THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

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Human Motor Control

Celebrating Mark Hallett's Research

BY DEVERA G. SCHOENBERG, NINDS

Internationally renowned classical pianist Leon Fleisher has **Mark Hallett** to thank for restoring his ability to play the piano. At the height of his career in the 1960s, Fleisher lost the use of his right hand when it became permanently cramped with its fingers curled under like claws. Back then, doctors were stumped and didn't know how to treat the problem. Fleisher was discouraged but eventually learned to perform one-handed repertoires.

After many misdiagnoses and failed treatments, he was finally diagnosed in 1991 with focal hand dystonia, or "musician's cramp," and referred to Mark Hallett in the National Institute of Neurological Disorders and Stroke (NINDS). Hallett was pioneering the use of botulinum toxin (Botox) to block the release of the neurotransmitter acetylcholine, which normally causes muscles spasms. He injected small amounts of Botox into the musician's hand, and soon Fleisher was playing the piano two-handedly again. Fleisher is still performing with symphony orchestras around the world today.

Not only was Hallett one of the pioneers in the therapeutic use of botulinum toxin, but he is also well known for differentiating a multitude of movement disorders using neurophysiological methods. His first major achievement was the classification of myoclonus (the sudden involuntary jerking of muscles) and using neurophysiological

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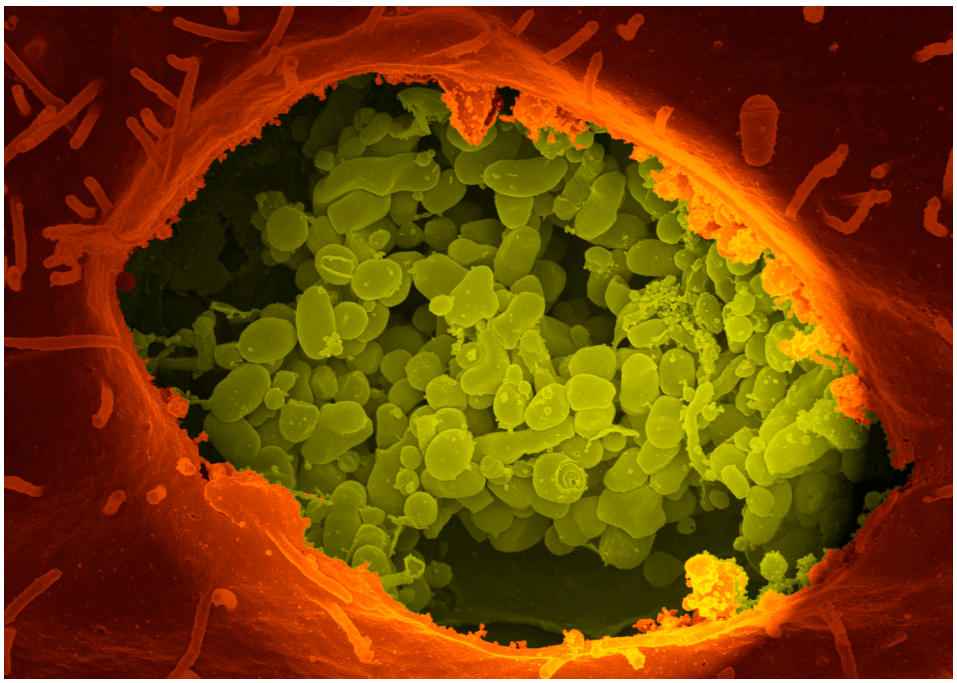
NIH Microscopy Lights Up Dulles Airport

Spectacular, Mega-magnified Images Reveal Cellular Mysteries

BY ALISA ZAPP MACHALEK, NIGMS



ROBERT HEINZEN, ELIZABETH FISCHER, AND ANITA MORA, NIAID

This dramatic magnified image of Q-fever bacteria, is one of the 46 NIH biological portraits in the *Life: Magnified* exhibit at the Washington Dulles International Airport (on the C concourse). More than a million ticketed travelers will see the exhibit, which runs through November 2014. This image and all the other portraits are in full color.

Brains, bone, muscle, blood—along with fish fins and flower parts—are among the biological players whose portraits light up the C-concourse walkway at Washington Dulles International Airport. These images—most of which are from scientists at or supported by NIH—comprise *Life: Magnified*, a gallery exhibit that showcases backlit, mega-magnified images of cells and other microscopic biological structures.

The show runs through November and is co-sponsored by the National Institute of General Medical Sciences, the American Society for Cell Biology, and the Metropolitan

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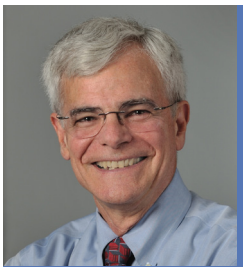


Enhancing Reproducibility of Research Findings

BY MICHAEL GOTTESMAN, DDIR

One of the signal characteristics of experimental research is that it is self-correcting: Other scientists may confirm the findings, apply more sophisticated approaches to enhance and extend the results, or demonstrate that the results or conclusions are flawed. There has been a growing concern, however, that more than a small minority of published preclinical studies using animal models cannot be easily replicated. Even studies of basic cell and structural biology, which depend on complex data sets that rely on technology-intense interpretation, may not be yielding valid conclusions.

The NIH, as the primary funder of biomedical research, has an obligation to ensure that as high a percentage as possible of published research results stands the test of time. In general, irreproducibility is not due to scientific misconduct or deliberate falsification, fabrication, or fraud. What we are talking about complex array of other factors that may result in an inability of scientists to reproduce the work of other scientists.

NIH has the ability to educate researchers about what can go wrong and how to avoid common pitfalls. In preclinical animal research, the list of possible problems is long, from poor statistical design to uncontrolled environmental influences. The NIH intramural program has been asked to help pilot a computer-based training module that outlines the kinds of problems that can beset animal studies. We will start by asking our fellows to beta test the current training module that was developed by **Shai Silberberg** (extramural program director in the National Institute of Neurological Disorders and Stroke) and then participate in focus groups to help us determine how to make this module more effective and user-friendly. Eventually we also expect to have, as part of the overall training in research integrity, a sophisticated course in experimental design. Our scientific directors have given strong support to training that improves the integrity and reproducibility of our science, and we trust that all of our staff will benefit from exposure to this training experience.

Another area that concerns me is the possibility for errors in interpreting data obtained from advanced technologies such as high-resolution structural models from nuclear magnetic resonance, crystallographic, mass spectroscopic, and cryo-electron microscopy data; high-resolution cell imaging and cell-based fluorescence resonance energy transfer and fluorescence-activated cell-sorting analyses; and studies using specialized cell lines and antibodies.

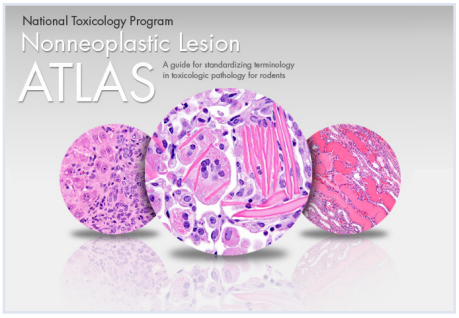
Intramural NIH is fortunate to have world-class experts in these technologies. I have assembled a committee that will help educate us about them. We are planning a one-day workshop at NIH—"New Advances in Structural and Cell-based Analyses: Potential and Pitfalls"—that should attract our trainees and staff to hear about the latest advances and the kinds of reproducibility problems that can arise. The workshop will also include our extramural academic and industrial colleagues and representatives from journals and professional societies, all of whom share concerns about data reproducibility. The goals are to educate researchers about what these techniques can accomplish; provide a cautionary note to scientists who are inexperienced in using these techniques but who plan to use them; and educate others who are reading results in the literature. A white paper and videos of the presentations will be made available for our staff and our extramural colleagues.

NIH Principal Deputy Director **Larry Tabak** has taken the lead in assembling a toolkit of approaches to enhance reproducibility and transparency of research findings. NIH institutes and centers are undertaking multiple pilots, including efforts to study and reduce factors that may motivate careless publication including "perverse incentives" (the promise of promotion, tenure, and, in rare instances, cash rewards to researchers who publish in certain journals) related to publication and funding.

NIH is also addressing the problem by altering the format of the "biographical sketch" that grant applicants must complete. The proposed format will emphasize the significance of advances resulting from the work and reflect individual contributions to successful research projects.

We are hoping that intramural NIH can help pilot important educational materials as they become available and lead the way in promoting reproducibility in research results. As always, your suggestions about how best to achieve these important goals would be welcome. ●

You might also be interested in reading a recent *Nature* article—"NIH Plans to Enhance Reproducibility"—that was co-authored by NIH Director Francis Collins and Lawrence Tabak (*Nature* 505:612–613, 2014).



NIEHS

New Online Resource

Nonneoplastic Lesion Atlas

BY ROBIN MACKAR, NIEHS

Having trouble determining exactly what kind of lesion a mouse or rat has? You no longer need to hold a magnifying glass over your old hardcover textbook. Instead you can consult a new online resource—the *Nonneoplastic Lesion Atlas*—to gain access to thousands of high-quality images and guidelines for the diagnosis of nonneoplastic lesions in experimental rodent models.

Developed by the National Toxicology Program (NTP), an HHS interagency program housed at the National Institute of Environmental Health Sciences (NIEHS), the atlas is a searchable Web-based guide that helps standardize lesion diagnosis, terminology, and documentation.

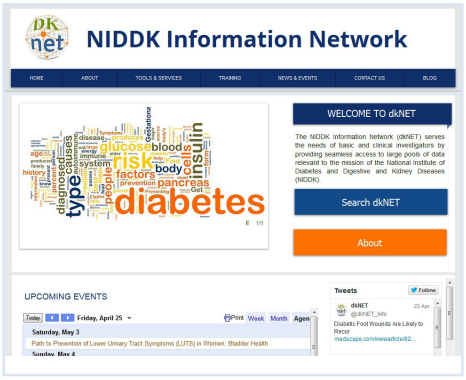
Nonneoplastic lesions are tissue changes that are pathological but not cancerous. Many nonneoplastic lesions occur normally with age, but they can become more pronounced when exposed to chemicals or other environmental agents. Such exposure complicates the diagnostic process; pathologists often differ in their opinions on how to describe or define particular lesions. Because many of these lesions have counterparts in NTP's toxicity and carcinogenicity studies, the atlas is a useful resource for the entire biomedical community.

"This atlas was developed as a resource that can be used as a teaching tool and as a reference for anyone who reads [or is involved in] NTP studies," said NTP Associate Director **John Bucher**. Standard guidelines that are readily available to pathologists are essential for evaluating noncancer findings in animal studies.

