A.S. Lobell, *PLoS Genet* **13:**e1007098, 2017)

NIDCD, NIMHD, NCATS: WHY A COMMON CANCER DRUG CAUSES HEARING LOSS

The chemotherapy drug cisplatin can cause permanent hearing loss in 40 to 80 percent of adult patients and at least half of pediatric patients. Using a highly sensitive technique to measure cisplatin in mouse and human inner-ear tissues, NIH scientists found that forms of cisplatin build up in the stria vascularis, which helps maintain the positive electrical charge in inner-ear fluid that certain cells need to detect sound. If cisplatin can be prevented from entering the stria vascularis during treatment, cisplatin-induced hearing loss might be prevented. (NIH authors: A.M. Breglio, A.E. Rusheen, E.D. Shide, K.A. Fernandez, K.K. Spielbauer, M.D. Hall, L. Amable, and L.L. Cunningham, *Nat Commun* **8:**article number 1654, 2017; DOI:10.1038/s41467-017-01837-1)

CC: CHEMICAL FROM CACTUS-LIKE PLANT MAY CONTROL SURGICAL PAIN

A promising approach to postoperative incision-site pain control uses a naturally occurring plant molecule called resiniferatoxin (RTX). RTX is found in *Euphorbia resinifera*, a cactus-like plant native to Morocco, and is 500 times as potent as the chemical that produces heat in hot peppers and may help limit the use of opioid medication while in the hospital and during home recovery.

NIH researchers found that RTX could be used to block postoperative incisional pain in an animal model. RTX has been found to be a highly effective blocker of pain in multiple other preclinical animal models and is in a phase 1 clinical trial at the NIH Clinical Center for patients with severe pain associated with advanced cancer. (NIH authors: S.J. Raithel, M.R. Sapio, D.M. LaPaglia, M.J. Iadarola, and A.J. Mannes, *Anesthesiology* **128:**620–635, 2017; DOI:10.1097/ALN.0000000000002006)

NICHD: IODINE DEFICIENCY MAY REDUCE PREGNANCY CHANCES

Women with moderate to severe iodine deficiency may take longer to become pregnant than women with normal iodine concentrations, according to a study by researchers at NIH and the New York State Department of Health (Albany, New York). Severe iodine deficiency has long been known to cause intellectual and developmental delays in infants.

The researchers analyzed data collected from 501 U.S. couples from 2005 to 2009. Women who had moderate-to-severe iodine deficiency had a 46-percent-lower chance of becoming pregnant than women who had sufficient iodine concentrations. Women who are concerned they may not be getting enough iodine may wish to consult their physicians before making dietary changes or taking supplements. (NIH authors: J.L. Mills, G.M. Buck Louis, J. Weck, A. Giannakou, and R. Sundaram, *Hum Reprod* DOI:10.1093/humrep/dex379)

NICHD: NIH RESEARCHERS REPORT FIRST 3-D STRUCTURE OF DHHC ENZYMES

The first three-dimensional structure of DHHC proteins—proteins that contain a 50-amino-acid chain called the DCCT domain, act as enzymes, and are involved in many cellular processes, including cancer—explains how they function and may offer a blueprint for designing therapeutic drugs. NIH researchers have proposed blocking DHHC-domain activity to boost the effectiveness of first-line treatments against common forms of lung and breast cancer. There are currently no licensed drugs that target specific DHHC enzymes. (NIH authors: M.S. Rana, P. Kumar, C.-J. Lee, R. Verardi, and A. Banerjee, *Science* **359:**eaao6326, 2018; DOI:10.1126/science.aao6326) See back page for image.

NIAID, NHGRI, NIAMS, NCI, NIDDK: MICROBES ON SKIN PROMOTE TISSUE HEALING, IMMUNITY

Beneficial bacteria on the skin of lab mice work with the animals' immune systems to defend against disease-causing microbes and accelerate wound healing. Untangling similar mechanisms in humans may improve approaches to managing skin wounds and treating other damaged tissues. NIH scientists observed the reaction of mouse immune cells to *Staphylococcus epidermidis*, a bacterium regularly found on human skin that does not normally cause disease. To their surprise, immune cells recognized *S. epidermidis* using evolutionarily ancient molecules called nonclassical major histocompatibility complex (MHC) molecules, which led to the production of unusual T cells with genes associated with tissue healing and antimicrobial defense. In contrast, immune cells recognize disease-causing bacteria with classical MHC molecules, which lead to the production of T cells that stoke inflammation. The researchers plan to next probe whether nonclassical MHC molecules recognize friendly microbes on the skin of other mammals, including humans, and

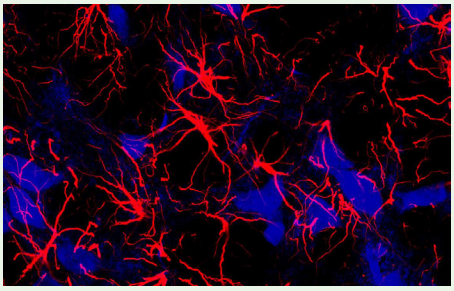
similarly benefit tissue repair. (NIH authors: J.L. Linehan, O.J. Harrison, S.-J. Han, A.L. Byrd, I. Vujkovic-Cvijin, A.V. Villarino, S.K. Sen, J. Shaik, M. Smelkinson, S. Tamoutounour, N. Collins, N. Bouladoux, A. Dzutsev, S.P. Rosshart, J.H. Arbuckle, T.M. Kristie, B. Rehermann,. Trinchieri, J.M. Brenchley, J.J. O'Shea, and Y. Belkaid, *Cell* DOI:10.1016/j.cell.2017.12.033)

NIA: COMPOUND PREVENTS NEUROLOGICAL DAMAGE, SHOWS COGNITIVE BENEFITS IN MOUSE MODEL OF ALZHEIMER DISEASE

The supplement nicotinamide riboside (NR)—a form of vitamin B3—prevented neurological damage and improved cognitive and physical function in a new mouse model of Alzheimer disease. The results of the study, conducted by researchers at NIA and an international team of scientists, suggest a potential new target for treating Alzheimer disease. The team plans further studies on the underlying mechanisms and preparations toward intervention in humans. (NIH authors: Y. Hou, S. Lautrup, S. Cordonnier, Y. Wang, D.L. Croteau, E. Zavala, Y. Zhang, K. Moritoh, J.F. O'Connell, B.A. Baptiste, M.P. Mattson, and V.A. Bohr, *Proc Natl Acad Sci U S A* DOI:10.1073/pnas.1718819115)

