THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

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How Cells Crawl

The Dynamics of Cell Motility

BY ADAM J. KUSZAK, NIDDK

No, Masur Auditorium hadn't become a campground. That orange dome-shaped tent sitting in the middle of the stage was a prop for a G. Burroughs Mider Lecture given as part of the Wednesday Afternoon Lecture Series. **Jennifer Lippincott-Schwartz** used it to demonstrate what happens to a cell's "skeleton," or more precisely its cytoskeleton, when it crawls.

Cells crawl for all sorts of reasons: to form new tissue during embryonic development; to heal wounds; to defend against invading microorganisms; to remodel bone; to regenerate nerves; and more. A cell's movement is driven by continuous remodeling of the cytoskeleton and is mediated by the lamellipodia (tiny filaments composed of a protein called actin) located at the lamella (front edge of the cell). When actin subunits are added to the lamellipodia in a process known as polymerization, a pushing force is generated. After the polymerization has occurred, the molecular motor, myosin II, is added to cause a contractile force. As the actin filament cytoskeleton pushes and contracts, the cell slowly crawls along.

Scientists typically use electron microscopy to get high-resolution, but static, images of the lamellipodia. Conventional confocal imaging can capture live, but blurry, images of cells crawling. Lippincott-Schwartz, a distinguished investigator in the National Institute of Child Health and Human Development (NICHD), has

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NHGRI-Smithsonian Collaboration

A New Model for NIH Outreach

BY KATHERINE WENDELSDORF, NIAID

In June, the "Genome: Unlocking Life's Code" exhibition opened at the Smithsonian National Museum of Natural History (Washington, D.C.). The exhibition celebrates the anniversaries of two historic landmarks: the 10th anniversary of the Human Genome Project's completion and the 60th anniversary of James Watson and Francis Crick's discovery of DNA's double-helical structure.

The exhibition is the brainchild of **Eric Green**, director of the National Human Genome Research Institute (NHGRI), and G. Wayne Clough, secretary of the Smithsonian Institution. It represents the most expansive collaboration to date between the NIH and the Smithsonian Institution. The high-tech exhibition uses interactive touch screens and high-definition graphics, three-dimensional models, custom animations, and videos of real-life stories to explain the basics of genomics and DNA sequencing technology and to examine both the benefits and the challenges that genomics presents.

MAGGIE BARTLETT, NHGRI

In June, the "Genome: Unlocking Life's Code" exhibition opened at the Smithsonian National Museum of Natural History, representing the most expansive collaboration to date between the NIH and the Smithsonian Institution.

One of the exhibition's displays features the stories of people who have taken part in genomic sequencing studies. Select a medical story, and a video of that individual appears

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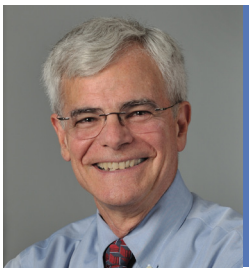


The NIH Intramural Research Program: Our Research Changes Medical Practice

BY MICHAEL GOTTESMAN, DDIR

Most of the readers of this column are aware of the enormous contributions to human health that the NIH has made by supporting basic biomedical research. For the NIH intramural research program (IRP) these contributions are reflected in numerous Nobel prizes to NIH scientists and trainees, other awards, and citations to articles by our highly visible scientists (http://www.irp.nih.gov/about-us/honors).

An equally lasting impact of intramural research has been felt in medicine's "standard of care" (what is supposed to happen when you enter a doctor's office for a check-up, diagnosis, or treatment).

The NIH IRP, including the Clinical Center and its talented clinically oriented scientists, has exemplified the importance of evidence-based medicine, dentistry, and even veterinary medicine. Almost every aspect of clinical practice has been profoundly affected by research done at the NIH.

Let's say you walk into the doctor's office for a check-up. Blood is drawn to screen for a variety of disorders, such as problems with lipid metabolism that could lead to heart disease, stroke, and kidney disease. The original description of low- and high-density lipoproteins and cholesterol, as well as their association with blood-vessel diseases, was worked out at the NIH by **Don Fredrickson** (NHLBI) and colleagues.

Next, the doctor does a blood count to determine numbers of red cells, white cells, and platelets; to detect malignant disorders of these cells; and to look for infection or bleeding. This procedure used to be a tedious counting process done with a hemocytometer and a microscope. Now diagnostic labs use a Coulter Counter or similar device. The counter was initially developed by Wallace Coulter, an engineer, to count particles in the paint used to protect the surfaces of U.S. Navy vessels. It occurred to him that the principle could be used to measure particles (cells) in blood. The NIH quickly picked up on this concept and developed it for clinical use.

Your doctor is likely to check that your vaccinations are up to date. If you were born in the past 20 years, you would have received in childhood an *Haemophilus influenzae* vaccine (developed by NICHD scientists **Rachel Schneerson** and **John Robbins** to prevent *H. influenzae* meningitis) and other vaccines—including one for hepatitis A—developed from NIH work. As an adolescent, you would have been vaccinated against human papillomavirus to prevent cervical cancer (NCI's **John Schiller** and **Doug Lowy** developed that vaccine). Later in life, you will receive a high-dose Herpes zoster vaccination to prevent shingles, thanks to the work of **Steve Straus**, **Phil Brunell**, and others in NIAID.

Chest pain is a common complaint. If the pain is severe and acute, your doctor will tell you to take a nitroglycerin tablet (and aspirin) and get to an emergency room, as per a protocol developed at the NIH to reduce the damage from occluded coronary vessels. NHLBI's **Andrew Arai**, in collaboration with Suburban Hospital (Bethesda, Md.), is working on a quick way to use functional magnetic resonance imaging (fMRI) to determine whether there is restricted blood supply to the heart during chest pain. We expect that use of coronary fMRI in emergency rooms will eventually provide definitive diagnostic information in minutes instead of hours. Incidentally, much of the software for interpreting both heart and brain MRIs was developed by NHLBI scientists.

The doctor might discover that a contributing cause of your chest pain is a severe anemia requiring a blood transfusion to improve oxygen delivery to your heart and other vital organs. Rest assured that the blood you receive will not be contaminated with hepatitis virus, thanks to the pioneering work of the Clinical Center's **Harvey Alter**, or human immunodeficiency virus (HIV), thanks to **Robert Gallo** (NCI) who helped develop the first blood test for HIV. If your anemia is due to bone-marrow failure (aplastic anemia), the standard treatment with immunosuppressive agents is thanks to the work of **Neal Young** (NHLBI).

The future of medicine will include a large dose of genomic analysis. Need I point out that the genetic code was deciphered by **Marshall Nirenberg** (NHLBI) and NIH colleagues; that the BLAST (Basic Local Alignment Search Tool) algorithm that we use to find related DNA sequences in existing databases was worked out by **Stephen Altschul** and **David Lipman** (NCBI, NLM); that many of the genes associated with human genetic diseases were first identified at the NIH and continue to be, through **William Gahl's** (NHGRI) Undiagnosed Diseases Program and other studies of rare diseases; and that use of genomic analysis of bacterial genomes, introduced by **Julie Segre** (NHGRI), **Tara Palmore**

(CC), and **Evan Snitkin** (NHGRI), will revolutionize the study of epidemics of multidrug-resistant pathogens.

There are hundreds of rare human diseases whose study has been advanced at NIH; important improvements have been made in treating severe psychiatric disorders such as bipolar illness (lithium was first used for this purpose at NIH, and **Carlos Zarate** in NIMH has introduced ketamine for rapid treatment of depression); fluoride, shown to prevent tooth decay, was first tested by NIDCR; the use of artificial, surgically implanted mitral valves to replace defective heart valves was an NHLBI first; and the development of single- and multiagent chemotherapy to treat cancer was pioneered at the NCI.

