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NIH Research Festival

Collaboration and Innovation

BY CATHERINE EVANS, NCI

Nobel laureate Marshall Nirenberg inspired countless scientists around the world, including this year's Research Festival organizers. The festival, which took place October 5–8, 2010, exemplified Nirenberg's interest in the diversity of scientific research and his dedication to the spirit of collaboration.

The Research Festival "serves a very important role in helping cross-collaborations and letting people know what's going on in other institutes," said Festival co-chair Richard Nakamura (NIMH).

The plenary session, which featured six scientific talks reflecting Nirenberg's varied interests, was dedicated to the legendary scientist; 120 presentations at concurrent symposia and more than 600 posters represented a broad range of NIH research including many trans-NIH projects; and more than 400 vendors displayed the latest in biomedical equipment, technologies, and services. The week ended with a memorial for Nirenberg as well as the opening of the NIH Office of History's exhibit—in a hallway near Lipsett Amphitheater in Building 10—that highlighted his career.

"The idea of dedicating the 2010 Research Festival plenary session to the memory of Marshal Nirenberg was to illustrate how his pioneering accomplishments have transformed today's biomedical research," said Festival co-chair Richard Leapman (NIBIB). "We also wanted to highlight the thread of Nirenberg's scientific

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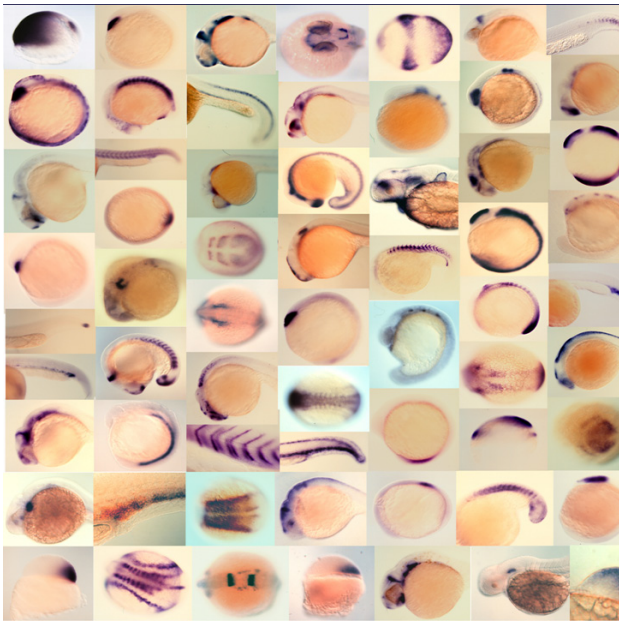
Something Fishy

Zebrafish Researchers Get a New Home

BY SARAH FREEMAN

There's something fishy going on at NIH. Tens of thousands of tiny, transparent, striped fish are taking over the three subterranean levels of Building 6—in a new 10,000-square-foot Shared Zebrafish Facility. It not only dwarfs any of the 10 existing zebrafish facilities on campus, but it is one of the largest in the world.



MICHAEL TSANG, NICHD

Montage of expression patterns as visualized by in situ hybridization for different zebrafish genes. The images represent different stages of embryos (from the gastrula to three-day-old larvae) that are hybridized with different probes.

Currently more than a dozen researchers from NHGRI, NICHD, NCI, NHLBI, NEI, and NIAAA use zebrafish, a.k.a. *Danio rerio*, as an animal model to gain insights into vertebrate development and human diseases. The minnow-size tropical freshwater fish are easy to breed and produce hundreds of eggs that are fertilized externally. The eggs develop—outside the mother—into larvae in under three days and become full-blown adults, capable of reproducing, in just three to four months. The fish are transparent so it's easy for scientists to observe and manipulate their development.