NINDS: STARLIKE CELLS MAY HELP THE BRAIN TUNE BREATHING RHYTHMS

Traditionally, scientists thought that star-shaped brain cells called astrocytes were steady, quiet supporters of neurons, their talkative, wirelike neighbors. Now, an NIH study suggests that astrocytes may also have their say. It showed that silencing astrocytes in the brain's breathing center caused rats to breathe at a lower rate and tire out on a treadmill earlier than normal. The researchers plan to continue their studies to understand how astrocytes help control other aspects of breathing. (NIH authors: S. Sheikhbahaei and J.C. Smith, *Nat Commun* 9:article number 370, 2018; DOI:10.1038/s41467-017-02723-6)



JEFFREY C. SMITH LAB, NINDS

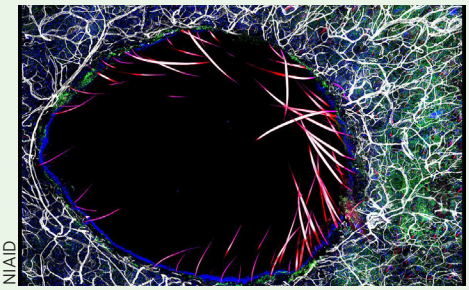
NINDS: A fresh look at the brain and breathing: An NIH study in rats shows that star-shaped brain cells, called astrocytes (red), may play an active role in breathing.

NEI: EYE COULD PROVIDE "WINDOW TO THE BRAIN" AFTER STROKE

Research into curious bright spots in the eyes on stroke patients' brain images could one day alter the way these individuals are assessed and treated. A team of scientists at NEI found that a chemical routinely given to stroke patients undergoing brain scans can leak into their eyes, highlighting those areas and potentially providing insight into their strokes.

The eyes glowed so brightly on those images due to gadolinium, a usually safe, transparent chemical often given to patients during magnetic resonance imaging (MRI) scans to highlight abnormalities in the brain. In healthy individuals, gadolinium remains in the bloodstream and is filtered out by the kidneys. However, when someone has experienced damage to the blood-brain barrier, gadolinium leaks into the brain, creating bright spots that mark the location of brain damage. Previous research had shown that certain eye diseases could cause a similar disruption to the blood-ocular barrier, which does for the eye what the blood-brain barrier does for the brain. The NEI team discovered that a stroke can also compromise the blood-ocular barrier and that the gadolinium that leaked into a patient's eyes could provide information about his or her stroke.

The findings raise the possibility that, in the future, clinicians could administer a substance to patients that would collect in the eye just like gadolinium and quickly yield important information about their strokes without the need for an MRI. (NIH authors: E. Hitomi, A.N. Simpkins, M. Luby, L.L. Latour, and R. Leigh, *Neurology* DOI:10.1212/WNL.0000000000005123)



NIAID

NIAID, NHGRI, NIAMS, NCI, NIDDK: Immunofluorescent image of immune cells surrounding a skin wound, enriched in the beneficial bacteria *S. epidermidis*.

Read longer versions of these briefs online and others at https://irp.nih.gov/catalyst/v26i2/research-briefs:

- **NIAAA: Steep Increase in Alcohol-Related ER Visits**
- **NIEHS: High Exposure to Radiofrequency Radiation Linked to Tumor Activity**
- **NIEHS: Defending Against Environmental Stressors May Shorten Lifespan**
- **NEI, NCI, NHGRI: Stem Cell Therapy for Eye Disease Closer to the Clinic**
- **NIAID, CC: MERS Antibodies Produced in Cattle Safe; Treatment Well Tolerated**
- **NIAID, CC: NIH Study Supports Use of Short-Term HIV Treatment Interruption in Clinical Trials**
- **NIAID: Flu Infection Study Increases Understanding of Natural Immunity**
- **NICHD: Induced Labor After 39 Weeks May Reduce Need for C-Section**
- **NIAID: EBOLA Virus Infects Reproductive Organs in Monkeys**

NIH's Early Homes

CONTINUED FROM PAGE 1

THE NEW YORK PUBLIC LIBRARY

The Hygienic Laboratory was established in 1887 at the United States Marine Hospital (Stapleton, Staten Island, New York) just as the germ theory of infectious disease was taking hold. The lab moved to Washington, D.C., in 1891.

1879 to 1891) soon began petitioning for an entire building.

In 1891, the laboratory moved to Washington, D.C., where it took over the top floor of the Butler Building, which had been the mansion of Benjamin Butler, a Union general during the Civil War and later a congressman and a governor of Massachusetts. Kinyoun and other MHS officers conducted studies here to distinguish variola virus from vaccinia virus, produced diphtheria antitoxin and rabies vaccine, and conducted water- and air-pollution research. Kinyoun also studied the newly discovered plague bacillus and was the first American to prepare and test smallpox immune serum in humans. It's no wonder he wrote in a 1896 report, "A laboratory of this character should not be placed in a building used for public offices. It is not only disagreeable to the other occupants, but in no little degree dangerous."

Finally, in 1901, Congress authorized $35,000 to erect an entire laboratory building and an animal facility. They would be constructed on Navy Hill, a five-acre section of the federal reservation that had been occupied by the United States Naval Observatory from 1844 to 1893. (The Naval Museum of Hygiene was housed in the former observatory from 1894 to 1902; then the Naval Medical School moved in.)

The North Building, as the laboratory's building was called, was located at 25th and E Streets NW and overlooked the Potomac riverfront industrial zone that included asphalt works, the Christian Heurich Brewery, and the malodorous Civil War–era wooden building of the municipal dog pound. The laboratory was to pursue investigations of infectious diseases and matters pertaining to public health.

While construction progressed in 1902, Congress solidified the laboratory's role as the federal government's center of research with two acts. The first changed the name of the MHS to the "Public Health and Marine Hospital Service" (PH-MHS). The second—the Biologics Control Act—made the laboratory responsible for regulating the commercial production of "biologics," the sera and vaccines produced as a consequence of the new science of bacteriology. To support the added mandate of public health, the laboratory created divisions of chemistry, pharmacology, and zoology in addition to the existing division of "pathology and bacteriology."