The atlas includes five anatomical systems—hematopoietic, or blood; hepatobiliary, which includes gall bladder and liver; integumentary, or skin; nervous; and urinary—and will eventually contain eight systems and 56 sections that each focus on a particular organ or tissue.

"Having a resource that toxicologists and pathologists all over the world can use to speak the same language when diagnosing nonneoplastic lesions in rats and mice will be invaluable to NTP and to the field," said **Robert Sills**, head of the NTP Cellular and Molecular Pathology Branch. Sills conceived the atlas and worked with his team to bring the project forward.

To find out more about NTP's *Nonneoplastic Lesion Atlas*, go to http://ntp.niehs.nih.gov/nnl. ●



dkNET

One-stop Shopping for Biomedical Resources

BY AMY F. REITER, NIDDK

Want a one-stop Web-based "shop" for finding biomedical resources such as data, reagents, organisms, and tools? The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has created one: the NIDDK Information Network (dkNET), which allows all intramural investigators to simultaneously search multiple databases that may be difficult to find using regular search engines. The information in dkNET is relevant to anyone interested in doing research on kidney, urologic, hematologic, digestive, metabolic, and endocrine diseases; diabetes; and nutrition.

"Scientists generate enormous amounts of data, but often there is no coherent means for finding it," said NIDDK program director **Ronald Margolis**, who is leading the dkNET effort. "dkNET uses advanced informatics tools to establish an online 'data-mart' for NIDDK investigator-generated data."

Launched in April, NIDDK–along with researchers at the University of California, San Diego (UCSD) and elsewhere–created dkNET as a catalog of NIDDK-supported online resources. dkNET contains information on some 1,900 resources, including links to such digital networks as the Nuclear Receptor Signaling Atlas, the GenitoUrinary Molecular Anatomy Project, and the Diabetic Complications Consortium.

Until recently, there has been "no good way of tracking and making collectively searchable all of the existing digital resources," said UCSD neuroscientist Maryann Martone, who is one of the dkNET architects. She helped develop SciCrunch—a Web structure that allows researchers to cost-effectively build and share data repositories—which is now serving as the backbone for dkNET.

Sharing data and tools will enrich the research landscape in serendipitous ways, according to Margolis. "Researchers will be able to compare their data [with] already existing data and to validate their research, add to the existing store of knowledge, [and] generate new ideas."

The site is easy to navigate, includes tutorials, and even has online "office hours" to answer user questions. To find out more, go to http://dknet.org. ●

SPECIAL FROM THE FELLOWS AT NIAID

Fellows Advised to Seize Unexpected Opportunities...and Even Fake It?

BY REBECCA BAKER, OD

Learn what you love, get involved with interesting opportunities outside the lab, and integrate your life with your career goals. That was the message to postdoctoral fellows at the National Institute of Allergy and Infectious Diseases (NIAID) who attended an annual retreat recently.

The retreat, held in the Cloisters (Building 60) on May 12, was led by NIAID Fellows Advisory Committee co-chairs **Shu Hui Chen** and **Kristen Kindrachuk** and the director of NIAID's Office of Training and Diversity, **Wendy J. Fibison**. The retreat offered advice on such topics as communication; building a professional network; charting a unique career path; focusing on transferrable skills; and building new areas of experience through short-term detail assignments.

Keynote speaker Peter Fiske, a nationally recognized author and lecturer on leadership and career development for young scientists and engineers, presented "Putting Your Science to Work: Career Strategies for Early-Career Scientists" and "The Neuroscience of Selling." He addressed the antipathy scientists often feel about selling themselves and cited research from 2002 Nobel-prize winner Daniel Kahneman, which shows that most decisions are based on rapid and intuitive thinking and not on the logical and deliberate thinking methods cultivated by scientists. Effective communication addresses both kinds of thinking. High-impact presentations, Fiske pointed out, tell a story that makes the scientist appear trustworthy, authoritative, interesting, sympathetic, safe, and funny and are targeted to the personality and needs of the audience.

But what about scientists who feel they can't sell themselves? Fiske's advice was to practice their presentations and, surprisingly, to "fake it." According to Harvard social scientist Amy Cuddy, individuals can fool themselves as well as others into thinking they feel calm and powerful just by adopting certain physical postures.

Fiske also offered fellows a rousing round-up of their skills: the capacity for deep thought; the ability to give and accept criticism; a knack for problem-solving; a talent for public speaking, communication, and persuasion; and the ability to work in situations where there is ambiguity.

He warned, however, that "the curse of being smart" can limit scientists who are too narrowly focused, who are averse to risk or failure, or who can't understand the intelligence of other types. Because they are keenly aware of the difficulties of pursuing the academic career path, scientists often act out of anxiety rather than self-confidence when seeking careers outside the lab. Fiske encouraged fellows to find a job that's the best fit for them by identifying not only their skills, but also their values and interests.

Echoing this advice, NIAID Scientific Director **Kathryn Zoon** highlighted the unpredictable turns her own career has taken. Her work, she said, has been driven in unexpected ways by technological developments, new laws governing recombinant DNA technology, the serendipity of working in a lab that identified and characterized interferon, and the recognition that interferon could be valuable as a therapeutic. She attributes her success to her willingness to embrace unexpected opportunities.

Zoon acknowledged the tough realities that trainees face: having to compete in a crowded field of Ph.D. scientists; enduring a long training time; and not being adequately prepared for careers outside of academia. But she went on to list the many career opportunities—both at and away from the bench—at NIH that are available to fellows: staff scientists, staff clinicians, statisticians, epidemiologists, scientific review officers, tenure-track and tenured scientist positions, and policy and administrative positions. She reminded fellows to seek the help of their mentors and emphasized that mentors' jobs are not to build armies of "mini-me's," but rather to help trainees identify and make progress toward their career goals.

Workshop panelists suggested that fellows find volunteer opportunities both in and outside of NIH in order to gain new experiences and document interests and skills. Trainees were also urged to expand their networks by conducting informational interviews and finding many mentors in their current field as well as the field they wish to enter.

The workshop's refrain: NIH is the best place to be a fellow, with opportunities everywhere just waiting to be seized. ●

BILL BRANSON

NIAID fellows attended a retreat recently that offered advice on being effective communicators, networking, and charting a unique career path. Here, several retreat participants are practicing their networking skills: (from left) **Rebecca Baker**, **Jessica Chertow**, and **Yolanda Williams-Bey.**

Rebecca Baker was a postdoctoral fellow in NIAID (2010–2014) and is now a health-science policy analyst in the Office of Clinical Research and Bioethics Policy in NIH's Office of the Director.

Getting the Most Out of Your NIH Training Experience

An Interview with FelCom Co-Chairs Kenneth E. Remy, M.D., and Lucie A. Low, Ph.D.

BY PATRICIA FORCINITO (NIDCR) AND WENDY KNOSP (NIDCR)

This year, the Fellows' Committee (FelCom) is run by co-chairs **Kenneth E. Remy** and **Lucie A. Low,** who respectively represent the clinical- and basic-science fellows. Remy arrived at the NIH in 2011 as an adult-critical-care clinical fellow after completing a three-year pediatric-critical-care fellowship at Columbia University (New York) with a research interest in sepsis. His leadership experience as president of the National Internal Medicine–Pediatrics Residents' Association made him a natural choice for the Clinical FelCom co-chair position to which he was elected in 2012.

Low came to the NIH in 2012 as a visiting fellow at the National Center for Complementary and Alternative Medicine, where she studies the neuroscience of chronic pain. She has a strong background in leadership and communications and was the vice president of finance for the Canadian Association of Postdoctoral Scholars as well as a *Nature* magazine careers columnist (2011–2012). Shortly after her arrival at the NIH, Low was elected as the FelCom Basic Science co-chair.

The *NIH Catalyst* interviewed Remy and Low recently. The following is a lightly edited transcript of their remarks.

WENDY KNOSP, NIDCR

FelCom co-chairs Ken Remy (left) and Lucie Low are enthusiastic about what FelCom can do for fellows.

CATALYST: What does it take for a FelCom co-chair to be successful?

KR: You need to be able to advocate for yourself as well as for all NIH fellows in an appropriate manner. To be successful you must think critically, take initiative, effectively communicate your innovative ideas, and be a team player.

LL: Success requires good organizational and communication skills and the ability to be a good listener. It is important to advocate for yourself and for the group you represent with appropriate initiative and tact.

CATALYST: Why should fellows join FelCom?

LL: FelCom is the voice of the fellows. It has the power to get attention and be heard as we advocate for fellows' rights. Here you will find people who can help you. If you get involved, you will gain transferrable and marketable skills to help you in your next career move.

KR: FelCom represents over 3,000 NIH fellows who are performing cutting-edge experiments, providing high-quality patient care, and identifying areas for improvement in these endeavors to improve the health of the country. FelCom provides opportunities for clinical- and basic-science fellows to interact, bringing bench science and patient care together, allowing for the cross-pollination of ideas, and making exciting discoveries. FelCom provides a unique opportunity to enhance your NIH experience and take an active role in helping improve the system.

CATALYST: What's next in your careers?

KR: I plan to pursue my research interests in red-blood-cell "storage lesion" (deterioration in red blood cells during storage), host response, and sepsis. I want to continue as a physician–scientist in an academic medical center and do research, practice adult- and pediatric-critical-care, and teach.

LL: I'm still exploring my options and deciding whether to attempt to get a faculty position and continue doing the research I love, or pursue other options.

CATALYST: What advice do you have for fellows?

LL: Speak up; get involved; make your training experience what you want it to be. FelCom has a lot of resources to help you and point you in the right direction.

KR: Explore and meet folks outside of your lab. Consider having a few advisors to help you along your desired career path.

CATALYST: What do you do for fun?

LL: I'm a member of the NIH Sailing Association, I go skydiving every weekend, and I am training for "Tough Mudders" obstacle races. I enjoy challenges!

KR: I am happily married with a two-year-old daughter and twins on the way. If I had more time I would play music, act, dress as a clown and visit hospital patients, play sports, do another medical mission (I am the ICU captain for Heart Care International and travel twice a year to Peru), or get more involved in my church.

CATALYST: Is there anything about you that would surprise people?

LL: I used to be a semiprofessional singer. If I weren't a scientist, I'd like to be a Ninja or an astronaut.