And given that the NIH IRP is one of the most credible sources of medical research in the world, it's not surprising that many treatments, once thought to be effective, failed NIH's rigorous clinical studies (for example, NIDDK tested pancreatic islet-cell transplantation for diabetes; NCI evaluated bone-marrow transplantation after high-dose chemotherapy for breast cancer). I am sure that there are many other examples of how the NIH IRP has influenced health care throughout the world, saving lives and preventing squandering of valuable resources.

At a time when everything that the government does is under increased scrutiny, the NIH IRP seems like a particularly good investment of funds and people.

Sending me any additional examples you have of how the IRP has improved medical care would be much appreciated. ●

NIH Medical Arts

We're Much Alive and Changing the Way We Do Business

BY MEDICAL ARTS STAFF

Despite what you may have heard, the Division of Medical Arts is still in business and continuing to provide services to its NIH customers. We have served the NIH community for more than 50 years and distinguished ourselves by winning numerous awards for our work. Our services are unmatched by outside providers.

But Medical Arts is a fee-for-service organization, and our budget depends on billable work requests from Institutes and Centers (ICs). Recently, there have been fewer requests for our services because ICs have smaller budgets and have had to cut or postpone projects that would have required Medical Arts' help; advances in technology have allowed ICs to do some things themselves that they used to rely on Medical Arts for; and some ICs are procuring similar services from outside vendors.

Medical Arts, therefore, is restructuring and changing the way we do business. We are reducing our space; refining our technology; and modifying the way our designers and artists work. In essence, Medical Arts is becoming a storefront that will manage and provide the services that support the NIH's mission, to the extent that revenue continues to cover expenses.

As we transition through this restructuring into FY2014, we will continue to provide:

Express services such as scientific and event posters, programs and brochures, plaques, campus photos, and custom framing

Medical and visual information services:

• Designs for identity graphics, publications, posters, brochures, signage, and exhibits

• Three-dimensional modeling and animation ranging from simple moving diagrams to photorealistic animations revealing even the most complicated processes

• Digital animations for presentations that can illuminate surgical procedures, educate patients, and communicate complex research by showing a series of steps instead of a single static image

• Illustrations for journal covers and publications; medical and biological drawings; and accurate technical charts, diagrams, and depictions of laboratory equipment

We encourage our customers to continue using our services during the transition. As the budget is developed for FY2014, we will have a better understanding of our ability—and of our customers' needs—to ensure the future viability of the Medical Arts capabilities. We will keep you posted and will adjust our business plan accordingly.

Medical Arts will be able to complete the services outlined in established Inter/Intra-Agency Agreements. These formal agreements have resulted in vital collaboration with other government agencies. You, the Medical Arts customer, can be assured that service levels will not decline.

We also encourage ICs that are procuring similar services from outside entities to try using Medical Arts instead during the transition. Our team is ready to do whatever it takes to get the job done—creatively, efficiently, and expertly. No outside provider can match our unique qualifications, convenience, expertise, and understanding of the NIH community. Medical Arts is dedicated to meeting your needs—each and every time. ●

For more information, visit medarts.nih.gov or call 301-496-3221.

FROM THE FELLOWS COMMITTEE

The NIH Fellows Editorial Board: A Secret No More

BY JENNIFER SARGENT, NIAMS

The NIH Fellows Editorial Board (FEB) may be one of the best-kept secrets of NIH's intramural research training program. But it shouldn't be.

The FEB provides a free, confidential scientific-editing service to all fellows at the NIH and FDA for manuscripts ranging from primary data articles to literature reviews to grant proposals. The volunteer editors are fellows and professionals who edit the documents for grammar, form, and clarity and review figures, legends, and other elements. They do not, however, consider the scientific merit of submissions.

Each manuscript is assigned to an associate editor and three or four primary editors who lead an open discussion with the rest of the board and prepare the final edits and reports. Each author receives a letter that summarizes the editorial suggestions and a copy of the marked-up manuscript.

The manuscript-editing service benefits more than just the authors. Whether FEB editors are planning to stay at the bench or transition to a career in scientific publishing, editing, or writing, they gain valuable experience as they hone their own editorial skills. FEB alum **Ranjini Prithviraj**, a former postdoctoral fellow at the National Institute of Neurological Disorders and Stroke, is now a managing editor at the American Chemical Society (Washington, D.C.). Being an FEB editor trained her to "read, understand, and critique manuscripts" outside of her field and work as part of an editorial team, she said.

FEB was founded in 2002 by the National Cancer Institute's Center for Cancer Research; in 2005, FEB was expanded NIH-wide. To date, some 500 fellows have served as volunteer editors and have reviewed more than 720 manuscripts. About 40 FEB members—led by Senior Editor **Andrew Broadbent**, a Visiting Fellow at the National Institute of Allergy and Infectious Diseases—are active at any given time. In addition, consulting editors, many of whom are former FEB members, provide assistance when needed.

For more information, visit FEB at http://ccr.cancer.gov/careers/feb or e-mail NCIeditors@nih.gov. ●

NIH CLINICAL CENTER'S NEW COURSE FOR PH.D. STUDENTS

BY JANET HULSTRAND, CC

MARIA NEKHAYONAK, CC

In July, 27 Ph.D. students from 16 institutions took part in the new "Clinical and Translational Research Course for Ph.D. Students," a two-week course that introduces talented young scientists to "bench-to-bedside" research. They met with intramural Ph.D. investigators who served as translational researcher role models, participated in a mock institutional review board, and learned how to file investigational drug applications with the FDA. "This was a diverse group of very bright and engaged students," said **Juan J.L. Lertora**, faculty lead for the program. Ph.D. students conducting research at the NIH and U.S. academic institutions are encouraged to apply. "This course has reminded me that my original goal of improving human health is not absurd or unrealistic," said Bridget Queenan, a neuroscience graduate student at Georgetown University (Washington, D.C.). "It's the only thing worth doing." For more information, visit http://www.cc.nih.gov/training/phdcourse/index.html.

History Mystery Solved

Invention that Revolutionized Epithelial Cell Research

BY MICHELE LYONS, OFFICE OF NIH HISTORY

No, it wasn't a prototype for a flux capacitor.

The "History Mystery" photo that appeared in the May-June issue of the *NIH Catalyst* (http://irp.nih.gov/catalyst/v21i3/nih-in-history) elicited 14 responses to our plea for help in identifying the equipment used by the late **Roderic E. Steele**, a researcher in the National Heart, Lung, and Blood Institute (NHLBI) from 1975 to 1988.

Three were whimsical guesses—a flux capacitor (the time-travel machine featured in the *Back to the Future* trilogy); an early breast pump; and a device to deliver electroshock therapy. But most respondents provided real clues. We thank everyone who helped identify this object (for individual comments, see http:// irp.nih.gov/catalyst/v21i5/nih-in-history).

So what is it? It turns out that it's equipment for a porous-bottom culture dish (PBCD) that Steele helped to develop for research on epithelial cells.

"This product truly revolutionized the way the epithelial cell community studied cells, particularly for performing transport assays," said **Gregory Germino**, Deputy Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). "The conductivity meter would have been used to measure resistance, a measure of how 'tight' the cell junctions had become, and also how much ionic activity could be induced by various interventions."

