

The Shutdown

Its Impact on NIH

BY RICH MCMANUS, OD

ON OCTOBER 23, 2013, NIH DIRECTOR **Francis Collins** held an hour-long town hall meeting in which he condemned the effects of an “unnecessary and ultimately pointless shutdown” that closed the government October 1–16 and idled 75 percent of the NIH workforce. He outlined a steadily deteriorating political landscape that has included multiple threats of shutdown, then the reality of budget sequestration, culminating in a 16-day shutdown coinciding with the start of FY2014. Federal regulations barred any but “excepted” employees—those with responsibility for the preservation of life (human and animal) and property—from coming to work. Collins also answered questions submitted by the audience and via e-mail.

There was, however, a silver lining to the shutdown debacle, Collins said. “NIH was mentioned over and over again” in the media as a national treasure worth preserving; several members of Congress even introduced bills to reopen NIH during the shutdown.

Looking to the new year, Collins noted “the only certainty these days is uncertainty,” but held out hope that congressional budget negotiators can reach a solution that includes the abolition of sequestration.

Collins said he was inspired by “the enthusiasm and commitment” of an NIH workforce that returned on October 17. He enumerated triumphs including a decision not to ditch the October grant-submission

CONTINUED ON PAGE 14

The Human Microbiome Project

... And the Intramural Connection

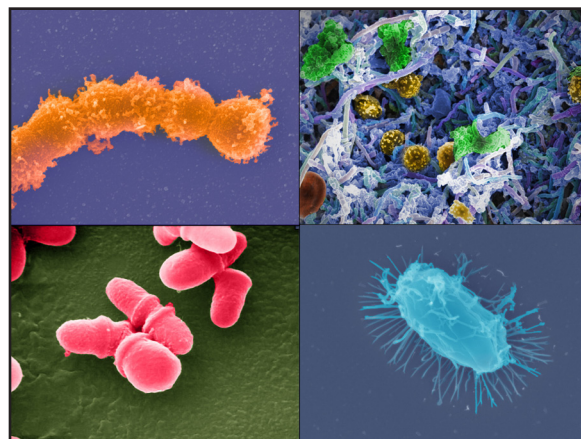
BY JOSEPH TIANO, NIDDK

THERE ARE 10 TIMES AS MANY bacteria, viruses, fungi, and protozoa—collectively known as the microbiome—living on and inside the human body as there are human cells. Although scientists have been aware of the microbiome for more than 30 years, they knew little about its diversity and role in human health and disease. Researchers tended to focus on disease-causing bacteria, and only 10 to 20 percent of these bacteria can be cultured in the laboratory.

In 2005, at an international meeting in Paris, scientists proposed using state-of-the-art genomic sequencing techniques to catalogue all the bacteria living on and inside the human body. They also discussed forming a consortium to catalogue the intestinal microbiome and its role in human health and disease.

On December 19, 2007, the NIH launched the Human Microbiome Project (HMP), a two-phased, eight-year, \$194 million initiative to support such an effort. The Intramural Research Program has been involved since the get-go and continues to participate.

Phase One of the HMP focuses on a survey of the microbiome in five areas of the body—the digestive tract, mouth, skin, nasal cavity, and vagina—and consists of two kinds of cohort studies: the Healthy Cohort Study and a collection of Demonstration Projects.



JONATHAN BAILEY, NHGRI

The Human Microbiome Project, which was launched by NIH in 2007, provided the first glimpse of the microbial diversity of healthy humans and is exploring the possible relationships between particular human diseases and the microbiome. (Clockwise from top left): *Streptococcus* (Credit: Tom Schmidt); microbial biofilm of mixed species, from human body (Credit: A. Earl, Broad Institute/MIT); *Bacillus* (Credit: Tom Schmidt); *Malassezia lophophyllis* (Credit: J.H. Carr, CDC).

CONTINUED ON PAGE 10

CONTENTS

FEATURES • [11](#) The Shutdown [11](#) Microbiome [16](#) HIV and AIDS: Anthony Fauci [17](#) NEI: What Wei Li Is Learning from Squirrels [19](#) An Unlikely Route to Translational Research

DEPARTMENTS • [21](#) DDIR: Recovering from the Shutdown [23](#) News You Can Use: NIH Library Offers Customized Services [24](#) Training Page [25](#) New Methods: New Microscopes That Capture Live Cellular Processes in 3-D [28](#) Research Briefs [29](#) Abbreviations [121](#) SIG Beat: Special Feature on Proteostasis [125](#) Announcements [161](#) Back Page: Sammys Winners



Recovering From the Shutdown: The Toll on Biomedical Research

BY MICHAEL GOTTESMAN, DDIR

NIH IS THE LARGEST PURELY BIOMEDICAL research facility in the world, with about 2,500 individual research projects and close to 1,500 clinical protocols. But during the 16-day federal government shutdown in October, the NIH Intramural Program (IRP) was profoundly affected. Its loss of progress is a big deal. Only 15 to 20 percent of IRP staff was “excepted” from furlough so they could protect life (mostly in the Clinical Center, where 75 percent of the staff were allowed to work), guarantee safety (infrastructure support including security and the power plant), and protect large investments in materials and property (in the lab, that meant animals, cell cultures, and expensive equipment).

There was also a skeleton crew of senior leadership (most institute and center directors, scientific directors, clinical directors, and NIH deputy directors) to oversee the shutdown. Other staff were called back as needed to ensure that the huge intramural investment of time, labor, and money in science was not wasted. Owing to the hard work of the NIH community, we weathered this manmade disaster and are now happily back at work.

NIH intramural research includes lab-based, clinical, and population-based projects. During the shutdown, all new projects were put on hold and ongoing ones were halted so we could spare any large losses in investments. At the NIH Clinical Center, ongoing clinical protocols continued, but only 25 new patients—including seven children—with serious or life-threatening

illnesses were accepted into existing protocols—instead of the usual 200 new patients per week. Only one of seven new protocols was initiated. Elsewhere at NIH, all population-based and lab-based research was stopped. Still, every effort was made to assure that when the shutdown ended we could restart experiments as soon as possible.

The government shutdown’s impact on NIH was enormous.

Although NIH leadership has tried to ameliorate the effect of the shutdown on our physical property, the impact on the science conducted at the NIH and on our scientists was enormous. Biomedical research is a continuum of experimental activity in which past experiments are evaluated, current experiments are being conducted, and new experiments are being planned. All must occur concurrently; breaks in ongoing experiments sometimes ruin years of work, requiring researchers to start over.

Scientific effort doesn’t occur in a vacuum, but requires interaction with other scientists. It is a creative, interactive, intellectual activity that cannot simply be turned off and on like a faucet. Dedicated NIH scientists are thinking constantly about their work, analyzing their results, generating hypotheses, and designing and conducting new experiments. Not being able to do research is uncomfortable and demoralizing and leads to the loss of momentum.

The shutdown took a toll on our training programs and trainees too. In addition

to being a biomedical research enterprise, NIH is the largest training facility in the world for future biomedical researchers. Right now we have approximately 4,000 postdoctoral fellows, 800 postbaccalaureate students, 500 graduate students, and 45 medical students. For many of these trainees, time is of the essence. Their appointments are time-limited (less than one year for the medical students, up to two years for the postbac students, and usually three to four years for the postdocs and grad students). Loss of a few weeks of work and mentoring as well as loss of a few more weeks of momentum—while cell lines are started up again, animals are bred, and experiments that may have suffered in the shutdown are repeated—represent a significant percentage of a research experience that could affect their future careers.

There were other missed opportunities that we may not be able to recover. Because of travel restrictions on all government employees, arranging for travel to scientific meetings was already difficult. During the shutdown, all travel was cancelled, and many NIH scientists had to forgo important talks that they had been invited to give. Furthermore, we had to cancel many important lectures that were supposed to occur at the NIH in early October including a talk by Bill Gates, Nobel Laureate Shinya Yamana-ka, and Institute of Medicine President Harvey Fineberg. The Research Festival was delayed and certain aspects—such as the graduate student component—were eliminated.



NIH Library

“Custom Information Solutions” Service

BY MASHANA DAVIS, NIH LIBRARY

What are the long-term effects?

- Because of the delay and interruption in research, some of our scientists will lose their competitive edge and may miss opportunities to get their work published in the most highly visible journals and presented at important national and international meetings.

- There was major inconvenience because invitations, events, and other activities had to be rescheduled. This rescheduling means doubling the amount of work many people had to do for the same activity.

- There was some loss in research investment because experiments may have to be restarted. We have tried our best to ameliorate this problem, but it is inevitable that some research dollars were wasted at a time when budgets are very tight.

- Although we have done our best to sustain the NIH research enterprise, we are concerned about the effect on recruitment in the future when trainees and more senior faculty are making decisions about where to apply and what offers to accept.