Zebrafish research has been going on since the late 1960s. It really took off, however, in the mid-1990s when scientists recognized the tiny fish as a vertebrate model with

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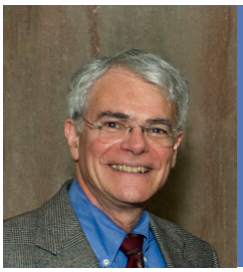

A Historic Intramural-Extramural Partnership to Nurture the Next Generation of Clinical Researchers

BY MICHAEL GOTTESMAN, DDIR

NIH IS EMBARKING ON AN EXCITING initiative to provide up to 11 years of protected research support for early-career clinical researchers. The program is designed to increase the diminishing pool of talented clinical and translational researchers at academic institutions and NIH. This effort is in response to numerous calls from high-level review groups as well as our own strong belief that we need to do more to encourage and foster clinical research careers in the current economic climate. By combining intramural and extramural research support, the new program will make careers in clinical research more attractive and perhaps recapture the "golden years" of NIH intramural research when talented investigators routinely spent formative time here before moving on to leadership positions in academic medical centers.

How will this initiative work? Careers begin in the intramural program with the opportunity to later move to an extramural setting. Interested NIH institutes and centers have specified areas of clinical research that they wish to support. We have sent a call out for clinical fellows and early-career clinical investigators to apply. A star-studded group of extramural clinical investigators—organized by the Center for Scientific Review—will evaluate applications and provide a list of the most highly qualified and relevant applications to NIH scientific and clinical directors. The scientific directors will determine—with my review and approval—which candidates will be placed on the NIH tenure track.

At NIH, our Boards of Scientific Counselors will regularly evaluate these newly hired researchers' programs. After five to seven years, if all goes well, each candidate will be reviewed again by a group of distinguished extramural clinical investigators, and by mutual agreement between the NIH and the candidates, a decision will be made as to whether they will stay on as tenured senior investigators at NIH (after appropriate intramural review) or be eligible for up to five years of extramural support (up to $500,000 a year plus overhead) in an extramural faculty position.

> The new program will provide early-career investigators with up to 11 years of protected research time.

Ideally, this program will provide early-career clinical investigators with up to 11 years of protected research time to establish their clinical research careers. To help ensure success, NIH will partner with the Lasker Foundation, which has agreed to help provide outstanding clinical mentors and a venue for meetings. To honor the contributions of Albert and Mary Lasker, who, as strong proponents of NIH-supported research, galvanized public and Congressional support for the NIH, we will call the participants "Lasker Clinical Research Scholars at the NIH." Additional partners in the private sector will be welcomed. We trust that these scholars will benefit from changes in NIH's ongoing management and oversight of clinical research activities, including access to protocol navigators to streamline their research activities.

The size of this program depends on investments in clinical research made by our institutes and centers. We hope to have up to five or more new Lasker Clinical Research Scholars each year, with a steady state of at least 20 to 30 investigators at NIH, and possibly more. It is hard to predict how many will stay here and how many will choose to leave for academia, but we expect that the Lasker scholars who leave will continue their collaborations with NIH as part of the overall effort to make the Clinical Center a national resource for all clinical investigators.

A program of this size and impact could not be birthed without the help of many individuals and committees. I thank the scientific directors, the clinical directors, the Extramural Program Management Committee, the Extramural Activities Working Group (EAWG), and the institute and center directors for their encouragement. And I especially want to thank Richard Wyatt and Charles Dearolf in my office, Deputy Director for Extramural Research Sally Rockey and Walter Schaffer in her office, and NINDS Director Story Landis, co-chair of the EAWG, for their hard work and creative input into this program. For more information visit http://www.nih.gov/science/laskerscholar. ●

NIH OBITUARIES

IN 2009 (Additions to December 2009 listing)

Matthias Kraus (died on December 1, 2009, at 55), who worked at NCI 1981-1995, was a pioneer in the study of ErbB proteins, members of the epidermal growth factor receptor family.

Ann L. Sandberg (died on December 31, 2009, at 71), who retired in 2005, was an immunologist whose work advanced the understanding of certain proteins that are now known to be instrumental in immunity.

Josiah Francis Wedgwood (died on November 27, 2009, at 59), an expert in primary immune deficiency and autoimmune diseases, was a pediatrician and section chief at NIAID.

IN 2010

Alexander Adler (died on June 22, 2010, at 90) was the founding editor of the *NIH Record* and a longtime NIH medical writer and administrator.

Jane M. Bell (died on July 17, 2010, at 76) began her career at NIH as an NCI chemist in 1955; joined the National Heart Institute in 1961; left federal service in 1967; and, in 1982, returned to NIH to work at NIA.