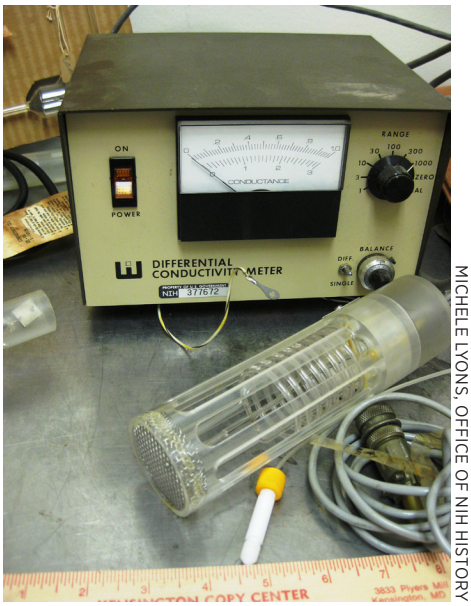
Epithelial cells are tightly packed together and line the body's major cavities, most organs, blood vessels, and the skin. Molecules—including nutrients, hormones, growth factors, ions, and oxygen as well as carbon dioxide and other waste products—are transported through the cells' upper and lower membranous surfaces. But such transport is difficult to measure when the cells are grown in a normal culture dish.

Steele's PBCD simulated a natural environment for the cells. The porous bottom allowed for the passage of transported solutes and provided a conductive pathway for electrical measurements.

Steele's journey to create the PBCD began with work he did in the 1970s at Stanford University (Stanford, Calif.). He was studying sodium transport and carbon dioxide production to determine how the chemical energy of cellular metabolism is converted to the electrochemical energy of active transport. Instead of using a conventional culture dish, he fashioned a PBCD out of a toad bladder, which he cut in half and suspended like a tiny trampoline across a glass chamber that could simultaneously measure sodium transport and oxygen consumption (*J Membr Biol* **34:**289–312, 1977).

By the spring of 1983, Steele was working with T. Andrew Guhl, an inventor and supervisor at Becton Dickinson, on commercializing the PBCD. Guhl wrote in a letter to Steele, "I envision this particular product to be the first [to incorporate] a porous membrane for cell-culture experiments involving feeding of the cell monolayer from the basal-lateral surface."

In 1986, Steele published a paper with **Joseph S. Handler** (NHLBI) in the *American Journal of Physiology* that described four porous bottoms they had tried—cellulose ester, polycarbonate, collagen, and placental amnion. The first three types were attached to a polycarbonate ring that formed the sides. The amnion bottoms were tucked between two hollow polyethylene stoppers stacked on top of each other in an "embroidery-hoop arrangement" (*Am J Physiol* **251:**C136–C139, 1986, and *Methods Enzymol* **171:**736–744, 1989).



MICHELE LYONS, OFFICE OF NIH HISTORY

NIH scientists helped the Office of NIH History discover that this conductivity meter was part of a system that the late NHLBI scientist Roderic E. Steele started developing in the 1970s: a porous-bottom culture dish that revolutionized research on epithelial cells.

The group continued their development of the PBCD, publishing an article in 1992 about a more complicated set-up (*J Tissue Cult Methods* **14:**259–264, 1992).

After Steele left NIH in 1988, he continued his association with Handler's lab. He eventually retired to California, where he died in 2011. His widow did not have any papers or objects to document his work. We were fortunate, however, that a few letters and handwritten data sheets mailed between Steele and Guhl were tucked into the box containing the PBCD. Usually, we are not so lucky as to have correspondence between a federal employee inventor and a commercial operation.

The expertise of the scientific community is an important resource for the NIH Stetten Museum, which covers a broad array of NIH history and research. Without your help, we would never identify everything in our collection. Thank you. ●

How Cells Crawl

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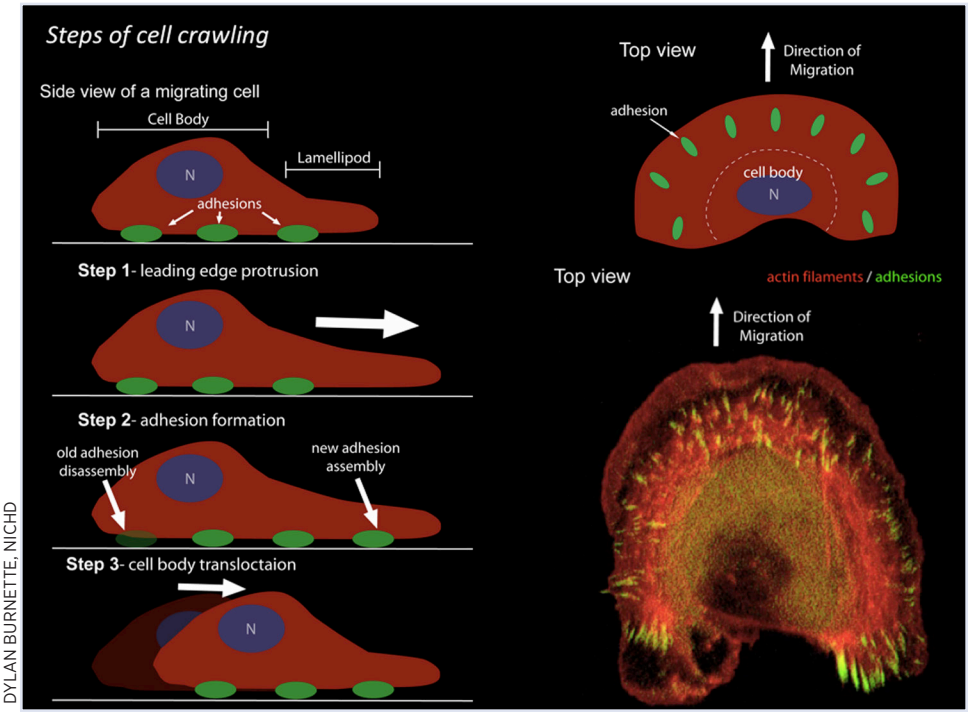


DYLAN BURNETTE, NICHD

played a leading role in advancing microscopy technologies to allow scientists to see high-resolution images of cells in action.

Her lab helped develop photo-activated localization microscopy (PALM), a technique that uses repeated activation, imaging, and bleaching of photo-switchable fluorescent probes to obtain resolutions of 10 to 20 nanometers, about 10 times the size of an average protein. PALM and other recent super-resolution imaging techniques have ushered a new era of investigations into cellular mechanics.

Lippincott-Schwartz wowed the audience with stunning videos of a live cell crawling. She explained how studies of actin's continual reorganization at the cell's lamella have yielded novel insights into the fundamental mechanics of cell motility. She and her NICHD colleagues found that actin arcs of the lamella were the base against which the lamellipodium's polymerizing actin filaments protrude (*Nature Cell Biol* **13:**371-382, 2011). Furthermore, the high spatial and temporal resolution analysis revealed that actin filaments evolve into the actin arcs as they interact with myosin II, demonstrating a heretofore unknown continuity between the lamellipodia and lamella actin networks.

She described how **Dylan Burnette**, the leading postdoctoral researcher on the project, studied the spatial relationship between actin and the focal adhesion protein zyxin and found a correlation between the contracting actin arcs and focal adhesion points (actin-rich structures that enable cells to adhere to the extracellular matrix). Moving actin arcs slowed down near newly forming focal adhesions, likened to "feet" at the point of contact between the cell and a surface. This interplay between actin arcs and focal adhesions in turn creates an anchored, stiff substrate against which the polymerizing actin filaments extend the plasma membrane. The combined dynamics of these systems cause the migrating cells to crawl.

Lippincott-Schwartz and Burnette wondered whether this "contractile apparatus" played other roles in a migrating cell's shape. Burnette visualized the arrangement of actin and myosin throughout the cell three-dimensionally. He saw that myosin II was localized to the actin arcs of a cell's dorsal side, not to the actin stress fibers connecting the dorsal surface to the ventral focal adhesions. His finding suggests that contractile force is localized to the actin arcs.

"What this system really looks like is a tent," said Lippincott-Schwartz as she walked over to the tent on center stage. The poles represent the actin stress fibers that go from the base to the top of the cell, she explained. As she pushed down on the tent, it flattened just as a crawling cell would.