My positive message to our current and future scientific staff is that even under the most severe of circumstances—a complete government shutdown—we have managed to persevere, the public has become more aware of the important work that we do, and we are back pursuing our mission of conducting research to improve the public health. We will be better prepared if this kind of lapse in funding happens again (hopefully not). ●

THE NIH LIBRARY PROVIDES READY access to thousands of resources, so much so that it may be difficult to find the best resources for your research needs. The Library recently introduced a new service, “Custom Information Solutions,” that can customize services and resources to address the specific needs of a group. Services include digitizing print materials; building databases to support research projects; developing portfolio-analysis reports; and creating customized Web search tools.

The National Institute on Aging (NIA) began using the service in 2011 in connection with its work on Alzheimer disease (AD). It began with a request to convert a spreadsheet of funding lines into a simple Web-enabled database.

Alzheimer disease research has become a global priority requiring enhanced coordination of funding strategies across both public and private funders. Supported by the “National Alzheimer’s Project Act” (<http://aspe.hhs.gov/daltcp/napa>), NIA first worked with the Alzheimer’s Association to develop a shared ontology known as the Common Alzheimer’s Disease Research Ontology.

Later, NIA began working with the NIH Library to develop a database to capture and track more than 6,000 Alzheimer-related grant-funded projects (2008 to the present) across all U.S. federal agencies and three non-federal funders. Discussions are now under way with other organizations and countries.

As a result of months of consultations and support from the NIH Library, the NIA decided to pursue the library’s proposed portfolio-analysis strategy. The first phase of this effort culminated in the July 2012 launch of the International Alzheimer’s Disease Research Portfolio, or IADRP (<http://iadrp.nia.nih.gov/cadro-web>).

The IADRP allows users to search funded projects by principal investigator, institution, funding agency, and funding announcement. Access to such information allows program officers and researchers from around the world to:

- Assess the changing landscape of Alzheimer disease research funded by different agencies and countries.

- Identify funding gaps as well as areas of possible overlap across funding agencies.

- Identify opportunities for coordination for Alzheimer disease research while leveraging critical resources.

For NIA, the funding information from the IADRP has helped to track and analyze research goals and strategic objectives.

In June 2013, the IADRP team, including NIH Library representatives **James King** and **Terrie Wheeler**, was presented with the NIH Director’s Award in recognition of “the planning and implementation of an AD research initiative in response to the National Alzheimer’s Plan.”

“Throughout the entire process, the NIH Library has gone above and beyond to provide outstanding customer service,” said NIA Senior Scientific Program Analyst **Charlene Liggins**.

The NIH Library is also collaborating with the National Institute of Allergy and Infectious Diseases to develop a pandemic influenza digital archive, which will be available to researchers within and outside NIH. ●

The NIH Library, located in Building 10, supports the information needs of the NIH research community. For more information about the library go to <http://nihlibrary.nih.gov/Pages/default.aspx>. For more information on “Custom Information Solutions,” visit <http://nihlibrary.nih.gov/Services/Pages/CustomInformationSolutions.aspx>.



FROM THE OFFICE OF INTRAMURAL TRAINING AND EDUCATION

Training to Work Well With Others

BY LORI CONLAN AND SHARON MILGRAM, OITE

ACCORDING TO THE BOOK *LAB DYNAMICS*, nearly two-thirds of scientists surveyed reported that interpersonal conflict had hampered progress on a scientific project one to five times in their career. So how can we train scientists to work well with others and manage conflicts in order to accomplish more science? After extensive discussions with mentors, trainees, students, fellows, career counselors, and experts in leadership development, the OITE developed workshops to provide an education in leadership and management.

The resulting *Workplace Dynamics* series (https://www.training.nih.gov/leadership_training) focuses on increased awareness of self and others using the Myers-Briggs Type Indicator; communication styles and influencing others; conflict dynamics; team theory; and diversity training. Our goal is to help participants gain self-awareness and an appreciation that others may tackle problems and approach conflict and group work differently. We augment the content and examples with lab-based examples, which resonate better with scientists. About 500 trainees have participated in the series, and we have begun offering the training at national meetings such as Experimental Biology. Some of our NIDDK and NHLBI fellows described their experiences with the series in their institute newsletters.

We learned that our trainees appreciate workshops but also like to receive information on resources on management topics. Many of these resources are available in the OITE Career Library on the second floor of Building 2 on the Bethesda campus as well as in the libraries of satellite campuses.

There are a variety of personality assessments, but we use the MBTI because it is widely used in academic and industry settings; we find that “Type Talk at Work” is

a good fit for scientists looking for more information on the MBTI.

Conflict is perhaps the most stressful topic, with many trainees feeling they lack resources for dealing with and defusing conflict in the workplace. We use the Thomas-Kilmann Conflict Mode instrument to help participants identify the conflict style they use and the styles they struggle with. Other resources on conflict management include *Becoming a Conflict Competent Leader*, which provides a way to explore the triggers that cause conflict and guidelines for approaching the conflict constructively instead of destructively; *Crucial Confrontations*, which provides tips on preparing for difficult conversations and tense negotiations; and the Center for Creative Leadership’s method, “Situation, Behavior and Impact,” to provide specific feedback to both the giver and the receiver.

We also include an introduction to diversity and difference because we all have a responsibility to develop a scientific workforce that is diverse and welcoming. Materials on diversity can be found in *Readings for Diversity and Social Justice, Third Edition*.

For trainees looking at an academic faculty job, there are even resources for them. The Burroughs Wellcome Fund and the Howard Hughes Medical Institute’s *Making the Right Moves* and Kathy Barker’s *At the Helm* offer practical advice on becoming a new faculty member and managing your staff.

Adapted with permission from L. Conlan and S. Milgram, “Workplace Dynamics: Understanding How to Work Together in Research Environments,” *Physiologist*, 56:76–77, 2013; available online at <http://www.the-aps.org/mm/Careers/Mentor/Managing-a-Lab-and-Personnel/Postdoctoral-Fellows/Supervising-staff-/Workplace-Dynamics>.

For Further Reading:

1. C. Cohen and S. Cohen, *Lab Dynamics: Management Skills for Scientists* (Cold Spring Harbor Press, New York, 2005)
2. Myers-Briggs Type Indicator: <http://www.myersbriggs.org>
3. MBTI articles: <http://www.capt.org/research/MBTI-bibliography-search.htm>
4. O. Kroeger, J.M. Thuesen, and H. Rutledge, *Type Talk at Work (Revised): How the 16 Personality Types Determine Your Success on the Job* (Dell, New York, 2002)
5. Thomas-Kilmann Conflict Mode Instrument (Xicom, Tuxedo, N.Y., 1974).
6. CPP Thomas-Kilmann Conflict Mode Instrument product page: <https://www.cpp.com/products/tki/index.aspx>
7. C.E. Runde and T.A. Flanagan, *Becoming a Conflict Competent Leader: How You and Your Organization Can Manage Conflict Effectively* (Jossey-Bass, San Francisco, 2006)
8. K. Patterson, J. Grenny, R. McMillan, and A. Switzler, *Crucial Confrontations* (McGraw-Hill, New York, 2004)
9. Center for Creative Leadership and S. Weitzel, *Feedback That Works: How to Build and Deliver Your Message* (Pfeifer, Somerset, N.J., 2007); <http://www.ccl.org/leadership/pdf/community/SBIJobAid.pdf>
10. M. Adams, W. Blumenfeld, C. Castaneda, and H.W. Hackman, *Readings for Diversity and Social Justice, Third Edition* (Routledge, New York, 2013)
11. Burroughs Wellcome Fund and Howard Hughes Medical Institute, *Making the Right Moves: A Practical Guide to Scientific Management for Postdocs and New Faculty* (Burroughs Wellcome Fund, Research Triangle Park, N.C., 2006); <http://www.hhmi.org/resources/labmanagement/moves.html>
12. K. Barker, *At the Helm* (Cold Spring Harbor Press, New York, 2010) ●

New Microscopes That Reveal Live Cellular Processes in 3-D

May Help Scientists Observe How Viruses Attack

BY JESSICA MEADE, NIBIB

NIH RESEARCHERS HAVE DEVELOPED two new high-resolution microscopes, both the first of their kind. The first—an instant linear structured illumination microscope (iSIM)—captures high-resolution images of small, fast-moving cellular structures in real time. The second—a dual-view inverted selective plane illumination microscope (diSPIM)—displays large cell samples in three dimensions (3-D) while decreasing the amount of harmful light that cells are exposed to during imaging.

Instant super resolution imaging

“Much of biology depends on the movement of very small proteins finding each other and interacting,” said **Hari Shroff**, chief of the High Resolution Optical Imaging Lab in the National Institute of Biomedical Imaging and Bioengineering (NIBIB). “We really need to look at how things move in a live cell.”

But it’s difficult to obtain good quality, high-resolution images in a living, moving cell. Traditional linear structured illumination microscopy (SIM), which can provide high resolution in a fixed cell, stumbles when it comes to imaging elements moving quickly in a live cell. The higher the resolution, the harder it is to eliminate the blur that comes from light diffraction and motion.

