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Secrets of Building 7

NIH's First State-of-the-Art Infectious Disease Laboratory

BY JAMIE KUGLER, NIDCR

It was once a proud building filled with innovative scientists who courageously tackled public-health problems. For 60 years, it provided a home for NIH scientists who worked on infectious diseases, identified new viruses, and developed vaccines against hepatitis, rotavirus, and adenoviruses.

Now NIH's Building 7 on the Bethesda campus awaits demolition, sitting empty and lifeless, a stark contrast for this storied structure that had hosted luminaries in the field of infectious diseases. But oh, what stories the walls could tell.

Infectious-disease research has always been a dangerous proposition. Before the advent of modern biosafety equipment, laboratory-acquired infections were a constant risk for scientists. While not all of these infections were deadly, 10 Public Health Service personnel died as a result of performing or assisting with infectious-disease research between 1928 and 1944. In 1944, two of them died at NIH facilities within six weeks of each other: **Richard G. Henderson**, in Building 5, of scrub typhus—an acute febrile infectious illness caused by the bacteria *Orientia tsutsugamushi*; and **Rose Parrott**, in Baltimore, of tularemia—a rodent-transmitted disease caused by the bacteria *Francisella tularensis*.

These deaths spurred Congress to appropriate $1.2 million for the construction of a state-of-the-art biosafety facility at NIH

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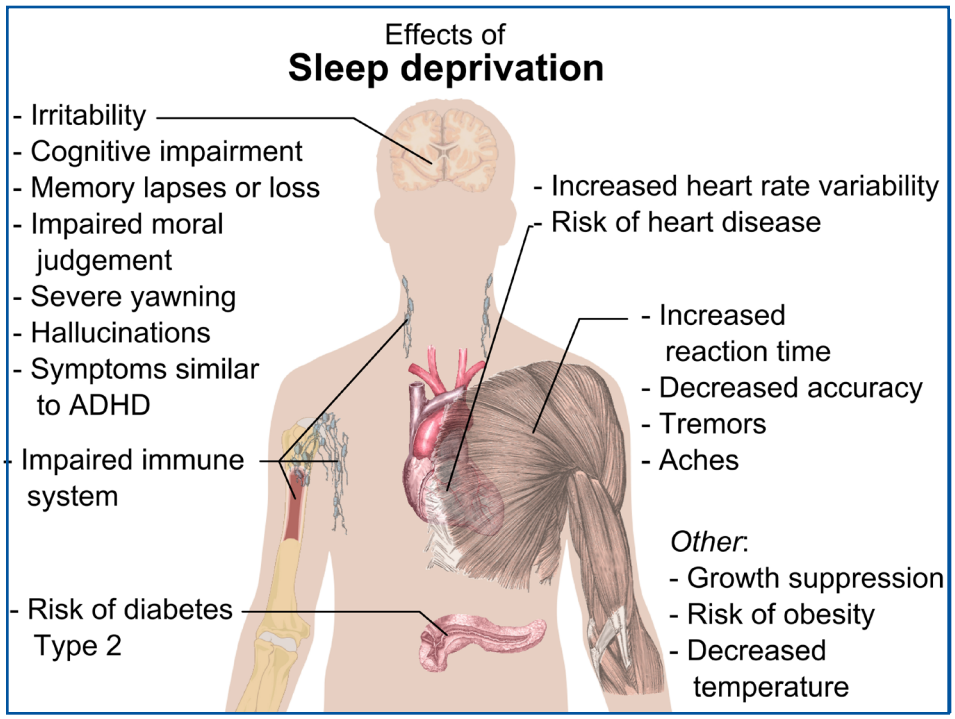
Sleep, Perchance to Research

NIHers Are Studying Sleep, Fatigue, and Circadian Rhythms

BY L.S. CARTER (OD), R. SCHEINERT (NIMH), J. TIANO (NIDDK), A. KUSZAK (NIDDK), AND R. BAKER (OD)



MIKAEL HÄGGSTRÖM, WIKIMEDIA COMMONS

Sleep plays an important role in physical health. It promotes the healing and repair of heart and blood vessels, helps maintain a healthy balance of hormones, and plays a role in learning. Ongoing sleep deprivation is linked to increased risk of heart disease, kidney disease, diabetes, obesity, high blood pressure, stroke, and other problems.

A sleep-deprived person may still function, but not as efficiently as someone who gets enough good-quality sleep, and they may be at increased risk for heart disease, kidney disease, diabetes, obesity, high-blood pressure, stroke, and a host of other problems. Lack of sleep may even affect one's ability to learn and remember information.

"Elucidating the nuts and bolts of what goes wrong [in sleep] is the cutting edge for much of the [sleep-related] research that is going on" at NIH and elsewhere, said **Michael Twery**, director of NIH's National Center on Sleep Disorders Research, which oversees the

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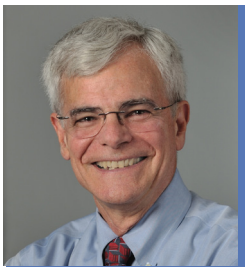


Long-term Planning for the IRP: An Update

BY MICHAEL GOTTESMAN, DDIR

You have probably been wondering what has been happening with the long-term planning process for the Intramural Research Program (IRP). As you recall, we initiated this process over a year ago in response to concerns about the declining buying power of the NIH intramural budget, important changes in the way in which we conduct biomedical research, and the need to sustain (and enhance) translational and clinical research in NIH's Clinical Center.

We are attempting to make this process as inclusive and transparent as possible and began by soliciting ideas from our entire scientific staff including the Assembly of Scientists. I have met many times with the scientific directors (SDs) as well as an ad hoc group of SDs, executive officers (EOs), and institute and center (IC) directors to formulate a process for long-term planning.

After five meetings with IC directors that included some smaller groups, we decided that the overall process would consist of three phases: (1) each IC would work with its Boards of Scientific Counselors (BSC) chairs, other outside expert advisors, and internal scientists to formulate IC-specific long-term plans; (2) the SDs and a small group of IC directors would synthesize these recommendations into trans-NIH initiatives; and (3) a subcommittee of the Advisory Committee to the Director (ACD), co-chaired by **Larry Tabak** and **Cato Laurencin**, would review materials provided by these various groups and make recommendations to the ACD at its December 12, 2014, meeting.

This timeline was ambitious, and I want to thank all of you for providing your time and input during the first two phases of this process. We had a well-attended, historic meeting of BSC chairs, IC directors, SDs, clinical directors, and EOs on May 16, 2014, to compare "visions." We noted some trans-NIH similarities and differences that represent the distinctive features of each IC.

> We are attempting to make the long-term planning process inclusive and transparent.

After receiving the IC-specific reports on July 31, the SDs assembled "The Future of the NIH Intramural Research Program: A Synthesis of Issues, Challenges, and Opportunities" that captured the trans-NIH features of all the IC reports. This document is being reviewed and edited by the NIH Director's Steering Committee of IC Directors.

The charge to the ACD has four components:

- Recommend how the IRP should ensure its distinctive role in biomedical research and how it should differ from extramural research institutions.
- Identify areas of opportunity that the IRP should focus on in the next 10 years to take advantage of its distinctive features.
- Identify what needs to be done to ensure the sustainability of the IRP's distinctive features, including the Clinical Center.
- Ensure the alignment of recommendations for the opportunities and needs in the IRP with the work of other ACD and internal NIH working groups regarding workforce demographics—age, sex, ethnic and racial diversity, and M.D.s versus Ph.D.s.

"The Future of the IRP" document, when completed, will address all these components and will have had input from each IC (with outside expert advice) and NIH as a whole. In particular, we will emphasize the IRP's distinctive characteristics that have evolved over time and in response to several outside reviews: the Clinical Center; the National Center for Biotechnology Information's and National Library of Medicine's databases; the sheer size and scope of research in the IRP; our ability to respond quickly to public-health emergencies (witness the Ebola vaccine trials taking place in the Clinical Center as this issue of the *NIH Catalyst* goes to press); our retrospective, investigator-oriented review process that should encourage high-risk, high-impact research; and the training environment that has populated academic medical centers with outstanding clinician-scientists and basic-scientists.

We have emphasized that the IRP environment includes a broad, critical mass of expertise consisting of some 1,000 principal investigators, 3,500 postdocs, and other

trainees who can collaborate quickly and share resources across IC and lab divisions.

The many discussions that went into the preparation of "The Future of the IRP" document helped frame the areas of scientific opportunity in which we are best poised to succeed. Although these areas are by no means intended to constrain the large range of scientific challenges embraced by our scientific staff, they are helpful in planning for facilities and recruitments.

The current list includes the development of precision medicine to enhance disease diagnosis, prevention, and treatment; cell-based therapies; research on the human microbiome and drug resistance; RNA biology and therapeutics; vaccine development; neuroscience and contributions to the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative; inflammatory diseases, clinical and molecular and cellular imaging; computational and structural biology; natural products as tools for basic research and treatment of disease; and the development of new animal models.

The NIH IRP seeks to be a dynamic research environment that will attract and train new generations of imaginative, highly talented, and diverse scientists who will lead biomedical research into the 21st century; reveal new principles of biology; provide a new understanding of human disease; and change treatment and prevention paradigms.

The long-term-planning effort to achieve this vision is still a work in progress. The opportunity for all of us to consider what kind of future the intramural program should have is valuable in its own right. There will be more to say later in the fall. ●

Let's Talk: Communicating Early with the FDA

Pre-IND Meetings May Help Shorten Drug-Development Time

BY ERIC BOCK, OD

The path from discovery to approval can be long, but meeting early with the Food and Drug Administration (FDA) may significantly shorten it.

In 2013, FDA researchers studied the clinical development times of all drugs approved between 2010 and 2012. On average, it took 10 to 15 years to develop a drug. When a clinical investigator of the drug met with the FDA before beginning clinical trials, the FDA researchers found that the average development was three to six years shorter.

"We think early communication can make a big difference regarding quality and efficiency," said **Anne Pariser**, an associate director in the Rare Diseases Program at FDA's Center for Drug Evaluation and Research.

Why? In short, the FDA can provide advice to help you be sure you are entering the process most efficiently. A clinical investigator must submit an investigational new drug (IND) application to the FDA before testing the drug in human subjects. The application typically requests information about the drug's nonclinical toxicology profile and any safety information available from prior human administration, drug formulation and characterization, proposed dosage, and the proposed clinical protocol and monitoring plan. The FDA wants to ensure that clinical-trial participants are protected from unnecessary risk; in reviewing the IND application, FDA focuses primarily on safety for first-in-human and early-phase clinical trials.

Before submitting the application, the investigator can request a pre-IND meeting with the FDA to ask for advice on clinical-trial design and to learn about necessary IND-enabling elements, including preclinical pharmacology and toxicology.