In March 1904, the 13 members of the laboratory moved into the North Building. Space was cramped, however, and the begging for more room began anew. Surgeon General Walter Wyman, who oversaw the PH-MHS, declared that the laboratory needed a shed for experimenting with disinfecting gases; an animal breeding house and an associated heating plant; a carpentry and blacksmith shop; and storage for wagons and other equipment. He also recommended that separate rooms be provided to study tetanus, tuberculosis, plague, and diphtheria; to monitor vaccines and sera; and to house delicate analytical balances. He complained in his annual report that the grounds were unsightly and full of weeds and not in keeping with the PH-MHS's position and dignity and contrasted poorly with the Navy's well-tended grounds.

In the meantime, the Naval Medical Hospital, with four pavilion-style wards, was being constructed (1903–1908) behind the old Naval Observatory. The hospital

LIBRARY OF CONGRESS

The Butler Building served as the Marine Hospital Service headquarters in the Capitol Hill area of Washington, D.C. The whole top floor belonged to the Hygienic Laboratory (1891–1904). The building was torn down in 1929 and was replaced by the Longworth Building, which contains offices for the U.S. House of Representatives.

complex included quarters for sick officers and nurses, a contagious disease building, and administrative structures.

A $75,000 extension to the North Building was completed in 1909, but in 1912, Congress expanded the laboratory's mission again—adding investigations into noninfectious disease—and shortened PH-MHS's name to the "Public Health Service" (PHS).

Laboratory Director **Milton Rosenau**, who had replaced Kinyoun in 1899, pointed out that the laboratory's responsibilities of regulating biologics, investigating infectious and noninfectious diseases, and addressing other public-health concerns required yet another building. Rosenau also renewed the plea for additional funds to build a proper animal house because the guinea pigs, horses, goats, and rabbits in the existing facilities were susceptible to epidemics themselves. A stone house for the animals was finally erected in 1915.

During World War I (1914–1918), the focus of the PHS and the Hygienic Laboratory shifted to manufacturing vaccines, evaluating industrial hygiene, and maintaining sanitation at the numerous military campsites around the United States. **George W. McCoy** became the lab's director in 1915 and served until 1937. Scientific contributions under his leadership included a vaccine against Rocky Mountain spotted fever and, later, the discovery that rickettsiae could be grown in the yolk sacs of fertile hens' eggs, an advance that enabled the mass production of a vaccine against epidemic typhus to protect Allied troops in World War II.

The laboratory also investigated the 1918 influenza epidemic; conducted fluoride and nutrition studies in the 1930s that later resulted in the addition of fluoride and nutrients to water and food; and established how certain diseases were transmitted by milk and developed a Milk Code for sanitation.

To accommodate the PHS's new responsibilities, the South Building was constructed in 1919—next to the North Building—for the divisions of zoology, chemistry, and pharmacology. The South Building was state-of-the-art, like the North Building before it, and was fireproof. But tragedy struck Hygienic Laboratory researchers in 1930 during an outbreak of parrot fever, or psittacosis. The disease was so contagious, and the methods of the time so ineffectual at isolating contagious material, that 11 laboratory workers became ill and one died. McCoy forbade anyone to work on the investigation except himself. The building had to be temporarily closed and fumigated with cyanide gas.

In May 1930, the Ransdell Act renamed the Hygienic Laboratory the "National Institute of Health" and gave NIH the ability to establish fellowships for research into basic biological and medical problems. (NIH became the National Institutes of Health—plural—in 1948.) The Ransdell Act also provided funds for more construction. This time a new laboratory building and the Administration Building (renamed the East Building in 1954) were built on Navy Hill. The new laboratory building became the South Building, while the old South Building was renamed the Central Building. The new South Building held the Division of Pathology and Bacteriology in a space larger than those of the Central and East Buildings combined. The East Building housed the director's office and library.

OFFICE OF NIH HISTORY AND STETTEN MUSEUM

The North Building on Navy Hill opened in March 1904 and was used by the Hygienic Laboratory (later renamed the National Institute of Health) until NIH's move to Bethesda, Maryland, in 1938. The building was destroyed in 1963 to make room for the E Street Expressway.

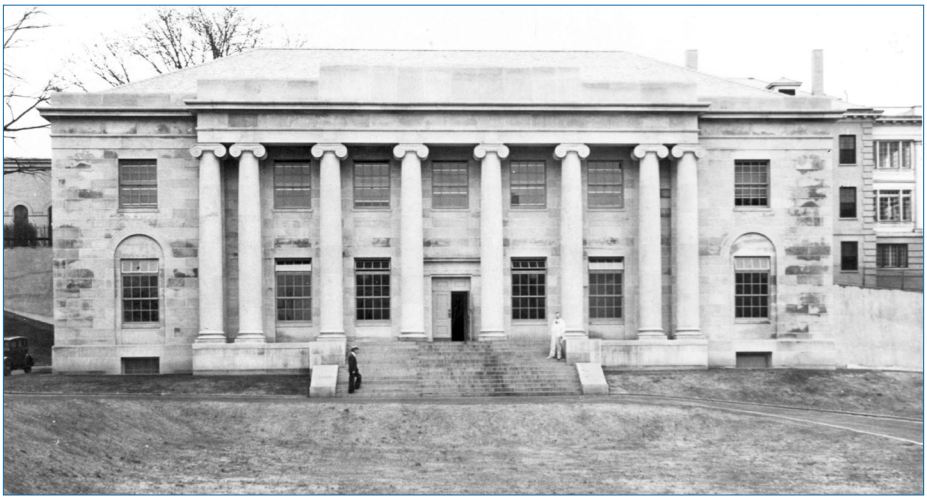
Once NIH had expanded into five buildings (including the animal facility) and the number of employees had risen to 150, the feeling of camaraderie, unfortunately, lessened; informal conversations about science as well as close collaborations were less likely to occur. And McCoy, as director, felt separated from what went on in the state-of-the-art laboratories furnished with the latest in scientific equipment.

And still the NIH was outgrowing its space. When Luke and Helen Wilson offered their 45-acre estate in Bethesda, Maryland, to the U.S. government, the PHS seized the opportunity to once again expand NIH's physical plant. By 1938, the NIH had moved to the Bethesda campus where it is today. The steps of Navy Hill's East Building became a convenient spot for the scientists in the various divisions to line up and pose for photographs before they departed for Bethesda.