KR: I was an actor and musician in a former life and founded a very successful organization called Clowns for Medicine. ●

Read more online at http://irp.nih.gov/catalyst/v22i4/felcom-getting-the-most-out-of-your-nih-training-experience

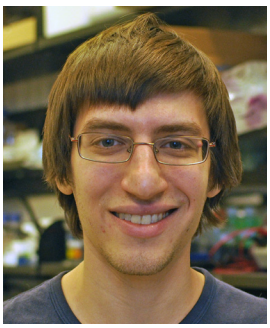
NIH's First Intramural Early Independent Scientists

Greg Alushin (NHLBI) and Donna Calu (NIDA) Speak Out

BY RACHEL SCHEINERT, NIMH

Greg Alushin (NHLBI) and Donna Calu (NIDA) are the first two *intramural* scientists to receive the NIH Director's Early Independence Award. The award—which has been in existence since 2011 and has traditionally been given to *extramural* investigators—is an opportunity for young scientists, who have recently received their doctoral degree or finished medical residency, to skip the postdoctoral years of training and advance directly into an independent research career. The NIH Common Fund provides each independent scientist with funding up to $250,000 in direct costs per year for five years.

The following is a lightly edited version of interviews the *NIH Catalyst* conducted with Alushin and Calu.



GREG ALUSHIN, PH.D.
Early Independent Scientist
Laboratory of Macromolecular Interactions, Cell Biology and Physiology Center, National Heart, Lung, and Blood Institute
Education: B.A. in biochemistry from Columbia University (New York); Ph.D. in biophysics from the University of California, Berkeley

How did you become interested in macromolecular interactions?

Steven Almo at the Albert Einstein College of Medicine in the Bronx introduced me to the idea that most things happening inside of a cell are orchestrated by groups of macromolecules—mostly protein-protein interactions. I found it exciting and fascinating that a relatively limited number of "ingredients" encoded in the genome could provide such diversity in biology.

What was your earlier research?

In graduate school I studied the interaction of kinetochore complexes with microtubules. One complex called NDC80 [kinetochore complex] is found in all eukaryotes. Using structural methods, I figured out how it binds microtubules and how that interaction can be regulated.

What is your current research focus?

I came here to do a postdoc with **Clare Waterman**. While I was in her lab I became more interested in the actin cytoskeleton. The structural transitions in actin may have a role in responsiveness to forces. We're trying to understand whether tension introduces a conformational change in actin and then what is the meaning of that for a cell.

Are you collaborating with anyone?

I am still collaborating with Clare, my mentor. We are also collaborating with **Jim Sellers**, trying to introduce tension into actin filaments. My other main collaboration is with Sharon Campbell at the University of North Carolina (Chapel Hill, North Carolina). We are working on the interactions of a particular focal adhesion protein, vinculin.

What made you apply for the Early Independence Award?

Clare really encouraged me. I think it allowed me to get to my long-term goal to incorporate structural biology and cell biology much more quickly than I would have otherwise.

What advice would you give someone who wishes to follow your path?

You have to have that entrepreneurial spirit. Independent research is a major undertaking, so you have to really know what you want to do. For me it was really important to work out arrangements with different people to get access to equipment and expertise.

What is your next scientific or career goal?

I would like to become a full professor or the equivalent here. Scientifically, my long-term goal is to understand what it is that makes the interactions between proteins so important for organizing a cell in allowing it to be alive. It's a really big question.

What has been your proudest moment so far in your scientific career?

For me, the discoveries are definitely the most exciting thing. I just had a paper published in *Cell* based on my work at the end of graduate school with Eva Nogales at the University of California at Berkeley. We figured out a conformational change that occurs in tubulin when it hydrolyzes [guanosine-5'-triphosphate] inside the microtubule. And getting this [Early Independence] award was a great honor.

What are your interests outside the lab?

Climbing is my main hobby. I started rock climbing, ironically, after I moved away from the West Coast. My fiancée got me into it about a year ago. Now, I climb with a couple of other people from NIH. It's a fun challenge.

DONNA CALU, PH.D.
Early Independent Scientist
Neurophysiology of Reward Seeking Section, Behavioral Neuroscience Research Branch, National Institute on Drug Abuse (Baltimore)
Education: B.S. in neurobiology and physiology from University of Maryland (College Park, Md.); Ph.D. in neuroscience from the University of Maryland School of Medicine (Baltimore)

How did you become interested in behavioral neuroscience?

My passion for understanding the brain mechanisms underlying associative learning likely stems from my experience as a young adult working with children both with and without learning disabilities. Observing how these children learn about their environments led me to ask questions about how the brain encodes and supports learned behaviors.

What was your research before you came to NIH?

During graduate school I became fascinated by the way in which the brain controls behavior. Using predictions derived from classic learning theories, I sought to understand how brain activity could mediate simple associative-learning processes.

What made you apply for the Early Independence Award?

As a graduate student and postdoc I was given the freedom to explore my research interests with a considerable amount of independence. My mentors, by giving me this flexibility so early in my career, have facilitated this unique opportunity for me to pursue the route of early independence. I am tremendously thankful for their ongoing support.

What made you decide to come to NIH?

I was drawn to the opportunity to address my research questions alongside the leaders in the addiction field, using groundbreaking techniques such as in vivo electrophysiology and optogenetics. The resources coupled with NIDA's highly collaborative environment have made it a fantastic place to enhance my training while starting a lab.

What is your current research focus?

The aim of our research is to identify the neural correlates and brain mechanisms underlying individual differences in reward learning and motivation. The goal is to understand how these processes may be involved in or predictive of addiction-related behaviors. We combine modern techniques including in vivo electrophysiology, optogenetics, and molecular and transgenic methods with classic behavioral procedures in order to examine in real time the contribution of brain reward circuitry in driving learning and motivational processes.

Ultimately, we seek to understand how individual differences in learning-associated neural correlates (evident prior to drug exposure) may predict drug-seeking behavior and to determine how drugs of abuse influence these brain mechanisms to shape addiction-related behaviors.

What is most exciting about your work?

By combining in vivo electrophysiology with optogenetics, we can first identify brain signals that correlate with observed behavior. Then, by silencing endogenous neural activity and observing changes in behavior, we can directly test the role those signals play in learning. It's exciting to watch neurons in the brain fire in real time as rats experience surprising rewards. I also enjoy analyzing the neural data to understand how the brain encodes meaningful environmental events.

What has been your proudest moment so far in your scientific career?

The moment I finished presenting my public thesis defense. Looking out and seeing my family, friends, and colleagues there to share that moment with me, I was overwhelmed with feelings of accomplishment and gratitude. That moment will be hard to top.

What is your advice to other young scientists?

Be patient and savor the little victories along the way.

What is your next scientific or career goal?

I very much enjoy the line of research we are currently pursuing in my lab, and I plan to continue to follow the data in order to examine emerging questions.

What are your interests outside the lab?

I love spending time with my children and my family, listening to music, dancing, and enjoying the outdoors. ●

For general information about the NIH Director's Early Independence Award, go to http://COMMONFUND.NIH.GOV/EARLYINDEPENDENCE/INDEX. For details on how intramural scientists can apply, contact Charles Dearolf (dearolfc@mail.nih.gov or 301-402-1225). Note: Alushin was also recently named to the *Forbes* List of 30 Under 30 (http://www.irp.nih.gov/catalyst/v22i3/world-changers).

Intramural Research Briefs

NIAID: PARASITE LEVELS IN BLOOD DO NOT DETERMINE SEVERITY OF MALARIA

Although malaria kills some 600,000 African children each year, most cases of the mosquito-borne parasitic disease in children are mild. Repeated infection does generate some immunity, and episodes of severe malaria are unusual once a child reaches age 5. However, the relative contributions of such factors as the concentration of malaria-causing parasites in a person's blood—parasite density—to disease severity and to development of protective immunity are not well understood.

Researchers from NIAID and Tanzania regularly examined 882 Tanzanian children beginning at birth and continuing for an average of two years. No simple relationship between parasite density and malaria severity emerged. Moreover, data from this study suggest that one or two mild episodes of malaria are not sufficient to eliminate the risk of severe malaria, a finding contrary to predictions made by some mathematical models. The researchers note that this prospective study is the first to provide direct evidence that severe malaria risk is stable over several infections. The findings suggest a new approach to malaria vaccine development based on naturally acquired immunity. Such a vaccine would prevent severe disease and death in children, without necessarily reducing exposure to the malaria parasite. (NIAID authors: B.P. Gonçalves, C.-Y. Huang, D.R. Prevots, M. Fried, and P.E. Duffy, *N Engl J Med* **370**:1799–1808, 2014)

NIDA: THE DRUG ECSTASY CAN BE FATAL

A moderate dose of 3,4-methylenedioxymethamphetamine (MDMA), commonly known as Ecstasy or Molly, which is typically nonfatal in cool, quiet environments, can be lethal in rats exposed to conditions that mimic the hot, crowded social settings where the drug is often used by people, according to a study conducted by NIDA scientists.

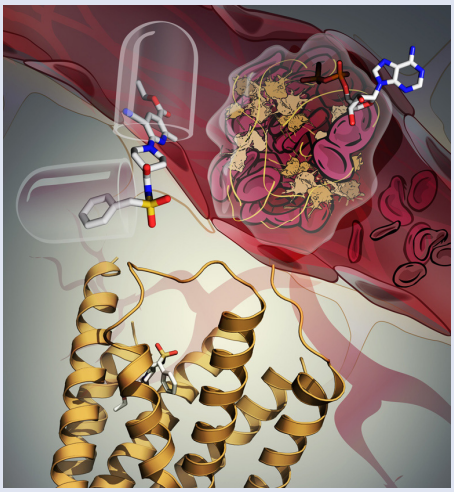
When rats were alone and in a room-temperature environment, a moderate dose of MDMA modestly increased brain and body temperature and moderately diminished the rats' ability to eliminate excessive heat. However, when researchers injected the same dose into rats that were either in a warmer environment or in the presence of another rat in the cage, brain temperature increased, causing death in some rats. These fatal temperature increases were because the drug interfered with the body's ability to eliminate heat.

These findings suggest that medical interventions aimed at increasing the efficiency of whole-body cooling by targeting blood-vessel constriction in the skin could be therapeutically relevant for counteracting the development of MDMA-induced hyperthermia. (NIDA authors: E.A. Kiyatkin, A.H. Kim, K.T. Wakabayashi, M.H. Baumann, and Y. Shaham, *J of Neurosci* **34**:7754–7762, 2014)

NIDCR, NIAID: TGF-BETA REGULATES IMMUNE-SYSTEM BALANCE

Without regulatory T cells (Treg cells), you'd likely die from out-of-control inflammation. Treg cells prevent your immune system from attacking your own tissues. NIH scientists reported that they've figured out that the indispensable ingredient for making Treg cells in the thymus is transforming growth factor–beta (TGF-beta).