"Any investigator can request a meeting with the FDA," said Pariser. "These early meetings are particularly important for the development of drugs for rare diseases."

Pre-IND meetings with the FDA are not required but are encouraged to avoid unnecessary delays. For example, if an investigator's IND application is missing important information, the FDA will place the application on "clinical hold," and the investigator cannot begin clinical trials until the clinical hold has been addressed. The delay could have been avoided had the investigator requested a pre-IND meeting and learned what was needed for the application to be considered complete.

To schedule a pre-IND meeting, an investigator must submit a written request to the FDA. Should the request be granted, FDA tries to schedule the meeting within 60 days of receipt of the request. The clinical investigator should submit the background package for the meeting as well as questions to be addressed at least four weeks before the meeting. Pariser recommended scheduling the meeting prior to conducting animal-toxicity studies. However, the timing of a pre-IND meeting depends on where the sponsor is in the development process.

Pariser co-chaired a Joint Task Force with **Juan Lertora**, director of clinical pharmacology at the NIH Clinical Center. The task force encourages and facilitates early interactions with FDA regulatory staff. ●

For more information visit http://www.fda.gov/Drugs/DevelopmentApprovalProcess. The document *Guidance for Industry: Formal Meetings between the FDA and Sponsors or Applicants* is at http://1.usa.gov/1qgJ5rpf. A version of this article first appeared in the August issue of the *NIH Clinical Center News* (http://www.cc.nih.gov/about/news/newsletter.html#story5).

Three NIH Scientists Elected to the National Academy of Sciences

Carolina Barillas-Mury (NIAID), Shiv Grewal (NCI), Marius Clore (NIDDK)

BY RACHEL SCHEINERT, NIMH

Whether they are investigating mosquito midgut cells to better understand the transmission of malaria, identifying failing chromatin mechanisms that may lead to cancer, or exploring the structure of macromolecular "dark matter," the newest NIH members of the National Academy of Sciences (NAS) are making a big impact. On April 29, the NAS announced the election of 84 new members, including three NIH scientists: **Carolina Barillas-Mury** (National Institute of Allergy and Infectious Diseases, NIAID), **Shiv Grewal** (National Cancer Institute, NCI), and **Marius Clore** (National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK). The three scientists shared their research at an NIH minisymposium held in Masur Auditorium (Building 10) in June.

Carolina Barillas-Mury, a section chief in NIAID's Laboratory of Malaria and Vector Research, has shown that the mosquito's immune system can learn to fight off malaria-causing parasites.

"Imagine we're all sitting inside a midgut mosquito cell," she began. She pointed to a set of double doors on one side of the auditorium and asked the audience to picture a parasite entering. If it tripped the alarm, a security system would spray it with yellow paint. Then when it tried to escape through the opposite set of doors, it could be easily identified and stopped. But any parasite that could avoid being tagged would avoid the detection system and escape unharmed.

It turns out that previous exposure to the parasite results in more sentinel cells that help the mosquito immune system learn to fight the invaders. Barillas-Mury hopes that her work might pave the way for preventing malaria infections by making mosquitoes malaria-proof.

She also hopes her election to the NAS will pave the way for other Hispanic and women scientists to be successful. She joked that although she loves her home country, Guatemala—and visits her 80-year-old mother there twice a year—dreaming of becoming a research scientist was "like saying you're going to be an astronaut in a country without a space program." When she received the news that she had been elected to the NAS, the culmination of that dream, the first thing she did was call her mother.

The first thing **Shiv Grewal** did when he got the news about his election to NAS was to think of his father, who was also a scientist. Sadly, he had passed away when Grewal was young. "He would understand what this means," said Grewal who was driving to work when he got the news and had to pull over to take the call. The same week, he was also elected to the prestigious American Academy of Arts and Sciences.

As an NIH Distinguished Investigator and chief of NCI's Laboratory of Biochemistry and Molecular Biology, Grewal studies how eukaryotic genomic information is organized into distinct chromatin domains, what the molecular architecture and mechanisms of these domains are, and how genetic mutations can have deleterious consequences, including cancer. His lab is focused on RNA-based targeting of chromatin modifiers akin to an "on/off" switch for reading and expressing the genome.

"NIH has always been the place to do chromatin research," said Grewal, who has come full circle since starting his career at NIH. When he was doing his postdoctoral research at NCI, he demonstrated epigenetic control of gene expression. Later, in 2002, his defining the important role of RNA interference in histone-modification patterns was named *Science*'s breakthrough of the year.

"Define your scientific question early on," Grewall offered as advice to young scientists. "Pick a core key question, build a system, and dedicate yourself."

NIDDK Distinguished Investigator **Marius Clore**—who is section chief in NIDDK's Laboratory of Chemical Physics and also a member of the American Academy—is dedicated to using nuclear magnetic resonance spectroscopy (NMR) to examine proteins. He has been called a pioneer in developing NMR into a powerful tool for studying the structure, dynamics, and interactions of proteins.

Clore is using a specialized NMR method called paramagnetic relaxation enhancement (PRE) to decipher what he calls "dark matter"—all the mysterious properties of protein-protein, protein-DNA, and protein-ligand recognition. PRE is a technique that allows for measuring longer distances between labeled atomic nuclei, to detect and study the mechanisms of sparse and transient macromolecular interactions.

Clore also advised young scientists to dedicate themselves to their work. "Whatever you're doing, do it 100 percent," he said. He gives 100 percent to his extracurricular pursuits, too: He has a third-degree black belt in taekwondo and is an avid cyclist. One of his proudest achievements was conquering La Marmotte, a 108-mile bike race winding through the French Alps.

Barillas-Mury, Grewal, and Clore represent the "extraordinary richness of talent at the NIH," said **Michael Gottesman**, deputy director for intramural research. The three now join the 55 other NIH intramural scientists who are NAS members. ●

Several NIHers are elected to the NAS each year. The list is posted at http://irp.nih.gov/about-us/honors/the-national-academies.

Karl Deisseroth: Optical Deconstruction of Biological Systems

Stanford Neuroscience Pioneer Thrills WALS Audience at Nirenberg Lecture

BY KEVIN RAMKISSOON, NHLBI

Karl Deisseroth of Stanford University (Stanford, California) has been changing the face of neuroscience and behavioral research one pioneering technique at a time.

"He has, more than anyone [else] we can point to in the last decade, developed and applied, and then distributed, remarkable technologies to help us understand neuroscience in ways that have been truly enlightening," said NIH Director **Francis Collins** in introducing Deisseroth as the speaker at the fourth annual Marshall W. Nirenberg Lecture on June 11, 2014, in Masur Auditorium (Building 10). "*Nature*, in its article about him about a year ago, called him the 'Method Man' because of the way in which he continually comes up with creative approaches that open new windows into understanding how the nervous system works."

Deisseroth, a Howard Hughes Medical Institute Investigator and professor of bioengineering and of psychiatry and behavioral sciences at Stanford, is the recipient of many awards and is a member of the National Academy of Sciences.

During the lecture, Deisseroth shared results and exciting advances in optogenetics technology; fiber phototometry; and CLARITY (which stands for clear, lipid-exchanged, acrylamide-hybridized rigid, imaging/immunostaining–compatible tissue hydrogel), a method his lab developed for keeping three-dimensional tissue intact. His team and others have been using these techniques to map neural networks, discern the molecular identities of cells that are naturally active in the course of behavior, and gain insight into what can go wrong in disease.

BILL BRANSON

Karl Deisseroth (Stanford) chatted with NIHers after his WALS-Nirenberg lecture on optogenetics in June.

Optogenetics combines light and genetically encoded light-sensitive proteins to control cell behavior. At the heart of optogenetics are microbial opsins, light-responsive receptor proteins that can sense light and modulate cell activity. Deisseroth and his colleagues brought optogenetics to the forefront of science in 2005, when they inserted a light-sensitive gene, *channelrhodopsin-2* (from pond algae), into selected mammalian neurons and showed that the light pulses could trigger the neurons to fire at their normal speed of a few milliseconds. Although this work was not the first demonstration of a genetically encoded method to gain optical control of neurons, the precise triggering of a single protein on a physiologically relevant timescale overcame significant challenges faced by earlier multicomponent techniques (*Nat Neurosci* **8:**1263–1268, 2005).

In the decade since, Deisseroth's research has progressed rapidly. Technological advances have facilitated the selective targeting of opsins to certain neurons in the mouse brains. His lab developed a fiber-optic neural interface to both control and distinguish between patterns of activity that contribute to motivated behavior, reward learning, and anxiety. Deisseroth is a psychiatrist who focuses on treatment-resistant depression, so he is particularly interested in the neural-circuit underpinnings of these behaviors.

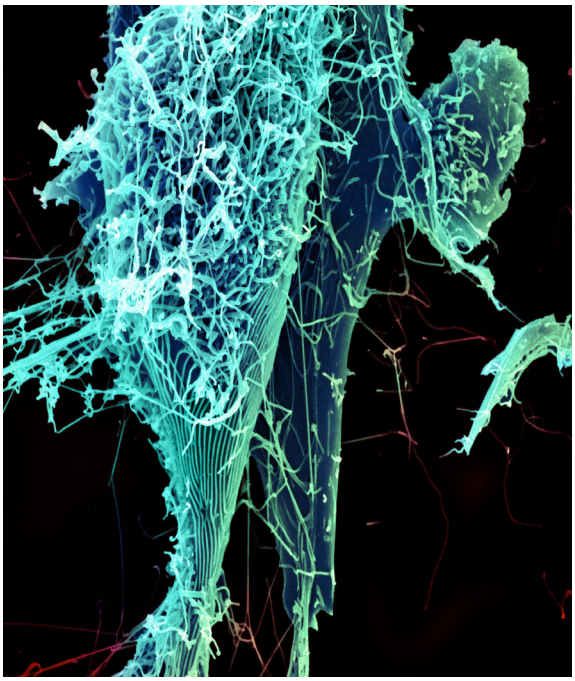
Perhaps one of the most important technologies that Deisseroth's group devised is CLARITY, a method to make the whole brain transparent so it could be easily imaged (*Nat Methods* **106:**508–513, 2013). Before CLARITY, scientists had to reconstruct three-dimensional images from slices of neural tissue, because imaging an entire brain was impossible: The lipid layers that surround the cells obscure the view.

Deisseroth's team figured out a way to remove the lipids without disrupting the rest of the brain structure. They created a mesh-like hydrogel to hold the other components in place and then incubated the brain in detergent to solubilize lipids. Once the fat is removed, the brain is transparent—and able to be more easily imaged—as well as permeable to macromolecules, which facilitates molecular phenotyping of cells.