CONTINUED ON PAGE 12

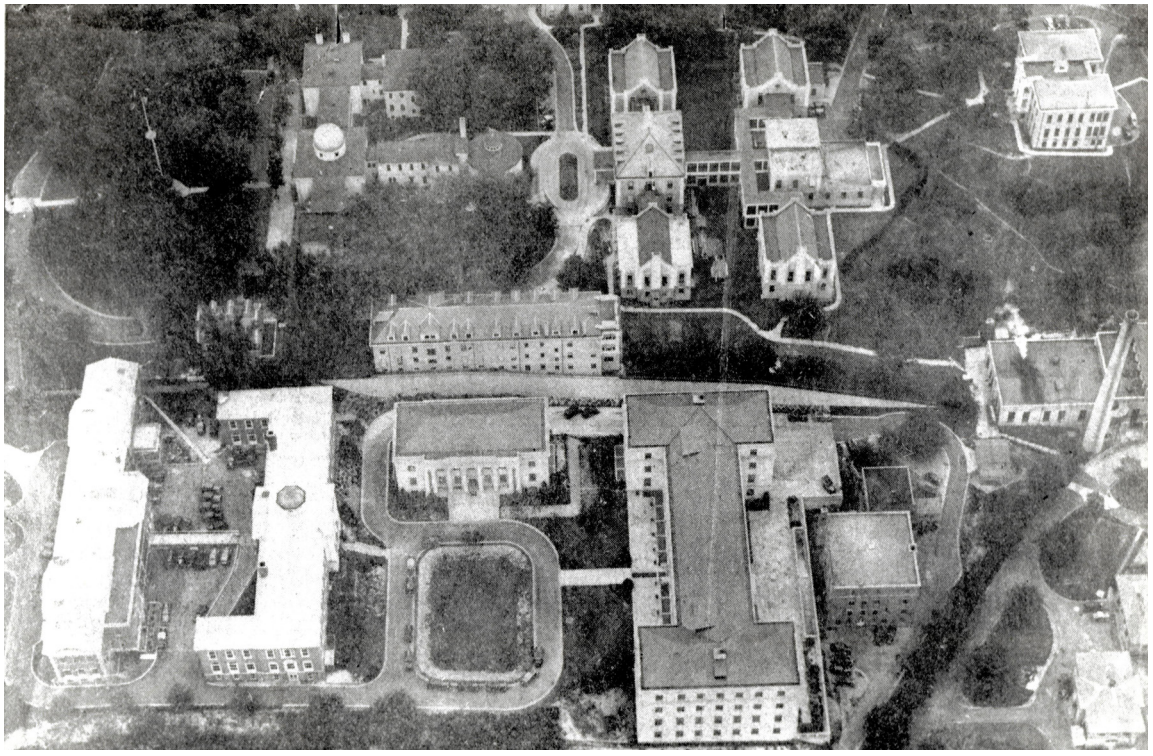
NIH's Early Homes

CONTINUED FROM PAGE 11



OFFICE OF NIH HISTORY AND STETTEN MUSEUM

The Administrative Building (later renamed the East Building) was used by NIH from 1934 to 1938. During World War II, the Office of Strategic Services, which was the predecessor of the Central Intelligence Agency, was headquartered here.



OFFICE OF NIH HISTORY AND STETTEN MUSEUM

NIH buildings on the Navy Hill campus as viewed from the Goodyear blimp Enterprise (1936). Buildings (lower half of photograph, from left): North Building; Central Building (old South Building); East Building (formerly the Administration Building); South Building. Behind the East Building (from left): The Old Naval Observatory, the Navy Hospital, and wards and housing.

NIH moves out, CIA moves in: In 1942, four years after NIH moved away from the Navy Hill campus, the Naval Medical Hospital and the Naval Medical School, which had been on Navy Hill since 1903, moved out. All their hospital operations were transferred to the National Naval Medical Center in Bethesda, Maryland. During World War II, several of the vacant Navy Hill buildings were used by the Office of Strategic Services (OSS) under William "Wild Bill" Donovan. His OSS, which ended operations in 1945, was the predecessor to the Central Intelligence Agency (CIA), which began in 1947. The CIA headquarters relocated to Langley, Virginia, in 1961. In 1963, to accommodate construction of the E Street Expressway, a large chunk of Navy Hill was demolished including the North Building and the animal building. The U.S. Navy Bureau of Medicine and Surgery, which moved to Navy Hill in 1942, remained there until 2012, when it moved to Falls Church, Virginia. The U.S. Department of State has been using the E Street campus to house a variety of operations since 1987. ●

United States Naval Observatory

Before Microscopes, There Were Telescopes

BY VICTORIA A. HARDEN AND MICHELE LYONS

BILL BRANSON, NIH

The United States Naval Observatory on Navy Hill (1844–1893), now unoccupied, made significant contributions to astronomy in the 1800s.

Lying between 23rd and 25th Streets, and E Street and the Potomac River, the site originally called Potomac Hill was a bastion of 19th century science. In 1844, the building now known as the Old Naval Observatory was completed. The American Prime Meridian was set here in 1850 and used as the reference point for establishing the boundaries of many western states. In 1877, the moons of Mars were discovered by a Naval assistant astronomer—one of the major astronomical discoveries of the 19th century. Naval researchers contributed to the Transit of Venus expeditions in 1874 and 1882, and they also attempted to measure the speed of light. By 1893 the observatory needed additional space and moved to its current location at 3450 Massachusetts Avenue, NW, in Washington, D.C. ●

FINAL NOTE: In 2016, OSS and CIA alumni succeeded in getting the buildings added to the National Register of Historic Places as the "E Street Complex (Office of Strategic Services and Central Intelligence Agency Headquarters)." The historical interpretation of the site is devoted to Donovan and the OSS, although the State Department is the current occupant of the remaining buildings. In 2017, it was through the Office of the State Department Historian that NIH staff members from the Office of NIH History and Stetten Museum were able to tour the site, which had been off-limits since NIH left nearly 80 years ago. The Office of NIH History will be working with the State Department Historian to rectify the gap in interpretation of the site. To learn more, read the application to the National Historic Registry at http://www.osssociety.org/pdfs/oss_nr_final_to_hpo.pdf.