Shroff and research fellow **Andrew York** (NIBIB), along with other NIH scientists, developed the iSIM to address these problems. Building on traditional SIM technology, the iSIM allows real-time, 3-D super resolution imaging of live cellular processes such as blood cells racing through a zebrafish embryo. This kind of imaging is impossible with other microscopes (*Nature Meth* **10**:1122–1166, 2013).

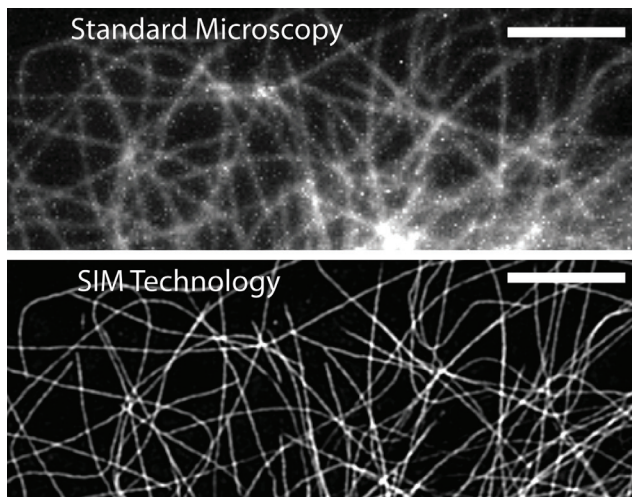
Most high-resolution microscopes, including SIMs, use imaging software to capture, store, and combine multiple camera exposures into crisp, exquisitely detailed images. Shroff and his lab equipped an iSIM microscope with powerful lenses and mirrors to produce high-resolution images from the original exposures more quickly.

“Before, we relied on computer software and algorithms to do things like sort through hundreds of images, eliminate out-of-focus light, and combine the individual images together,” said Shroff. The process was time consuming and could take hours or even days. “Now, we can do most of that optically with the microscope itself.” In addition, the iSIM data use only one percent of the hard-drive space that other types of high-resolution microscopes do.

The diSPIM

The second microscope builds on technology called selective plane illumination microscopy (SPIM) that uses a thin beam of light to illuminate only a single plane of tissue at a time. (Traditional microscopes expose a whole sample to light that can damage or even kill biological samples.) The SPIM then rotates the sample so it can be imaged from many angles to create a 3-D effect.

But the rotation process slows the imaging speed, making it difficult to capture live cellular motion. Ironically, the sample is still at risk of light damage because it is repeatedly illuminated as each plane is imaged.



The resolution differences between standard microscopy (top) and SIM technology (bottom) can be clearly seen.

COURTESY: NIBIB

To fix this problem, Shroff, NIBIB staff scientist **Yicong Wu**, and colleagues from NIH and other institutions developed the dual-view inverted SPIM (*Nature Biotechnol* DOI:10.1038/nbt.2713). The diSPIM can image cellular processes at high speed without causing extensive light damage. Two detection cameras, set at a 90-degree angle to each other, capture perpendicular views of each sample. With relatively simple modifications, traditional single-camera SPIMs can be converted into the dual-camera diSPIM.

But to combine the images from the two cameras, the scientists had to create a new post-processing software algorithm.

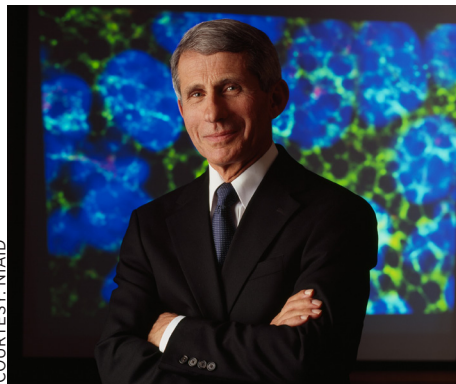
With the diSPIM microscope, scientists can obtain high-resolution images of live cellular processes—such as fast-moving viruses, migrating cancer cells, and interacting neurons—in a 3-D environment.

“As scientists, it’s up to us to find ways to observe cells as accurately as possible,” Shroff said. “There are a lot of biological processes that we can’t understand without observing them and that’s something these devices can help us do.” ●

HIV and AIDS: Much Accomplished, Much to Do

Says NIAID Director Anthony Fauci, One of the First to Study AIDS

BY REBECCA G. BAKER, NIAID



In a recent lecture, NIAID Director and AIDS pioneer Anthony Fauci celebrated the many advances made in HIV and AIDS research but said there was still “much to do.”

EVEN THOUGH MORE THAN FOUR MILLION lives have been saved, “it’s clearly too soon for a victory lap” in the fight against human immunodeficiency virus (HIV) and AIDS, said **Anthony Fauci**, one of the first scientists to begin studying HIV and AIDS when the illness emerged in the early 1980s. A pioneer in understanding human immunological diseases, Fauci has led extensive basic and translational research exploring HIV and AIDS.

At the September 11, 2013, Clinical Center Grand Rounds Great Teachers Lecture, Fauci recalled his early research in the immune-mediated and infectious diseases; saluted his NIH mentors; and offered a tour de force of the current state of HIV and AIDS prevention and treatment and research efforts toward a cure.

Fauci has been the director of the National Institute of Allergy and Infectious Diseases (NIAID) since 1984 and serves as one of the key consultants to the White House and Department of Health and Human Services on global AIDS issues as well as on emerging infectious disease threats such as pandemic influenza.

He waxed eloquent about his former colleagues in NIAID’s Laboratory of Clinical

Investigation, leaders in immunological research: his mentor and lab chief, the late **Sheldon “Shelly” Wolff**; **John Gallin** (now the director of the NIH Clinical Center); and **Charles Dinarello** (no longer at NIH, but considered one of the founding fathers of cytokine biology). When Fauci began reading reports of AIDS cases, he soon made the bold decision to redirect his lab’s focus from investigating fundamental questions of immunology to studying HIV and AIDS. He assembled a research team—**Clifford Lane** (NIAID) and **Henry Masur** (Clinical Center)—to investigate HIV and AIDS, and together they made breakthroughs in understanding how HIV destroys the body’s immune system and in developing strategies to restore immune defenses. Other NIH pioneers included **Robert Gallo**, who co-discovered HIV and identified it as a cause of AIDS, and scientists in the National Cancer Institute’s (NCI) AIDS Therapy Program. These included **Robert Yarchoan**, **Sam Broder** (later became director of NCI), and **Hiroaki Mitsuya**, who together developed the first FDA-approved antiretroviral therapies (ART).

Globally, about 35 million people are living with HIV infection, and 2.3 million are newly infected each year. Fauci expressed pride in research advances that have led to therapies that have prevented 4.2 million deaths. He outlined successful prevention strategies, including condom use and behavior modification, pre-exposure prophylaxis, voluntary medical circumcision for adult men, and early intervention with ART. Untreated HIV almost always progresses to AIDS.

Fauci is discouraged that it has been difficult to implement the strategies even though they are known to be effective. In the United States, for example, only 82 percent

of the estimated one million HIV-infected people have been diagnosed. Of the total infected, only 66 percent receive care and 33 percent receive ART. Thanks to treatment, an estimated 25 percent of all HIV-infected persons in the United States have a suppressed viral load. But many effective treatments and preventions fail to achieve their full potential because “people are not adhering to something that works,” Fauci said. “We need to link human behavior research with biomedical interventions.”

Regarding the possibility of a cure for HIV, Fauci explained that if one is found, it must be simple, safe, and expandable to millions of people. In addition, he called for “new tools for prevention.”

One of the new tools might one day be an HIV vaccine. Indeed, scientists at NIH and elsewhere are working to develop one, but they face many challenges. In classical vaccinology, vaccinologists develop vaccines by copying “the body’s immune response to the pathogen,” Fauci explained. “But it’s not the same with HIV because the body is not capable of responding adequately.”

The world’s first HIV vaccine trial was led by Lane at NIH in 1988. Recently an HIV vaccine trial in Thailand has shown some promise, but, Fauci cautioned, “It’s not ready for prime time.”

Fauci celebrated the many advances in HIV and AIDS research, trumpeting them as “great news about the translation of basic science to effective clinical interventions.” Yet there remains “much to do, both to implement what we already have and in the discovery of new interventions.”●

To watch a videocast of Fauci’s talk “HIV/AIDS: Much Accomplished, Much To Do,” go to <http://videocast.nih.gov/launch.asp?18075>.

Understanding the Human Retina

Through the Eyes of a Ground Squirrel

BY DUSTIN HAYS, NEI

WHY IS NIH SCIENTIST WEI LI studying a fanciful species of ground squirrels to understand the human eye? For one thing, both humans and the thirteen-lined ground squirrel (*Spermophilus tridecemlineatus*), so named for its beautiful pattern of white stripes, can see in color. That's something that most mammals can't do. And when the ground squirrels hibernate, their eyes experience the same kind of metabolic stress that human eyes do when they have certain retinal disorders.