CLARITY allows high-resolution imaging of very fine cellular structures, such as axons. Deisseroth further refined the method using light-sheet microscopy to illuminate only the region of the tissue being imaged at a particular time (*Nat Protoc* **9:**1682–1697, 2014). When combined with commercially available CLARITY-optimized microscope objectives, both the speed and the image quality of tissue images have been greatly enhanced.

Deisseroth enthusiastically shares the tools with, and provides training to, the scientific community (http://clarityresourcecenter.org). The end result is an ever widening field of scientists using optognetics to help elucidate the inner workings of the brain. ●

The Nirenberg Lecture commemorates the late Marshall Nirenberg, who shared the Nobel Prize for Physiology or Medicine in 1968 for deciphering the genetic code. To watch a videocast of Karl Deisseroth's June 11, 2014, lecture go to http://videocast.nih.gov/launch.asp?18552.



H. FELDMANN, P. JAHRLING, E. FISCHER, A. MORA, NIAID

After multiplying inside a host cell, the stringlike Ebola virus is emerging to infect more cells. Ebola is a rare, often fatal disease that occurs primarily in tropical regions of sub-Saharan Africa. The virus is believed to spread to humans through contact with wild animals, especially fruit bats. It can be transmitted between one person and another through bodily fluids.

FDA LEAVES BETHESDA CAMPUS

Sadly, the Building 29 complex on NIH's Bethesda campus is no longer home to the Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research (CBER) and Center for Drugs Evaluation and Research (CDER). The complex's occupants were relocated to FDA's new White Oak campus in Silver Spring, Maryland, as part of an effort to consolidate operations. The CBER and CDER divisions were once part of NIH's Division of Biologic Standards before becoming part of FDA in 1972.

The Building 29 complex consists of three interconnected buildings located just south of the Clinical Center: Building 29, built in 1960; 29A, built in 1968; and 29B, constructed in 1994. Building 29 will remain vacant for the time being while the cost of renovation is being assessed; Building 29A will be used as swing space to facilitate ongoing renovations of Building 10; Building 29B will be occupied by NICHD, NIAID, and NIMHD.

Both 29 and 29A were originally referred to as the Center for Biologics Annex and have been determined eligible for listing in the National Register of Historic Places. They not only hosted the research labs of illustrious NIH women scientists such as **Margaret Pittman** and **Ruth Kirschstein**, but also were the only facilities in the United States dedicated to the regulation of biological medicines.

To read a recent story in the *NIH Record*, go to http://nihrecord.nih.gov/newsletters/2014/08_29_2014/story1.htm.

OLD INFECTIOUS AGENTS DISCOVERED ON CAMPUS

In July, 327 vials of infectious agents—including six safely sealed glass vials of Variola (smallpox) virus—that were stored in a cold room in an FDA laboratory in Building 29A, were discovered as the scientists were packing up to move to FDA's new White Oak facility. The discovery was handled appropriately and the smallpox was safely and securely transferred to the Centers for Disease Control and Prevention's (CDC) high-containment facility in Atlanta. The materials dated back to the 1950s and were under NIH control until 1972, when the labs' responsibility for regulating vaccines and other biologics were transferred to the FDA. Back in the 1950s, some of the materials in question were routinely used in research and not considered select agents at the time.

"This incident underscored the need to keep close track of all potentially pathogenic materials," NIH Director **Francis Collins** wrote in an all-staff e-mail. NIH quickly developed a plan to "conduct a comprehensive search of all facilities to be certain that no other select agents, toxins, or hazardous biological materials are improperly stored in any NIH facilities." The "clean sweep" of all NIH intramural labs is underway and expected to be completed by the end of September. So far, the clean-sweep operation has found more misplaced pathogens, and NIH officials promptly reported the discoveries to the CDC.

"Good lab practices demand that we only store materials we need," said Deputy Director for Intramural Research **Michael Gottesman**, who is overseeing the clean-sweep operation. "Dangerous materials should be properly handled and registered."

ERADICATING EBOLA

As the Ebola virus continues to spread in West Africa, NIH has begun a clinical trial to test an investigational vaccine, co-developed by the National Institute of Allergy and Infectious Diseases (NIAID) and GlaxoSmithKline—to prevent the disease. NIH intramural and NIAID-supported extramural researchers have also been working for decades to improve the understanding of the Ebola virus and to develop diagnostics, therapeutics, and vaccines. In addition, the NIH Clinical Center has a special clinical studies unit with high-level isolation capabilities and is prepared to accept Ebola patients if necessary. And NIAID Director **Anthony Fauci**, through media interviews, is helping to educate the public about the disease. To read more, visit the NIH Director's Blog and search for Ebola: http://directorsblog.nih.gov. ●

Native Voices: Native Peoples' Concepts of Health and Illness

Exhibit at the National Library of Medicine

BY LIAM EMMART, INTERN

Sweat lodges, herbal medicine, and a model Hōkūle`a, a Native Hawaiian voyaging canoe. These are just a few of the elements in the National Library of Medicine's (NLM's) Native Voices exhibit, which explores the connection between wellness, illness, and cultural life through a combination of interviews with Native people, artwork, objects, and interactive media.

The exhibit displays the NIH's "growing admiration for many of the ideas and practices of Native Peoples and highlights their beliefs about the importance of nature, tradition, and community in healing," explained NLM Director **Donald Lindberg** in an introductory video.

Despite advances in Western medicine in treating many types of illness, traditional Native healing practices have recently been recognized by the U.S. Department of Veterans Affairs (VA) for their value in therapeutic healing treatments and their potential to teach modern medicine a few valuable lessons. The exhibit features riveting interviews with Native Americans, Alaska Natives, and Native Hawaiians, collectively called Native Peoples, on their concepts of health and illness.

Although traditional healing methods may be unable to cure terminal illnesses such as cancer, the American Cancer Society credits them with reducing pain and stress while improving the quality of life. This holistic approach to treatment underlines the idea that "wellness of the individual is inseparable from harmony within the family and community and pride in one's heritage," according to one of the exhibit displays. Ceremonies such as the Hawaiian Ho'oponopono, a kind of family conference that focuses on restoring and maintaining healthy relationships within a family or with God, are valuable for maintaining a community's order, peace, and trust.

Many traditional healing ceremonies reaffirm one's commitment to living a healthy and productive life. They form the basis of treatment and create a dialogue to release people from feelings of guilt.

For example, the Navajo Enemy Way Ceremony helps restore a returning soldier's "state of balance, or beauty, within the universe." The ceremony helped the Code Talkers: Navajos, Choctaws, Cherokees, and other Native Peoples who used their languages to enable the U.S. military to transmit coded messages during both world wars. The Code Talkers not only were subjected to the normal stresses of war—they also had the added stress of being ordered to take oaths of silence about their crucial wartime contributions.

Fortunately, they were allowed to participate in spiritual ceremonies including the Navajo Enemy Way Ceremony, which helped them "sustain connections with family, community, and Native culture." The VA also recognizes that this type of holistic, community-oriented healing approach is helpful to any veteran who is recovering from post-traumatic stress disorder.

Although ceremony and community-focused healing distinguish traditional healing methods from Western medicine, many facets of each approach are similar. For instance, Native games—built on tests of strength and displays of survival skills—and modern medicine's push to exercise both emphasize the value of being fit and healthy.

Traditional healing practices also offer Western medicine ideas for new methods of engaging with not only the individual but also with their communities. ●

MONICA MENDOZA, U.S. AIR FORCE PHOTO

Michael Hackwith, (U.S. Marine Corps, retired) Lakota spiritual leader, and sweat lodge [Inipi], 2010. The sweat lodge ceremony was first practiced by the Plains Indians and has spread to many other tribes. A sweat lodge is typically a tent-like structure that traps heat under blankets or animal hides, promoting wellness by cleansing and purifying the body and spirit.

NATIVE VOICES
NATIVE PEOPLES' CONCEPTS OF HEALTH AND ILLNESS

To view NLM's "Native Voices: Native Peoples' Concepts of Health and Illness" exhibit online, go to http://www.nlm.nih.gov/nativevoices. The exhibit is also open to visitors from 8:30 a.m. to 5:00 p.m., Monday–Friday (except federal holidays), in Building 38.

Intramural Research Briefs

NIDCR: REGENERATING TEETH

NIDCR researchers were part of an NIH-Harvard team that was the first to demonstrate the ability to use a low-power laser light (LPL) to coax stem cells inside the body to regenerate tissue. They used a small dose of LPL to activate dental stem cells in rat molars that had cavities, to generate dentin, the bonelike tissue that is major component of teeth. The researchers also outlined the molecular mechanism involved: They found that LPL treatment generated a type of molecule known as reactive oxygen species, which stimulated dentin production by activating transforming growth factor–beta, a signaling protein that can promote dental stem-cell differentiation. The researchers also showed that LPL induced adult human dental stem cells to form dentin in the laboratory. The findings may lead to new approaches to develop low-cost, noninvasive therapies for treating dental disease and tooth damage. The lead author, who was a postdoc at Harvard at the time of the study, is now at NIDCR. (NIDCR authors: P.R. Arany, A. Cho, and A. Kulkarni, *Sci Trans Med* **6**:238ra69, 2014)

NIAID: EXPERIMENTAL CHIKUNGUNYA VACCINE

An experimental vaccine to prevent the mosquito-borne viral illness chikungunya elicited neutralizing antibodies in all 25 adult volunteers who participated in a recent early-stage clinical trial conducted by NIAID's Vaccine Research Center (VRC). Chikungunya infection is characterized by severe joint pain accompanied by headache and fever. There are currently no vaccines or specific drug treatments for chikungunya. The chikungunya virus has been documented in 40 countries; it appeared in the Western Hemisphere in late 2013. Vaccine-induced antibodies persisted in all volunteers for at least 11 months after the final vaccination, suggesting that the vaccine could provide durable protection. (NIAID VRC authors: L.-J. Chang, K.A. Down, G.J. Nable, J.E. Ledgerwood, and others, *Lancet* DOI:10.1016/S0140-6736(14)61185-5)

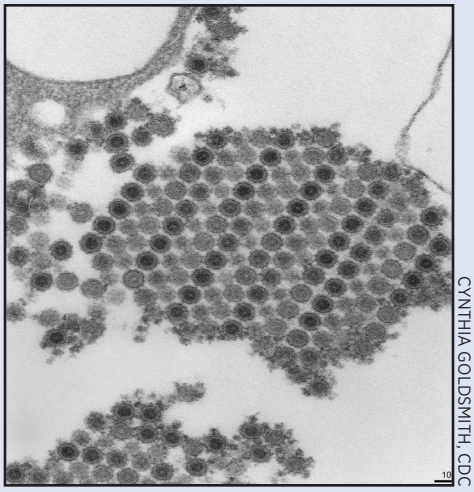
NCI, NICHD: SUBCELLULAR IMAGING VISUALIZES BRAIN RECEPTORS

NCI and NICHD scientists have created high-resolution images of the glutamate receptor, a protein that plays a key role in neuronal signaling. The advance opens a new window to study protein interactions in cell membranes in exquisite detail. The scientists used an imaging technique called cryo-electron microscopy (cryo-EM), an emerging tool for obtaining protein structures in various states. Cryo-EM is a more versatile approach for obtaining protein structures than the commonly used method of X-ray crystallography, a process that requires scientists to force the protein to crystallize in a fixed shape.