By understanding the pathways and molecular players involved in Treg-cell function, scientists might one day be able to develop therapies for people with oral cancer or other types of cancer, or autoimmune diseases, such as Sjögren syndrome and multiple sclerosis. (NIDCR authors: J.E. Konkel, W. Jin, B. Abbatiello, W. Chen; NIAID author: J.R. Grainger, *Proc Natl Acad Sci U S A* **111**:E465–73, 2014)



KATYA KADYSHEVSKAYA, SCRIPPS RESEARCH INSTITUTE

The P2Y12 receptor (ribbon) plays a key role in blood-clot formation: When it is stimulated by an ADP molecule, blood platelets cluster and clots form (top right). NIDDK scientists discovered that the receptor's three-dimensional structure undergoes pronounced rearrangement when its function is blocked by an antithrombotic drug (upper left).

NIDDK: STRUCTURE OF BLOOD-CLOTTING RECEPTOR IDENTIFIED

NIDDK scientists were part of a team that published two papers in *Nature* describing the discovery of the three-dimensional structure of a receptor that plays a key role in blood clotting. When the receptor, named P2Y12, is stimulated by adenosine diphosphate (ADP) molecules, platelets cluster and a thrombus forms. The receptor is one of the most prominent clinical drug targets for the inhibition of platelet aggregation. But, until now, scientists have not understood how the receptor works. The study indicates that the P2Y12 receptor's structure undergoes a pronounced rearrangement when the ADP is replaced by an antithrombotic drug.

Antithrombotic drugs limit the formation of blood clots that can lead to heart attacks and strokes. Understanding how the P2Y12 receptor responds to drug molecules is the first step toward improving antithrombotic drugs and developing potential treatments for nervous system disorders, chronic pain, and other conditions. (NIDDK authors: Z. Gao, S. Moss, S. Paoletta, E. Kiselev, K. Jacobson, *Nature* **509**:115–118, 2014; NIDDK authors: Z. Gao, S. Paoletta, K. Jacobson, *Nature* **509**:119–122, 2014) ●

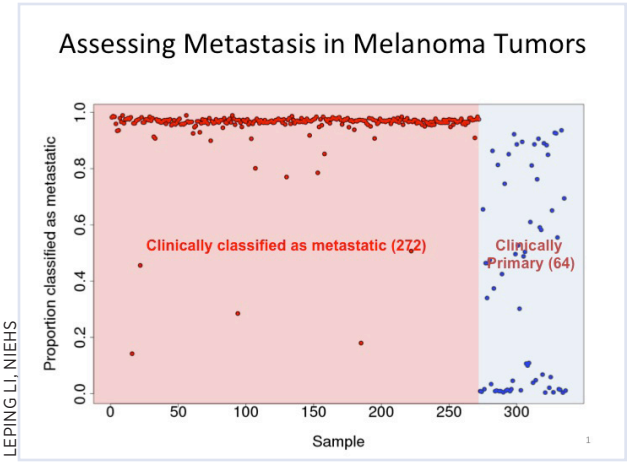
CONTRIBUTORS: KRYSTEN CARRERA, NIDDK; GERIANN PIAZZA, NIDCR

Read more online at http://irp.nih.gov/catalyst/v22i4/research-briefs.

New Software Program Evaluates Potential for Metastasis

NIEHS Scientist Leping Li Develops New Approach for Classifying Cancer Cells

BY ROBIN ARNETTE, NIEHSS



LEPING LI, NIEHS

Assessing Metastasis in Melanoma Tumors: Leping Li (NIEHS) analyzed gene-expression data from 336 TCGA melanoma samples using the new GA/KNN software program. Nearly all of the 272 clinically classified metastatic tumors were scored as likely to be metastatic, while the 64 primary tumors separated into three categories: one-third had characteristics like metastatic tumors, one-third correlated with primary tumors, and one-third fell somewhere in-between.

Pathologists have traditionally used the physical characteristics of melanoma cancer cells to classify them as primary or metastatic. Recently, however, computational biologist **Leping Li** at the National Institute of Environmental Health Sciences (NIEHS) developed another approach to classifying the cancer cells.

Melanoma is the most serious type of skin cancer and develops in the pigment-producing melanocytes in the basal layer of the epidermis. Primary melanoma represents the original site of the tumor; the metastatic form means the tumor has spread and has become life-threatening.

Li has developed an algorithm, based on gene-expression data, that evaluates each tumor's resemblance to metastatic tumors. He presented his work as part of the NIH Director's Seminar Series, April 4, on NIH's Bethesda campus.

It all started in 2000, when Li was a member of the NIEHS Laboratory of Structural Biology. He and several senior researchers wrote a software program called Genetic Algorithm/K-Nearest Neighbor (GA/KNN), a classification tool for categorizing genes found by microarray analysis (*Bioinformatics* **17:**1131–1142, 2001).

Li offered the program on his Web site as freeware (http://1.usa.gov/1olDU75) and soon after joined the NIEHS Biostatistics Branch, receiving tenure in 2012.

In the fall of 2013, Li was examining *The Cancer Genome Atlas* (*TCGA*), a cancer database funded and managed by the National Cancer Institute and the National Human Genome Research Institute. As he looked at the gene-expression and mutation data for a variety of tumor types, he realized the tools he developed back in 2000 could be applied to the new, more accurate NextGen Sequencing data.

"What if the clinical classification says one thing," Li began, "but the gene-expression data [say] something else?"

Li made several modifications to the GA/KNN software and decided to test it on melanomas because they are highly metastatic. He analyzed gene-expression data from 336 *TCGA* melanoma samples: 272 were clinically classified as metastatic and 64 as primary.

Ninety-eight percent of the 272 metastatic tumors displayed gene-expression patterns that were similar to one another. But to his surprise, nearly two-thirds of the nonmetastatic primary melanomas exhibited expression patterns that were typical of metastasis.

In addition, the updated GA/KNN revealed 39 genes that seemed to be taking part in metastasis. During the tumors' switch from primary to metastatic, the genes' expression levels either increased or decreased, suggesting that these genes take part in metastasis. Most of them are known to be involved in ectoderm and epidermis development. Several others haven't been reported in the literature and form the basis of Li's research.

"Our analysis may provide useful information for treatment and disease management for melanomas in the future," Li said. "It may also offer insight into the molecular mechanisms that underlie metastasis."

Although the newer version of GA/KNN isn't publically available yet, Li's software tweaks will give researchers another tool in the fight against cancer, said NIEHS Biostatistics Branch Chief **Clarice Weinberg**, who helped create the original computer program.

"Leping's creative development of algorithms may provide important clues based on mining gene-expression data," she said. They "could ultimately give clinicians a way to focus on the most dangerous cancers." ●

LEPING LI, NIEHS

To see a videocast of Li's presentation, "Gene Selection and Sample Classification with Applications to TCGA Data," at the April 4, 2014, NIH Director's Seminar Series, go to http://videocast.nih.gov/launch.asp?18378. For more on Li's work, visit http://irp.nih.gov/pi/leping-li.

NIH Microscopy at Dulles Airport

CONTINUED FROM PAGE 1

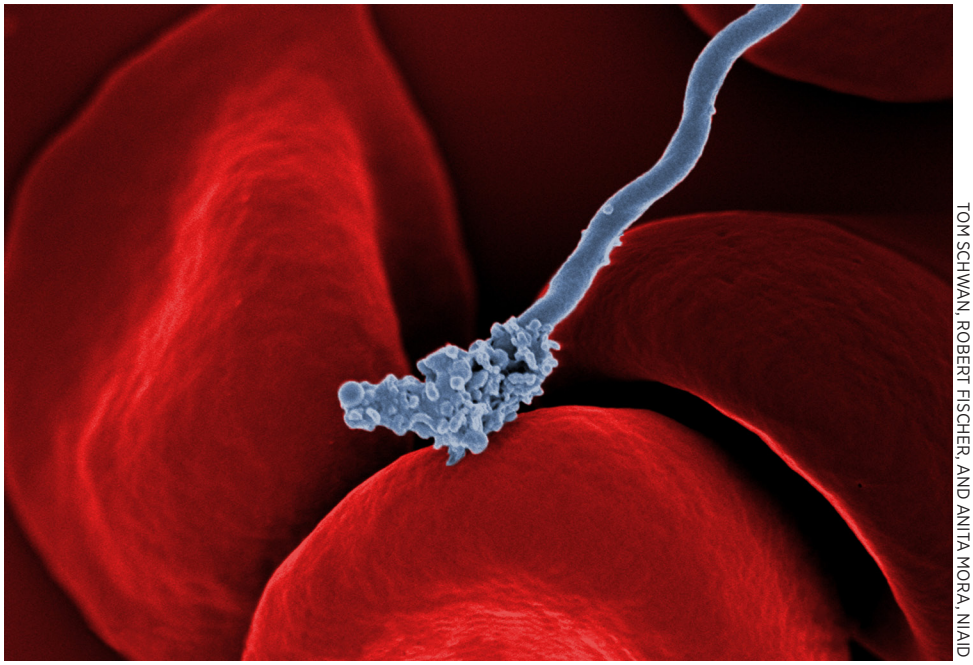
Washington Airports Authority's Arts Program. More than a million ticketed travelers will see the exhibit at Dulles. It's likely that even more people will see it on a screen. The online version of *Life: Magnified* is at http://www.nigms.nih.gov/education/life-magnified/, where users can read enhanced captions and freely download high-resolution versions of all of the images for research, education, and other noncommercial purposes.

In addition, news of the exhibit has been picked up by various scientific journals and media outlets including the *Washington Post*, *Scientific American*, *National Geographic*, *The Atlantic*, *NBC News Online*, and even *BuzzFeed* and *My Modern Met*.

Of the 46 images in the collection (selected from more than 600 submissions), 11 are from intramural labs: National Institute of Allergy and Infectious Diseases (NIAID); Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); National Heart, Lung, and Blood Institute (NHLBI); and the National Eye Institute (NEI). About 20 different organisms are represented in the exhibit, including humans, common biomedical models, a few more exotic creatures—a gecko, an anglerfish, and a lone star tick—and eight pathogens.