As a senior investigator at the National Eye Institute (NEI) and chief of the Retinal Neurophysiology Unit, Li studies how the synaptic circuits in the retina are normally wired and how they are altered by disease. On September 12, 2013, he presented his work at the annual Sayer Vision Research Lecture, which features scientists who have made major contributions to vision research.

The retina, the light-sensitive layer lining the inside of the eye, contains two types of photoreceptors: rods, which are sensitive to changes in light, and cones, which are sensitive to color. The ground squirrel retina and the central region of the

human retina are dominated by cone photoreceptors. The retinas of most mammals are made up mostly of rod photoreceptors, which are good for night vision but cannot discern color.

Li and NEI staff scientist **Shan Chen** were lauded in 2012 when they reported in *Nature Neuroscience* the discovery of a unique type of neuron in the retina of the thirteen-lined ground squirrel that helps encode color vision (*Nat Neurosci* **15**:954–956, 2012). For years, researchers suspected the existence of an interneuron that modulates signals from cone photoreceptors that principally capture blue light. Li conceived of a technique to hunt for such cells among retinal interneurons called amacrine cells, of which there are 30 types. Chen painstakingly probed individual amacrine cells, measuring their response to alternating blue and green light. Li and Chen eventually found one type—the S-cone amacrine cell—that attenuates transmission from blue cones. They suspect that the newly identified cells likely have a similar function in humans.

Li also suspects that hibernation-induced metabolic stress is similar to the metabolic stress that occurs in retinal eye diseases. When ground squirrels hibernate in winter, their retinas are subjected to a long period of challenging metabolic conditions. The retinal neurons power down during hibernation, but their function is quickly restored when the animals awaken. Li wants to know how these seemingly fragile circuits rebound so quickly.

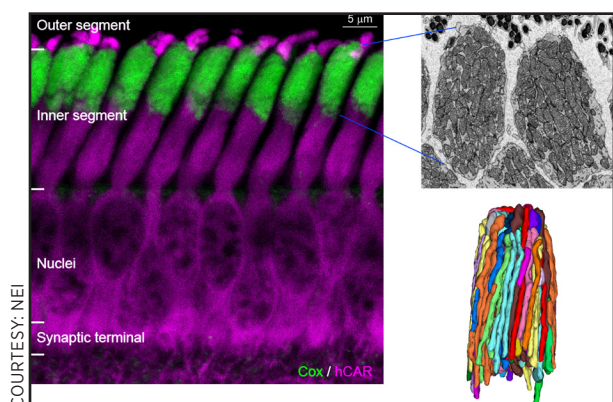
Li is using serial block face scanning electron microscopy (SBEM) to explore the structural changes that occur in the

ground squirrels' retinal mitochondria during hibernation. SBEM allows for three-dimensional reconstruction of subcellular structures through repeated fine-resolution scans. After each scan, a very thin layer (less than 30 nanometers) of the cell is cut away and the underlying surface is scanned. A computer program then assembles hundreds of scans to construct a three-dimensional representation—a little like reconstructing a loaf of bread from individual slices.

Li's preliminary SBEM work shows that the mitochondria inside the photoreceptors look like tightly packed cable strands. He suggested that this orientation may help conduct light, similar to the way a fiber optic cable works. He is collaborating with **Robert Balaban**, the scientific director of the National Heart, Lung, and Blood Institute, to correlate retina structural changes with functional changes such as enzymatic activity.

Uncovering the mechanisms that ground squirrels use to recover from hibernation may help us understand metabolic stress that occurs in human diseases of the retina such as diabetic retinopathy, age-related macular degeneration, and retinitis pigmentosa, Li said. "Our hope is that these tricks will point to therapeutic solutions for humans." ●

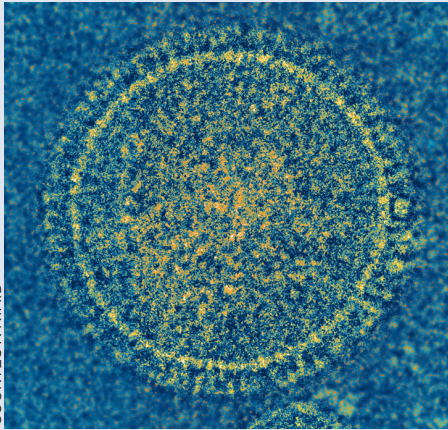
The Sayer Vision Research Fund was established in 2006 at the Foundation for the National Institutes of Health by Jane M. Sayer, a research scientist with NIDDK. In partnership with NEI, the fund supports the Sayer Vision Research Lecture Series, given by a scientist of national or international prominence in a discipline with relevance to vision research. From time to time, the fund also supports an award to a promising young NIH investigator in eye research, of which Wei Li is the first recipient. For more information visit <http://www.nei.nih.gov/news/special/sayer.asp>.



Ground squirrel photoreceptor mitochondria: (left) cross section of the ground squirrel retina, focusing on the photoreceptor layer and cones; (top right) scanning electron microscopy image of photoreceptor mitochondria; (lower right) 3-D reconstruction of mitochondria in a single cone photoreceptor.



Intramural Research Briefs



COURTESY: NIAID

The respiratory syncytial virus (RSV) is responsible for a common childhood illness. NIAID and VRC scientists have developed a candidate vaccine that show promise in animals and plan to conduct early-stage clinical trials in the future.

NHLBI: ENTEROVIRUSES NEED CHOLESTEROL TO REPLICATE

Researchers at NHLBI discovered that the Enterovirus genus of viruses—which includes human pathogens such as polioviruses, Coxsackie viruses, and rhinoviruses (which cause the common cold)—depend on cholesterol for replication. These viruses actively rewire the endocytic membrane trafficking pathways of host cells to maximize cholesterol absorption and delivery to their replication platforms. By targeting the viral and host factors that are required for cholesterol absorption and delivery to the replication platforms (as identified in this study), scientists may be able to develop panviral therapeutics that can block the replication of many different enteroviruses in humans. (NHLBI authors: M. Santiana, W.-L. Du, Y.-H. Chen, N. Altan-Bonnet; *Cell Host Microbe* 14:281–293, 2013)

NICHD: NEW DRUG COULD SLOW PROGRESS OF FATAL CHILDHOOD DISORDER

Batten disease is a fatal, inherited disorder of the nervous system that typically begins in childhood. NICHD researchers have identified a potential new drug that could help in the treatment of a form of the disease. When tested in mice, the drug slowed the loss of coordination seen in the disorder and extended the animals'

life span. The drug is derived from hydroxylamine, a molecule chemically similar to ammonia. Hydroxylamine is toxic, but a slight change in the molecule's chemical structure results in a nontoxic molecule, called NtBuHA, short for *N*-(*tert*-Butyl)-hydroxylamine. The researchers hope NtBuHA will be useful for treating a particular subtype of the disease, infantile Batten disease. Children with this form of the disease have a genetic deficiency of the enzyme palmitoyl-protein thioesterase-1, which ordinarily breaks down ceroid, a waxy substance. The researchers are also evaluating two other drugs—cysteamine bitartrate and acetylcysteine—for the treatment of the disease. (NICHD authors: C. Sarkar, G. Chandra, S. Peng, Z. Zhang, A. Liu, and A.B. Mukherjee; *Nature Neurosci* 16:1608–1617, 2013)

NIAID, VRC: CANDIDATE VACCINE AGAINST RESPIRATORY SYNCYTIAL VIRUS

An experimental vaccine to protect against respiratory syncytial virus (RSV), a leading cause of illness and hospitalization among very young children, elicited high concentrations of RSV-specific antibodies when tested in animals, according to NIH researchers. The scientists built on their previous findings about the structure of a critical viral protein to design the vaccine. Earlier this year, the VRC team obtained atomic-level details of an RSV protein—called the fusion (F) glycoprotein—bound to a broadly neutralizing human RSV antibody. Before it fuses with a human cell, the F glycoprotein contains a region vulnerable to attack by broadly neutralizing antibodies.

The researchers used this information to design and engineer F glycoprotein variants that were then used as vaccines in experiments in mice and rhesus macaques. It turned out that the more stable the protein, the higher the concentration of neutralizing antibodies elic-

ited by vaccination. Early-stage clinical trials are planned. (NIH researchers: J.S. McLellan, P.D. Kwon, B.S. Graham, and others; *Science* 342:592–598, 2013; and NIH researchers: J.S. McLellan, P.D. Kwon, B.S. Graham, and others; *Science* 340:1113–1117, 2013)

NIDDK, CIT: MOLECULAR STRUCTURE OF AMYLOID PLAQUES

Alzheimer disease (AD) is thought to be caused by abnormal protein deposits called amyloid plaques in the brain. Until recently not much has been known about the molecular structures of the amyloid-beta (A-beta) fibrils within these plaques. NIDDK and CIT investigators, together with colleagues from the University of Chicago, have now developed methods for determining the molecular structures of A-beta fibrils in brain tissue of AD patients, based on solid-state nuclear magnetic resonance spectroscopy. The investigators examined fibrils grown from brain tissue of two AD patients with different clinical histories and found that each patient had developed a single fibril structure, but that fibril structures in the two patients were different from each other. Moreover, fibrils that developed in brain tissue were different from fibrils grown in the test tube.