NEWS FROM AND ABOUT THE SCIENTIFIC INTEREST GROUPS

NEW SIG: Genetic Counseling Scientific Interest Group

The Genetic Counseling Scientific Interest Group (GC SIG) is open to anyone who provides genetic counseling at a government or military institution in the local community. The SIG will provide a forum for counselors to share practice and research ideas, participate in continuing education, and form collaborations with one another. The group can also serve as a resource for the broader NIH community by delivering lectures or collaborating on the development of research protocols. The SIG will meet several times a year for seminars, journal clubs, guest lectures, and group discussions. For more information or to join the GC SIG LISTSERV, contact Katie Lewis (NHGRI; lewiskatie@mail.nih.gov). ●

Scientific Interest Groups

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

Pioneering Gene Therapy for Radiation-Induced Dry Mouth

Ongoing Clinical Trial Explores Saliva-restoring Gene Transfer

BY CATHERINE EVANS, NIDCR

For most individuals who survive head and neck cancers, the relief of successful treatment can be tempered by a troubling side effect of some cancer therapies: chronic dry mouth. Because radiation treatment kills both tumor cells and healthy saliva-producing cells, saliva production can dwindle or even shut down completely. People with dry mouth may find it hard to speak or chew, taste, and swallow food. They may have pain from slow-to-heal ulcers and be at increased risk for tooth decay and other infections. Treatments can help, including saliva substitutes, salivary stimulants, and ice chips that moisten the mouth. But there's no cure for radiation-induced dry mouth.

"You get tired of patting somebody on the back and saying, 'There's nothing more I can do for you,'" said emeritus scientist **Bruce Baum**, who retired from the National Institute of Dental and Craniofacial Research (NIDCR) in 2011.

Frustrated by his inability to provide lasting relief for such patients, Baum began exploring experimental treatments to repair damaged salivary glands about three decades ago. By the early 1990s, the concept of gene therapy—giving patients working versions of genes to correct a disease-causing defect—was gaining traction as an experimental approach to treating diseases such as cancer and rare genetic conditions.

Inspired by a colleague's success in transferring and expressing genes in rat lungs in 1991, Baum thought that gene transfer might also work in the salivary gland. He came up with the idea of using a modified virus to deliver a corrective gene directly into the damaged gland to restore the flow of saliva. But the journey from concept to clinical trial would take many years and multiple studies to complete.

HWEI L. ONG, NIDCR

About three decades ago, NIDCR emeritus scientist Bruce Baum began exploring experimental treatments to repair salivary glands damaged by radiation treatment. He came up with the idea of using a modified virus to deliver a corrective gene directly into the damaged gland to restore the flow of saliva.

Baum's work is among many parallel efforts in gene therapy, where safety and logistical concerns have delayed the clinical debut of several promising approaches. Only in the past year have a handful of these therapies—two for blood cancers and one for an inherited form of blindness—received U.S. Food and Drug Administration approval. The therapy for blindness is the only one in which a corrective gene is directly administered to the patient. This so-called in vivo delivery method is the approach Baum and colleagues have been developing over 25 years to treat radiation-induced dry mouth. Their experimental therapy was the first-ever salivary-gland gene therapy tried in humans. The treatment worked better than expected, encouraging the investigators to explore additional applications for its use. Now, a second NIDCR clinical trial is underway to assess the safety and effectiveness of a similar approach using an improved gene-delivery vehicle.

From concept to clinic: A working salivary gland resembles a bunch of grapes, with globe-shaped structures made of acinar cells linked to stemlike duct cells. Water from the bloodstream flows across the acinar cells through pore-forming proteins called aquaporins located in the cell membranes. Water mixes with various proteins secreted from the cells, creating saliva that can be transported via the ducts into the mouth. Radiation damages or kills acinar cells, leaving mostly duct cells, which lack aquaporins and can't secrete water.

Baum guessed that delivering a gene for one of the pore-forming proteins, called aquaporin 1, into damaged salivary glands might enable existing cells to transport water and restore saliva production. He chose a genetically altered adenovirus as the gene-delivery vector. When infused into the salivary gland, the viral vector deposits aquaporin DNA into glandular cells and instructs them to start producing the protein.

Through the 1990s and early 2000s, Baum and his colleagues developed and tested the concept. NIDCR virology expert **John Chiorini** was brought on in 1998 to optimize the viral vector. The team eventually showed that the aquaporin 1 gene therapy could restore saliva flow in radiation-damaged glands of rats and miniature pigs. The next step was to test it in humans.

"No one had tried gene therapy in the human salivary gland. It was a new frontier with unknown risks," said Chiorini, now the chief of NIDCR's Adeno-Associated Virus Biology Section. "It wasn't clear whether the human salivary gland would function the same way as the animal models. We intended to do a proof-of-concept trial in patients with radiation-induced dry mouth just to see if the gene transfer even worked in humans."

Once the researchers received FDA

approval for a clinical trial, the first patient was treated in 2008.

In 2012, the group published their initial results (*Proc Natl Acad Sci U S A* **109:**19403–19407, 2012). Of the 11 participants, five had increased saliva flow and reduced sensation of dry mouth, responses that peaked in the weeks after the gene transfer. Remarkably, and to the great surprise of the investigators, the improvements in these patients persisted for several years after the one-time treatment. This outcome convinced the team that their concept could work and even bring long-lasting relief to some people.

Expanding horizons: The researchers designed a second clinical trial using a different gene-delivery vehicle based on an adeno-associated virus. The newer viral vector was designed to transfer the same aquaporin 1 gene to the salivary glands.

"We think the patients who didn't respond in the first trial developed an immune response to the adenovirus," said Chiorini. "Although they experienced virtually no adverse objective or subjective effects, at a microscopic level, it looks like their bodies rejected the viral vector or cells transduced by the vector." Adeno-associated virus is thought to be less likely to elicit immune responses and to have longer-lasting effects than the previously used adenoviral delivery vehicle.

SANDRA AFIONE, NIDCR

NIDCR virology expert John Chiorini was brought on in 1998 to optimize the viral vector. The gene-transfer approach to treating radiation-induced dry mouth worked in animals and has been successful in clinical trials, too.

The new clinical trial began in July 2016, with four patients treated to date. So far, there's been no sign of an immune response. Chiorini and his colleagues expect to continue enrolling participants over the next year or so, with the aim of treating up to 17 additional participants who have radiation-induced dry mouth.

For Baum, the first trial's unexpected success was the realization of a dream many scientists can only hope for. "To see this go from a pie-in-the-sky idea to helping patients, I couldn't have asked for anything more from my career," he said. "I felt like I could retire from research because I'd achieved what I set out to do."

There's evidence the experimental therapy could help an even broader group of patients. Chiorini and colleagues have been studying Sjögren syndrome, an autoimmune disease that causes dry eyes and dry mouth, among other symptoms.

"Our research suggests that at least some Sjögren's patients have a similar defect as those with radiation-damaged glands: the inability to move water," Chiorini said. The team validated the idea in an animal model and will soon launch a clinical trial to test aquaporin 1 gene therapy in Sjögren patients. If it succeeds, the treatment could provide a path to relief for many more people suffering from dry mouth and may have even wider implications.