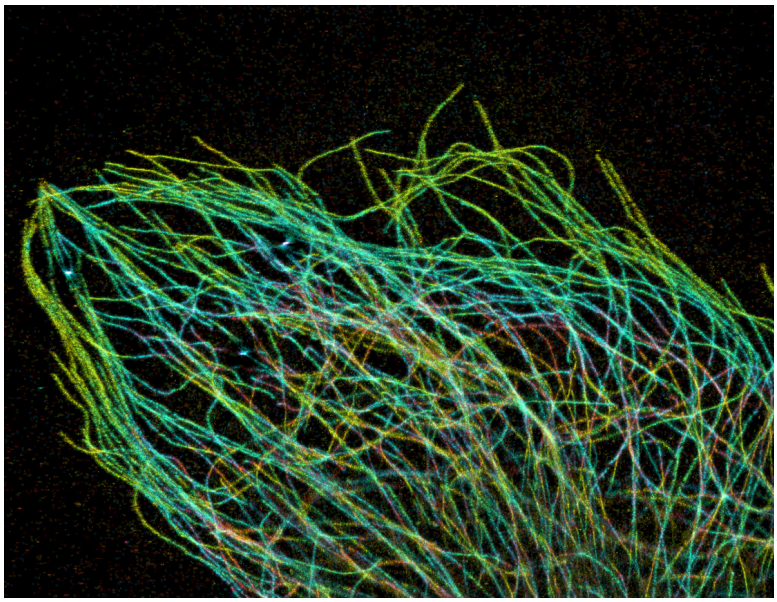
The exhibit organizers hope that after the exhibit is over, some of the images will be displayed on the NIH campus.

The following images are among those produced by the NIH intramural program.



TOM SCHWAN, ROBERT FISCHER, AND ANITA MORA, NIAID

Relapsing fever bacterium on red blood cells: The long, spiral-shaped bacterium in this image causes relapsing fever, a disease characterized by recurring high fevers, muscle aches, and nausea. The relapses result from the bacterium's unusual ability to change the molecules on its outer surface, allowing it to dodge the human immune system. The disease is transmitted through the bite of a tick (not the same species that transmits Lyme disease) and is found in parts of the Americas, the Mediterranean, central Asia, and Africa.



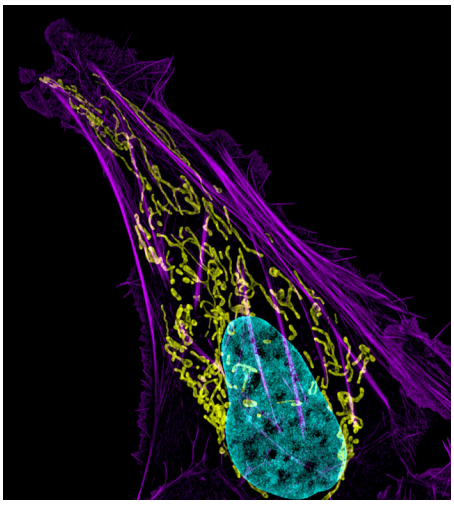
AKORN KANCHANAWONG AND CLARE WATERMAN, NHLBI

Tiny strands of tubulin, a protein in a cell's skeleton: Just as our bodies rely on bones for structural support, our cells rely on a cellular skeleton. In addition to helping cells keep their shape, this cytoskeleton transports material within cells and coordinates cell division. One component of the cytoskeleton is a protein called tubulin, shown here as thin strands.

See all the intramural images, in color, in the online edition of the *NIH Catalyst* at http://irp.nih.gov/catalyst/v22i4/nih-microscopy-lights-up-dulles-airport.

B. JOSEPH HINNEBUSCH, ELIZABETH FISCHER, AND AUSTIN ATHMAN, NIAID

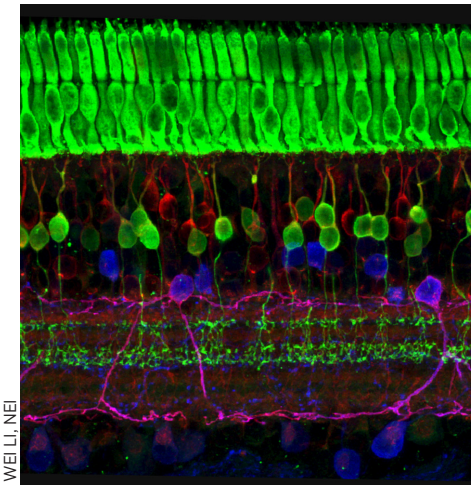
Bubonic plague bacteria (fluffy shapes) on part of the digestive system in a rat flea (banana-like shapes): Here, bubonic plague bacteria are shown in the digestive system of a rat flea. Carried by rodents and spread by fleas, the bubonic plague killed a third of Europeans in the mid-14th century. Today, it is still active in Africa, Asia, and the Americas, with as many as 2,000 people infected worldwide each year. If caught early, bubonic plague can be treated with antibiotics.



D. BURNETTE AND J. LIPPINCOTT-SCHWARTZ, NICHD

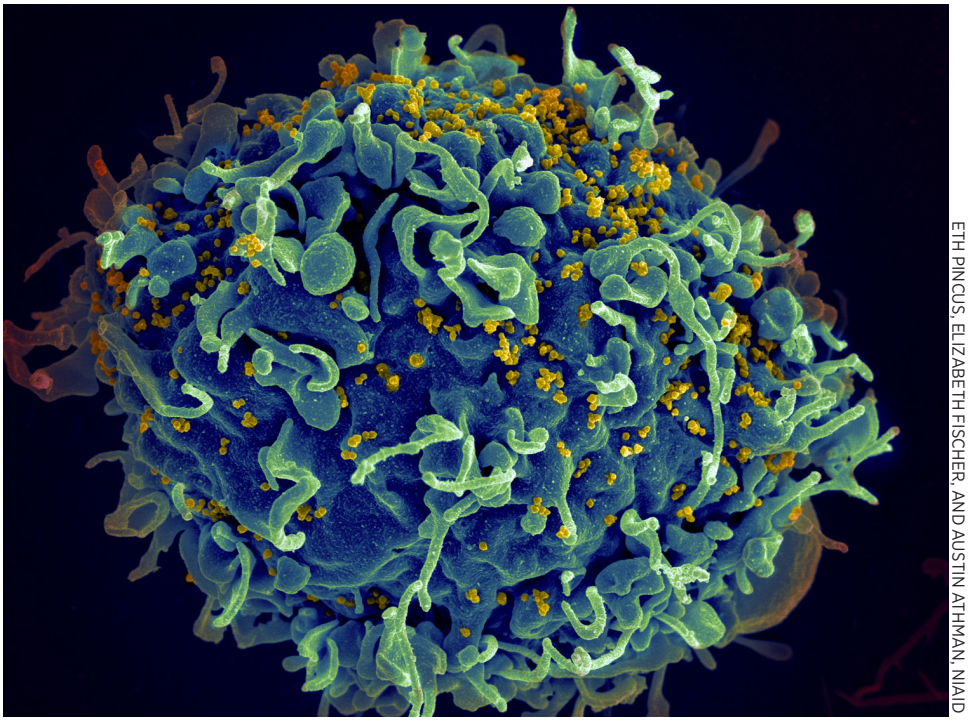
Bone cancer cell (nucleus as ovoid shape): This image shows an osteosarcoma cell with DNA (dark spots in nucleus), mitochondria (spiral shapes), and actin filaments (hairlike strands flanking the mitochondria). One of the few cancers that originate in the bones, osteosarcoma is extremely rare, with fewer than a thousand new cases diagnosed each year in the United States.

See all the intramural images in color at http://irp.nih.gov/catalyst/v22i4/nih-microscopy-lights-up-dulles-airport.



WEI LI, NEI

The eye uses many layers of nerve cells to convert light into sight: This image captures the many layers of nerve cells in the retina. The top layer is made up of cells called photoreceptors that convert light into electrical signals to relay to the brain. The two best-known types of photoreceptor cells are rod- and cone-shaped. Rods help us see under low-light conditions but can't help us distinguish colors. Cones don't function well in the dark but allow us to see vibrant colors in daylight.



ETH PINCUS, ELIZABETH FISCHER, AND AUSTIN ATHMAN, NIAID

HIV, the AIDS virus (tiny ball shapes), infecting a human cell: This human T cell is under attack by the human immunodeficiency virus (HIV), the virus that causes AIDS. The virus specifically targets T cells, which play a critical role in the body's immune response against invaders like bacteria and viruses.

Extending Organ Survival

A Path Toward Animal-to-Human Transplants

BY CRAIG HICKS, NHLBI

Genetically modified pigs may one day offer new hope to thousands of people waiting for heart transplants, thanks in large part to an NIH intramural research team led by **Muhammad Mansoor Mohiuddin** at the National Heart, Lung, and Blood Institute (NHLBI).

"At any given time, about 3,000 people are on the waiting list for a heart transplant," said Mohiuddin, who is chief of the Transplantation Section in NHLBI's Cardiothoracic Surgery Research Program. "But only 2,000 donor hearts become available each year. Human organs alone will never be able to meet this demand." Many people on the transplant waiting list will die before they receive a replacement heart, he said.

One day, clinicians may be able to transplant pig hearts into people either as a substitute for donor organs or as a "bridge" for patients awaiting a human heart transplant.

The use of animal organs in humans, or xenotransplantation, is a potential alternative to conventional transplantation of human donor organs. Artificial hearts might one day provide an alternative, but for now they pose risks such as blood clots, internal bleeding, infection, and mechanical malfunctions.

Pigs are an ideal source for xenotransplantation because their organs are similar in size to those of humans; there are fewer ethical issues because pigs are used for food; their breeding cycle is short; and it's relatively easy to genetically modify them.

But the pig and human immune systems are different—a pig heart would be rejected within minutes. Mohiuddin and his team, however, are using genetic engineering and specialized drugs to overcome this barrier.

The genetic modifications allowed the researchers to use novel drugs to suppress parts of the immune system. These drugs avoid complications associated with traditional pharmacological approaches to preventing rejection.

The research team collaborated with Revivicor Inc., a Virginia-based regenerative-medicine company, to develop a three-part approach: knocking out certain pig genes for an antigen that stimulates an immune response; inserting a human gene, *hCD46*, into the pig to prevent activation of the recipient's innate immune system that would otherwise kill heart-graft cells; and altering the genes responsible for proteins that prevent blood clots in pigs but are incompatible with human blood.

To test the pig hearts, the researchers placed each into a baboon's abdomen and surgically connected two major blood vessels from the pig heart with two corresponding abdominal vessels in the baboon. The transplanted heart beats but doesn't replace the baboon's heart. This procedure allowed the researchers to overcome known obstacles from graft rejection while minimizing the risk to the baboons. The baboon immune system is similar to that of humans.

Ethical considerations, federal law, and NIH policy require responsible care and use of research animals. Mohiuddin's team designed their studies to be sure the baboons survived even if the transplanted cardiac tissue was rejected.

ROBERT F. HOYT, NHLBI

NHLBI surgeon–researchers Muhammad Mohiuddin and Philip Corcoran are doing research that may one day allow clinicians to transplant genetically engineered pig hearts into humans.