Phyllis W. Berman (died on May 23, 2010, at 82), was a child development psychologist in NICHD from the early 1980s until 1993.

Monique C. Braude (died on January 2, 2010, at 84) was a pharmacist at NIDA from the mid-1950s until she retired in 1987.

Sally D. Breul (died on March 16, 2010, at 88) was a researcher at NIDA from the 1970s through the early 1990s.

Robert N. Butler (died on July 4, 2010, at 83), who became the founding director of NIA in 1976, started his career at NIMH in 1955. He won the Pulitzer Prize for his book *Why Survive? Being Old in America*. He left NIH in 1982 to become the director of the new department of geriatrics at Mt. Sinai School of Medicine (New York).

Joan Shih Carducci (January 22, 2010, at 76) was a chemist at NHLBI from 1987 to 2000, until she retired to run a cooking school and write a cookbook.

Robert M. Chanock (died on July 30, 2010, at 86) was a world-renowned virologist and former chief of the Laboratory of Infectious Diseases, NIAID. He joined the NIAID Laboratory of Infectious Diseases in 1957. He and colleagues were the first to identify and characterize human respiratory syncytial virus; discovered the four parainfluenza viruses; isolated new strains of rhinovirus and coronavirus; and isolated and characterized *Mycoplasma pneumoniae*.

Hank Fales (died on October 28, 2010, at 83) was a research chemist and chief of NHLBI's Laboratory of Chemistry. He helped to expand the field of mass spectroscopy.

John E. (Jack) Folk (died on December 27, 2010, at 85) was a scientist emeritus in NIDCR, who spent his entire career at the NIH. After joining the National Institute of Dental Research in the early 1950s, he made groundbreaking advances by discovering and characterizing several new enzymes. He retired in 2000, but continued to volunteer as a chemist in NIDDK and NIDA.

Ira Green (died on October 22, 2010, at 84) was a world-leading immunologist and former senior investigator in NIAID's Laboratory of Immunology.

Carl Henn (died on July 27, 2010, at 48), in the Office of Acquisition and Logistics Management, had 23 years experience in federal contracting, 20 with NIH.

Leon A. Heppel (died on April 9, 2010, at 97) played a crucial role in cracking the genetic code when he was at NIH in the 1950s by developing techniques for synthesizing pieces of RNA. He left NIH in 1967.

Harvey Itano (died on May 8, 2010, at 89) was an NIAMS researcher whose studies provided a breakthrough on sickle cell disease. He worked at NIH until 1970, when he was recruited to the University of California, San Diego, School of Medicine.

James W. Jacobson (died on December 23, 2010, at 67) was a research administrator who had spent the past 18 years at NCI, most recently as acting associate director of its cancer diagnosis program.

Karen A. Johnson (died on August 19, 2010, at 64) was a research oncologist and chief of the breast and gynecologic cancer research group in NCI's Division of Cancer Prevention.

Alan I. Kay (died on June 17, 2010, at 75) was a Washington-area real estate magnate whose company oversaw the construction of NIH's Children's Inn, which opened in 1990.

David B. Keister (died on July 15, 2010, at 70) was a malaria researcher and parasitologist at NIAID from 1966 to 2006.

Jin H. Kinoshita (died on August 20, 2010, at 89) was a pioneer in the biochemical study of cataracts and former scientific director at NEI.

Howard A. Moss (died on October 16, 2010, at 81), a senior scientist in NIMH (1960s–1980s), did research in developmental psychology.

Jeffrey Nadler (died on November 26, 2010, at 60) served as acting director of the therapeutics research program in NIAID's division of AIDS in 2007–2010.

Marshall W. Nirenberg (died on January 15, 2010, at 82), a geneticist in NIAMS, won the Nobel Prize in Physiology or Medicine in 1968 for deciphering the genetic code.

Mary Frances Picciano (died on August 29, 2010, at 64) was a senior nutrition research scientist in the Office of Dietary Supplements. Her husband, John Milner, is chief of NCI's nutritional science research group.

Elaine Ron (died on November 20, 2010, at 67) was a senior investigator at NCI and one of the leading experts in radiation epidemiology and in the causes of thyroid cancer.