The glutamate receptor serves as a channel to allow ions into the nerve cell, which induces nerves to send signals. The dysfunction of this receptor has been implicated in some types of cancer as well as in neurodegenerative and psychiatric disorders, including Parkinson disease and depression. Understanding how the ion channels operate could lead to the creation of medications that inhibit or enhance these receptor motions. (NCI authors: J.R. Meyerson, P. Rao, S. Subramaniam; NICHD authors: J. Kumar, S. Chittori, M.L. Mayer, *Nature* DOI:10.1038/nature13603)

NIA, NHLBI: SIX NEW GENETIC RISK FACTORS FOR PARKINSON DISEASE

Using data from some 18,000 patients, NIH scientists have identified more than two-dozen genetic risk factors involved in Parkinson disease, including six that had not been previously reported. The NIH researchers collaborated with multiple public and private organizations to collect and combine data from existing genome-wide association studies, which allow scientists to find common variants in the genetic codes of large groups of individuals. The combined data included approximately 13,708 Parkinson disease cases and 95,282 control subjects, all of European ancestry. The investigators identified potential genetic-risk variants, which increase the chances that a person may develop Parkinson disease. Their results suggested that the more variants a person has, the greater the risk, up to three times as high, for developing the disorder. Some of the newly identified genetic risk factors are thought to be involved with Gaucher disease, regulating inflammation and the nerve-cell chemical-messenger dopamine as well as alpha-synuclein, a protein that has been shown to accumulate in the brains of some people with Parkinson disease. Further research is needed to determine the roles of the variants identified in this study. (NIA authors: M.A. Nalls, D.G. Hernandez, M.F. Keller, S. Arepalli, C. Letson, C. Edsall1, H. Pliner, A.B. Singleton; NHLBI author: A.L. DeStefano, *Nat Genet* DOI:10.1038/ng3043)



CYNTHIA GOLDSMITH, CDC

NIAID's Vaccine Research Center (VRC) tested a promising experimental vaccine to prevent the mosquito-borne viral illness chikungunya. Above: This transmission electron micrograph (TEM) depicts numerous chikungunya virus particles Each virion is approximately 50 nanometers in diameter.

CONTRIBUTORS: SOMA CHOWDHURY, FDA; KRYSTEN CARRERA, NIDDK

Read more online at http://irp.nih.gov/catalyst/v22i5/research-briefs.

NIAID: NASAL TEST DETECTS PRION DISEASE

NIH and Italian scientists have developed a nasal brush test that can rapidly and accurately diagnose Creutzfeldt-Jakob disease (CJD), an incurable and ultimately fatal neurodegenerative disorder. CJD is a prion disease in which normally harmless prion protein molecules become abnormal and gather in clusters, leaving spongelike holes, in the brain. Other prion diseases include bovine spongiform encephalopathy, or mad cow disease, in cattle.

Human prion diseases can be transmitted via blood transfusions, transplants, and contaminated surgical instruments. Up to now, a CJD diagnosis required testing brain tissue obtained after death or by biopsy in living patients. The new diagnostic test, which involves collecting olfactory neurons in the nasal cavity, would let doctors clearly differentiate prion diseases from other brain diseases. (NIAID authors: C.D. Orru, M. Bonginni, A.G. Hughson, B.R. Groveman, and B.Caughey, *N Engl J Med* **371**:519–529, 2014)

NIAMS, NHLBI, NHGRI, NIDCD: GENE LINKED TO FATAL INFLAMMATORY DISEASE

NIH investigators have identified a gene that underlies a very rare but devastating autoinflammatory condition in children. Several existing drugs have shown therapeutic potential in laboratory studies, and one is currently being studied in children with the disease, which the researchers named SAVI, short for stimulator of interferon genes protein–associated vasculopathy with onset in infancy. (NIH authors: Y. Liu, A.A. Jesus, B. Marrero, R. Goldbach-Mansky, and others, *N Engl J Med* DOI:10.1056/NEJMoa1312625)

NEI, NCI: GENE CRITICAL TO THE EARLY DEVELOPMENT OF CILIA

NEI and NCI researchers have described the functions of a gene responsible for anchoring cilia, the sensory hairlike extensions present on almost every cell of the body. In mice without the gene *Cc2d2a*, cilia throughout the body failed to grow, and the mice died during the embryonic stage. The finding adds to an expanding body of knowledge about ciliopathies, a class of genetic disorders that result from defects in the structure or function of cilia. (NIH authors: S. Veleri, A. Swaroop, and others, *Nat Commun* **5**:4207, 2014)

NCI: EXTREME OBESITY MAY SHORTEN LIFE EXPECTANCY UP TO 14 YEARS

Adults with extreme obesity have increased risks of dying at a young age from cancer and many other causes including heart disease, stroke, diabetes, and kidney and liver diseases, according to results of an analysis of data pooled from 20 large studies of people from three countries. The study, led by NCI researchers, found that people with extreme obesity had a dramatic reduction in life expectancy compared with people of normal weight. Extreme obesity is defined as a body mass index (BMI) of 40.0 or higher; normal weight is a BMI of 18.5-24.9. (NCI authors: C.M. Kitahara, P. Hartge, et al., *PLoS Med* **11**:e1001673, 2014)

NHGRI, NCI, CIT, NHLBI: NEW GENETIC ASSOCIATION WITH CORONARY ARTERY DISEASE

Researchers at NHGRI, working with groups from NCI, NHLBI, and CIT, have found an innovative way to identify genes associated with coronary artery calcification by next-generation sequencing of RNA from subjects enrolled in the ClinSeq study, substantiated with DNA and protein evidence. Results from this research suggest that the *TREML4* gene is associated with coronary calcification. (NIH authors: S.K. Sen, L.G. Bieseker, and others, *Am J Hum Genet* **95**:66–76, 2014)

NIDDK: UNDERSTANDING THE MOLECULAR BASIS OF A SICKLE-CELL DRUG

NIDDK researchers have identified a molecular basis for a key beneficial effect of the drug hydroxyurea in patients with sickle-cell disease (SCD). Hydroxyurea increases fetal hemoglobin concentrations in the red blood cells of patients with SCD, thus diluting the concentration of sickled red cells and so decreasing the tendency of red cells to block blood flow to tissues. The drug is the only one approved by FDA for treating SCD.

Researchers had previously identified expression of the *SAR1* gene as crucial to the drug's ability to increase fetal hemoglobin concentrations in red blood cells. In the latest study, suppression of *SAR1* expression in red blood cell precursors prevented hydroxyurea from stimulating fetal hemoglobin production. Researchers also found that overexpression of *SAR1* activated a genotoxic stress pathway and promoted fetal hemoglobin production. These findings suggest that molecular pathways involved in *SAR1* expression may provide targets for designing new fetal hemoglobin–stimulating drugs that may be useful for the treatment of SCD and thalassemia. (NIH authors: J. Zhou, K. Chin, W. Aerbajinai, C. Kumkhaek, H. Li, G.P. Rodgers, *Blood* **124**:1146–1156, 2014)

NCATS: FIRST DRUG CANDIDATE ACQUIRED BY BIOPHARMACEUTICAL COMPANY

A drug candidate—Aes-103—developed by NCATS researchers and collaborators to treat sickle-cell disease (SCD), has been acquired by Baxter International's BioScience business. Aes-103, the first drug specifically developed to target the underlying molecular mechanism of SCD, binds directly to hemoglobin and changes its structure, thereby reducing the sickling of red blood cells. This is the first time a company has acquired a drug candidate developed with NCATS's Therapeutics for Rare and Neglected Diseases (TRND) program resources. Currently, the only FDA-approved drug to treat SCD is hydroxyurea, which not everyone responds to favorably. To read more about NCATS and its TRND program, visit http://www.ncats.nih.gov/trnd.html. ●

Sleep

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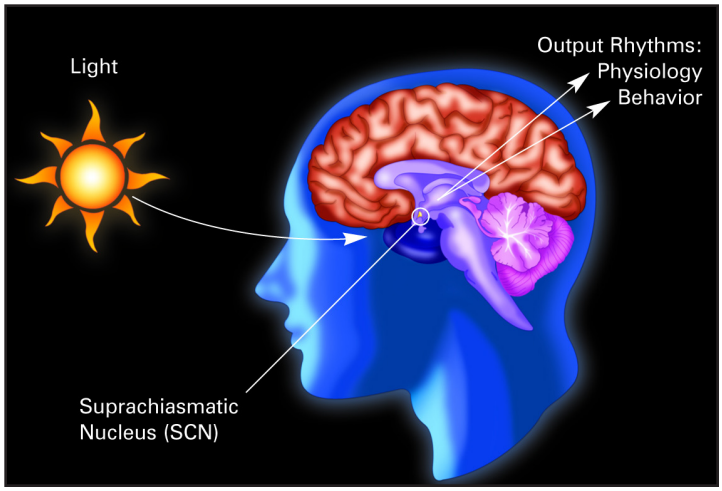

NIGMS

NICHD investigator David Klein and a colleague found that a tiny subunit of the hypothalamus called the suprachiasmatic nucleus (SCN) was essentially a circadian pacemaker, or what he calls "the mind's clock." The SCN helps control sleep by coordinating the actions of billions of miniature "clocks" throughout the body. These aren't actually clocks, but rather are ensembles of genes inside clusters of cells that switch on and off in a regular, 24-hour cycle.

support of research and research training related to sleep disorders and stewards several forums that facilitate the coordination of sleep research across NIH, other federal agencies, and outside organizations.

At NIH, there are more than 50 researchers studying sleep, fatigue, and circadian rhythms. The *NIH Catalyst* interviewed four of them and provided descriptions of the work of many others. (Read more online, including an interview with Twery, at http://irp.nih.gov/catalyst/v22i5/sleep-perchance-to-research.)

The Mind's Clock: David C. Klein

BY RACHEL SCHEINERT, NIMH

For someone who says, "I was never really interested in sleep" research, neuroendocrinologist **David Klein** (National Institute of Child Health and Human Development) has significantly contributed to the field by identifying the molecules and brain regions that regulate the internal clock in all vertebrates.