The work represents the first detailed analysis of the molecular structures of the deposits that develop in AD patients' brains. Information gathered from examining molecular structures of A-beta fibrils may provide a way to accurately diagnose mild cognitive impairment in still-living AD patients, allowing for early intervention and potential inhibition of disease progression. The findings pave the way for new patient-specific strategies to improve diagnosis and treatment of this common and debilitating disease. (NIH authors: J.-X. Lu, W. Qiang, W.-M. Yau, C.D. Schwieters, and R. Tycko; *Cell* 154:1257–1268, 2013) ●

CONTRIBUTORS: KRISTEN CARRERA, NIDDK; NICHOLAL ZAGORSKI, NHLBI

Read more online at <http://irp.nih.gov/catalyst/v21i6/research-briefs>.



From Zoo to Bedside

An Unlikely Route to Translational Research

BY JENNIFER SARGENT, NIAMS

KOALAS—THOSE DOCILE, UNDENIABLY cute Australian marsupials—are a threatened species. Ever since the British colonization of Australia in the late 1700s, these adorable creatures have suffered immensely, and their populations have been reduced as a result of their native habitats being destroyed.

But a new, more insidious danger has emerged in the last century—a cancer-causing virus. Today, leukemia and associated lymphomas are the leading cause of death in koalas in northeastern Australia and in zoos around the world.

Surprisingly, some human-related NIH research may help to rescue the koalas. **Maribeth Eiden**, chief of the Section on Directed Gene Transfer at the National Institute of Mental Health (NIMH), is developing viral-based vectors for delivering genetic material to cells in the human central nervous system (CNS). Her findings may lead to the optimization of gene-delivery vectors in humans as well as ways to prevent deadly viral attacks in koalas.

The deadly koala virus, discovered in 2000, is the endogenizing koala gamma-retrovirus (KoRV), which has been integrating into the koala genome over the past 100 years. KoRV is closely related to other retroviruses known to cause blood cancers such as the gibbon ape leukemia virus (GALV). KoRV is also found in healthy animals, so its association with cancers has remained enigmatic.

Eiden's lab and a team of scientists from the Los Angeles and San Diego Zoos showed that koalas infected with the virus substrain KoRV-B had a higher incidence of malignant tumors than did noninfected koalas (*Proc Natl Acad Sci U.S.A.* **110**:11547–11552, 2013). The researchers then developed an assay using the polymerase chain



R. STOWE, WIKIMEDIA COMMONS

NIMH scientist Maribeth Eiden is doing research that may lead to the optimization of gene-delivery vectors in humans as well as ways to prevent deadly viral attacks in koalas. Above: A koala at the Greater Los Angeles Zoo.

reaction to screen for pathogenic KoRV-B as part of an effort to prevent disease transmission among koalas (between individual animals and from mothers to their offspring).

Great news for koalas, but how does this relate to human gene therapy?

For over two decades, Eiden has been re-engineering GALV and other viruses to construct vectors for human gene therapy. She is interested in the viral envelope proteins that infect cells by targeting specific host receptors. And that's where studying koalas comes into play.

KoRV and GALV are closely related, share many of the same genes, and even use the same receptor to infect human cells. Eiden found, however, that the newly discovered pathogenic KoRV-B uses a different receptor to infect cells and that that receptor is expressed in the human CNS. She is now examining the KoRV-B envelope proteins with the goal of honing the GALV-based vectors to more specifically target the CNS.

Although Eiden and her group are primarily interested in understanding retroviruses and modifying vectors for continual improvement of human therapeutics, this collaborative project is a shining example of the impact the NIH intramural research has in unlikely places . . . even at the zoo. ●

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
DOE: Department of Energy
FAES: Foundation for Advanced Education in the Sciences
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
NIHES: National Institute of Environmental Health Sciences
NIHMS: 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
ODS: Office of Dietary Supplements
OITE: Office of Intramural Training & Education
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health
OTT: Office of Technology Transfer

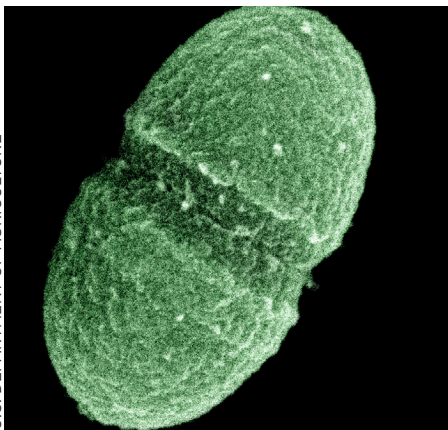
Microbiome

CONTINUED FROM PAGE 1

The second phase of the HMP which started on September 8, 2013, focuses on a survey of the biological properties of the microbiome, such as gene expression profiles, proteins, and metabolites, produced by the microbiome under specific conditions such as in preterm birth or in diabetic patients.

The goal for the Phase One Healthy Cohort Study was to create a reference microbiome that represents the normal collection of bacteria living on and inside healthy American adults. It has provided the first glimpse of the microbial diversity of healthy humans; the major findings are described at the end of this article in an interview with **Lita Proctor** and online at <http://www.hmpdacc.org>.

The goal for the Demonstration Projects was to explore the relationships between human diseases and the microbiome. Researchers collected and sequenced microbiome samples from volunteer patients and compared them with the reference microbiomes from healthy volunteers. The microbiome from individuals with a disease—such as Crohn's Disease, eczema, or esophageal adenocarcinoma—is significantly different from those of healthy individuals. Scientists are trying to determine whether the microbiome differences are a cause or effect of disease.



The bacterium, *Enterococcus faecalis*, which lives in the human gut, is just one type of microbe that is being studied as part of NIH's Human Microbiome Project.

Intramural Microbiome Research

What follows are descriptions of three intramural research projects in the HMP.

Julie Segre, senior investigator, NHGRI, and Heidi Kong, investigator, NCI-CCR: The microbiome of the skin

These researchers have played a large role in helping us to understand the microbiome of the skin. Our skin is a diverse ecosystem analogous to Earth's various ecosystems (oily versus dry, for example).

What Segre and colleagues have found is that the moist areas of the body have the greatest number of bacteria but the least diversity, while the dry areas of the skin have the fewest bacteria but the most diversity. Segre's laboratory studies atopic dermatitis (eczema) in young children, and she hopes understanding the microbiome of the skin will lead to improved treatments. Atopic dermatitis is characterized by asymptomatic periods punctuated by periods of severe skin inflammation. Segre and Kong found that the microbial population changes during dermatitis flares, and they are exploring whether the microbial diversity can be used to predict when dermatitis flare-ups will occur. In addition, there are multiple treatments for atopic dermatitis and not all children respond similarly. Because there is no adequate diagnostic to predict which treatment will work best, Segre and Kong are investigating whether the microbial diversity of atopic dermatitis can be used to identify the most effective treatment.

Jason Brechley, senior investigator, NIAID: Microbiome of the intestine

It may not seem intuitive, but the gut microbiome plays an important role in human immunodeficiency virus (HIV) infection. Although antiretroviral therapy has proven successful in controlling the replication of HIV in the blood and in reducing the incidence of acquired immunodeficiency syndrome (AIDS), the life expectancy of

infected, but treated, individuals is shorter than that of healthy individuals. Recent data have shown that the cause of death in HIV patients is strongly associated with inflammation and microbial translocation from the gastrointestinal (GI) tract lumen. During the acute phase of HIV infection there is a significant depletion of GI-tract-resident CD4+ T cells, apoptosis of gut epithelial cells, and a shift away from the normal immune-regulating cells. These changes make the gut epithelium susceptible to microbial translocation into the body, causing chronic low-grade systemic inflammation that over time can result in cardiovascular disease. Using an animal model of HIV, Brechley has found that bacteria that translocate across the gut epithelium are not representative of the gut microbiota and that bacteria of the phylum Proteobacteria (including invasive strains such as *brevundimonas* and *diaphorobacter*) tended to translocate preferentially.

These studies led to a proposal for using probiotics (healthful bacteria) to increase the percentage of beneficial, noninflammatory microbes in the gut, thus reducing the percentage of invasive proteobacteria. The probiotics produce factors that act on the gut epithelium to restore its structural integrity, reduce inflammation, and prevent microbial translocation. Ongoing studies in Brechley's laboratory aim to understand how HIV infection alters the gut microbial composition and metabolism.

Yasmine Belkaid, senior investigator, NIAID: Microbiome of infection barrier sites (skin and gut)

Harmful bacteria and viruses gain entry to the body by traversing its protective barriers such as the skin, mucosal epithelium of the nasal passages, and the gut epithelium. Until recently it was thought that these protective barriers (especially the skin) functioned independently of the resident or commensal microbiota known to reside on them. We



now know that the commensal microbiota of the barrier sites are integral in keeping harmful bacteria from entering our body.