She hypothesized that such a system underlies the flattening of a cell's leading edge, allowing the cell to move into the tight spaces of surrounding substrates. Her studies have generated exciting insights into a critical process in developmental biology and cancer metastasis.

Although Lippincott-Schwartz and Burnette have captured astounding images of cellular movement using super-resolution microscopy, they are focused on advancing the mechanistic understanding of cell motility rather than repeatedly imaging the same processes with new microscopy techniques.

Lippincott-Schwartz and her trainees are also applying high-resolution imaging techniques to their investigation of the diverse systems of mitochondrial fusion, Golgi organization, glucose uptake, and hepatocyte metabolism. They are poised to make many more great leaps forward in understanding dynamic cellular functions. ●

To view the video of Lippincott-Schwartz's talk, "Navigating the Cellular Landscape with New Optical Probes, Imaging Strategies, and Technical Innovations," visit http://videocast.nih.gov/launch.asp?17997.

Why Do Tumors Keep on Growing?

Cancer Therapy Kills Only Part of a Tumor

BY REBECCA BAKER, NIAID

"I WANT TO GET YOU TO CHANGE YOUR thinking about how we evaluate cancer," **Antonio "Tito" Fojo** told the audience that had gathered in Lipsett Amphitheater (Building 10) on June 12 for the Great Teachers Tenth Annual John Laws Decker Memorial Lecture. Cancer therapy, he said, kills only part of a tumor—the part that's sensitive to a cancer-fighting drug. The rest is resistant and continues to grow.

Fojo, a senior investigator in the National Cancer Institute, strives to identify the mechanisms of drug resistance so that one day it can be prevented. He conducts basic science and translational research as well as clinical studies in the hopes of finding better therapies. He also excels at teaching clinical fellows to rigorously evaluate cancer therapies, work toward improved patient outcomes, and provide empathetic patient care.

In recognition of his skill in training physicians, the NIH Clinical Fellows Committee selected him as the recipient for this year's Distinguished Clinical Teacher Award.

During his lecture, "Novel Paradigms in Cancer That May Lead to Better Therapies," Fojo pointed out the blind spots in modern-day cancer treatments: Even after years of research by NIH scientists and others, clinicians still rely on the same small arsenal of nonspecific cancer-fighting drugs to treat patients. And he bemoaned the proliferation of "me too" drugs that mimic successful therapeutics by targeting, ineffectively, the same signaling pathways.

Fojo challenged the audience to think more critically about cancer treatments and develop better ones. He also highlighted NIH's innovative research that explores how to get the immune system to attack tumors.

But better research wasn't all that was on Fojo's mind—empathetic patient care was, too. "The most important thing NIH clinical fellows can learn is how to take care of patients [who] are enrolled in clinical trials," he said. Fellows need to learn "how to listen to a patient, empathize with the patient, and be able to attend [to] their needs in diverse ways." ●

The Decker Lecture is named in honor of John Laws Decker, director of the Clinical Center (CC) 1983–1990, who was lauded by colleagues for both his bedside manner and his careful design of clinical trials. He oversaw major advances at the CC including the development of the positron emission tomography program and the clinical use of magnetic resonance imaging. To view the June 12, 2013 lecture, visit http://videocast.nih.gov/launch.asp?17996. For more on Fojo, visit http://www.irp.nih.gov/pi/antonio-fojo.

ERNIE BRANSON

At the Great Teachers Tenth Annual John Laws Decker Memorial Lecture, held in June, NCI senior investigator Antonio "Tito" Fojo explained how cancer therapy kills only part of a tumor—the part that's sensitive to a cancer-fighting drug. The rest is resistant and continues to grow.

NEWS FROM AND ABOUT THE NIH SCIENTIFIC INTEREST GROUPS

BCIG: A MIMIC-II STORY

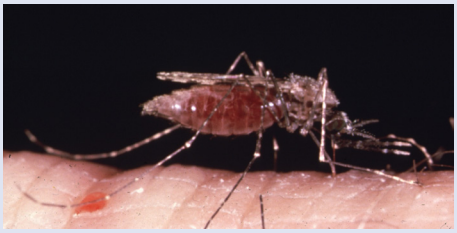
Monday, September 23, 10:30–11:30 a.m.
Natcher Conf. Center (Building 45), Room B

The NIH Biomedical Computing Interest Group (BCIG) presents "Knowledge Discovery for Critical Care: A MIMIC-II Story" by Mengling Feng (Harvard–MIT), Thomas Brennan (MIT), and Leo Anthony Celi (Harvard–Beth Israel). The data generated in the process of medical care have historically been underused and wasted. This waste was due in part to the difficulty of accessing, organizing, and using data on paper charts. In addition, variability in clinical documentation methods and quality made the problem even more challenging. Without a practical way to systematically capture, analyze, and integrate the information contained in the massive amount of data generated during patient care, medicine has remained largely an ad hoc process in which the disconnected application of individual experiences and subjective preferences continues to thwart continuous improvement and consistent delivery of best practices to all patients.

The intensive-care unit (ICU) presents an especially compelling case for clinical data analysis. The value of many treatments and interventions in the ICU is unproven, and high-quality data supporting or challenging specific practices are embarrassingly sparse. Over the past decade, the Massachusetts Institute of Technology, Beth Israel Deaconess Medical Center (BIDMC), and Philips Healthcare, with support from the National Institute of Biomedical Imaging and Bioinformatics, have partnered to build and maintain the Multi-parameter Intelligent Monitoring in Intensive Care database, which now holds clinical data from more than 40,000 de-identified stays in BIDMC ICUs and is shared online with researchers via PhysioNet. This system uses individual data to benefit the care of populations and population data to benefit the care of individuals.

For more information, contact Jim DeLeo at jdeleo@nih.gov. ●

Intramural Research Briefs



T. WELLEMS, NIAID

The female *Anopheles gambiae* mosquito can transmit malaria parasites as she takes a blood meal. NIH researchers recently tested an investigational malaria vaccine and found it to be safe and protective.

NIAID, CC: INVESTIGATIONAL MALARIA VACCINE FOUND SAFE AND PROTECTIVE

An investigational malaria vaccine has been found to be safe, to generate an immune response, and to offer protection against malaria infection in healthy adults, according to the results of an early-stage clinical trial conducted at NIH. The vaccine, known as the PfSPZ vaccine, was developed by scientists at Sanaria Inc. (Rockville, Md.) The PfSPZ vaccine is composed of live but weakened sporozoites of the species *Plasmodium falciparum*, the most deadly of the malaria-causing parasites.

An important challenge in the continued development of PfSPZ vaccine is that the vaccine currently is administered intravenously—a rare delivery route for vaccines. Previous studies at lower doses showed that the more common intradermal (into the skin) and subcutaneous (under the skin) routes did not yield as strong an immune response as the intravenous route. Several follow-up studies are planned, including research to evaluate the vaccine's different dose schedules, possible protection against other Plasmodium strains, and the durability of protection. The researchers may also evaluate whether higher doses administered subcutaneously or intradermally provide the same protection as found in this study. (NIH authors: R.A. Seder and others, *Science* DOI:10.1126/science.1241800)

NCI: HOW CANCER CHROMOSOME ABNORMALITIES FORM IN LIVING CELLS

For the first time, scientists have directly observed events that lead to the formation of chromosome abnormalities, called translocations, often found in cancer cells. Despite many years of research, just exactly how translocations form in a cell has remained a mystery. To better understand this process, NCI researchers created an experimental system in which they induced breaks in the DNA of different chromosomes in living cells. Using sophisticated imaging technology, they were then able to watch as the broken ends of the chromosomes reattached correctly or incorrectly inside the cells. The scientists were able to demonstrate that translocations can occur within hours of DNA breaks and that their formation is independent of when the breaks happen during the cell-division cycle. (NCI authors: V. Roukos, T.C. Voss, C.K. Schmidt, D. Wangsa, and T. Misteli, *Science* **341**:660–664, 2013)

NIA: DIABETES DRUG IMPROVES HEALTH AND EXTENDS LIFESPAN IN MICE

Long-term treatment with the type 2 diabetes drug metformin improves health and longevity of male mice when started at middle age, reported an international team of scientists led by NIA researchers. Metformin is known to enhance insulin sensitivity, prompting the conversion of glucose to energy and preventing its build-up in the liver. Metformin also reduce risk of health problems associated with metabolic syndrome, a condition characterized by an increased chance for heart disease, stroke, and 2 diabetes. (NIA authors: A. Martin-Montalvo, E.M. Mercken, S.J. Mitchell, H.H. Palacios, T.M. Ward, R.K. Minor, M. Bernier, Y. Yu, and R. de Cabo, *Nat Commun* **4**:2192, 2013)

Read more Research Briefs (and expanded versions of these) online at http://irp.nih.gov/catalyst/v21i5/research-briefs.