"I was interested in endocrinology, and the pineal gland had the shortest chapter [in textbooks] … so I figured I could make the biggest contribution," he joked. The pineal gland is a small melatonin-producing structure in the center of the vertebrate brain. Melatonin, discovered by a team of researchers led by Yale dermatologist Aaron B. Lerner in 1958, is a hormone that regulates circadian rhythms.

When Klein joined the NIH in 1969, NIH neuroscientist **Julius Axelrod** was already investigating the synthesis of melatonin. "I was competing with a man with a Nobel prize," said Klein. (Axelrod, who worked in the National Heart Institute and the National Institute of Mental Health, shared the Nobel Prize in Physiology or Medicine in 1970 for his discovery of the actions of neurotransmitters in regulating the metabolism of the nervous system.)

Soon, however, Klein made the breakthrough discovery that the daily rhythm of melatonin production is regulated by arylalkylamine N-acetyltransferase, an enzyme responsible for serotonin acetylation. Basically, this enzyme, which Klein coined the "timezyme," controls melatonin production, turning it on and off very rapidly.

Klein playfully handled a large, brightly colored crystalline model of the "timezyme" while he explained its unique structure. Concentrations of "timezyme," and subsequently melatonin, increase at night in all vertebrates. Because not all animals sleep at night, melatonin is not a simply a signal to sleep but truly a signal of time, even used for seasonal timing in some species.

In collaboration with neuroanatomist Robert Moore, Klein found that a tiny subunit of the hypothalamus called the suprachiasmatic nucleus (SCN) was essentially a circadian pacemaker, or what Klein calls "the mind's clock." This brain region contains melatonin receptors and works as "the master oscillator" that keeps the circadian clocks in the body synchronized with one another and to the 24-hour day. The SCN also controls the endogenous sleep rhythms of when to sleep and for how long. If the SCN is destroyed, circadian rhythmicity is abolished as well as the ability to synchronize patterns of daily activity with the light cycle.

Klein believes he has influenced the field of sleep research by raising awareness of the SCN; in 1991, he, Moore, and a colleague co-edited *Suprachiasmatic Nucleus: The Mind's Clock*, a book devoted to explaining the significance of the SCN.

Today, melatonin is a widely used, self-administered sleep aid. There are claims that melatonin helps you to fall and stay asleep, and maintain healthy sleep patterns. However, Klein points out that many of these claims have not been scientifically proven. Currently, Klein's laboratory is focused on characterizing the transcriptome (the very small percentage of the genome that is transcribed into RNA molecules) of the pineal gland. Using high-throughput DNA and RNA sequencing techniques, they have found hundreds of genes that are significantly altered over a 24-hour cycle. These genes, some of which exhibit a 100-fold difference in day-night expression, control many functions including the fate and phenotype of pinealocytes, the cells responsible for producing melatonin.

The Link Between Obesity and Sleep: Giovanni Cizza

BY JOSEPH P. TIANO, NIDDK

Investigator Giovanni Cizza (National Institute of Child Health and Human Development) spent a large part of his career as a clinical investigator at the NIH addressing two important questions surrounding sleep and obesity. First, what happens to the metabolism of people who are sleep deprived for social reasons when they are given an opportunity to sleep longer? Second, why are individuals with narcolepsy (who cannot regulate their sleep cycle and so sleep at random times throughout the day) about 15 pounds heavier than healthy control subjects?

To answer the first question—How do sleep-deprived people respond to adequate sleep?—Cizza enrolled obese people who self-reported sleeping fewer than 6.5 hours per night in a study and coached them to increase their sleep time to at least 7.5 hours per night for 15 months. Before and immediately after the intervention, they spent time at the NIH undergoing many baseline and follow-up tests assessing metabolism, body weight, insulin sensitivity, hormone concentrations, and neurological function. Cizza found that sleeping longer improved the participants' neurocognitive functions (such as memory) and executive functions (learning and decision making) by up to 10 percent. Some of the results on body weight and metabolism were published in the August 2014 issue of the electronic journal *PLOS ONE*. (*PLOS ONE* **9:**e104176, 2014)

For the the second question—Why do individuals with narcolepsy weigh more than healthy control subjects?—Cizza hypothesized that individuals with narcolepsy have decreased energy expenditure compared with healthy control subjects. After all, mice with narcolepsy weigh more than healthy mice because they expend less energy and therefore burn fewer calories. The extra calories are stored as fat. To test the hypothesis in humans, Cizza has so far recruited about 20 subjects with matched control subjects and put them in a room-sized metabolic chamber for 24 hours to measure their oxygen consumption and carbon-dioxide production, which reflect energy expenditure. He'll report his findings when the study is complete.

BILL BRANSON

NICHD investigator Giovanni Cizza (now at the FDA) spent a large part of his career addressing important questions on the relationship between sleep and obesity. Pictured: Cizza is standing next to a recruiting poster—for a sleep and weight study—that features Pablo Picasso's painting of a woman sleeping in a chair.

Cozying Up with Sleeping Flies: Susan Harbison

BY ADAM J. KUSZAK, NIDDK

Susan Harbison didn't foresee the day she would be meticulously measuring the genetics of sleep in flies when she started her career as an aerospace engineer analyzing structural stress factors on Navy helicopters. Later, after going back to school to get a Ph.D. in genetics and doing postdoctoral work in neuroscience and genetics, she found her calling—quantitative genetics.

Now she is an Earl Stadtman Investigator in the National Heart, Lung, and Blood Institute's (NHLBI's) Laboratory of Systems Genetics, where she is trying to derive computational models describing how gene networks influence sleep.

She focuses on the Drosophila (fruit fly) model because so many powerful genetic tools exist to study it. Furthermore, sleep in Drosophila has all the behavioral characteristics of mammalian sleep. Immobile periods of five minutes or more and a drooping posture (resulting from muscle relaxation) define fruit-fly sleep. A fruit fly will try to make up for lost sleep. An increased arousal threshold is also observed—for instance, experimental vials need to be tapped with greater force to rouse a sleeping fruit fly, just as you might need to be forcefully shaken awake from a deep slumber. A fruit fly's sleep cycle is diurnal, and fruit flies also spend a significant portion of their lives asleep just as we do, in some cases as much as a combined 15 hours in a 24-hour period.

"I measured things [such as] sleep duration, the number of sleep-bouts or naps, the average sleep-bout length, [and] waking activity, which is a measure of how hyperactive the flies are," Harbison told NHLBI Director **Gary Gibbons** in a recent interview that appears on the NHLBI Web site.

Sleep

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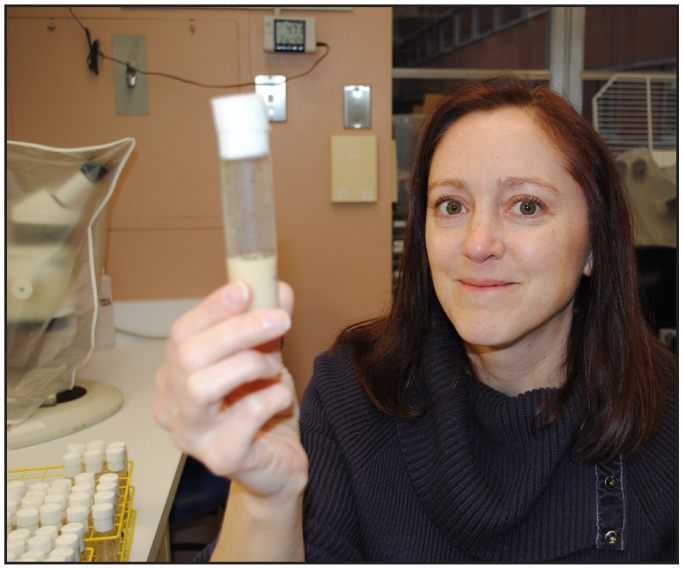


NHLBI

The recent recipient of a Presidential Early Career Award for Scientists and Engineers, NHLBI investigator Susan Harbison was recognized for her work into the genetic and environmental changes—such as drug exposure—affect sleep patterns in Drosophila (fruit flies). Since sleep in Drosophila has all the behavioral characteristics of mammalian sleep, she hopes that the identification of gene networks may have implications for humans.

To measure sleep in fruit flies, she used an infrared-based Drosophila activity-monitoring system. Each fruit fly is placed in a three-inch-long glass tube. "When the fly walks back and forth, he breaks the infrared beam, and that tells us whether or not he's active," Harbison explained to Gibbons. The data generate a series of text files that include numbers of counts per minute. "We can decipher [sleep phenotypes] from that."

Harbison has generated some exciting results using a genome-wide association study (GWAS) in which she probed 2.5-million genetic variants in a collection of inbred fruit flies whose ancestors were captured in the wild. She identified single-nucleotide polymorphisms, many of which have human homologues that may be associated with natural variations in sleep.

Now the big problem facing Harbison is determining which candidate genes contribute most to sleep behavior. In fruit flies of identical genotypes, she found that sleep patterns were affected by changes in the environment. She also observed differences in sleep patterns between male and female fruit flies: Males have bursts of activity at dawn and at dusk that might be related to courtship behavior; females are active at a lower level throughout the day and take shorter naps than males do. Sleep deprivation also affects glycogen content in males and triglycerides in females.

Human sleep disorders are correlated with learning and memory impairment, neurological diseases, cardiovascular problems, and hypertension, to name a just a few. Within this complex web the question of whether sleep is needed for one particular function before all others remains a puzzle. "There's not one theory of sleep that everyone is jumping on," said Harbison. Indeed, the GWAS candidate genes identified in her work represent aspects of all the current theories on the need for sleep, providing no shortage of big questions to ask.

To listen to Harbison's interview with NHLBI Director Gary Gibbons, go to http://1.usa.gov/1qjfX22. To view Harbison's presentation that she gave on April 1, 2014, as part of the Demystifying Medicine series, go to http://videocast.nih.gov/launch.asp?18362.

Why Sleep? Carolyn Beebe Smith

BY REBECCA BAKER, OD

Why do we need to sleep? Senior Investigator **Carolyn Beebe Smith** in the National Institute of Mental Health (NIMH) is exploring this essential question by imaging the brain during wakefulness and sleep and correlating its protein metabolism with learning and memory.

It's thought that sleep is needed to maintain, repair, and reorganize brain cells. In animals, the formation of brain proteins increases during sleep. Sleep also seems to enable synaptic remodeling processes that promote neuronal plasticity during development, learning, and memory formation.

Smith is conducting a clinical trial, using positron-emission tomography (PET), to examine the formation of brain proteins while people are awake, deprived of sleep, and asleep; and to assess brain-protein syntheses in waking and sleep combined with a learning task—a computerized visual-discrimination task. Participants are injected with a radiolabeled amino acid detectable by a PET scan. Persistence of radiolabeled amino acids in the brain indicates that they are being incorporated into new proteins. New protein synthesis serves as a correlate for the synaptic remodeling events required for learning and memory consolidation.