Belkaid's laboratory, in collaboration with Julie Segre (NHGRI) and Heidi Kong (NCI-CCR) was instrumental in demonstrating the importance of the skin microbiome as a barrier against infection. She compared the response of two groups of mice to infection. The first group was housed normally and were host to the normal array of commensal microbiota; the second group was housed from birth in a highly controlled environment free of germs, including commensal microbiota. When the two groups were exposed to the pathogenic bacteria *Leishmania major* (which is transmitted by sandflies and causes cutaneous leishmaniasis), the normal group mounted a normal immune response whereas the sterile-environment group failed to mount such a response. Additional experiments demonstrated that the skin's commensal microbiota are essential in priming the skin's immune system to respond to noncommensal pathogenic microbiota.

Major Findings of the HMP

An edited interview with Lita Proctor, HMP program officer, NHGRI

What has been the most unexpected finding?

The sheer magnitude of the genetic potential in the thousands of microbes living on and inside the human body. Humans are hosts to 10,000 different bacterial species; each individual carries around 1,000 different species. The global pool of unique microbial genes associated with the 10,000 microbial species is estimated to be around eight million. (Humans have about 23,000 genes.)

What benefits can patients expect to see?

Indirect benefits of the HMP are already being realized. Fecal microbiota transplantation, the process of transplanting fecal bacteria from a healthy individual into a recipient, is often used to treat the symptoms

of *Clostridium difficile* infection (such as antibiotic-associated diarrhea). Doctors are using the technology developed for the HMP to perform sequenced-based analysis of donor and recipient stool to predict how individuals will respond to tailored treatments. The long-term benefits of the HMP are predicted to be wide-ranging. But at this early stage, researchers cannot say with certainty what specific benefits will arise. They know very little about the human microbiome and its role in healthy and unhealthy individuals.

What does the future hold for the HMP?

The HMP is only the tip of the iceberg for understanding the diversity of the human microbiome and its role in healthy and unhealthy individuals. The next step is to broaden the human subject sampling. The 300 normal, healthy individuals who contributed to the reference microbiome had a mean age of 26, were all Americans, and were mostly white. Such a small and biased sample disregards the effects of age and cultural practices on the diversity of the microbiome. For example, it is known that diet influences the diversity of the gut microbiome and that humans begin accumulating a microbiome following birth. It is unknown how (or if) the microbiome diversity changes as individuals age. These are all questions that still need to be addressed. ●

For more information, go to:

- <http://commonfund.nih.gov/hmp>
- PLOS Series: <http://www.ploscollections.org/article/browseissue.action?issue=info:doi/10.1371/issue.pcol.v01.i13>

TO READ AN EXPANDED VERSION OF THIS ARTICLE, GO TO <http://irp.nih.gov/catalyst/v21i6/the-human-microbiome-project>

THE MICROBIOME CLOUD

BY HILLARY HOFFMAN, NIAID

The NIH Microbiome Cloud Project (MCP), led by NIAID and NHGRI, addresses one of the greatest challenges facing microbiome scientists: large-scale data analyses. A team of scientists from NIH, academia, and industry is developing a cloud, or Internet-based, platform that brings together Human Microbiome Project (HMP) data and analysis tools. The HMP produced 14 terabytes of genetic information about the microbes that naturally colonize our bodies. That's enough data to fill more than 3,000 standard DVDs.

Mining microbiome datasets promises to help scientists better understand the role of the microbiota in health and disease and identify new targets for drugs and vaccines, but scientists need proper tools to make sense of these complex data. By bringing together the data and tools in the cloud, the MCP will give researchers access to vast amounts of data with high-performance computing power.

In September 2013, NIAID and NHGRI launched the first phase of the MCP, which makes a five-terabyte portion of HMP sequencing data publicly available on the Amazon Web Services cloud. Cloud storage facilitates analysis by reducing the need for time-consuming data downloads. The MCP team is developing the next phase of the project, which will add analysis tools, more data, and supporting documentation such as online tutorials. Before the platform is released to the public, it will be evaluated by a team of NIH scientists and extramural researchers.

To access any of the cloud-based HMP datasets, visit <http://aws.amazon.com/datasets/1903160021374413>. For more information about the MCP, contact Yentram Huyen (huyen@mail.nih.gov), Maria Giovanni (mg37u@nih.gov), or Vivien Bonazzi (bonazziv@mail.nih.gov).

Proteostasis

One Name, Many Fields: “Proteostasis” Research at NIH

BY JENNIFER SARGENT, NIAMS

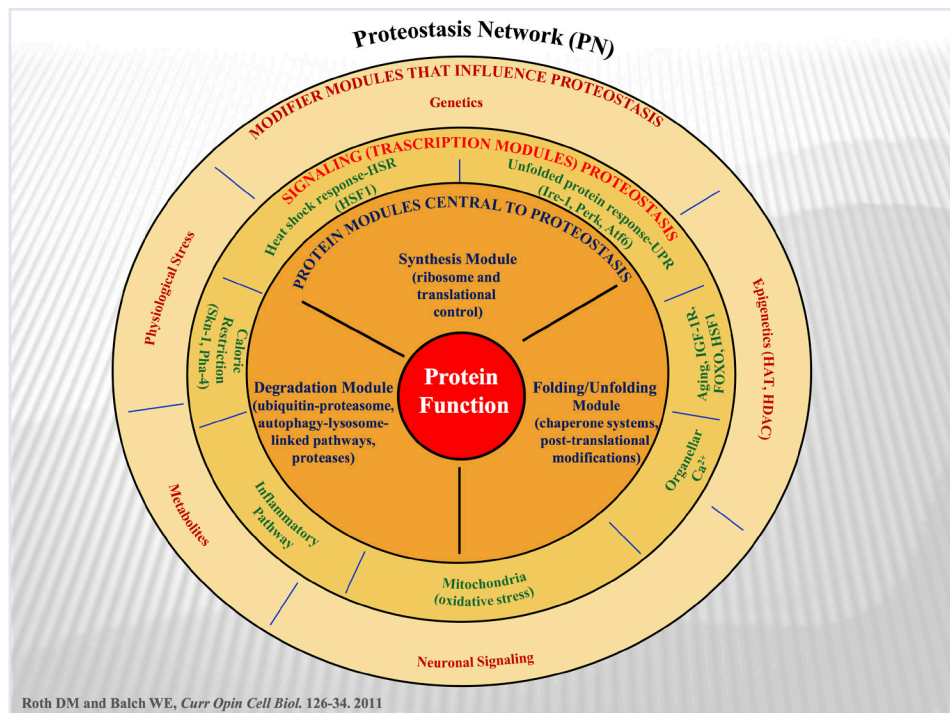
PROTEOSTASIS, A SEEMINGLY straightforward fusion of the words “protein” and “homeostasis,” is actually a fertile and multifaceted concept. Ask any 10 scientists to define it, and you’re bound to get 10 different answers, and those opinions may change from year to year.

In effect, proteostasis is greater than the sum of its parts, encompassing the study of all areas of protein health and fitness that contribute to maintaining cellular integrity and function. Derailed proteostasis leads to protein misfolding and aggregation that is implicated in many neurodegenerative diseases such as Alzheimer disease, Parkinsonism, amyotrophic lateral sclerosis, type 2 diabetes, cancer, cardiomyopathy, cystic fibrosis, cataracts, prion disease, immune problems, metabolic deficiencies, alcoholic liver disease, and other chronic maladies. It is well established that proteostasis naturally declines during aging.

At the NIH, the processes underlying such conditions traditionally have been studied in isolation, with fields of study delineated by disease classifications. But **Andras Orosz**—a program director at the National Institute of Alcohol Abuse and Alcoholism and driving force behind the recent formation of the Proteostasis Scientific Interest Group (SIG)—thinks that it’s time we change our approach to understanding and treating these devastating chronic diseases.

He believes that “learning the basic biology of proteostasis is important for understanding a slew of debilitating protein misfolding and aggregation disorders and [for] developing cures.”

As such, the Proteostasis SIG brings together intramural research program (IRP)



COURTESY A. OROSZ, NIAAA

investigators from across multiple fields and institutes to share knowledge about the underlying molecular commonalities of different diseases.

Proteostasis, a term coined in a landmark *Science* paper in 2008, is a broad concept that is relevant to all fields that involve protein synthesis, folding, processing, and turnover (*Science* 319:916–919, 2008). Some major subgroups that fall under the proteostasis umbrella include protein synthesis and degradation systems; chaperone proteins that bind to nascent polypeptide chains and partially folded proteins to ensure proteins attain correct conformation; and post-translational modifications that can modulate protein activation states, specify intracellular location, or tag a protein for degradation by the proteasome. As many as 2,000 proteins are involved in the proteostasis network.