NIAAA: CHRONIC ALCOHOL USE SHIFTS BRAIN'S CONTROL OF BEHAVIOR

Chronic alcohol exposure leads to brain adaptations that shift behavior control away from an area of the brain involved in complex decision-making and toward a region associated with habit formation, according to a new study conducted in mice by NIAAA scientists. The findings provide insight into how excessive drinking affects learning and behavioral control at the neural level. (NIAAA authors: L. DePoy, R. Daut, J.L. Brigman, K. MacPherson, N. Crowley, O. Gunduz-Cinar, C.L. Pickens, R. Cinar, G. Kunos, D.M. Lonvinger, M.C. Camp, and A. Holmes, *Proc Natl Acad Sci USA* DOI:10.1073/pnas.1308198110)

NIEHS, NCI: 3-D IMAGES SHOW FLAME RETARDANTS CAN MIMIC ESTROGENS

By determining the 3-D structure of proteins at the atomic level, NIH researchers have discovered how some commonly used flame retardants, called brominated flame retardants, can mimic estrogen hormones and possibly disrupt the body's endocrine system. (NIH authors: R.A. Gosavi, G.A. Knudsen, L.S. Birnbaum, L.C. Pedersen, *Environ Health Perspect* DOI:10.1289/ehp.1306902)

NINDS: NIH RESEARCHERS DISCOVER HOW BRAIN CELLS CHANGE THEIR TUNE

Using advanced microscopic techniques, NINDS researchers recently showed that brief bursts of chemical energy coming from the mitochondria may fine-tune brain cell communication. Problems with mitochondrial energy production and movement throughout nerve cells have been implicated in Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and other major neurodegenerative disorders. The researchers think these results will ultimately help scientists understand how mitochondrial problems can lead to disorders in brain cell communication. (NINDS authors: T. Sun, H. Quiao, P-Y. Pan, Y. Chen, Z-H. Sheng, *Cell Rep* **4**:413–419, 2013) ●

Other Research News

PUBLISH AND FLOURISH

It's difficult to get official numbers, but if you do a search via PubMed, you will see that NIH researchers are authoring approximately 500 peer-reviewed journal articles each month. Some of these articles are featured on flat-screen monitors at the Clinical Center. Some are featured in the "Hot Topics" section of the relatively new Intramural Research Program (IRP) Web site at http://irp.nih.gov/news-and-events/hot-topics.

It's a fantastic number, considering we have about 1,000 labs at the NIH. Now the journal *Nature* has provided some documentation. According to the *Nature* Publishing Index 2012 (http://www.natureasia.com/en/publishing-index/global/), the NIH ranks #6 in the number of papers published in the *Nature* family of journals. Only #6, you ask? Well, of course, NIH isn't competitive in physics, astronomy, engineering, and many other fields dominated by the top five on the list: Harvard, Stanford, Max Planck, Massachusetts Institute of Technology, and the French National Centre for Scientific Research (CNRS).

Also, the CNRS and Max Planck organizations represent a good deal of their nation's investment in research; their rankings are equivalent to counting all NIH-supported research (extramural and intramural) with a little NSF and NASA thrown into the mix.

Nevertheless, if you break down the *Nature* numbers, the NIH IRP ranked #2 for *Nature Genetics*, *Nature Neuroscience*, *Nature Medicine*, and *Nature Immunology*; #3 for N*ature Structural and Molecular Biology*; and #5 for *Nature Chemical Biology*.

The bottom line is that we are a productive bunch, and I hope we can keep up that productivity and maintain our rankings through the inevitable downsizing that will occur if budgets remain flat or additional cuts are mandated.

Michael Gottesman, DDIR

HELA GENOME ACCESS BROKERED BY NIH

NIH announced a privacy agreement with the family of the late Henrietta Lacks to allow for the limited use of genomic sequence data from cells derived from her tumor, commonly known as HeLa cells. HeLa cells are the most widely used human cell line in existence today and have been used in the development of modern vaccines, cancer treatments, in vitro fertilization techniques, and other medical advances. Lacks died of cervical cancer in 1951, before scientists were required to get permission to use a patient's cells in research.

This spring, German scientists sequenced the genome of a HeLa cell line and posted the data in a public database. The data had the potential to reveal private genetic information about the Lacks family. NIH Director **Francis Collins** and NIH Deputy Director for Science, Outreach, and Policy **Kathy Hudson** met with members of the Lacks family to discuss the research. They settled on an agreement for use of HeLa data: Published genomes will be stored in an NIH-controlled database, accessed only by researchers who agree to terms of use defined by a panel that includes Lacks family members. Collins noted the new policy allows for public data sharing while showing respect that NIH and scientists have for the contributions of the Lacks family. (K.L. Hudson and F.S. Collins, *Nature* **500**:141–142, 2013)

Rebecca Baker, NIAID

NIH DIRECTOR'S CHALLENGE INNOVATION AWARDS

The NIH Director's Challenge Innovation Awards program is supporting 10 intramural projects for research on antibacterial drug resistance. The program, which provides seed money to stimulate innovative, high-impact research, gives priority to applications that involve collaborations among PIs from multiple NIH Institutes and Centers. This year, $750,000 is supporting the projects, with awards ranging from $45,000 to $100,000 per year.

FY2013 and FY2014 Awards:

Anirban Banerjee (NICHD) with researchers from NIAID: Structural and Chemical Biology Approach to Targeting MraY—an Integral Membrane Enzyme in the Bacterial Peptidoglycan Biosynthesis Pathway

Robert Danner (CC) with researchers from NCI and NHGRI: Engineering a Multivalent Bacteriophage Targeting KPC+ *K. pneumoniae*

John Barrett (NHLBI) with researchers from CC and NIAID: Th17 Cells for Treatment of Carbapenem Resistant *Klebsiella pneumoniae*

Yasmine Belkaid (NIAID) with researchers from NCI, NHGRI, and NIAID: Role of the Microbiota in KPC-producing Klebsiella Pneumonia Infection

Karen Frank (CC) with researchers from NCI and NHGRI: Carbapenemase blaKPC Horizontal Transfer between Enterobacteriacae

Julie Segre (NHGRI) with researchers from CC: Microbiome Studies of CC Patients at Risk for Multidrug-Resistant Bacteria

Susan Buchanon (NIDDK) with researchers from NCI: Klebsiella Capsule as a Target for Novel Antibiotics: Genetics, Structure/function and Small Molecule Screens

Adrian Ferre D'Amare (NHLBI) with researchers from NCI: High-throughput Discovery of Antibiotics Against Bacterial Riboswitches

Matthias Machner (NICHD) with researchers from NCATS: Discovering "Smart" Drugs That Target Only Pathogenic Bacteria

Roger Woodgate (NICHD) with researchers from NCATS: Inhibitors of LexA/DinR Cleavage Combat Evolution of Antibiotic Resistance

The next competition is scheduled for FY2015. For more information, visit http://sigs.nih.gov/challenge/Pages/FundedProjects.aspx.