Some participants are allowed to nap after training and some are not. All are trained in the morning on the computerized visual-discrimination task and then tested eight hours later. Subjects who napped performed better on the test. PET scans performed during the nap indicate that protein synthesis is increased in the part of the visual cortex involved in the training. Smith's preliminary findings demonstrate that protein synthesis increases during memory consolidation, suggesting that synaptic remodeling and neuronal plasticity may be key functions of sleep. ●

To view the presentation Smith gave on April 1, 2014, as part of the Demystifying Medicine series, go to http://videocast.nih.gov/launch.asp?18362.

A FEW OTHER NIHERS DOING RESEARCH ON SLEEP, FATIGUE, AND CIRCADIAN RHYTHMS

CLINICAL CENTER

Gwenyth R. Wallen, R.N., Ph.D. , and others: sleep disturbance associated with pain and depression in sickle-cell disease and in people with alcoholism.

Leighton Chan, M.D.: natural history study of traumatic brain injury in which fatigue, depression, and daytime sleepiness are measured.

Lynn Gerber, M.D.: mechanisms and treatment of fatigue.

NATIONAL CANCER INSTITUTE

Mirit I. Aladjem, Ph.D., and **Kurt Kohn, M.D., Ph.D.:** created a computational model of a mammalian circadian clock to gain insight into the regulation of circadian rhythms and their role in cancer biology and treatment.

Gordon Hager, Ph.D.: ultradian and circadian cycling of hormones and glucocorticoid receptors.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Ann C. M. Smith, M.A., Honorary D.Sc.: effect of bright light or melatonin treatment on circadian sleep disturbance in children with Smith-Magenis syndrome.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Amisha V. Barochia, M.D., Nargues Weir, M.D., and **Stewart Levine, M.D.:** basic and clinical research on asthma including sleep study.

Susan Harbison, Ph.D.: See article.

James Taylor VI, M.D.: genetic factors and high prevalence of sleep disturbances in sickle-cell disease.

John Tisdale, M.D., Courtney Fitzhugh, M.D., and **James Taylor, M.D.:** research on sickle-cell disease that includes sleep disturbances.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Nora Volkow, M.D.: used PET to show that sleep deprivation reduced dopamine (DA) receptor availability.

Lorenzo Leggio, M.D., Ph.D., and others: sleep disturbances in people with alcoholism who are undergoing inpatient alcohol detoxification.

Matthew Pava, Ph.D., and **David Lovinger, Ph.D.:** how the endocannabinoid system modulates sleep and wake states in mice.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Giovanni Cizza, M.D., Ph.D.: See article.

David Klein, Ph.D.: See article.

Margaret F. Keil, Ph.D, C.R.N.P.: sleep deprivation on neuroendocrine function, physical growth, and cognitive and behavioral development in recently adopted children (from orphanages in other countries).

Lynnette K. Nieman, M.D.: whether taking cortisol, melatonin, or both can help alleviate jet lag.

Jack A. Yanovski, M.D.: role of the *PAX6* gene in sleep patterns in people with certain rare syndromes.

Paul Albert, Ph.D.: developed statistical model to measure the sleep-wake cycle in adolescents.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASE

Yaron Rotman, M.D.: physiology of fatigue and contributions of circadian rhythms in people with chronic liver disease.

Monica C. Skarulis, M.D.: characterizing the hormones, metabolism, sleep patterns, and more in people with and without weight problems.

Kong Chen, Ph.D.: using a metabolic chamber to measure human energy expenditure day and night (including during sleep).

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Serena Dudek, Ph.D.: discovered that caffeine strongly enhanced synaptic responses in the hippocampus CA2 region, which could be a potential target for drugs to combat fatigue and sleep disturbances.

Honglei Chen, M.D., Ph.D.: reported that longer daytime napping was associated with a higher risk for Parkinson disease.

Janet Hall, M.D.: research on neuroendocrine interactions underlying normal human reproduction.

NATIONAL INSTITUTE OF MENTAL HEALTH

Carolyn Beebe-Smith, Ph.D.: See article.

Ashura Buckley, M.D., and **Susan Swedo, M.D.:** how abnormal sleep patterns may contribute to autism spectrum disorders.

Kathleen Merikangas, Ph.D.: demonstrated that sleep duration and difficulties are associated with serious health consequences in adolescents.

Susan Swedo, M.D., and **Ashura Buckley, M.D.:** how abnormal sleep patterns may contribute to autism spectrum disorders.

Audrey E. Thurm, Ph.D., and **Ashura Buckley, M.D.:** pilot study—which includes measuring brain activity during sleep—on the markers of autism spectrum disorders in at-risk toddlers.

Thomas Wehr, M.D.: reported in 1992 that humans would revert back to a pre-industrial era of two four-hour shifts of sleep a night if they were not exposed to artificial lighting.

Carlos A. Zarate, M.D.: examining riluzole—FDA-approved drug for treating amyotrophic lateral sclerosis (ALS)—to see if it can reduce excessive sleeping in patients with bipolar disorder.

NATIONAL INSTITUTE OF NURSING RESEARCH

Jessica Gill, R.N. Ph.D.: sleep disturbances and mechanisms of post-traumatic stress disorder, depression, and post-concussive syndrome.

Leorey N. Saligan, Ph.D., R.N., C.R.N.P.: fatigue in people with and without cancer; identified genes that can predict fatigue risk for patients receiving cancer therapy.

Read more complete descriptions of everyone's work and an interview with Michael Twery online: http://irp.nih.gov/catalyst/v22i5/sleep-perchance-to-research.

Building 7

CONTINUED FROM PAGE 1

to prevent more "martyrs"—scientists who contracted the diseases they were studying and died. Building 7 was originally named "Memorial Laboratory" in honor of Henderson and Parrott. Although the building no longer goes by that name, the road running past it is still called "Memorial Drive."

Building 7, which has 12-inch steel-reinforced concrete walls, boasted a state-of-the-art biosafety system when it opened in 1947, complete with superheated grids to sterilize air as it passed through the ventilation system and carefully controlled airflow directed from "clean" to "dirty" parts of the building. Ultraviolet lights installed in all labs were turned on each night to help sterilize surfaces.

The only entryways and exits from the laboratories were through decontamination locks, where employees were required to shower and change clothes—coveralls were supplied for wear within the laboratories—before entering the "dirty" labs or the "clean" outside world. The building even had concrete window canopies, obviating the need for internal fabric shades that might become contaminated.

The inhabitants soon realized that there was "one oversight," recounted the late **Robert Chanock** in a 2001 oral history interview. He was chief of the Laboratory of Infectious Diseases (LID) in the National Institute of Allergy and Infectious Diseases (NIAID). "They forgot to [seal] the space around the pipes that ran through the building and from one floor to another," meaning that contaminated air from the infectious-disease laboratories escaped into the rest of the building. The Building 7 researchers were studying Q fever, an infection caused by *Coxiella burnetii* bacteria that is spread by exposure to infected livestock, and characterized by high fever and pain in the head, neck, chest, and muscles. Most of the researchers, however, had been vaccinated against the disease to avoid becoming accidentally infected.

But only months after the new building opened, there was an outbreak of Q fever that sickened eight unvaccinated victims: five laboratory workers; **Joseph Smadel**—later the director of Intramural Research at NIH—who only visited the lobby; and the landlords of one of the infected workers—they were exposed to the bacteria when doing their tenant's laundry. While no fatalities resulted from this outbreak, it was clear that Building 7 was no safer than any other laboratory at the time. In addition, renovations to correct the ventilation defect were impossible without demolishing the building. Despite these defects, it was still the safest possible environment in which to work on infectious diseases in the 1940s.

No further large-scale outbreaks occurred, mostly because the LID ceased research on highly virulent organisms. Individual researchers did, however, acquire nonfatal laboratory-associated infections from time to time. For instance, then–NIAID researcher **Richard Wyatt**, who worked in the building from 1971 to 1983, was once infected with norovirus while centrifuging fecal filtrates.

Important research began in Building 7 almost as soon as the first laboratories moved in in 1947. The building's first inhabitants were LID researchers led by **Charles Armstrong**, who was already well-known for his work on the prevention of botulism poisoning from improperly canned foods. He also identified the mosquito-borne virus behind the 1933 St. Louis, Missouri, encephalitis outbreak.

Another early inhabitant was **Robert Huebner**—Armstrong's protegé—who had done extensive fieldwork on Rickettsialpox and Q fever at the behest of the Public Health Service. "Q" stands for "query," meaning the causative agent was unknown when the disease was discovered in the 1930s; although the pathogen was discovered in 1937, the name stuck. Huebner spent the 1950s in Building 7, analyzing patient samples and isolating 70 new viruses as well as describing the clinical symptoms associated with each.

Alexis Shelokov, another early inhabitant, brought some of the first tissue-culture techniques to NIH, enabling Huebner and others to grow viruses in culture for the first time.

Janet Hartley, later head of the Viral Oncology section of the NIAID's Laboratory of Viral Diseases, began her scientific career as a bacteriologist in Huebner's laboratory, where she worked while obtaining her

OFFICE OF NIH HISTORY

NIH's Building 7, on the Bethesda campus, boasted a state-of-the-art biosafety system when it opened in 1947: superheated grids sterilized air as it passed through the ventilation system; labs had ultraviolet lights that were turned on each night to sterilize surfaces; access to the laboratories was through decontamination locks; and concrete window canopies instead of fabric shades (that might become contaminated). Above: At night, the building "glows" with ultraviolet light.

Ph.D. at George Washington University in Washington, D.C.

"In those days in Building 7, all the investigators wore blue jumpsuits. Everybody," recalled Hartley in a 1995 oral history interview. "I met with Bob Huebner, who was a big man, and his blue jumpsuit was a little too small for him…. But he was so full of enthusiasm for what they were doing—that you know I could think there is no place that I've been that I want to work more than this place."

The 1950s also brought batches of promising young officers from the Public Health Service to Building 7. Some of them, such as **Wallace P. Rowe**, who worked with Huebner to help discover adenoviruses and was later chief of the Viral Diseases section, became so enamored of the ongoing research that they spent their careers there.

In 1957, Chanock and **Albert Kapikian** began their laboratories in Building 7; both were recruited by Huebner and would continue their work in Building 7 until NIAID built biosafe labs in Building 50 years later. Chanock studied respiratory viruses. In 1962, he identified respiratory syncytial virus (RSV), the most common cause of serious lower respiratory infections in infants. In the 1970s, he developed the first nasal anti-influenza vaccines.

Kapikian studied nonbacterial gastroenteritis and in the early 1970s identified norovirus and rotavirus using the electron microscope in the sub-basement. **Robert Purcell**, who joined LID in 1963, identified the virus that causes hepatitis A in 1973. He eventually developed a vaccine against it that was commercially released in 1995.