Shahriar (Shah) Saleh (died on December 3, 2010, at 62) was a professional engineer who worked for NIH for more than 20 years. He was also a highly respected master of Persian classical music performance and theory.

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FROM A SUMMER INTERN

An Eye-Opening Experience

BY ANDREW ZUREICK, DARTMOUTH COLLEGE CLASS OF 2013

The crowded Metro train screeched to a stop. "Medical Center, red line to Shady Grove," the driver announced over the loudspeaker. I threw my backpack over my shoulder, climbed the monstrous escalator, and walked out into the almost unbearbable summer heat toward the entrance to the National Institutes of Health in Bethesda, Md. After having my badge scanned at the front gate, I made my way to the National Eye Institute in Building 10, NIH's Clinical Center. I boarded a packed elevator, rode up to the tenth floor, and headed down the long hallway to my laboratory, the doors of which were decorated with postcards from all over the world and Biosafety Level 2 signs.

Dr. Igal Gery stood outside the lab waving and smiling. Though nervous and intimidated by the radioactive materials warnings at first, I continued into the lab and met my new co-workers. Before I knew it, Barbara Vistica, our lab technician and microbiologist, was explaining the lab's research. We had spoken over the phone a few months earlier, so I remembered words like "uveitis" and "transgenic mice," but most of what she said went over my head.

After I set up my new desk and computer, Dr. Gery gave me a tour of the Laboratory of Immunology, which spanned most of the hall. The essentials—the –80° C freezer, the bathroom, the many elevators, the copy machine, etc.—were just as important as knowing where the pipette tips and 1.5-milliliter tubes were stored. Later I was inundated with a stack of articles from the *Journal of Immunology*. And Dr. Gery lent me an immunobiology textbook to help me catch up on the field.

During my first two weeks, I trained with Barbara and Dr. Cuiyan "Yan" Tan, a postdoctoral fellow, and read articles on PubMed (based in NIH's National Library of Medicine). I still felt overwhelmed, but Dr. Gery sat down with me often to answer my questions. My lab experience so far had been limited to high school coursework and a biology class at Dartmouth, so Barbara and Yan supervised me until I felt comfortable with performing assays and other techniques.

By the third week I felt comfortable working by myself and interacting with researchers in and out of the lab. The casual dress code and classical radio station that filled the lab with music helped me relax. Soon I began planning my project for the summer intern poster day scheduled for early August. I decided to build off a study that Yan had submitted for publication just prior to my arrival. It focused on patterns of cytokine production by T helper 9 cells and their effects on inflammation of the eye. Running assays and performing experiments using real-time polymerase chain reaction were challenging tasks for a newbie like me, but I began to see a general pattern that formed the basis of my upcoming presentation. I took great care in always vortexing tubes and withdrawing correct amounts of whatever diluent or buffer solution I worked with. The seven-hour experiments were grueling at first, but I soon became accustomed to the pace.

I attended many of OITE's information sessions for summer interns; one was on designing posters and another on giving scientific presentations. Dr. Gery read through drafts and coached me on how to express my research concisely and accurately. Both he and Barbara helped me anticipate questions I might be asked.

Finally, poster day came. The Natcher Building's hallways and atriums were packed with parents, students, researchers, and doctors who had come to see the hundreds of posters. Wearing a blazer with my new NEI pin and carrying my poster in a large tube, I was filled with indescribable energy as I entered the building. I visited many of my friends' posters before setting up mine for the afternoon session. My presentation went well and, despite the fatigue of talking for two hours to the people walking by, I felt very satisfied to have completed my first research experience.

I also had many opportunities to learn at NIH outside the lab. The OITE program coordinator explained that high school and college students come to the NIH not only to gain work experience, but also to learn, to have fun, and to make the most of Bethesda. Dr. Gery knew this and was flexible, often exclaiming, "Work, work, work! Enjoy, enjoy, enjoy!" I joined a summer interns journal club on hormones in disease and development, attended many seminars on topics as diverse as stem cells and optoelectronics, and went to OITE's huge fair that featured representatives and admissions officers from more than 100 medical schools and graduate programs.