"Everything we're learning from these studies can benefit the broader community of scientists who are trying to advance gene therapy as a platform for treating many kinds of genetic and acquired diseases," Chiorini said. "As an NIH investigator, it's a privilege to take part in high-risk, conceptual, pioneering science that might ultimately change patients' lives." ●

This article appeared in the *NIDCR Science Briefs* and is reprinted with permission (bit.ly/2nOS8U1).

News You Can Use

CONTINUED FROM PAGE 5

Deep phenotyping is something the Clinical Center does very well."

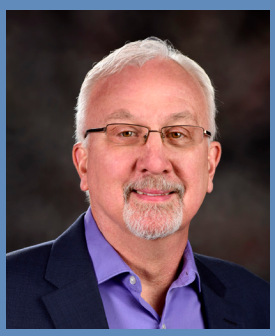
TGAC's lead staff clinician, **Alexander Katz** (NHGRI), will help bring additional existing cohorts into the TGAC and assist interested investigators with small phenotyping projects under its existing clinical protocol.

"Across NIH, there are [already] at least 10,000 sequenced individuals," said Siegel. But many of those individuals will need to give consent to be re-contacted, he explained. Siegel and Biesecker also hope to incorporate many additional cohorts from around the NIH–including any new patients who come through the NIH Clinical Center—a task that will require significant additional genomic sequencing.

Another important partner is the Walter Reed National Military Medical Center (Bethesda, Maryland), "which has a really great sequencing center," said Siegel. In addition, TGAC hopes to include data from the Environmental Polymorphisms Registry at the National Institute of Environmental Health Sciences (Research Triangle Park, North Carolina) as well as from organizations outside the NIH.

Tyra Wolfsberg, associate director of NHGRI's Bioinformatics and Scientific Programming Core, is leading the team that is developing the TGAC web portal. Data from the ClinSeq cohort are already available to NIH investigators through this portal; data from the ITMI cohort will be added next. Although the pilot-phase TGAC database will be accessible only to intramural investigators, the leaders of this effort hope to be able to make the resource available to the wider scientific community in the future. For more information about TGAC, visit https://tgac.nhgri.nih.gov or contact Alexander Katz at alexander.katz@nih.gov. ●

Recently Tenured

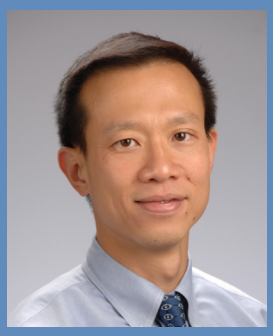


PAUL W. DOETSCH, NIEHS

IAIN FRASER, NIAID

CLAUDIA PALENA, NCI-CCR

MARK PURDUE, NCI-DCEG



WAI T. WONG, NEI

PAUL WILLIAM DOETSCH, M.S., PH.D., NIEHS
Senior Scientist, Genome Integrity and Structural Biology Laboratory, National Institute of Environmental Health Sciences

Education: University of Maryland, College Park, Maryland (B.S. in biochemistry); Purdue University College of Pharmacy, West Lafayette, Indiana (M.S. in medicinal chemistry and pharmacognosy); Temple University School of Medicine, Philadelphia (Ph.D. in biochemistry)

Training: Research fellow, Department of Pathology, Dana-Farber Cancer Institute, Harvard Medical School (Boston)

Before coming to NIH: Professor of biochemistry, of radiation oncology, and of hematology and medical oncology at Emory University School of Medicine (Atlanta); associate director for basic research at Emory's Winship Cancer Institute

Came to NIH: In 2017

Selected professional activities: Programmatic Panel Member (equivalent to grants council) for Department of Defense Peer-Reviewed Cancer Research Program; editorial boards of *DNA Repair*, *Biochemistry Research International*, and *Nucleic Acids Research*

Outside interests: Cycling (including bike trips abroad); studying military history; reading; following the University of Maryland Terrapins basketball and lacrosse teams

Website: https://irp.nih.gov/pi/paul-doetsch

Research interests: More than two decades ago, my team at Emory discovered transcriptional mutagenesis (TM), which we believe may be involved in the development of cancer and other diseases. TM occurs when DNA damage in the transcribed strand of an active gene is bypassed by a RNA polymerase; the genes can miscode at the damaged site and produce mutant transcripts leading to mutant proteins that can alter cellular phenotype in the absence of DNA replication.

Also when I was at Emory, my team discovered and characterized several DNA-repair enzymes, elucidated the regulation of repair pathways, and defined relationships between DNA-damage management and genetic events that lead to basic processes important in tumor development. This information is being used for understanding cancer-cell resistance to radiation and chemotherapy as well as to develop new therapeutic strategies for cancer treatments.

At NIH, my research will continue to focus on the biochemistry, molecular biology, and genetics of DNA repair; how DNA repair is regulated; and how the transcriptional machinery interacts with DNA damage caused by environmental exposure to chemicals or radiation. We have established that TM occurs in bacterial and mammalian cells and can induced a phenotypic change. If a phenotype caused by TM results in DNA replication or cell-cycle entry, one of the resulting daughter cells may acquire a permanent DNA mutation and thus permanently establish an altered phenotype. This mechanism has been termed retromutagenesis (RM). We will be investigating how TM and RM may have a deleterious impact on human health such as contributing to the etiology of diseases and giving rise to antibiotic-resistant pathogenic bacteria.

Another area of emphasis will be to continue our studies on DNA-base-excision repair (BER). While much is known about the biochemical steps comprising BER, little is known about how the pathway is regulated or the consequences of its dysregulation. To ensure optimal protection of the genome from diverse endogenous and environment insults, the BER pathway is coordinated with other repair systems through interactions with components of other pathways. Thus, dysregulation of BER components could affect several repair pathways and contribute to human disease. The goal of our studies is to define BER-component-pathway interactions and the mechanisms and consequences of dysregulation, especially within the context of tumor development.