In what was almost an anatomical arrangement, "the respiratory viruses were on the third floor, hepatitis was on the second floor, and the diarrhea viruses were on the first floor," recalled Wyatt who is currently the deputy director, Office of Intramural Research.

Permanent staff turnover was low. When Rowe died of colon cancer in 1983 at age 57, the array of laboratory chiefs in Building 7 had remained constant for 15 years. To honor him, a room on the fourth floor was renovated and became the Wallace P. Rowe Conference Room. Lab meetings were held there until 2001 when NIAID moved to Building 50.

After NIAID left, Building 7 was renovated to provide temporary space for researchers whose own labs were undergoing major renovations. In 2003, the National Eye Institute (NEI) and other laboratories that had been housed in Building 6 moved into Building 7. Although the shower rooms and other remnants of biosafety features were gone, the remaining structural oddities made an impression on the new inhabitants: Closets had doors that led outside; restrooms had unusual proportions because they were once the entryways to laboratories; the old ventilation system became overloaded when new heating, ventilation, and air conditioning equipment was installed; and the new fans dislodged fine black dust, which settled over the laboratory benchtops overnight.

In January 2009, a pipe burst in Building 7's attic, sending sheets of water cascading through the labs on the south side of the building. There was no structural damage to the building, but the water nearly destroyed the expensive equipment sitting on the benchtops and flooded many drawers, ruining what was inside. The toll of age on the pipes was obvious. Because they could not be fixed, plans for other laboratories to move into the building were cancelled. By the end of 2009, NEI and all the other occupants were gone. In 2016, Building 7 and nearby Building 9 will be demolished to free up space for a new research facility. ●

More photos and stories about Building 7 are online at http://irp.nih.gov/catalyst/v22i5/secrets-of-building-7

NIH ABBREVIATIONS

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

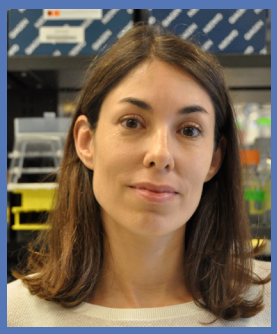
Recently Tenured

CHRISTIAN C. ABNET, NCI-DCEG

BRIAN BROOKS, NEI

CHRISTOPHER B. BUCK, NCI-CCR

YIE LIU, NIA



ROSA PUERTOLLANO, NHLBI

CHRISTIAN C. ABNET, PH.D., M.P.H.; NCI-DCEG

Senior Investigator and Acting Chief, Nutritional Epidemiology Branch

Education: University of Oregon, Eugene, Ore. (B.S. in biology); University of Wisconsin, Madison, Wis. (Ph.D. in environmental toxicology); University of Minnesota, Minneapolis (M.P.H. in epidemiology)

Training: Cancer Prevention Fellowship, NCI

Came to NIH: In 1998 for training; in 2005 became an investigator in NCI

Selected professional activities: Editorial board, *Cancer Epidemiology, Biomarkers and Prevention*; steering committee, Barrett's Esophagus and Esophageal Adenocarcinoma Consortium; chair, fellowship selection committee, International Agency for Research on Cancer

Web site: http://irp.nih.gov/pi/christian-abnet

Research interests: The major focus of my work is to understand the etiology of esophageal and gastric cancer. I am studying the complex pattern of the worldwide occurrence of these two malignancies across diverse populations—in China, Iran, Brazil, and Eastern and Southern Africa—that have high rates of these diseases. I am interested in how etiologic factors such as nutritional deficiencies, tobacco and alcohol use, and other lifestyle factors contribute to these cancers.

My research also examines the genetic contribution to worldwide differences in the incidence of gastric and esophageal cancer. The advent of genome-wide association studies has allowed my lab and I to pursue powerful genetic studies of these cancers in high- and low-incidence populations.

In 2010, my colleagues and I reported that a single locus encompassing *PLCE1* gene was the top hit for both these cancers among Chinese individuals in our study. I am carrying out additional studies of gastric cancer in Chinese populations and complementary studies of esophageal and gastric cancer outside China. This comprehensive examination across continents may provide the fullest understanding of the genetic contribution to the apparent etiologic differences in these malignancies.

Lastly, I am interested in the role of oral health and the oral microbiome and the risk of upper gastrointestinal cancers. In addition, I am leading studies to assess the impact of tobacco on the oral microbiome and its association with tobacco-related diseases.

If you have been recently tenured, the *NIH Catalyst* will be contacting you soon about including you on these pages.

BRIAN BROOKS, M.D., PH.D.; NEI

Senior Investigator, Pediatric, Developmental, and Genetic Ophthalmology Unit

Education: University of Maryland, College Park, Md. (B.S. in zoology); University of Pennsylvania, Philadelphia (M.D.; Ph.D. in pharmacology)

Training: Residency in ophthalmology and fellowship in pediatric ophthalmology at the University of Michigan (Ann Arbor); fellowship in clinical genetics at NHGRI

Came to NIH: In 2002 for training; moved to NEI in 2005 under the Physician-Scientist Development Program; in 2008 became tenure-track investigator in NEI

Selected professional activities: Founding director, National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE); board of senior consultants for the NIH-wide Undiagnosed Diseases Program

Outside interests: Camping with the family; bicycling; swimming; reading

Web site: http://irp.nih.gov/pi/brian-brooks

Research interests: The goal of my research is to understand the causes and mechanisms of inherited eye diseases—especially those that affect children—and to use that knowledge to develop prevention strategies and treatments. Currently, my lab is focused on the genetics of uveal coloboma (a potentially blinding congenital eye malformation) and identifying potential treatments

for albinism (an inherited disorder associated with reduced melanin pigment in the hair, skin, and/or eyes). Both conditions are developmental defects that can cause blindness in children.

To better understand the genetics of uveal coloboma, I am integrating basic laboratory experiments—including work in mouse and zebrafish disease models—with detailed clinical characterization of patients and their families at the NIH Clinical Center. This research will lead to improved molecular diagnosis, genetic counseling, and, perhaps, prevention and treatment strategies for patients.

In the field of albinism, my lab and I have identified an FDA-approved compound, nitisinone, that improves melanin pigmentation in a mouse model of one form of albinism called oculocutaneous albinism (OCA-1B). We are currently testing whether this drug is effective in humans with OCA-1B. We are also collaborating with the NIH Intramural Sequencing Center to identify other novel therapeutics for albinism.

CHRISTOPHER B. BUCK, PH.D.; NCI-CCR

Senior Investigator, Lab of Cellular Oncology

Education: University of Colorado, Boulder (B.A. in molecular, cellular, and developmental biology); Johns Hopkins School of Medicine, Baltimore (Ph.D. in cellular and molecular medicine)

Training: Postdoctoral training in NCI

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

Selected professional activities: Co-organizer of the annual Think Tank meeting for NCI's Center of Excellence in HIV/AIDS and Cancer Virology

Outside interests: Loves food; currently obsessed with almost all things fermented; likes mountain hiking; has great appreciation for many forms of modern music

Web site: http://irp.nih.gov/pi/christopher-buck

Research interests: Our group studies polyomaviruses. Most healthy adults chronically shed polyomavirus virions in their urine and from the surface of their skin. Although these lifelong infections generally don't cause symptoms in healthy individuals, under conditions of immune impairment, polyomaviruses can cause disease.

The human polyomavirus BK virus (BKV) causes kidney and bladder damage in organ-transplant patients, whereas its close relative the John Cunningham virus (JCV) causes a lethal brain disease in patients on immunosuppressive therapies and in individuals suffering from AIDS or human immunodeficiency virus.

At least one skin-dwelling polyomavirus species, Merkel cell polyomavirus, causes a rare but highly lethal form of skin cancer called Merkel cell carcinoma. Virus-discovery efforts led by our lab have uncovered the existence of three additional polyomaviruses—human polyomaviruses 6, 7, and 10—that are commonly shed from human skin.

By applying basic-science knowledge of capsid (protein shell of a virus) biology, our group has pioneered the development of polyomavirus-based gene-transfer vectors. These vectors, also known as pseudoviruses, deliver reporter genes to the cell nucleus via pathways that resemble the infectious entry of authentic virions. In addition to their utility for studying the mechanics of infectious entry in vitro and in vivo, these tools have a variety of other applications. For example, we use pseudoviruses to perform high-throughput analyses of neutralizing-antibody responses.

A primary goal of our current work is to understand how polyomaviruses evolve to evade antibody-mediated neutralization. This work has opened the door to the clinical development of virus-like particle vaccines against BKV and JCV.

YIE LIU, PH.D.; NIA

Senior Investigator, Laboratory of Molecular Gerontology

Education: Harbin Medical University, Harbin, Heilongjiang, China (B.A. in medicine); Karolinska Institute, Solna, Sweden (Ph.D. in human genetics)

Training: Postdoctoral fellow, National Cancer Institute of Canada, University of Toronto, Toronto

Before coming to NIH: Senior research scientist at Oak Ridge National Laboratory (Oak Ridge, Tenn.)

Came to NIH: In 2006

Selected professional activities: Associate editor, *Mechanism of Aging and Development*; member, NIH Stadtman Committee

Outside interests: Playing the accordion

Web site: http://irp.nih.gov/pi/yie-liu

Research interests: I am interested in the mechanisms of telomere damage-induced cellular senescence and organismal aging. Most eukaryotic chromosomes terminate in telomeres, which are structures of repetitive DNA sequences and their associated proteins. Telomeres allow cells to distinguish natural chromosome ends from damaged DNA and protect chromosomes against degradation and fusion. Telomere integrity in cells thus plays an essential role in controlling genomic stability. Loss of genetic material at chromosome ends (telomere shortening) is frequently observed in the elderly, in cellular senescence, and in premature-aging syndromes. Furthermore, telomere dysfunction contributes to genomic instability that leads to cell death, defects in cell proliferation, and malignant transformation, which might in turn contribute to age-related disorders and a higher incidence of cancer during aging.

My lab and I use a combination of molecular, genetic, and biochemical approaches to probe the impact of oxidative stress and DNA damage on telomere length

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Recently Tenured

CONTINUED FROM PAGE 17

and to explore the key DNA-repair genes that modulate telomeric DNA damage. We are also in the process of determining the role of Fanconi anemia (FA) proteins and helicases in maintaining telomere length. FA is an inherited blood disorder that leads to bone-marrow failure. We recently discovered that an FA protein functions as a scaffold to recruit various endonucleases to telomeres. We will continue to investigate how FA proteins as well as oxidative DNA damage and deficiencies in DNA repair contribute to telomere defects in aging and human disorders.