My time at NIH was rewarding in part because of the many scientific techniques I picked up, but mainly because of the people I met. NIH teems with scientists who have a passion I hope to develop. Spending a summer learning from them helped me to understand both the difficulty and the beauty of the scientific process. ●

This essay is adapted with permission from one that appeared in the Winter 2010 issue of *Dartmouth Medicine* magazine. Zureick, a sophomore at Dartmouth College in Hanover, N.H., hails from Bloomfield Hills, Mich.

Striking Gold in Rodent Urine Collection

BY CHRISTOPHER WANJEK

There are horse whisperers, people who can befriend a feral or traumatized horse through empathetic body language and keen insight into equine instinct and mentality.

And then there's Dalton Saunders, the man who can make mice pee.

While the former is shrouded in pseudoscience, Saunders' technique is poised to collectively save thousands of research hours, if not thousands of research dollars, by simplifying the process of collecting mouse urine for laboratory tests.

Saunders, a laboratory technician in the NHLBI Genetics and Development Biology Center, stumbled onto his simple technique upon realizing what myriad researchers and animal handlers before him have noticed: Nervous rats and mice lifted from their cages for blood collection or immunization tend to urinate or defecate. Why not put that urine to good purpose, he thought.

Rodent urine collection is essential for biochemical, nutritional, metabolic, physiological, and general behavioral studies. A few drops are all one needs for qualitative analysis using Multistix reagent strips. One of the most common collection techniques is called the metabolism cage method; essentially, one places the animal in a special cage designed to collect a clean urine sample and, well, waits. And waits.

As any parent will attest, merely placing a child on a potty won't necessarily have an immediate and desired outcome. So, using such cage collection devices can be a tedious and time-consuming affair, especially when many rodents are involved. The metabolism method is best used for studies requiring a day's worth of urine.

A paper by Biji Kurien of the Oklahoma Medical Research Foundation, published in *Laboratory Animals* in 2004, lists over a dozen methods that researchers use to quicken the process of urine collection. Yet each method has its limitations in terms of ease of collection, amount of urine collected, contamination with feces, stress to the animals, or what can best be categorized as animal noncompliance.

From the old to the new. The Dalton Saunders method of collecting urine from mice (right) is gentle and painless as well as quicker and much more effective than the old metabolic cage method (left).

The charm in the Saunders method is its ease and regularity. In one test of this method, he could collect clean urine samples from 50 mice in about a half hour. Each mouse dutifully complied; the samples ranged from five to 200 microliters, all suitable for analysis.

Saunders calls his technique the single-animal method, or SAM. First he playfully lifts the mouse out of its cage, perhaps by its tail. With one hand he then pulls back a bit of the mouse's fur on its neck, which serves to splay its arms and legs, and places the mouse belly-down on a ready sheet of sterile Parafilm. The abrupt handling prompts the mouse (or rat) to urinate yet leaves no visible signs of stress or discomfort.

The technique was a few years in the making.

Saunders first perfected the art of oral gavage, the process of inserting food or medicine down an animal's throat. Saunders needed to firmly hold the animal with mouth open and limbs splayed, with one hand, while he inserted a pipette with the other hand. This same "judo" hold on the mouse is the first part of SAM.

Saunders presented this work at the 2010 NIH Research Festival on October 5. His co-presenters were Robert Adelstein, Mary Anne Conti, and Yingfan Zhang, all from the Laboratory of Molecular Cardiology. He later presented the poster at the American Association for Laboratory Animal Science national meeting in Atlanta, and he gave away all 500 of his poster printouts.

Saunders has taught his technique to several people at the NIH, and he said he'll teach you, too, if you're up to the call. His group is preparing an article on SAM for a peer-reviewed publication. ●

Editor's note to parents: Although the SAM technique doesn't induce stress in mice, please don't try this at home with your toddler.

We are always looking for ideas to include in this column. If you have developed any new methods that you would like to have considered or have suggestions about new methods developed by others at NIH, please let us know by e-mailing catalyst@nih.gov.