In December 2013, Mohiuddin and his team were the first to demonstrate that interspecies transplanted hearts could survive more than a year in large animals; previously reported survivals were less than four months (*Am J Transplan* **14:**488–489, 2014; http://onlinelibrary.wiley.com/doi/10.1111/ajt.12562/full).

In April 2014, they further reported survival of 600 days (*J Thorac Cardiovasc Surg* DOI:10.1016/j.jtcvs.2014.06.002; http://dx.doi.org/10.1016/j.jtcvs.2014.06.002).

The next step, Mohiuddin said, is to fully replace a baboon's original heart with a genetically engineered pig heart. If he and his intramural colleagues are successful, they could pave the way for xenotransplantation clinical trials for heart patients. ●

Others involved in the research: NHLBI: Keith Horvath, Avneesh Singh, Philip Corcoran, and Robert Hoyt; NHLBI Animal Surgery and Resources, Office of Research Services, Division of Veterinary Resources (DVR): Marvin Thomas, Michael Eckhaus, Tannia Clark, Billeta Lewis, and DVR technicians.

BILL BRANSON

The K.T. Jeang Memorial Garden, named in honor of the late Kuan-Teh Jeang (NIAID), features this granite medallion that is inlaid with the logo of *Retrovirology*, an open-access journal he founded.

K.T. JEANG MEMORIAL AND GARDEN

On May 15, 2014, a memorial lecture was held to honor the memory of the late **Kuan-Teh Jeang**, the accomplished virologist who died in January 2013. Jeang was the chief of the Molecular Virology Section of NIAID's Laboratory of Molecular Microbiology. His research focused on gene regulation of the human immunodeficiency virus (HIV) and how human T-cell lymphotrophic virus type 1 (HTLV-1) causes leukemia. The lecture was given by Yuan Chang (University of Pittsburgh), who along with her husband and research partner, Patrick Moore, discovered the viral causes of four different human cancers. In 1994, the Chang-Moore lab identified and isolated Kaposi's sarcoma-associated herpesvirus, the cause of Kaposi's sarcoma, a cancer epidemic among HIV/AIDS patients. After the lecture, a ceremony was held to dedicate the Jeang Memorial Garden, located between NIH Buildings 31 and 6.

DATA SCIENCE

Welcome to **Philip E. Bourne**, Ph.D., NIH's first permanent associate director for data science. Based in the Office of the Director, he will lead an NIH-wide priority initiative to take better advantage of the exponential growth of biomedical research datasets, which are an area of critical importance to biomedical research.

Before coming to NIH, Bourne was at the University of California at San Diego (La Jolla, California), where he was the associate vice chancellor for innovation and industry alliances of the Office of Research Affairs and a professor in the Department of Pharmacology and the Skaggs School of Pharmacy and Pharmaceutical Sciences. He also was the associate director of the Research Collaboratory for Structural Bioinformatics Protein Data Bank.

Bourne's focus is on relevant biological and educational outcomes derived from computation and scholarly communication. He wants to further the free dissemination of science through new models of publishing and better integration and subsequent dissemination of data and results.

NIH BEAR

There was a lot of nervous (and frivolous) chatter throughout NIH and on Twitter on Thursday, June 19, when a 125-pound young-adult black bear (*Ursus americanus*) clambered up a tree near the Medical Center Metro station. Authorities erected a fence around the base of the tree and then fired rounds of miniature firecrackers in an effort to scare him down. When he finally climbed down, he scampered onto the wooded NIH campus (the fence was intended to steer him away from Rockville Pike traffic). He was located about 25 minutes later, shot by a trained wildlife biologist with a tranquilizer dart, and then loaded onto a stretcher and into a small truck. He was taken to a forest in western Montgomery County in Maryland and released. Somehow in all the fuss, he managed to find time to tweet about his experiences. You can find the tweets—and see whether he's still tweeting—on Twitter at @NIH_Bear. ●

NEWS FROM AND ABOUT THE NIH SCIENTIFIC INTEREST GROUPS

NEW SIG: MIND-BODY MODALITIES

The new Mind-Body Modalities (MBM) Scientific Interest Group (SIG) brings together scientists and clinicians who are interested in research in and the practice of mind-body modalities (including meditation, acupuncture, yoga, and Reiki). There is burgeoning interest and empirical support for the efficacy of mind-body modalities in improving health and well-being. Mind-body practices are also typically low-risk and applicable to both the prevention and the treatment of illness. In addition, mind-body practices raise interesting questions about the philosophy of science and epistemology.

The MBM-SIG will facilitate constructive dialogue and scientific and experiential inquiry about mind-body practices; discuss appropriate research and analytic methods to understand the mechanisms and efficacy of mind-body practices; and inspire active discussion about the epistemology and philosophy of science.

The SIG plans to hold monthly meetings that will include a brief demonstration of a mind-body practice, followed by a speaker presentation or a group discussion. Demonstrations will provide attendees some subjective experience with the technique so they will have a better basis for understanding its subjective effects. For more information join the SIG LISTSERV at MBM-SIG@list.nih.gov or contact Laura Case at laura.case@nih.gov.

NEW SIG: 3-D PRINTING AND MODELING

The 3-D Printing group provides information on 3-D printing and modeling resources, services, and technologies; offers a forum for the exchange of information and ideas; and promotes awareness of the benefits of 3-D printing technologies. The group will use a Web site (3Dprint.nih.gov) and LISTSERV to share digital models and disseminate information. Sponsors are NIAID's Bioinformatics and Computational Biosciences Branch, NICHD, and the NIH Library. The LISTSERV is 3D-SIG-L@LIST.NIH.GOV. Contact Ben Hope (hopeb@mail.nih.gov) for more information. ●

Human Motor Control

CONTINUED FROM PAGE 1

methods—such as electromyograms and electroencephalograms—to determine where the different kinds of myoclonus originated in the brain.

Hallett led the field in understanding the physiology of the bradykinesia (overall slowness of movement) experienced by Parkinson patients. He explained the pathophysiology of dystonia (involuntary muscle contractions that cause twitching and slow repetitive movements or abnormal postures) and was one of the first to use transcranial magnetic stimulation (TMS) to study the central nervous system.

To celebrate the accomplishments of both Hallett and the Human Motor Control Section (HMCS), a one-day symposium, entitled "Human Motor Control: 30 Years of Research at NIH and Beyond," was held at NIH on April 24, 2014. More than 100 neurologists and neuroscientists from around the world, many of them former fellows and colleagues, attended the gathering.

Presentations covered overviews of movement disorders; dystonia; TMS in disease and cognition; and neuroplasticity and learning. **Mahlon DeLong** (Emory University, Atlanta) presented "Overview of Movement Disorders"; **Günther Deuschl** (Christian-Albrechts University, Kiel, Germany) presented "Tremor, Physiology and the HMCS"; **Sabine Meunier** (Université Pierre et Marie Curie, Paris) presented "Dystonia: A Basal Ganglia or Cerebellar Dysfunction"; **Alvaro Pascual-Leone** (Harvard Medical School, Boston) presented "TMS to Treat Movement Disorders"; **Eric Wassermann** (NINDS) spoke on "TMS as a Probe in Cognition and Nonmotor Behavior"; and **Leonardo Cohen** (NINDS) discussed "Neuroplasticity, Learning, and Rehabilitation."

Hallett has been one of the key players in the field of movement disorders even before it became a subspecialty of neurology in the 1980s.

"At that time, therapy for movement disorders was largely limited to levodopa as a treatment for Parkinson's disease," according to an editorial in a 2011 issue of *Movement Disorders*. "The science of movement disorders was in its infancy." (*Mov Disord* **26:**935–936, 2011)

And Hallett was just the guy to help nurture and develop the profession. He had developed an early interest in movement disorders and had been nurtured by some of the best in the burgeoning field. After receiving his M.D. from Harvard Medical School and completing an internship in internal medicine at Peter Bent Brigham Hospital (Boston), he came to NIH for the first time in 1970 as a "yellow beret." During the Vietnam War, doctors were drafted and could fulfill their military obligation by entering either the armed services or the Public Health Service (PHS). The ones who opted for the PHS called themselves the "yellow berets"—in contrast to the "green berets"—who were proud to fulfill their military obligation in the "Battle of Bethesda."

Hallett joined **Ichiji Taskaki's** lab in the National Institute of Mental Health (NIMH) to work on the biophysics of nerve excitation. At NIMH he was influenced by **Ed Evarts**—a pioneer in the study of the motor system who perfected the technique of recording single nerve-cell activity—and one of Evarts's senior fellows, **Mahlon DeLong**—who later made several important discoveries about Parkinson disease and other movement disorders and became the chair of neurology at Emory.

Hallett returned to Boston in 1972 to do a residency in neurology at Massachusetts General Hospital (1972–1975) and research on the motor system. Then he did a yearlong fellowship with British neurologist C. David Marsden—one of the world's leading authorities on movement disorders—at the Institute of Psychiatry (London).

Back in Boston in 1976, Hallett headed the Clinical Neurophysiology Laboratories at the Peter Bent Brigham Hospital; developed a program in movement disorders and clinical neurophysiology; and worked his way up to associate professor at Harvard Medical School.

In April 1984, he returned to NIH and became the clinical director of NINDS, and founded the HCMS, to pursue the study of the physiology of normal human voluntary movement and the pathophysiology of different movement disorders. Already

N. DANG, NINDS

ERNIE BRANSON

Many gathered at NIH in April to celebrate the accomplishments of Mark Hallett, one of the pioneers in the therapeutic use of botulinum toxin and well known for using neurophysiological methods to differentiate a multitude of movement disorders. Inset (from left): **Harold Gainer** (NINDS), **Mark Hallett**, and **Shahram Khoshbin** (professor of neurology at Harvard Medical School). Khoshbin was Hallett's first fellow when they were both at Brigham and Women's Hospital (Boston) in the 1970s.

recognized as one of the leaders in movement-disorders research, Hallett was asked to join the founding board of the journal *Movement Disorders*, which was launched in 1986, a year after the Movement Disorders Society was established. The journal was the first to combine printed and video formats. The editors believed that the videos were a good way to "illustrate a movement that is unusual [and to] demonstrate the results of therapeutic trials." (*Mov Disord* **1:**1–2, 1986)

At NIH, Hallett first began training clinical neurophysiologists who were interested in movement problems and then movement-disorder neurologists who were interested in neurophysiology. More than 100 neurologists have completed fellowships under Hallett and have gone on to have successful careers.