IAIN FRASER, PH.D., NIAID

Senior Investigator and Chief, Signaling Systems Section, Laboratory of Systems Biology, National Institute of Allergy and Infectious Diseases

Education: Heriot-Watt University, Edinburgh, Scotland (B.S. in biochemistry); Imperial College, University of London, London (Ph.D. in biochemistry)

Training: Postdoctoral fellowship at the Vollum Institute (Portland, Oregon)

Before coming to NIH: Co-director, Alliance for Cellular Signaling, Molecular Biology Laboratory, California Institute of Technology (Pasadena, California)

Came to NIH: In 2008 as an investigator in NIAID; became chief of NIAID's Signaling Systems Unit, Laboratory of Systems Biology (LSB) in 2011

Selected professional activities: Editorial boards, *Scientific Reports* and *Scientific Data*; co-chair, NIH Systems Biology Interest Group; executive committee, NIH Oxford-Cambridge Scholars Program

Outside interests: Spending time with his wife and three children; walking and hiking; watching his kids play music and sports; playing golf

Website: https://irp.nih.gov/pi/iain-fraser

Research interests: My group's research focuses on how inflammation and the activation of macrophages influence human disease and other pathologies. Macrophages constantly evaluate host mucosal surfaces and peripheral tissues for signs of infection or injury. The host must find a balance between tolerating beneficial microorganisms and minor nonpathological microbial organisms versus launching an immune response against more serious infections. Emerging evidence suggests that this decision is made by the cell based on the combinatorial signals it receives through pattern-recognition receptor (PRR) pathways that have been activated by microorganisms and endogenous stimuli.

We use high-throughput genetic screening to identify key pathway regulators, and a combination of cell biology, biochemistry, and molecular biology to characterize their function. We seek to obtain a better understanding of how PRR-signaling pathways control the macrophage inflammatory state. Ultimately, we aim to develop strategies to regulate these responses in human inflammatory diseases.

We are also developing new integrated bioinformatics approaches to data analysis that are widely applicable and freely available to the research community. We conduct comparative studies in both mouse and human systems to identify the most-important targets for potential therapeutic intervention. And, in collaboration with our LSB and NIH colleagues, we seek to link novel findings from our screens to cases of human disease. Our recent findings suggest that innate immune responses are intimately linked to the cellular metabolic state.

To extend our understanding of how macrophages integrate and respond to complex signals during encounters with pathogens, we are building models of infection based on clinically relevant bacterial species. We are studying how the combined activation of multiple pathways, including ones considered antiviral, can mount a host response to clear a bacterial infection. In parallel, we are identifying mechanisms that pathogenic bacteria use to evade a host's defense mechanisms.

What we learn will be critical to understanding how the host response is shaped and influenced by multiple microbe-derived signals, and how the response is modified by the presence of additional endogenous stimuli. Such knowledge will have important implications for understanding immunopathologic responses to infection, designing better vaccines, and determining how some pathogens evade immune responses.

CLAUDIA PALENA, PH.D., NCI-CCR

Senior Investigator, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute

Education: National University of Rosario, Rosario, Argentina (B.S. in biochemistry; Ph.D. in biochemistry)

Training: Postdoctoral training in the Laboratory of Tumor Immunology and Biology, NCI-CCR

Came to NIH: In 2000 for training; in 2008 was appointed staff scientist; became tenure-track investigator in 2011

Selected professional activities: Editorial board member, *Journal of Experimental and Clinical Cancer Research*; editorial board member, *Frontiers in Oncology* (Cancer Molecular Targets and Therapeutics Section)

Outside interests: Spending time with family; listening to classical music

Website: https://irp.nih.gov/pi/claudia-palena

Research interests: The main goal of my research is to address the two central features of metastatic disease: tumor dissemination and resistance to therapy. My group is investigating how changes in the phenotype of a tumor between the epithelial and a mesenchymal-like state (a phenomenon called carcinoma mesenchymalization) could facilitate the dissemination of the tumor cells and make them resistant to anticancer therapies. My laboratory has identified the T-box transcription factor brachyury—a molecule normally expressed in the embryo but absent in normal adult tissues—as a novel tumor antigen, a driver of mesenchymalization and drug resistance in human carcinoma cells, and a target for T-cell-mediated immunotherapy. (T-box refers to a group of transcription factors involved in limb and heart development.) Our studies have shown that brachyury is overexpressed in various

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Recently Tenured

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human carcinomas, both in the primary tumor and in metastatic sites, and that high brachyury expression in the primary tumor site is associated with poor clinical outcome. The results of these investigations led to a team science effort—including my laboratory, scientists and clinicians from the intramural and extramural scientific communities, and collaborators in the private sector—that resulted in the translation of two brachyury-based cancer vaccines from preclinical stage into phase 1 and phase 2 clinical trials in patients with advanced carcinomas and the rare tumor chordoma.

Currently, my laboratory is investigating the various signals that induce changes in tumor phenotype. We have recently demonstrated, for example, that brachyury overexpression induces the secretion of interleukin-8 (IL-8) and the expression of IL-8 receptors, and that IL-8 signaling is critical for maintaining the mesenchymal characteristics of human tumor cells. These findings may have implications for cancer therapy: A blockade of IL-8 could be a new way to target mesenchymal-like, invasive carcinoma cells.

MARK PURDUE, PH.D., NCI-DCEG

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

Education: Queen's University, Kingston, Ontario, Canada (B.S. in life sciences; M.S. in community health and epidemiology); University of Toronto (Ph.D. in epidemiology)
Training: Postdoctoral training at NCI-DCEG
Came to NIH: In 2004 for training; was appointed tenure-track investigator in 2009
Selected professional activities: Associate editor for *Cancer Epidemiology*; editorial board member for *Cancer Epidemiology, Biomarkers and Prevention*
Outside interests: Enjoys traveling and outdoor activities with his wife and two children
Website: https://irp.nih.gov/pi/mark-purdue

Research interests: I apply molecular and classical epidemiologic methods to study the causes of cancer and improve the assessment of exposure to cancer-causing agents. I am particularly interested in investigating the etiology of non-Hodgkin lymphoma (NHL) and kidney cancer, and evaluating the carcinogenicity of trichloroethylene and other chlorinated solvents.

Non-Hodgkin Lymphoma: While severe immune dysregulation is an established risk factor for NHL, it is unclear whether subtle, subclinical immune-system function influences lymphomagenesis in the general population. In my research, I have found elevated circulating concentrations of the immune markers sCD23 and sCD30 to be associated with increased future NHL risk. As these have been proposed to be informative markers of B-cell activation, my findings support the hypothesis that mechanisms associated with sustained B-cell activation play a role in lymphomagenesis. I am also conducting similar research to better understand the etiology of multiple myeloma, a highly lethal B-cell malignancy.