It's All about Balance

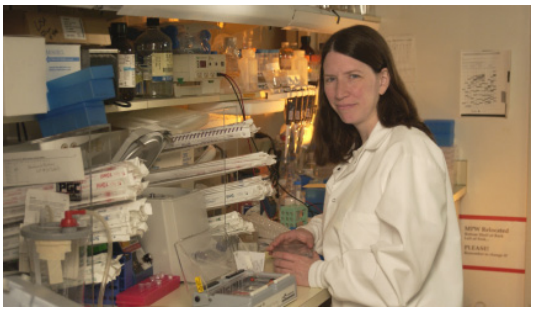
BY ANDREA MCCOLLUM, NIGMS

No one knows better than NHGRI senior investigator Pamela Schwartzberg that an immune system's attack against pathogens relies on a delicate balance of immune cell activation and cytokine production. Any disruptions in this balance, such as alterations in intracellular signaling molecules, can lead to devastating immune diseases.

In an Anita Roberts lecture entitled "Integrating T-cell Signals," Schwartzberg, who is head of NHGRI's Cell Signaling Section, described how altered intracellular signaling is associated with immune disorders. Her laboratory dissects T-lymphocyte signaling pathways to determine how altered signaling affects T-cell activation and interaction with other immune cells. "Regulating the balance [of T cells] is critical for being able to mount an immune response," she said. The immune system doesn't work right when the molecules involved in T-cell activation are affected by mutations or polymorphisms.

One such mutation occurs in the signaling lymphocytic activation molecule (SLAM)-associated protein (SAP). SAP binds to SLAM-family receptors in T cells to act as a scaffold for recruiting signaling molecules. The resulting cascade of signals activates T cells and stimulates cytokine production. But mutations in SAP can lead to diseases such as human X-linked lymphoproliferative syndrome (XLP), an inherited disorder of the immune system that affects males and is characterized by recurrent infections, an unusual susceptibility to B-cell lymphomas, and fatal mononucleosis infection. In individuals with XLP, there is a mutation in the *XLP* gene, which controls the response to the Epstein-Barr virus (EBV). EBV is a common virus that causes infectious mononucleosis; it has no long-lasting ill effects in the normal population but can kill males with XLP.

Schwartzberg uses mouse models "to provide clues to human immunodeficiency and how the immune system functions," she explained. SAP-deficient mice, for instance, offer insights into XLP pathophysiology. SAP deficiency can disrupt T-cell development and T-cell-receptor signaling, alter cytokine production, and render the immune system unable to respond to pathogens. Live-imaging studies done in collaboration with Ronald Germain (NIAID) have shown that SAP-deficient mice have shorter intercellular interactions between T and B cells. This type of decreased interaction may explain why T cells in people with XLP are unable to kill EBV-infected B cells.



MAGGIE BARTLETT, NHGRI

At a recent Anita Roberts lecture, NHGRI senior investigator Pamela Schwartzberg described how altered intracellular signaling can disrupt the balance of the immune system.

In more recent work, Schwartzberg is leading a study with the Center for Human Immunology (CHI), a trans-NIH initiative that aims to understand how healthy as well as diseased human immune systems function. The CHI study was initiated last year and included 150 NIH employee volunteers who were vaccinated with the H1N1 influenza vaccine. A systems biology approach was used to analyze the normal human immunome and characterize how the immune system responds to the vaccine. Early, adaptive, and memory immune responses were measured in blood drawn from the participants before the flu shots were administered and every day for 70 days thereafter. On day one, there was a striking change in gene expression, indicating modifications in the innate immune system. The changes, which involved a drop in the lymphocyte count, are being cross-correlated with functional responses to vaccination such as cytokine production. By day seven, there were fewer changes and what changes there were involved lymphocyte-specific signaling genes. The researchers were surprised to see the innate immune system respond so quickly; in yellow fever vaccine studies, for example, the initial immune system responses don't occur until seven days after the vaccine is given.