Over the past 30 years, Hallett and the HMCS have distinguished themselves in the study of the:

- Physiology and classification of myoclonus (little is being done at NIH now)
- Processes behind human motor learning (currently the focus of NINDS senior investigator **Leonardo Cohen** and NINDS staff clinician **Eric Wassermann**, who both trained under Hallett)
- Pathophysiology of psychogenic movement disorders (now directed by clinical fellow **Carine Maurer**)
- Pathophysiology of disorders of volition (conscious control of movement)
- Pathophysiology of Parkinson disease (now being led by Staff Clinician **Codrin Lungu**)
- Pathophysiology of tremor, including essential tremor (**Dietrich Haubenberger,** a former fellow, is returning from Austria to become head of the new NINDS Clinical Trials unit and leader for this project)

In addition to his NIH responsibilities, Hallett has held leadership positions in several professional organizations including the presidency of the Movement Disorder Society, the American Association of Electrodiagnostic Medicine, the International Federation of Clinical Neurophysiology, and the Brainstem Society. He has been on the editorial boards of 18 journals and was editor-in-chief of *Clinical Neurophysiology* and *World Neurology* and associate editor of *Brain* and *Brain Stimulation*. He also chaired the medical advisory boards of the Benign Essential Blepharospasm Research Foundation and the International Essential Tremor Foundation for many years.

He has also published more than 650 manuscripts and won many awards. Hallett gave up being the NINDS clinical director in 2000 so he could devote all his time to research. He remains chief of HCMS.

In the years since Hallett founded HMCS, "there has been an astonishing growth in the field of movement disorders," according to the 2011 *Movement Disorders* editorial. "Gene mutations responsible for Parkinson's disease [and] many other movement disorders have now been identified…. The introduction of deep-brain stimulation has given us the opportunity to probe the basal ganglia and other deep-brain structures of patients with movement disorders and has greatly increased our understanding of how the basal ganglia are organized in physiologic and pathologic conditions. There have been major advances in the fields of molecular biology, genetics, pathology, neuroimaging, clinical trial design, and so forth." (*Mov Disord* **26:**935–936, 2011)

"Mark has had an exceedingly stellar career and has completely pioneered the field of movement disorders," said current NINDS clinical director **Avindra Nath**. Most fortunate for everyone is that Hallett is still pioneering newer aspects of movement disorders and the fellows keep coming to study with the "master." ●

Read more online at http://irp.nih.gov/catalyst/v22i4/human-motor-control

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

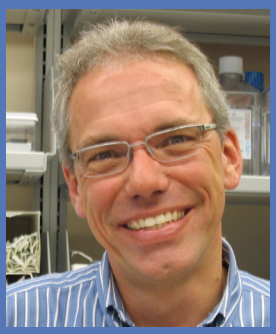
Recently Tenured


LESLIE BAIER, NIDDK


MARK HOON, PH.D., NIDCR


STEPHANIE STUDENSKI, NIA


BRYAN TRAYNOR, NIA


ADRIAN WIESTNER, NHLBI

LESLIE BAIER, PH.D., NIDDK

Senior Investigator, Phoenix Epidemiology and Clinical Research Branch

Education: Lawrence University, Appleton, Wis. (B.A. in biology and chemistry); University of Michigan Medical School, Ann Arbor, Mich. (Ph.D. in cell and molecular biology)

Training: Postdoctoral fellowship at Arizona State University (Phoenix)

Came to NIH: In 1993

Selected professional activities: Adjunct professor, University of Arizona College of Medicine (Tucson) and Arizona State University; mentors high school and undergraduate students, and postbaccalaureate and postdoctoral trainees

Outside interests: Dancing (recently traded her ballet pointe shoes for Zumba sneakers); making pilgrimages to Nordstrom with her daughters; playing endless games of *Candy Land* with her grandchildren

Research interests: My lab is identifying and characterizing susceptibility genes for obesity and type 2 diabetes among the Pima Indians of Arizona. This Native American population has high rates of obesity and the highest reported prevalence of type 2 diabetes of any population worldwide. Multiple studies have shown that heritable factors underlie a significant portion of the variation in risk for these disorders; environmental variables influence the expression of this genetic susceptibility. We are comparing the genetic details of Pima Indians with and without obesity and type 2 diabetes.

Using genome-wide association studies (GWAS), we have identified common genetic variants associated with type 2 diabetes, obesity, prediabetes, or preobesity traits in Pima Indians. We also identified several strong and reproducible associations not reported in other GWAS, a finding that suggests ethnic-specific heterogeneity in risk factors for these common diseases.

We are testing the hypothesis that multiple rare variants may underlie some proportion of the variance we have identified. We recently completed whole-exome sequencing on 180 Pima Indians and whole-genome sequencing on 135 Pima Indians. We also have genome-wide expression data from skeletal muscle and adipose biopsies from more than 200 nondiabetic Pima Indians. We are using the data to identify expression profiles that may predict the onset of diabetes. We are also merging expression data with GWAS data and whole-genome sequence data to identify factors that may contribute to these diseases.

Understanding genetically determined susceptibility factors could help us prevent the disease by identifying at-risk individuals. The research could also identify novel therapeutic and personalized targets, which may lead to improved treatments.

MARK HOON, PH.D., NIDCR

Senior Investigator, Laboratory of Sensory Biology, Molecular Genetics Unit

Education: University of Birmingham, U.K. (B.S. in biochemistry); University of Leeds, U.K. (Ph.D. in biochemistry)

Training: Postdoctoral training in microbiology at the Albert Ludwigs University of Freiburg (Freiburg im Breisgau, Germany)

Came to NIH: In 1992 for training; in 1999 became a staff scientist; in 2006 became a tenure-track investigator

Selected professional activities: Member of the Society for Neuroscience and of the American Pain Society

Outside interests: Long-distance running

Research interests: Several years ago I started as a tenure-track investigator in what was, for me, a completely new area of sensory biology. Previously, in the lab of **Nick Ryba**, I had studied the sense of taste. As a tenure-track investigator I made a change and set up a lab that investigated the biology of somatosensation (thermal and nociceptive stimulation and the sense of touch). We particularly want to understand how molecules and peripheral sensory neurons transform stimuli into membrane depolarization and how these cells transmit signals to neural relays in the brain. We have been using a variety of techniques including molecular genetics and behavioral

DMITRI ZAYKIN, PH.D., NIEHS

and electrophysiological testing, as well as cell-culture and biochemical assays.

Our studies have provided new information about the mechanisms by which somatosensory receptors transduce and transmit signals. Recently, we identified a neurotransmitter called natriuretic polypeptide B (Nppb) that is released in the spinal cord and carries the sensation of itch to the brain. We showed that mice lacking either Nppb or cells expressing its receptor in the spinal cord did not scratch themselves when administered itching agents, but were still sensitive to pain. These and related studies will allow us to continue to determine crucial molecules and cells required for specific types of somatosensory input, including those involved in sensing pain and touch. Ultimately, we would like to establish how the brain distinguishes different types of stimuli.

STEPHANIE STUDENSKI, M.D., M.P.H., NIA

Senior Investigator, Longitudinal Studies Section

Education: University of Kansas, Kansas City, Kansas (B.S.N. and M.D.); University of North Carolina, Chapel Hill (M.P.H.)

Training: Residency in internal medicine and fellowships in rheumatology–genetic disease and in geriatrics, Duke University Medical Center (Durham, N.C.)

Before coming to NIH: Professor of medicine and director of research, Division of Geriatric Medicine, University of Pittsburgh; staff physician at Geriatric Research, Education, and Clinical Center, VA Pittsburgh Healthcare System; previously held faculty positions at Duke University Medical Center and at University of Kansas Medical Center and was director of the latter's Center on Aging

Came to NIH: In 2014

Selected professional activities: Associate Editor, *Journal of Gerontology Medical Sciences*; member, NIA Council; former chair of study sections: Aging Systems and Geriatrics; Geriatrics and Rehab Medicine

Outside interests: Hiking; cooking; playing piano

Research interests: I am interested in the causes and consequences of and effective interventions for balance and mobility disorders in older adults. These problems increase in frequency as people age and can occur with stroke, arthritis, Parkinson disease, and hip fractures as well as with other conditions such as peripheral neuropathy (numb feet), vision loss, muscle dysfunction, and slowed neural-processing speed.

I use biomechanics, neuroimaging, body-composition techniques, and neuropsychologic testing. I led several clinical trials using novel forms of exercise—such as motor-learning practice and interactive video dance games–to promote balance and mobility in older persons. I have also led collaborations to pool data from multiple studies to estimate the effect of walking speed or muscle mass on survival and disability.

Subclinical changes in the aging brain contribute to alterations in walking behavior. Beyond evidence of regional gray-matter atrophy and white-matter disease, there are subtle changes in white-matter tracts (detected using diffusion tensor imaging) that contribute to changes in walking speed and gait variability. My clinical trials are designed to promote smoothness and efficiency of gait as well as sensorimotor processing. I have also assessed how regional brain white-matter disease affects responses to interventions.

BRYAN TRAYNOR, M.D., PH.D., NIA

Senior Investigator and Chief of the Neuromuscular Diseases Research Section, Laboratory of Neurogenetics

Education: University College Dublin Medical School (M.B., B.Ch., M.D.; Ph.D. in the genetics of amyotrophic lateral sclerosis, ALS); Harvard University and Massachusetts Institute of Technology, Cambridge (M.M.Sc. in drug discovery and clinical-trials design)

Training: Internal medicine residency, St. Vincent's University Hospital (Dublin); neurology residency and fellowship, National Neuroscience Center of Ireland, Beaumont Hospital (Dublin); neurology residency and ALS-neuromuscular fellowship at Massachusetts General Hospital and Brigham and Women's Hospital (Boston)

Before coming to NIH: Instructor and staff neurologist at Harvard Medical School (Boston) and Massachusetts General Hospital

Came to NIH: In 2005 as a clinical associate

Selected professional activities: Adjunct faculty member, Neurology Department, Johns Hopkins Medicine (Baltimore); member of the Scientific Review Committee of the ALS Association and of the Integration Panels for the Department of Defense's ALS research and Alzheimer research programs

Research interests: My laboratory is best known for its work on understanding the genetic etiology of amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) and related neurodegenerative disorders, such as frontotemporal dementia (FTD). We apply advanced genomic technologies to unravel the etiology of our diseases of interest.

We have had many notable successes: My lab published the first genome-wide association study of ALS (2007); was the first to identify an association signal for ALS on the short arm of chromosome 9 in the Finnish founder population (2010); discovered that mutations in the *VCP* gene

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Recently Tenured

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are responsible for a significant fraction of familial ALS (2010); and recently published that mutations in the *MATR3* gene are another cause of familial ALS (2014). In 2011, I led the international consortium that identified a pathogenic hexanucleotide repeat expansion in the *C9ORF72* gene as the underlying mutation in a large proportion of familial ALS and FTD, as well as in the more common sporadic forms of both diseases.