The decline of proteostasis with aging

When protein homeostasis degenerates and collapses, cells get old . . . and sick. Hallmark features of cellular aging include a buildup of proteotoxic stress, mistranslation of nascent polypeptides, and concentration of damaged, misfolded proteins and protein aggregates. This accumulation of cellular waste is toxic to cells. That’s when things start to fall apart.

Senior Investigator **Jay Chung**, head of the National Heart, Lung, and Blood Institute’s (NHLBI) Laboratory of Obesity and Aging Research, believes that the same molecular pathways that are affected under conditions of metabolic stress go awry in natural aging. The common thread between these seemingly disparate disorders boils down to the issue of unbalanced proteostasis. Chung says that understanding how these stresses affect protein quality control is



tantamount to understanding how and why aging-associated diseases such as Alzheimer disease and obesity-related health pathologies develop.

Central to quality control of proteins in the cell is the molecular chaperone heat shock protein 90 (HSP90). Chung has observed that post-translational modifications of HSP90 can be drastically altered in either aged or obese mice compared with healthy and younger animals. He has also demonstrated that calorie restriction, a method previously shown to increase longevity in mice, can reverse the post-translational modifications associated with aging and obesity, restoring proteostasis on a molecular level. The full spectrum of mechanisms by which age and caloric restriction affects proteostasis is under intense investigation.

Elsewhere in NHLBI, **Toren Finkel** and his team in the Laboratory of Molecular Biology are interested in understanding the basic mechanisms underlying natural aging. His lab recently showed that lowering the expression levels of a gene encoding a signaling molecule called mammalian target of rapamycin (mTOR) can increase the lifespan of mice by up to 20 percent. This feat would be equivalent to raising the average lifespan of a human being from 75 to 90 years (*Cell Rep* 4:913-920, 2013).

Finkel says that one potential mechanism by which mTOR controls life expectancy is through the proteostasis degradation pathway of autophagy. Autophagy, a process by which cells clear damaged organelles and proteins, is essential to maintaining healthy protein homeostasis.

Protein aggregates, amyloid, and prions

Protein aggregates are one type of cellular trash that can accumulate when the proteostatic balance is lost.

Amyloids are a form of protein aggregate comprising filaments of monomers bound by hydrogen bonds. Formation of amyloid is pathogenic in several neurological

disorders including Huntington, Lou Gehrig's, and Alzheimer diseases. Other neurodegenerative diseases, such as Creutzfeldt-Jakob disease and bovine spongiform encephalopathy, are caused by pathogenic amyloid structures comprising misfolded prion proteins.

While it is known that these disorders arise through disparate genetic mechanisms and that the aggregates are formed from different proteins, there are striking similarities in their three-dimensional structures. Understanding the basics of how and why these proteins aggregate may provide clues about how to break apart amyloid plaques and potentially reverse disease pathologies.

Reed Wickner, chief of the Laboratory of Biochemistry and Genetics in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), uses yeast prions as a model to study the dynamics of amyloid structures. One finding from his group that may yield clues about amyloid turnover is the identification of a protein, Batten-disease-related protein 2 (Btm2), that cures yeast cells of prions by sequestering prion aggregates to a cellular compartment.

Some 2,300 miles away from Bethesda, at the Rocky Mountain Laboratories (Hamilton, Mont.), which is part of the National Institute of Allergy and Infectious Diseases (NIAID), researchers are seeking to understand prion biology in mammalian systems. **Suzette Priola**, chief of the Transmissible Spongiform Encephalopathy (TSE)/Prion Molecular Biology Section, has identified a region of mammalian prion protein that controls interspecies transmission. Her group is also deciphering those events that trigger initial prion protein misfolding.

Molecular chaperones

Molecular chaperones are critical components of the proteostasis network. Senior Investigator **Daniel Masison**, in NIDDK's Laboratory of Biochemistry and Genetics, is exploring mechanisms by which chaperones

target specific prion aggregates. He has shown that heat shock protein 70 (HSP70) acts with co-chaperones to propagate prion replication by breaking up amyloid structures into fragments, each of which can then seed a new prion aggregate.

Masison collaborated with NHLBI's **Lois Greene** to demonstrate that overexpression of co-chaperone HSP104 resulted in complete disintegration of prion aggregates in hours.

Greene's laboratory is using real-time cell imaging to study mammalian prion biology as well as the function of chaperone proteins in the formation of clathrin-coated pits, a mechanism by which cells can internalize cargo-bound receptors on the cell surface.

Lisa Cunningham, head of the Section on Sensory Cell Biology in the National Institute on Deafness and Other Communications Disorders, is investigating a lesser-known role for HSP70. She and her team have discovered that HSP70 secreted by neighboring cells is a critical factor in protecting mechanosensory hair cells in ototoxic-mediated hearing loss. Traditionally the roles of chaperones and heat-shock proteins in protein folding and trafficking were thought to be limited to folding and stabilizing proteins within the cell in which they are synthesized.

Cunningham is working with the audiology team at the NIH Clinical Center to restore hearing in patients by inducing HSP70 expression in the inner ears.

Proteostasis and cancer

Leonard Neckers and his group at the National Cancer Institute's (NCI) Urologic Oncology Lab, like Chung, also are interested in the chaperone protein HSP90. Neckers has found that HSP90 is a critical factor for cell survival and proliferation in many types of cancers. Called the "cancer chaperone," HSP90 stabilizes proteins in the

CONTINUED ON PAGE 14

Proteostasis

CONTINUED FROM PAGE 13

cell, many of them protein kinases, that play important roles in cell growth, cell survival, apoptosis, and oncogenesis.

But stabilization is not always a desirable outcome. In certain types of cancers, HSP90 stabilizes oncogenic proteins, shielding them from degradation. Thus, overactive HSP90 can sustain cancer-cell growth and survival by extending the lifespan of toxic proteins. In the late 1990s, Neckers's lab identified the first small-molecule HSP90 inhibitor and helped develop the first-in-human drug targeting HSP90. Several chemically distinct HSP90 inhibitors are currently in phase 1 and phase 2 clinical trials and one is in phase 3 clinical trial.

Allan Weissman, chief of NCI's Laboratory of Protein Dynamics and Signaling (Frederick, Md.), works on the ubiquitin system, which he describes as "the major player in regulating levels of cellular proteins." Ubiquitination is a post-translational modification that can target proteins for proteasomal degradation. In 1999 Weissman and co-workers were the first to describe (RING)-finger proteins as ubiquitin ligases. RING fingers are a family of enzymes that tag proteins for degradation and constitute the majority of ubiquitin ligases. Although all the targets of RING-ubiquitin ligases have not yet been identified, Weissman has shown that overexpression of a specific RING-ubiquitin ligase leads to a marked enhancement of metastasis—the primary cause of death in cancer.

Proteostasis research at the NIH is far greater than what this article could summarize. As evidence of this emerging field's importance within the IRP, it made a splash with a well-attended workshop in June and symposium in September and was featured at the NIH Research Festival in November 2013. To learn more about the Proteostasis SIG and related activities, contact Andras Orosz at orosza@mail.nih.gov. ●

The Shutdown

CONTINUED FROM PAGE 1

cycle. Even though more than 200 peer-review meetings were scuttled by the shutdown, affecting some 11,000 grants, NIH will work double-time so as not to delay this process for another four months.

Collins concluded, "I am humbled and thankful to be associated with all of you . . . your professionalism is a delight to behold."

A videocast of the town hall meeting may be viewed (by NIHers only) at <http://videocast.nih.gov/launch.asp?18126>.

Impact on Intramural Program

The furlough of three-quarters of NIH's workforce for 16 days dealt a particularly hard blow to the Intramural Research Program, putting 2,500 research protocols and 1,500 clinical protocols on hold, said NIH Deputy Director for Intramural Research **Michael Gottesman**.

"Suddenly coming to a complete halt—that's a big blow to the whole research establishment," he said. Many experiments were lost and will have to be repeated; it will take a few weeks for most research projects to get back up to speed.

Troubling to Gottesman was the message a furlough sends to the wider research community. "NIH has compacts with all sorts of organizations. Our scientists collaborate, give talks—all as part of our official duties—and suddenly we were not reliably there to do that. All of a sudden, NIH looks like a less reliable partner."

Although the Clinical Center remained open, only 75 percent of its staff was on hand, he said, and attendance varied from institute to institute, based on the clinical studies under way. Of seven protocols due to begin during the shutdown, only one was allowed to go forward, based on its potentially life-saving effect. And only 25 of more than 400 scheduled patient visits were permitted during the shutdown.

"No one could be in a lab without a supervisor," Gottesman said. Not all lab chiefs, nor all scientific directors, hold "excepted" positions, he noted. Those who were permitted to work found themselves handling such routine duties as checking freezers and animal colonies.

"We were very careful with our animal [colonies]," Gottesman continued, allowing continued breeding and ensuring that animals were genotyped to preserve needed cage space. "We won't have to start from scratch with our animals."