Schwartzberg expressed her appreciation for the collaborative environment and "unique interactive atmosphere at NIH that allows scientists to carry out studies where we can . . . do cross-disciplinary research to provide insights into disease" as well as the delicately balanced immune system. ●

The Roberts Legacy: Anita B. Roberts spent 30 years at NCI before her death from gastric cancer in 2006. She became well known for her groundbreaking work on transforming growth factor–beta and its role in the growth of epithelial and lymphoid cells. In 2003, Thomson Scientific's Science Watch *listed her among the 50 most-cited scientists from 1982 to 2002 in a feature called "Twenty Years of Citation Superstars." The "Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH" honors the contributions Roberts and other successful female scientists have made to the NIH research community. To see an archived videocast of Schwartzberg's talk, which was given on October 28, 2010, or videocasts of other Anita Roberts lectures, go to http://videocast.nih.gov/PastEvents.asp?c=151.*

NIH ABBREVIATIONS

CC: NIH Clinical Center
CDC: Centers for Disease Control and Prevention
CIT: Center for Information Technology
CSR: Center for Scientific Review
FAES: Foundation for Advanced Education in the Sciences
FelCom: Fellows Committee
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCI: National Cancer Institute
NCCAM: National Center for Complementary and Alternative Medicine
NCRR: National Center for Research Resources
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
OIR: Office of Intramural Research
OITE: Office of Intramural Training and Education

NEWS FROM AND ABOUT THE NIH SCIENTIFIC INTEREST GROUPS

Metabolomics in Translational Research

Metabolomics, the comprehensive characterization of small molecules in biological systems, is an emerging field with tremendous potential to advance our understanding of human health and disease. To better understand the possibilities this field offers, the trans-NIH Metabolomics Special Interest Group was created to help stimulate interest and bring interested NIH program officials and intramural investigators together.

On September 17, 2010, the Metabolomics Special Interest Group held a symposium, "State of Metabolomics Technologies in Translational Research." The meeting convened more than 300 NIH-funded metabolomics researchers with NIH scientists who provided insights into how metabolomics technologies are being applied in translational research. Topics included various cutting-edge metabolomics technologies with a focus on the application for cancer detection, prognosis, inflammatory conditions, and cardiovascular diseases. To view the meeting summary and session presentations, visit http://www.palladianpartners.com/metabolomicstechnologies. A videocast of the meeting is available at http://videocast.nih.gov/Summary.asp?File=16132.

Name Change

The Endocrinology Interest Group is now the Reproductive and Adult Endocrinology Interest Group. The website site is still http://sigs.nih.gov/endocrinology. The group represents persons interested in basic and clinical endocrinology in the areas of endometriosis, fibroids, and infertility. It also covers other endocrine aspects of implications on traditionally non-endocrine fields that include immunology, psychiatry, gastroenterology, epidemiology, and cancer. Contact: Karel Pacak, karel@mail.nih.gov.

For a complete SIG list, go to http://www.nih.gov/sigs or see the July-August 2010 issue of *The NIH Catalyst*, pages 9–12, at http://www.nih.gov/catalyst/2010/10.08.01/catalyst_v18i4.pdf.

LOOK WHO'S VISITING NIH

Philip Chen (left) enjoyed Robert Gallo's talk.

Philip Chen (center) and his family attended the lecture.

Robert Gallo, who co-discovered that the HIV virus caused AIDS, was the guest speaker at the Fifth Annual Philip S. Chen, Jr., Distinguished Lecture on Innovation and Technology Transfer, held at NIH in November 2010. This annual lecture series honors Philip Chen for his almost 50 years of service to the NIH. Chen, who retired from NIH in 2006, established NIH's Office of Technology Transfer in 1986 to implement the Federal Technology Transfer Act.

real potential. The fish are particularly well suited for large-scale genetic screening; it's easy to map mutations from the thousands of progeny produced by each pair of adults.

"It's very difficult or impossible to do the sorts of screens we do in zebrafish in other commonly used vertebrate models" such as mice, said zebrafish researcher Brant Weinstein, director of NICHD's Program in Genomics of Differentiation.

Igor Dawid, in NICHD's Laboratory of Molecular Genetics, was the first NIH researcher to take serious notice of zebrafish. Until the early 1990s, he had relied on *Xenopus laevis* (African clawed frog) as his animal model. His zebrafish lab started out as a few cabinets in a small closet-size space on the fourth floor of Building 6B. Dawid's lab uses high-resolution imaging to see where, in a zebrafish embryo, specific genes are expressed. The lab is particularly interested in genes in the neural crest, which gives rise to diverse cell types, including craniofacial skeletal and connective tissue, the peripheral nervous system, and more.