ADRIAN WIESTNER, M.D., PH.D., NHLBI

Senior Investigator, Laboratory of Lymphoid Malignancies; Attending Physician, Hematology Branch

Education: University of Basel Medical School, Basel, Switzerland (M.D.; Ph.D. in genetics)

Training: Residency in internal medicine, University Hospital in Basel, Switzerland

Came to NIH: In 2000 as a hematology fellow in NHLBI; in 2003 became a clinical fellow at NCI; in 2004, joined NHLBI as a tenure-track investigator and attending physician

Selected professional activities: Medically responsible investigator and IND (investigational new drug sponsor) on clinical trials investigating novel agents for chronic lymphocytic leukemia

Outside interests: Traveling; playing tennis; skiing; sailing

Research interests: I am interested in B-cell lymphoproliferative diseases, especially chronic lymphocytic leukemia (CLL). CLL is the most common leukemia in the United States and affects mostly older adults. I want to better understand how the tumor cells grow and to develop novel agents and treatment strategies that we can test in clinical trials.

My lab is pursuing two complementary approaches. First, using leukemic cells from CLL patients who are enrolled in a natural-history study, we are studying signaling pathways that drive the proliferation and survival of the leukemia. We compared tumor cells isolated from blood, bone marrow, and lymph nodes, and we identified B-cell-receptor signaling as a key pathway in CLL. We have confirmed in several clinical trials that inhibitors of B-cell-receptor signaling may be useful as a targeted therapy. We are conducting a study using an inhibitor, called ibrutinib, in patients with a genetic lesion (deletion of chromosome 17p) that predicts poor survival with standard treatment. Preliminary results are encouraging and suggest that ibrutinib may overcome treatments limitations and improve survival.

In our second approach, we are trying to understand the effect of a given treatment on tumor cells. Although most clinical studies record the responses to and side effects of treatment, they rarely sample and analyze tumors before and during treatment.

At the Clinical Center such studies are possible, thanks to its unique infrastructure and our patients, who are often willing to undergo additional procedures to provide research samples. By analyzing tumor cells during therapy, we learn how they react, adapt, and become resistant to treatment. We have also obtained information that could lead to novel therapies, an avenue that we are actively pursuing.

DMITRI ZAYKIN, PH.D., NIEHS

Senior Investigator, Biostatistics Branch

Education: North Carolina State University, Raleigh, N.C. (Ph.D. in biomathematics, minor in statistics); Far Eastern State University, Vladivostok, Russia (M.S. equivalent—in biology and population genetics)

Before coming to NIH: Research fellow, Institute of Marine Biology (Vladivostok); visiting scholar, North Carolina State University; investigator, GlaxoSmithKline (Durham, N.C.)

Came to NIH: In 2004

Selected professional activities: Adjunct associate professor, Center for Neurosensory Disorders, University of North Carolina at Chapel Hill; member of the American Statistical Association and of the American Society of Human Genetics

Outside Interests: Listening to classical music; reading; weightlifting; science is also a hobby, not just a job

Research Interests: Our group uses statistical methodology to discover relationships between genetic variation and phenotypic traits. We use high-throughput genotyping data to reveal genetic polymorphisms involved in disease susceptibility, response to medications, and differential reactions to environmental exposures. Development of statistical methods to accompany technological advances is essential for treating and preventing disease and enhancing the quality of life.

We develop efficient approaches for detecting and characterizing genetic associations with discrete and quantitative traits while taking into account the large and expanding scale of genomic data, environmental exposures, and gene-environment interactions. We devise strategies that are useful, not only for genetic applications, but also for the analysis of other kinds of multidimensional data in which many statistical hypotheses are being evaluated. Some examples of where our techniques are applicable include studies involving epigenetic effects of exposures, metabolomics, and differential gene expression. Our collaborative research continues to bring modern statistical methodology to epidemiological studies of complex human diseases. ●

CONTRIBUTOR: ROBIN ARNETTE, NIEHS

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

HISTORY OF MEDICINE LECTURES

July and September; 2:00–3:00 p.m.
Lister Hill Auditorium (Building 38A)
Information: http://1.usa.gov/1iVBwVg

Tuesday, July 15: "Anatomy Acts and the Shaping of the American Medical Profession's Social Contract," Dale Smith (Uniformed Services University of the Health Sciences)

Tuesday, September 2: "Pictures of Nursing: The Zwerdling Postcard Collection," Julia Hallam (University of Warwick)

NIH GRADUATE AND PROFESSIONAL SCHOOL FAIR

Wednesday, July 16; 9:00 a.m.–3:30 p.m.
Exhibits: 10:00 a.m.–2:15 p.m.
Natcher Conference Center (Building 45)
Register: https://www.training.nih.gov/gp_fair

Explore programs for graduate and professional degrees; meet representatives from more than 150 colleges and universities; attend workshops. Check Web site for details.

"THINK BIG OR STAY WHERE YOU ARE"

Wednesday, July 16; 11:00 a.m.–12:30 p.m.
Wilson Hall (Building 1)

For more information on this career-development training, contact Victoria Gross (Victoria.Gross@nih.gov or 301-451-0746).

MEDICAL SCIENTIST TRAINING PROGRAM 50TH ANNIVERSARY SYMPOSIUM

Thursday, July 17; 8:00 a.m.–12:00 p.m.
Masur Auditorium (Building 10)
To register (free) : http://1.usa.gov/1mFSUZ7
Videocast at http://videocast.nih.gov.

Talks by current and former MSTP trainees; remarks by NIH Director F. Collins and others.

SUMMER POSTER DAY 2014

Thursday, August 7; 9:00 a.m.–3:00 p.m.
Natcher Conference Center (Building 45)
Information: http://1.usa.gov/1rdkV1M

Learn about the summer interns' projects and help them practice their communication and networking skills. Investigators, staff scientists, and scientific administrators are encouraged to come and engage the students in discussion.

FIFTY YEARS OF THE GENETIC CODE

A Symposium to Honor Marshall Nirenberg
Thursday, July 31; 8:30 a.m.–5:30 p.m.
New York Academy of Sciences (New York)
To register (not free): http://bit.ly/1ovBiCq

This symposium honors **Marshall Nirenberg** (1927–2010), who spent his entire scientific career at NIH and won the Nobel Prize in Physiology or Medicine in 1968 for deciphering the genetic code. The symposium will be held on the 50th anniversary of Nirenberg's July 31, 1964 presentation of a method to identify all 64 codons that make up the genetic code. For more information, visit the Web site, e-mail nyas@nyas.org, or call 212-298-8600.

INTERNATIONAL EXPO 2014

Tuesday, September 9; Noon to 4:30 p.m.
NIH FAES Education Center (Building 10)
Information: http://1.usa.gov/TMpCkK

Postdocs and graduate students interested in international careers can meet representatives from embassies, funding agencies, and globally minded science and health organizations.

NIH LIBRARY OPEN HOUSE

September 10; 10:00 a.m.–3:00 p.m.
NIH Library (Building 10)
Check for event updates: http://nihlibrary.nih.gov/Pages/openhouse_2014.aspx

See demonstrations of new technology and services that can help you accomplish more, including three-dimensional printing, bioinformatics software, tips for getting published, and more.

WALS RETURNS ON SEPTEMBER 3

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

The 2014–2015 Wednesday Afternoon Lecture Series (WALS) starts September 3 with epigeneticist Andrew Feinberg, M.D., M.P.H. (Johns Hopkins). The schedule will be posted soon at http://wals.od.nih.gov.

Read more online at http://irp.nih.gov/catalyst/v22i4/announcements.

INTRAMURAL AIDS TARGETED ANTIVIRAL PROGRAM (IATAP)

Application launch date: August 1, 2014
Application deadline: September 16, 2014

The IATAP review committee will consider new research projects for FY2015 and FY2016. Proposals should be concerned with the development of targeted antivirals for HIV, structural and functional studies of HIV proteins, or closely related areas in the molecular and cell biology of HIV. The program's funds are intended to encourage development of new projects by investigators who may not otherwise work in these areas. For information, contact IATAP Scientific Director William Eaton (eaton@helix.nih.gov or 301-496-6030) or Jackie Roberts (robertsjm@od.nih.gov or 301-496-1921).

POWERFUL PRESENTATIONS AND PUBLIC SPEAKING

September 12; 9:00 a.m.–4:30 p.m.
6001 Executive Blvd., Rockville, Md.
Registration required; Tuition is $570

Limited to 12 participants. For more information and to register, visit http://trainingcenter.nih.gov/ShowDetails.aspx?cidv=NIHTC4006-FY14 or contact the NIHTC at 301-496-6211 or training1@od.nih.gov.

NIH RESEARCH FESTIVAL

September 22–24, 2014; Building 10

For information and schedules, visit http://researchfestival.nih.gov or contact Jacqueline Roberts at 301-594-6747 or robertsjm@od.nih.gov.

FAES GRADUATE SCHOOL

Fall Term Registration
July 15–September 5, 2014
Late Registration until September 30
Web site: www.faes.org/grad

The Foundation for Advanced Education in the Sciences (FAES) Graduate School offers more than 120 undergraduate- and graduate-level courses, most of which are held in the evenings on the NIH Bethesda campus. For more information, visit the Web site, e-mail registrar@faes.org, or call 301-496-7976. ●

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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/v22i4

FROM THE ANNALS OF NIH HISTORY

Hamsters' Delight

OFFICE OF NIH HISTORY

The Office of NIH History has many collections of old photos and other materials depicting life at NIH. The photo above is from a collection that includes photographs, programs, and scripts of plays written and performed by the NIH thespian group "The NIH Hamsters." The group, which included researchers, physicians, and other staff, was formed in 1949 under the leadership of **Mary T. Beecher**, in the National Heart Institute, and disbanded in the 1960s. The plays were performed in Wilson Hall (Building One) and attended by NIHers as well as by members of the local Bethesda community. Here the actors and actresses are performing a hilarious play called "Twice Upon a Time," which an article in the March 24, 1952, edition of the *NIH Record* described as "the zaniest production ever [with] scientists and cavemen cavort[ing] through the courtesy of a time machine 100,000 years into the past." Highlights of the show included a "Clinical Cave with facilities for treating [only] five patients; ... a robot who attends official meetings; [and] the Gamster chorus that was especially good in a 'Blue Genes' number." If you recognize anyone in the photo, contact the *NIH Catalyst* (catalyst@nih.gov or 301-402-1449) and let us know. In upcoming issues of the *Catalyst*, we will be featuring other photos from the Office of NIH History's collections.

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