Kidney Cancer: My leadership on genome-wide association studies (GWAS) of renal-cell carcinoma (RCC) has led to important advances in our understanding of genetic susceptibility to this malignancy. I reported the first GWAS findings for RCC, identifying variation in the *EPAS1* gene as well as a nongenic region on chromosome 11q13.3 to be associated with risk. Through subsequent investigations, I identified an additional 10 genetic-susceptibility regions. These findings have provided new insight into biologic pathways affecting the development of kidney cancer. I am working to expand the size of the GWAS and am conducting investigations of gene-environment interaction with established RCC risk factors such as body-mass index, hypertension, and smoking.

Chlorinated Solvents: The industrial cleaning chemical trichloroethylene (TCE), classified by the International Agency for Research on Cancer as a kidney carcinogen, may also affect the risk for NHL. Other chlorinated solvents are also suspected to cause cancer, most notably the dry-cleaning agent tetrachloroethylene. I have been leading occupational epidemiologic studies to better understand the carcinogenicity of these chemicals. In case-control investigations using very detailed retrospective-exposure assessment methods, I found that high exposure to TCE and tetrachloroethylene is associated with increased risks of NHL and kidney cancer respectively. I am continuing to investigate the carcinogenicity of these agents within a retrospective cohort of dry-cleaning workers and in other epidemiologic studies.

If you have been recently tenured, *The NIH Catalyst* will be in touch with you soon to do an article about you on these pages.

WAI T. WONG, M.D., PH.D., NEI

Senior Investigator and Chief, Neuron-Glia Interactions in Retinal Disease Section, National Eye Institute

Education: Massachusetts Institute of Technology, Cambridge, Mass. (B.S. in biology; B.S.E. in chemical engineering); Washington University, St. Louis (M.D.; Ph.D. in neuroscience)

Training: Internship in surgery, transitional year program, Presbyterian Hospital (Philadelphia); residency in ophthalmology, Scheie Eye Institute, Department of Ophthalmology, University of Pennsylvania (Philadelphia); fellowship in medical retina, National Eye Institute

Came to NIH: In 2005 for training; became a staff clinician in 2007; was appointed tenure-track investigator in 2011

Selected professional activities: Principal investigator on several clinical trials in retinal diseases; editorial board of *Scientific Reports*

Outside interests: Playing squash and other racket sports; traveling; visiting museums

Website: https://irp.nih.gov/pi/wai-wong

Research interests: My lab is exploring the fundamental biological mechanisms that underlie retinal diseases and is translating these findings into proof-of-concept clinical studies to discover new therapies. We are trying to understand the interactions between the cellular components (neuronal and glia) of the retina. Because many retinal diseases—such as diabetic retinopathy, retinal vein occlusions, and age-related macular degeneration—involve a key inflammatory component, we have focused on how the microglial cell (the resident immune cell in the retina) interacts with other retinal cells in the healthy and diseased retina.

To examine how microglia contribute to normal neuronal function in the uninjured adult retina, we depleted microglia in a genetic model over a sustained period of time. We found no significant changes in the laminar appearance or thickness in the retina, densities of neuronal populations, or morphology of retinal neurons and macroglia. But we did find that sustained microglial depletion resulted in the progressive deterioration in the electroretinographic response, which was correlated with synaptic degeneration. Our study was the first to show that microglia are required to maintain synaptic integrity in the central nervous system and in the healthy function of the retina.

We are trying to understand how microglia undergo change in the aging retina and contribute to age-related retinal disease. In our previous work, we demonstrated that retinal microglia in mouse models undergo senescent changes in morphology, dynamic-process motility, and distribution. We discovered that aged microglia display an altered response to injury signals: They are slower to respond to acute injury but also slower to revert back to a resting state after injury resolution.

We are also studying how microglia are altered in retinal disease, how they may drive disease progression, and how they can be inhibited in preclinical experiments and in clinical trials. In earlier studies, we found that—in a mouse model for retinitis pigmentosa (RP)—microglia contributed to the overall rate of photoreceptor degeneration in RP via phagocytosis and pro-inflammatory mechanisms. We also recently discovered that tamoxifen, a drug previously associated with retinal toxicity, paradoxically conferred protection on photoreceptors via its ability to suppress microglia activation. Together these studies outline the contributions that retinal microglia can make to photoreceptor degeneration and highlight some candidate pathways and pharmacological agents that can be exploited for the therapeutic strategy of microglial modulation to ameliorate photoreceptor loss in a variety of retinal diseases. ●

ABBREVIATIONS

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
NIEHS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
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

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

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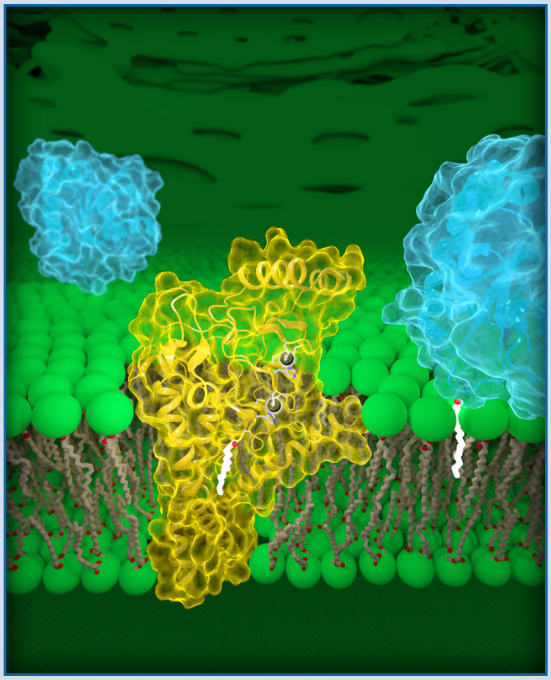
https://irp.nih.gov/catalyst/v26i2

CATALYTIC RESEARCH

NICHD: First 3-D Structure of DHHC Enzymes

The first three-dimensional structure of DHHC proteins—proteins that contain a 50-amino-acid chain called the DCCT domain, act as enzymes, and are involved in many cellular processes, including cancer—explains how they function and may offer a blueprint for designing therapeutic drugs. Researchers from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development led a study in which they proposed blocking DHHC-domain activity to boost the effectiveness of first-line treatments against common forms of lung and breast cancer. There are currently no licensed drugs that target specific DHHC enzymes. Shown: Molecular view of DHHC palmitoyltransferases. Human DHHC20 (yellow) is embedded in the Golgi membrane (green), a compartment located inside cells. DHHC20 attaches a fatty-acid chain (white) to a target protein (blue, foreground), which anchors the protein to the Golgi membrane. Read more at https://irp.nih.gov/catalyst/v26i2/research-briefs. ●



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