On any given day, NIH as a whole manages around 384,000 animals, including more than 330,000 mice, said **Terri Clark**, director of the Office of Animal Care and Use. There had been concerns that a prolonged shutdown would have led to a need to euthanize many mice due to overcrowding. But that did not happen, she said. A small number were culled and euthanized in the normal course of breeding operations that occurred during the shutdown.

Only critical animal studies already in midstream or experiments of particularly high value, as determined by the scientific directors, were allowed to go forward.

Gottesman was reluctant to name heroes during the shutdown. "There are more than I could enumerate," he said. "It's hard to single out individuals. Even those who did what they were supposed to do by staying home did their part."

"What was amazing to me, though, was that as soon as people came back, spirits lifted enormously." ●

This article was adapted, with permission, from one that appeared in the November 8, 2013 issue of the *NIH Record*. To read the entire article go to http://nihrecord.od.nih.gov/newsletters/2013/11_08_2013. To read more of Gottesman's thoughts on recovering from the shutdown, see his essay on page 2.



**SPECIAL NIH LECTURES:
2013 NOBEL PRIZE WINNERS IN CHEMISTRY**

Michael Levitt: “The Birth and Future of Computational Structural Biology”

Monday, November 18, 2013

4:00–5:00 p.m.

Masur Auditorium (Building 10)

Arieh Warshel: “Computer Simulations of Biological Functions”

Wednesday, November 20, 2013

1:00–2:00 p.m.

Masur Auditorium (Building 10)

CHEN LECTURE ON INNOVATION AND TECHNOLOGY TRANSFER

Friday, November 22, 2013

10:00–11:00 a.m. (reception follows)

Lipsett Amphitheater (Building 10)

Clifton Barry (NIAID) and Carol Nacy (co-founder and CEO of Sequella, Inc): “TB: It Takes More than a Village to Raise a Remedy.”

WEDNESDAY AFTERNOON LECTURE SERIES

Most Wednesdays, 3:00–4:00 p.m.

Masur Auditorium (Building 10)

Schedule at: <http://wals.od.nih.gov>

November 20: Annual Astute Clinician Lecture, Marston Linehan (NCI): “The Genetic Basis of Kidney Cancer: Targeting the Metabolic Basis of Disease”

December 4: Susan Rosenberg (Baylor): “How Bacteria and Cancer Cells Regulate Mutagenesis and Their Ability to Evolve”

December 11: Steve Holland (NIAID): “The Protean Manifestations of GATA2 Deficiency across the Lifespan”

December 18: Clyde Yancy (Northwestern): “Patient-centered Outcomes Research: New Directions, Major Challenges, Transformative Potential”

Read more online at <http://irp.nih.gov/catalyst/v21i6/announcements>.

FROM BIG DATA TO LITTLE KNOWLEDGE

Friday, December 13, 2013

3:30–5:00 p.m.

Building 50, Room 1328/1334

Vladimir Cherkassky (University of Minnesota), will present a critical discussion of the popular view “more data generates more knowledge” and on the methodological aspects of data-analytic knowledge discovery in the context of applications in health care and life sciences. All are welcome to a pre-event social at 3:00 p.m. by the coffee shop outside the meeting room. For more information, contact Jim DeLeo (jdeleo@nih.gov or 301-496-3848).

DEMYSTIFYING MEDICINE 2014

Tuesdays, starting January 7, 2014

4:00–6:00 p.m.

Building 50 Conference Room

The “DeMystifying Medicine” course, in its 12th year, 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. For more information, 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.

INVESTIGATIONAL NEW DRUG (IND)

What You Need to Know for Successful Interactions with the FDA

Thursday, December 12, 2013

8:00 a.m.–4:00 p.m.

Lipsett Amphitheater (Building 10)

Registration deadline: December 5, 2013

This program is offered by the NIH Clinical Center-FDA CDER Joint Task Force and emphasizes regulatory requirements for clinical trials of new and repurposed drugs, with a special focus on rare diseases. To register, go to https://ocrtme.cc.nih.gov/_layouts/Form-Server.aspx?XsnLocation=https://ocrtme.cc.nih.gov/Forms/INDRegistrationForm.

For more information, contact Juan Lertora (lertoraj@cc.nih.gov or 301-496-9425).

**A NEW FABRIC FOR CLINICAL RESEARCH:
APPLICATION TO THE PAIN PROBLEM**

Monday, December 16, 2013

9:00–10:00 a.m.

Lipsett Amphitheater (Building 10)

This year’s Stephen E. Straus Distinguished Lecture in the Science of Complementary Health Therapies will be presented by Robert Califf (Duke University Medical Center), who will examine the advent of “big data” and how they unite patients, families, providers, administrators, and researchers; and the impact of big data on the management of chronic pain. For more information, go to <http://nccam.nih.gov/news/events/lectures> or contact Prachi Patel (patelp2@mail.nih.gov or 301-594-1030). The event will also be videocast: <http://videocast.nih.gov>.

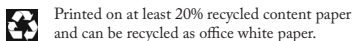
VOLUNTEER OPPORTUNITIES AT NATIONAL MUSEUM OF HEALTH AND MEDICINE

The National Museum of Health and Medicine (<http://www.medicalmuseum.mil>), in Silver Spring, Md., is seeking volunteer docents to conduct outreach activities, support public programs, or lead tours of the permanent exhibits, “Innovations in Military Medicine,” “Anatomy and Pathology,” “Civil War Medicine,” “Biomedical Engineering,” and “Human Identification and Microscopes.” Prerequisites include being at least 21 years of age and having an open, flexible schedule (weekday and weekend opportunities are available). Training will be provided. To become a volunteer or to request more information, call 301-319-3312.

KUDOS:

Congratulations to **Ron Germain** (NIAID), **Warren Leonard** (NHLBI), and **Daniel Pine** (NIMH) who are among the 70 new members elected to the Institute of Medicine this year. This honor reflects the scientists’ exemplary contributions to the medical sciences, health care, and public health. Read more online at <http://irp.nih.gov/catalyst/v21i6/announcements>. ●

Official Business
Penalty for Private Use \$300



CATALYTIC REACTIONS?

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

More Online

To read expanded versions of the *NIH Catalyst* articles, go to (<http://irp.nih.gov/catalyst/v21i6>).

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

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

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

OTHER NEWS

Sammies Honored at the White House



OFFICIAL WHITE HOUSE PHOTO BY PETE SOUZA

President Barack Obama met with the Samuel J. Heyman Service to America Medal (Sammies) finalists and winners in the East Room of the White House, October 23, 2013. Receiving the top honor of “Federal Employee of the Year” was the team comprising **Julie Segre** (NHGRI), **David Henderson** (CC), **Tara Palmore** (CC), and **Evan Snitkin** (NHGRI) for their work in stopping “the spread of a deadly hospital-acquired infection through the first-ever use of genome sequencing.” Sammie finalists included Deputy Director for Intramural Research **Michael Gottesman** and NIDA Director **Nora Volkow**. For more information, go to http://servicetoamericamedals.org/SAM/recipients/profiles/fym13_segre-palmore.shtml. To read the *NIH Catalyst* story on the work of the Segre team, go to <http://irp.nih.gov/catalyst/v20i6/intramural-detectives>. ●

PUBLISHER

MICHAEL GOTTESMAN
Deputy Director for Intramural Research, OD

EDITORS

JOHN I. GALLIN
Director, NIH Clinical Center
HENRY METZGER
Scientist Emeritus

MANAGING EDITOR

LAURA STEPHENSON CARTER

WRITER-EDITOR

CHRISTOPHER WANJEK
Director of Communications, OIR

COPY EDITOR

SHAUNA ROBERTS

EDITORIAL INTERN

JENNIFER SARGENT

CONTRIBUTING WRITERS

REBECCA BAKER, LORI CONLAN
KRYSTEN CARRERA
MASHANA DAVIS, DUSTIN HAYS
HILLARY HOFFMAN, RICH MCMANUS
JESSICA MEADE, SHARON MILGRAM
JOSEPH TIANO
NICHOLAS ZAGORSKI

PHOTOGRAPHERS/ILLUSTRATORS

JONATHAN BAILEY, J.H. CARR,
A. EARL, A. OROSZ, TOM SCHMIDT,
R. STOWE, PETE SOUZA

EDITORIAL ADVISORY BOARD

DAN APPELLA, NIDDK
DAVID DAVIES, NIDDK
MICHAEL ESPEY, NIDDK
ELISE C. KOHN, NCI
SUSAN LEITMAN, CC
GERMAINE BUCK LOUIS, NICHD
DAVID MILLER, NIEHS
BERNARD MOSS, NIAID
HYUN PARK, NCI
PAUL PLOTZ, NIAMS
SARAH RHODES, NIMH
JULIE SEGRE, NHGRI
ANDY SINGLETON, NIA
GISELA STORZ, NICHD
RONALD SUMMERS, CC
RICHARD WYATT, OIR