ROSA PUERTOLLANO, PH.D.; NHLBI

Senior Investigator, Protein Trafficking and Organelle Biology

Education: Universidad Autónoma de Madrid, Madrid (B.S. in biology and biochemistry; M.S. in molecular genetics); Consejo Superior de Investigaciones Cientifícas, Madrid (Ph.D. in molecular biology and biochemistry)

Training: Postdoctoral training in the Cell Biology and Metabolism Branch, NICHD

Came to NIH: In 1999 for training; NIH visiting fellow at NICHD (2001–2004); then became tenure-track investigator in NHLBI

Selected professional activities: Editorial boards of *Traffic, ISRN Cell Biology*, and *Advances in Biology*; faculty member of the Faculty of 1000 Cell Biology

Outside interests: Reading; traveling; spending time with her five-year-old son

Web site: http://irp.nih.gov/pi/rosa-puertollano

Research interests: The selective recycling of lipids and proteins is critical to healthy cellular function. Many genes associated with human diseases encode components of the cellular machinery that sorts lipids and proteins for selective trafficking along endocytotic pathways that lead to lysosomal degradation. My lab seeks to understand how defects in intracellular trafficking—specifically, in endosomal-lysosomal pathways—contribute to human diseases. Loss-of-function mutations in ion channels called mucolipins result in a lysosomal storage disorder that is characterized by severe neurological and ophthalmologic abnormalities.

Well-regulated storage and release of ions, such as calcium, are important for membrane trafficking and signaling. But we know little about the regulation of ion concentration within endosomal organelles. By using a combination of biochemistry and confocal and electron microscopy, my lab and I have found that mucolipins appear to regulate changes in the luminal ion composition of endosomal organelles. Our goal is to uncover pathological cascades beginning with alterations in basic homeostatic mechanisms of intracellular compartments that may be common to many diseases.

In another project we are attempting to elucidate the molecular mechanisms that regulate the localization and activity of two transcription factors--TFEB and TFE3—that control the expression of autophagic and lysosomal genes. We recently showed that these factors are regulated by the energy-sensing so-called mechanistic target of rapamycin protein-kinase complex. We are exploring the role of lysosomes as signaling centers that synchronize environmental cues with gene expression, energy production, and cellular homeostasis. ●

More on the IRP Web site

You can link to each principal investigator's Web site via the links provided above. You will also find links to "Research in Action" stories and videos featuring the work of Brooks and Puertollano (accessible through their Web sites). For a complete listing of "Research in Action" stories, go to http://irp.nih.gov/our-research/research-in-action.

NINR DIRECTOR'S LECTURE WITH PENN'S MEDOFF-COOPER

"Innovations in High-Risk Infant Care: Creating New Pathways"

Tuesday, September 16, 10:30–11:30 a.m.

Balcony C, Natcher Conf. Center (Bldg. 45)

Internationally recognized Dr. Barbara Medoff-Cooper (University of Pennsylvania School of Nursing) will discuss her research on infant development, feeding behaviors in high-risk infants, infant temperament, and developmental care of infants with complex congenital heart disease. For more information, visit http://www.ninr.nih.gov/directorslecture. For reasonable accommodation, e-mail info@ninr.nih.gov or call 301-496-0256.

2014 NIH RESEARCH FESTIVAL

September 22–24, 2014

Plenary: September 22, 10:00 a.m.–noon

Masur Auditorium, Lipsett Amphitheater, and FAES Academic Center (Building 10)

The theme for this year's showcase of intramural research is "The Era of the Brain." The festival features an opening plenary session with a "State of the NIH Intramural Research Program" message by NIH Director **Francis Collins**, the FARE Awards Ceremony, and scientific presentations by **Antonello Bonci** (NIDA) and **Mark Hallett** (NINDS); concurrent symposia, posters (even ones by institute directors and scientific directors), exhibits on resources, the Technical Sales Association tent show, and more. For information, visit http://researchfestival.nih.gov or contact Jacqueline Roberts at 301-594-6747 or robertsjm@od.nih.gov.

NINTH ANNUAL CHEN LECTURE

"Purine Receptor Drugs: Future Treatment for Chronic Diseases?"

Friday, October 3, 2014, 10:00–11:00 a.m.

Masur Auditorium (Building 10)

The Philip S. Chen, Jr., Distinguished Lecture on Innovation and Technology Transfer will feature **Kenneth A. Jacobson (NIDDK)**. For reasonable accommodation, contact Joe Kleinman at 301-496-0472 or the Federal Relay (1-800-877-8339). Also online at http://videocast.nih.gov.

2014 IATAP WORKSHOP

Presentations by investigators
October 16–17, 2014; starts at 8:30 a.m.
Conference Room 127, Building 5

The Intramural AIDS Targeted Antiviral Program (IATAP) Investigators will present brief summaries of their research. For more information, contact Jacqueline Roberts at 301-594-6747 or robertsjm@od.nih.gov.

INTRODUCTION TO THE PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH

October 14, 2014–March 9, 2015
Mondays and Tuesdays, 5:00–6:30 p.m.
Lipsett Amphitheater (Building 10)
Registration deadline: October 8, 2014

This free course offers training on how to conduct clinical research. For information, visit http://clinicalcenter.nih.gov/training/training/ippcr.html or e-mail Daniel McAnally at daniel.mcanally@nih.gov or call 301-496-9425. An e-mail confirmation will be sent to registrants.

2014 NIH-JAPAN SYMPOSIUM

October 23: 8:00 a.m.–6:00 p.m.
(posters 3:30–6:00 p.m.)
October 24: 8:30 a.m.–12:30 p.m.
Poster deadline: September 30, 2014
Lipsett; FAES Classrooms (Building 10)

The NIH-Japan symposium will focus on highlights of biomedical science from NIH and Japan; promote the career development of young scientists; and feature lectures by NIH senior investigators as well as by scientists from several universities in Japan. For more information, contact Yoshi Yamada at 301-496-2111 or yyamada@dir.nidcr.nih.gov.

SANTIAGO RAMÓN Y CAJAL EXHIBIT

Scheduled to open in early November
First Floor Atrium, Porter Neuroscience Research Center (Building 35)

Original ink-on-paper drawings by Spanish physician and scientist Santiago Ramón y Cajal will be on display at NIH beginning in early November. Awarded the Nobel Prize in Physiology or Medicine (1906), Cajal's "neuron doctrine" is considered to be the beginning of modern neurobiology. A selection of his drawings will be on loan to the NIH's DeWitt Stetten, Jr. Museum of Medical Research for six months, courtesy of the Cajal Institute (Madrid). More details will be shared with the NIH community soon.

WEDNESDAY AFTERNOON LECTURES

Most Wednesdays, 3:00–4:00 p.m.
Masur Auditorium (Building 10)

WALS features prominent scientists from leading universities. Visit http://wals.od.nih.gov.

COURSES ON SCIENCE OF SEX AND GENDER IN HUMAN HEALTH

Web site: https://sexandgendercourse.od.nih.gov/index.aspx

NIH's Office of Research on Women's Health is pleased to offer online courses designed to enable researchers, clinicians, and students integrate knowledge of sex and gender differences and similarities into their research and practice. The series covers how differences between women and men influence disease manifestation, treatments, and outcomes.

PICK THE RIGHT TOOL FOR THE JOB: EXPERT GUIDANCE ON USING MODERN TECHNOLOGIES IN BIOMEDICAL RESEARCH

"Data analysis, interpretation, and presentation in cell biology: potentials and pitfalls"
Monday, November 24, 8:30 a.m.–4:30 p.m.
Lipsett Amphitheater (Building 10)

This workshop is the first in a series to educate NIH trainees and staff about what advanced technologies can accomplish and the kinds of reproducibility problems that can arise; provide a cautionary note to scientists who plan to use but are inexperienced in using these techniques; and educate others who are reading results in the literature. For more information, contact Paul Liu at pliu@nhgri.nih.gov or 301-402-2529.

Read more online at http://irp.nih.gov/catalyst/v22i5/announcements.

NCATS LAUNCHES CHEMICAL TOXICITY DATA MODEL COMPETITION

Registration deadline: Nov. 14, 11:59 p.m. ET.
Winning models showcased: January 2015.
To register and for more information:
https://tripod.nih.gov/tox21/challenge/

NCATS' Toxicology in the 21st Century (Tox21) Data Challenge 2014 is a crowdsourcing competition to develop computational models that can better predict chemical toxicity. The Tox21 initiative (http://www.ncats.nih.gov/research/reengineering/tox21/tox21.html) is designed to improve current toxicity assessment methods, which are slow and costly.

DEMYSTIFYING MEDICINE 2015

Tuesdays, January 6–May 5, 2015
4:00–6:00 p.m.
Building 50 Conference Room

The "DeMystifying Medicine" course bridges the gap between advances in biology and their application to human disease. Each class features presentations by a clinician, a researcher, and often a patient. Topics include attention-deficit hyperactivity disorder, Ebola, malaria, infertility, and more. For a complete schedule and instructions on how to sign up, visit http://demystifyingmedicine.od.nih.gov or contact Win Arias at ariasi@mail.nih.gov.

NEW NIH INTRAMURAL RESEARCH RECORDS SCHEDULE

The NIH Office of Management Assessment (OMA) and Office of Intramural Research led a trans-NIH effort to redesign the NIH Intramural Research Records Schedule to better align policy with intramural research practices. The effort resulted in a significant streamlining of the research record-retention schedules; a reduction in the number of scheduled items from approximately 95 to 12; and criteria for evaluating the historical significance of records. OMA is conducting training and information sessions for records liaisons. A listing of the liaisons can be found at http://1.usa.gov/1t5lJDf. For questions regarding the new schedule, contact Kim Johnson, officer, at johnsonk4@mail.nih.gov or 301-496-2463. ●

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CATALYTIC REACTIONS?

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

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

READ EXPANDED VERSIONS OF THE ARTICLES IN THIS ISSUE OF THE NIH CATALYST ONLINE AT http://irp.nih.gov/catalyst/v22i5

FROM THE ANNALS OF NIH HISTORY

Intelligence Tests

BOTH: OFFICE OF NIH HISTORY

This Houghton Mifflin test material was part of the "Form L Revised Stanford-Binet Scale," used by National Institute of Mental Health researchers in the 1950s to test the intelligence of children taking part in certain clinical studies. The Stanford-Binet Intelligence Scale was first developed in 1905 by French psychologist Alfred Binet and his collaborator Theodore Simon to test the attention, memory, and verbal skill of schoolchildren and thereby measure their intelligence. It was revised in 1908 and 1911. In 1916, Stanford University psychologist Lewis Terman released the "Revised Stanford-Binet Scale." The "Form L" refers to Terman's version of the test; there's also a "Form M," named for his graduate student Maud Merrill. The test is now used for clinical and neuropsychological assessment, educational placement, and more. ●

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

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