NHGRI-Smithsonian Collaboration

CONTINUED FROM PAGE 1

MAGGIE BARTLETT, NHGRI

The high-tech exhibition, developed by the Smithsonian and NHGRI staff, uses interactive touch screens and high-definition graphics, three-dimensional models, custom animations, and videos of real-life stories to explain the basics of genomics and DNA sequencing technology and to examine both the benefits and the challenges that genomics presents.

on a large screen. The people describe their participation in the research and how the results were able to impact their lives.

Visitors are also invited to explore genetic and environmental disease risk with a "wheel of chance." This interactive activity illustrates that genetic risk factors alone do not determine whether one gets a particular disease. It is important for people to grasp the concept that a combination of genetic, environmental, and random factors influences their chances of developing a particular disease.

The exhibition was developed by museum and NHGRI staff. NHGRI's Division of Policy, Communications, and Education, and its Education and Community Involvement Branch (ECIB) directed NHGRI's involvement in the project. ECIB leads NHGRI's involvement in helping to build the public understanding of the role of genomics in human health and of the accompanying ethical, legal, and social issues. ECIB provides educational information on genetics and genomics, distributes information on new genomic technologies, and increases awareness of genomic advances.

NHGRI expects to be able to reach millions of people through the exhibitions. The museum hosts roughly seven million visitors a year, ranging from school-aged children to retirees, from all over the world. "If I published 100 papers a year, no way would seven million people read them," **Lawrence Brody**, chief of NHGRI's Genome Technology Branch, pointed out.

NHGRI wants to "enhance the public's genomic health literacy [and] encourage understanding of how genomic research is important to individuals, their families and communities," said ECIB education-outreach specialist **Christina Daulton**.

In addition to disseminating information, the exhibition also *gathers* it. Visitors can voluntarily answer survey questions such as "Is there anything about your genome that you want to remain a mystery?" and "If you could find out one thing about your genome, what would it be?" This Social Genomics Project led by intramural researchers provides the public an opportunity to consider the questions and see how other people have responded. It is expected that thousands of people will participate. ●

The exhibition will be at the National Museum of Natural History through September 2014. Afterwards, it will tour North America through 2018. For more information, visit http://www.mnh.si.edu/exhibits/genome or http://unlockinglifescode.org.

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
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
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

Making Progress Against Rare Adrenal Tumors

BY REBECCA LAZERATION, NICHD

People suffering from rare diseases often feel isolated and have few opportunities to share their experiences with one another. But at NIH recently, people with two types of rare adrenal tumors—pheochromocytoma and paraganglioma—met at a gathering that included physicians and scientists to learn about the latest in research and treatments. On June 20 and 21, the second annual International Patient Symposium on Pheochromocytoma, hosted by the Pheo Para Alliance (Arlington, Va.), was held in Building 60 and featured 27 speakers including several from NIH.

Pheochromocytomas are rare, usually benign, tumors that originate inside the adrenal glands; paragangliomas are similar tumors that form outside the adrenals. These difficult-to-diagnose tumors—which can occur at any age but are most common between the ages of 30 and 50 years old—can trigger the release of excess adrenaline and dopamine, causing dangerously high blood pressure, pounding headaches, and heart palpitations. Two to eight people per million are diagnosed with these tumors each year. The conventional treatment is the surgical removal of the tumor sometimes accompanied by chemotherapy.

"Right now, 50 percent of cases go undiagnosed and treatments are suboptimal or not effective," said **Karel Pacak**, a senior investigator and a leading pheochromocytoma researcher in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Pacak, who focuses on improving the diagnosis and treatment of pheochromocytoma and paraganglioma, advanced imaging strategies, and novel therapeutic options, went on to describe recent research on the genes associated with the onset of these tumors and NIH's exploration of diagnostic imaging techniques such as positron emission tomography scans.

Other NIH scientists presenting at the symposium included NICHD staff clinician and genetics counselor **Margarita Raygada**, National Cancer Institute senior investigator **Tito Fojo** (see article about his work on page 7), and Clinical Center radiologist **Aradhana Venkatesan**.

Raygada is interested in the improved management of chronic genetic conditions and described the seven major gene mutations that predispose an individual to pheochromocytoma and paraganglioma. The mutations are typically passed on from parent to child, but can occur spontaneously, she said. "Every single patient who has pheochromocytoma [or] paraganglioma has to be offered genetic testing" to determine whether other members of the family are at risk of having mutated genes.

Fojo, an expert in the mechanisms of chemotherapeutic drug resistance, presented an overview of the different types of chemotherapy used to treat certain pheochromocytoma and paraganglioma tumors. His findings suggest that tumors created by a mutation in the *SDHB* gene respond well to chemotherapy, whereas tumors resulting from other mutations do not.

Venkatesan, a radiologist and imaging clinician, described a relatively new treatment that has become an alternative to the surgical excision of adrenal tumors: radiofrequency ablation (RFA), which uses high-energy radio waves to heat and destroy cancerous cells. RFA has been in use for a long time to treat nerve-related chronic pain, heart arrhythmias, and some cancers, but has only recently been expanded to treat adrenal tumors. Venkatesan has demonstrated that RFA is successful in destroying small and large tumors, but because it's been in use for such a short time, she strongly advises patients who are considering it to "seek out experienced locations" such as the NIH Clinical Center.

BILL BRANSON

Karel Pacak, a senior investigator in NICHD, was one of several NIH researchers who presented their work on improving the diagnosis and treatment of rare adrenal tumors—pheochromocytoma and paraganglioma—at the International Patient Symposium on Pheochromocytoma, held at NIH in June.

"It is important that we at the National Institutes of Health work with research and patient groups in the United States and around the world" to advance the research, Pacak said. "Together we stand a chance; separately we fail." ●

YOUR IDEAS WELCOME

We are always looking for ideas for stories about intramural research and investigators, behind-the-scenes activities that enable research to happen, new methods developed at NIH, and more. Don't hesitate to get in touch. E-mail catalyst@nih.gov or call Managing Editor Laura Carter at 301-402-1449.

Recently Tenured


DONALD COOK, NIEHS


STEVEN VOGEL, NIAAA


KYLIE WALTERS, NCI


KATHERINE WARREN, NCI


NICHOLAS WENTZENSEN, NCI

DONALD COOK, PH.D., NIEHS

Senior Investigator, Immunogenetics Group, Laboratory of Respiratory Biology

Education: McGill University, Montreal (B.S. and Ph.D. in microbiology and immunology)

Training: Department of Pathology, University of North Carolina at Chapel Hill School of Medicine (Chapel Hill, N.C.)

Before coming to NIH: Principal scientist, Schering-Plough Research Institute (Kenilworth, N.J.); assistant professor, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center (Durham, N.C.)

Came to NIH: In 2005

Selected professional activities: Editorial board for *American Journal of Respiratory Cell and Molecular Biology and Frontiers in Chemoattractants*; adjunct assistant professor, Department of Immunology, Duke University School of Medicine

Outside Interests: Training for short triathlons; playing blues on the piano

Research Interests: My lab uses gene-targeted mice lacking chemokines, cytokines, or signaling molecules to understand the molecular and cellular mechanisms that trigger immune responses to inhaled allergens. We focus on pulmonary dendritic cells that initiate immune responses to aeroallergens. By purifying discrete populations of dendritic cells from the lung, we have been able to assign specific functions to them.

We also study how these functions are affected by gene-environment interactions. We have found that bacterial products, such as lipopolysaccharide and flagellin, are found in house dust and promote allergen-specific immune responses. We also examine how environmental agents affect the function of airway epithelial cells.

We are testing the hypothesis that communication between airway epithelial cells and nearby dendritic cells determines the nature of immune responses to inhaled allergens. An improved understanding of these signaling pathways may lead to therapeutic strategies that target specific types of asthma, including steroid-resistant asthma.

STEVEN S. VOGEL, PH.D., NIAAA

Senior Investigator; Chief, Section on Cellular Biophotonics, Laboratory of Molecular Physiology

Education: City College of New York (B.S. in biology); Columbia University, New York (Ph.D. in biochemistry and molecular biophysics)

Training: Postdoctoral training at NIDDK, NICHD, and NINDS

Before returning to NIH: Associate professor and director of the Cell Imaging Core Laboratory at the Medical College of Georgia (Augusta, Ga.)

Came to NIH: In 1989 for training; in 2003 joined NIAAA

Selected professional activities: University of Virginia FRET Microscopy Workshop Faculty

Outside interests: Playing acoustic 6– and 12–string guitar; bicycle commuting

Research interests: In cells, proteins act together to form assemblies that mediate cellular processes. Considering that protein complexes are so ubiquitous and that they perform so many functions, it is no surprise that many human diseases arise from inappropriate protein interactions. A major obstacle to understanding these diseases, however, is the paucity of robust methods for studying protein interactions under physiological (natural) conditions.

Through my research, which lies at the intersection of physics, bioengineering, and neurobiology, I have been developing new forms of fiber-optic microscopy and spectroscopy to better monitor protein interactions inside living cells and animals. These approaches are based primarily on Förster resonance energy transfer (FRET) and fluctuation correlation spectroscopy (FCS). I am especially interested in the interactions of synaptic proteins that are involved in regulating memory, behavior, and addiction.

My long-term goal is to use FRET and FCS to help identify drugs that can target

and correct abnormal protein interactions inside cells. The technology that we are developing will provide tools for delineating the steps in protein-complex conformational changes; a means of rapidly identifying sites of protein interactions; a way to help decipher which protein partners interact within large assemblies of proteins; and the means for confirming whether specific interactions occur under physiological conditions even when those interactions occur deep within the brain of a living mouse.

KYLIE WALTERS, PH.D., NCI-CCR

Senior Investigator; Head, Protein Processing Section, Structural Biophysics Laboratory

Education: Wesleyan University, Middletown, Conn. (B.A. in molecular biology and biochemistry and concentration in biophysics); Harvard University, Cambridge, Mass. (Ph.D. in biophysics)

Training: Postdoctoral training in pathology at Harvard Medical School (Boston)

Before coming to NIH: Associate professor of biochemistry, molecular biology, and biophysics, University of Minnesota (Minneapolis)

Came to NIH: In July 2013

Selected professional activities: Has served as NIH Membrane Biology and Protein Processing study section member since 2008

Outside interests: Enjoys outdoor activities with husband and two children; swimming; kayaking and canoeing; running

Research interests: We use nuclear magnetic resonance (NMR) and other biophysical techniques to reveal the three-dimensional structure and dynamic properties of proteins and complexes associated with cancer biology. We are interested in ubiquitin signaling pathways, especially those involved in protein quality control. Ubiquitins, small regulatory proteins, regulate gene transcription, protein degradation, cell death, and other cellular activities. We study how misfolded proteins are recognized and cleared from cells and how targeted ubiquitinated proteins are identified and processed by the proteasome.

The proteasome is the major machinery in eukaryotes (organisms whose cells contain a nucleus and other organelles) for regulating protein degradation. It contains enzymes called proteases, which degrade protein substrates. The proteasome can be "capped" by multiple regulators. We focus on the 19S regulatory particle, which contains the proteins that recognize and process ubiquitinated substrates. Human pathologies associated with malfunctions of the ubiquitin-proteasome pathway include autoimmunity and inflammation, neurodegeneration, and cancer. The proteasome inhibitors bortezomib and carfilzomib are used to treat certain hematological cancers; other inhibitors are being tested in clinical trials. Our long-term goal is to reveal quality-control mechanisms in the ubiquitin-proteasome pathway in order to manipulate the lifespan of oncoproteins and tumor suppressors.

KATHERINE WARREN, M.D., NCI-CCR

Senior Investigator; Head, Pediatric Neuro-Oncology Section, Pediatric Oncology Branch

Education: North Adams State College, North Adams, Mass. (B.S. in medical technology); Tufts University School of Medicine, Boston, Mass. (M.D.)

Training: Residency in pediatrics at Children's National Medical Center (Washington, D.C.); fellowship in pediatric hematology and oncology at NCI

Came to NIH: In 1993 for training; became a tenure-track investigator in 2003

Selected professional activities: Active in the Pediatric Brain Tumor Consortium (holds leadership positions) and the Children's Oncology Group

Outside interests: Spending time with family; traveling

Research interests: I am interested in developing better treatments for children who have central nervous system tumors (CNS) tumors. Pediatric and adult CNS tumors differ, so data from adults may not apply to pediatric patients. We are conducting clinical trials to test new agents for treating CNS tumors in children; exploring new methods of treatment delivery to tumors; noninvasively evaluating and imaging the brain to assess tumor characteristics; and studying neurotoxicity resulting from treatment.

A significant proportion of pediatric brain tumors are benign or low-grade, and the five-year survival rate is over 70 percent. But the survival rate is dismal for children with malignant tumors such as diffuse intrinsic brainstem gliomas, high-grade gliomas, and recurrent malignant tumors.

Treatments for pediatric CNS tumors include surgery, radiation, and chemotherapy. Chemotherapy is not always successful, however, because the blood-brain barrier limits the delivery of the drugs to the tumor site. And such treatment has little, if any, effect on malignant gliomas and recurrent malignant tumors or against the brainstem tumor diffuse intrinsic pontine glioma (DIPG). Surgery is not an option for DPIG because the tumor is in the brainstem, which controls vital functions such as heartbeat and breathing. Most children with DIPG die within one year of diagnosis.

Although hundreds of clinical trials have been performed with DPIG over three decades, there's been no progress in improving outcomes. We know little about the biology of this disease partly because biopsies are not routinely obtained in the United States so there's a scarcity of tissue available for study. My research has focused on developing new agents for treatment; doing noninvasive evaluations; using autopsy tissue to study tumor biology; and developing novel approaches to deliver chemotherapeutics directly.

CONTINUED ON PAGE 14

Recently Tenured

CONTINUED FROM PAGE 13

NICOLAS WENTZENSEN, M.D., PH.D., M.S., NCI-DCEG

Senior Investigator, Hormonal and Reproductive Epidemiology Branch

Education: Heidelberg University Ruperto Carola, Heidelberg, Germany (M.D. and Ph.D. in applied tumor biology); Johannes Gutenberg University of Mainz, Mainz, Germany (M.S. in epidemiology)

Training: Residency in general surgery and postdoctoral research in applied tumor biology and molecular epidemiology, Heidelberg University; postdoctoral research in NCI-DCEG

Came to NIH: In 2007 as a visiting fellow; became tenure-track investigator in 2009

Selected professional activities: Senior editor, *Cancer Epidemiology, Biomarkers and Prevention*; member of the Practice Improvement in Cervical Screening and Management Working Group and co-author of the 2012 consensus cervical cancer screening-guidelines publications; member of the steering committee, working-group leader, and writing-team member for the 2012 American Society for Colposcopy and Cervical Pathology management-guidelines update; faculty of various international scientific conferences

Outside interests: Running; listening to classical music; playing guitar

Research interests: I am interested in the origins of gynecologic cancers and improving screening and prevention efforts. My research focuses on understanding the heterogeneous etiology of cervical, endometrial, and ovarian cancers and their precursors. I am analyzing risk factors that drive the development of these malignancies and looking at biomarkers that could identify women at high risk.

Although most cervical cancers are caused by human papillomavirus (HPV) infections, only a small subset of women infected with HPV progress to invasive cancer. We are conducting profiling studies on more than 2,000 tissue samples collected from women with cervical HPV infections, precancer, and cancer to elucidate the transitions from cervical HPV infection to precancer and from precancer to invasive cancer.

We are also interested in improving colposcopy-guided biopsy procedures, which are used to screen for cervical cancer but tend to be inaccurate and frequently miss the worst lesions on the cervix. We conducted the Biopsy Study, to quantify the inaccuracy of colposcopies. We also hope to expand our understanding of the clonal relationship of multiple lesions on the cervix.

In addition, we are exploring the etiology of ovarian cancer, which is complex, poorly understood, and often fatal. Because the low prevalence of ovarian cancer limits molecular epidemiology studies, we are pooling cases from several NIH-based and extramural cohorts. We are conducting large epidemiologic studies and profiling ovarian tumor tissues. We hope to improve the classification of ovarian tumors and evaluate new early-detection approaches that can be translated into clinical or screening applications. In other studies, we are investigating how inflammatory markers and endogenous hormone exposures to ovarian epithelium promote tumor growth. ●

NIH Director Visits Camp Fantastic

ERNIE BRANSON

NIH Director **Francis Collins** donned a dragon hat recently when he visited Camp Fantastic (Front Royal, Va.) to help campers celebrate the theme Medieval Magic. The weeklong camp lets children in all stages of cancer treatment shed their cancer image and feel like normal kids again. Camp Fantastic is the hallmark program of Special Love, a nonprofit organization that provides cancer families a network of support. Camp medical director **Stephen Chanock** (newly appointed scientific director for NCI-DCEG) and other NIH volunteers make it possible for children to attend the camp at any stage of their treatment. Shown here, Collins enjoys eating dinner with the campers.

THE ANITA B. ROBERTS FALL LECTURE

Tuesday, September 17, 2013, 1:00 p.m.
Lipsett Amphitheater (Building 10)

Wei Yang, section chief of NIDDK's Laboratory of Molecular Biology, will give the fall seminar honoring the memory of Anita B. Roberts, former chief of NCI's Laboratory of Cell Regulation and Carcinogenesis. Yang's talk, "Seeing Is Believing: Functional Biology at Atomic Resolution," is sponsored by the NIH Women Scientist Advisors Committee and the Office of Research on Women's Health. Individuals who need reasonable accommodations to participate should contact Margaret McBurney at 301-496-1921 and/or Federal Relay, 1-800-877-8339, five days before the lecture.

NIH SUPPLY CENTER BLOWOUT SALE!

Hurry! The NIH Supply Center and its Self Services Stores (SSS) are discounting a huge of amount of stock to make room for new items. Office and laboratory items are being reduced weekly. Get these products while supplies last. Our goal is to provide more responsive support to our customers. Self Service Store campus locations (Monday–Friday, 8:00 a.m.–4:00 p.m.): BLDG 10, Room B2B41 (301-496-2051); Building 31, Room B1A47 (301-496-4430). View the list of reduced items at http://nihsc.od.nih.gov/Promotions.aspx.

WEDNESDAY AFTERNOON LECTURE SERIES

SPECIAL: Begins Monday, September 9
Most Wednesdays, 3:00–4:00 p.m.
Masur Auditorium (Building 10)

The NIH Director's Wednesday Afternoon Lecture Series, colloquially known as WALS, is the highest-profile lecture program at the NIH. Each season includes some of the biggest names in biomedical and behavioral research. For more information, contact Jackie Roberts (301-594-6747 or robertsjm@od.nih.gov) or visit the WALS Web site at http://wals.od.nih.gov. Here's a sampling:

MONDAY, September 9: Cori Bargmann (The Rockefeller University), "Neuromodulatory Circuits and Motivated Behavior"

September 11: Jeffrey Esko (University of California, San Diego), "Proteoglycans: Arbiters of Lipoprotein Metabolism"

September 25: Moyses Szklo (Johns Hopkins Bloomberg School of Public Health), "Epidemiology: Back to Translation"

October 2: Taekjip Ha (University of Illinois at Urbana-Champaign), "Genome Maintenance up Close and Personal: Eavesdropping on Single Molecular Conversations"

October 3 (Thursday): Shinya Yamanaka (Kyoto University and Gladstone Institutes), "Recent Progress in iPS Cell Research towards Regenerative Medicine"

CARDIOVASCULAR REGENERATIVE MEDICINE

September 25–26, 2013
Natcher Conference Center (Building 45)

The NHLBI Symposium on Cardiovascular Regenerative Medicine, will bring together experts in basic stem cell biology, as well as clinical cardiovascular medicine, to discuss advances and potential clinical applications. For more information and to register, go to http://www.nhlbi.nih.gov/news/events/2013-nhlbi-cvregenmed.

NIH RESEARCH FESTIVAL

October 7–11, 2013
FAES Academic Center (Building 10)
Masur Auditorium (Building 10)

Find out what's going on in NIH research: Attend lectures, minisymposia, poster sessions, and more during this weeklong festival. Don't miss the special poster session on Monday, October 7, at which the scientific directors will showcase their work (4:00-6:00 p.m.). For more information and schedules, visit http://researchfestival.nih.gov or contact Jacqueline Roberts (301-594-6747 or robertsjm@od.nih.gov).

NATIONAL GRADUATE STUDENT RESEARCH CONFERENCE

October 6–8, 2013
FAES Academic Center (Building 10)
Natcher Conference Center (Building 45)

Ninety advanced graduate students from across the United States will share their own cutting-edge research and learn about scientific advances being made at NIH. NIH investigators will have the opportunity to recruit participants as postdoctoral fellows. Agenda: career- and professional-development workshops; a panel of former NIH trainees discussing their careers; and NIH Research Festival poster sessions. NIH investigators and postdocs are encouraged to visit the posters to discuss potential collaborations and learn firsthand about novel techniques and approaches that could enhance their investigations. For more information visit https://www.training.nih.gov/events/recurring/nih_national_graduate_student_research_festival.

INTRODUCTION TO THE PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH

October 15, 2013–March 24, 2014
Monday and Tuesday evenings
5:00–6:30 p.m., Bethesda campus
Registration deadline: October 8, 2013

This free course is for physicians and other health professionals planning a career in clinical research. A certificate will be awarded on successful completion of the course. Topics include: basic epidemiologic methods; ethical and legal issues; the role of institutional review boards; the monitoring of patient-oriented research; infrastructure; developing and funding research studies; and more. It's suggested that participants acquire a copy of the textbook, *Principles and Practice of Clinical Research, Third Edition*. For more information or to register, visit http://www.cc.nih.gov/training/training/ippcr/application.html or call 301-496-9425. An e-mail confirmation will be sent to those accepted into the program. ●

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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 *NIH Catalyst* pages.

More Online

To read expanded versions of the *NIH Catalyst* articles, go to (http://irp.nih.gov/catalyst/v21i5).

OTHER NEWS

Town Hall Meeting at NIH

BILL BRANSON

U.S. Secretary of Health and Human Services **Kathleen Sebelius** (right) visited the NIH on August 1 for a tour that included the Children's Inn and an NCI lab; meetings with NIH leaders; and a Town Hall Meeting for NIH staff. At the Town Hall Meeting, hosted by NIH Director **Francis Collins** (left), Secretary Sebelius recognized the "dazzling" contributions of NIH researchers despite budget cuts and uncertainty. As she answered questions submitted in advance by members of the NIH community, she reaffirmed her commitment to funding medical research and celebrated NIH advancements including studies of "super-bug" hospital infections at the NIH Clinical Center and improved cancer treatments resulting from genomic sequencing.

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

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