The NIH zebrafish program has grown dramatically in the past decade, but the aging facilities—which range in size from 200 to 600 square feet—can't accommodate the number of fish it takes to do large-scale genetic screenings. One genetic screen, for example, requires as many as 60,000 fish living in more than 6,000 1.8-liter tanks.

"Screening for mutants takes space," said Dawid. "The new facility will secure the future of the [zebrafish] program."

Tom Sargent, head of NICHD's Section on Vertebrate Development, has also transitioned his research from frog to zebrafish models and welcomes the opportunity to work in the new space. "I got frustrated in the frog field by the inability to do easy genetics," he said. "The fish were like a dream come true." He studies a gene thought to be a mediator in cell-cell signaling in early craniofacial development.

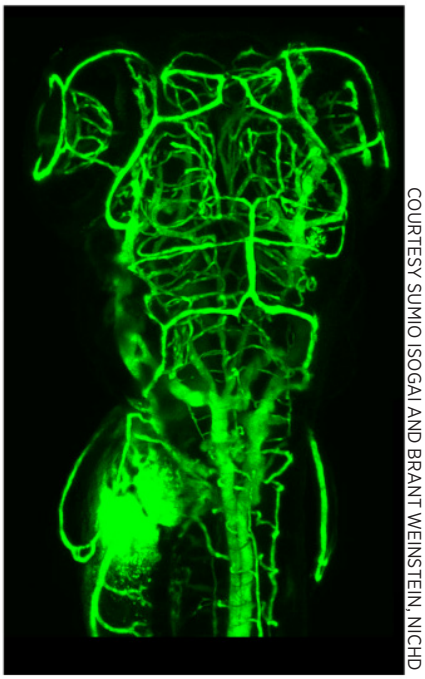
Other NIH scientists are seizing the opportunity to do large genetic screens in the new facility. Harold Burgess, head of NICHD's Unit on Behavioral Neurogenetics, plans to create a library of 250 genetically engineered zebrafish lines that can be studied to gain a better understanding of the neural basis of behavior. He runs five-day-old fish, which have about 100,000 brain cells that are organized similar to the adult brain, through a battery of behavioral tests. "Vertebrates share the [same] basic architectural blueprint of brain anatomy," he said. "If we understand how a zebrafish brain works, we can understand how a mammalian brain works." His lab developed computer software that uses fluorescent tools and high-resolution imaging to measure in real time how the zebrafish brain processes information.

For example, Burgess is investigating the zebrafish "startle response," which occurs reflexly after an unexpected stimulus. He hopes that his work will shed some light on certain human mental disorders in which the startle reflex is abnormal.

Zebrafish are also shedding light on how vascular systems develop. Researchers led by Brant Weinstein have developed transgenic zebrafish lines that express green fluorescent proteins, which are visible with high-resolution multiphoton time-lapse imaging. The scientists can thus map every twist and turn of the developing network.

Weinstein's lab is also carrying out large-scale genetic screens to find mutations in genes that determine blood-vessel growth and patterning. "We've been able to learn more about how we get the progenitors that form the vessels, what cues help promote or inhibit vessel formation, and how vessels get properly patterned," he said. The lab's findings may one day be used to grow new blood vessels around damaged hearts or prevent the development of blood vessels that feed tumors.

Other researchers are using zebrafish to better understand some of the causes of cancer. Paul Liu, head of NHGRI's Oncogenesis and Development Section,



COURTESY SUMIO ISOGAI AND BRANT WEINSTEIN, NICHD

investigates the genetic control of blood-cell formation, a process that goes awry in leukemia and other blood cancers. Zebrafish embryos are ideal for such work: For the first 24 hours, blood cells can be seen forming before the blood begins circulating. Zebrafish embryos can continue to develop in the absence of blood cells for up to two weeks after the eggs are fertilized. Researchers can thus observe how genetic mutations affect blood-cell formation at all stages of embryonic development, even in embryos with mutations that cause them to become "bloodless" (without circulating blood).

Liu's lab uses both mouse and zebrafish models. "These two systems are complementary to each other," he explained. "We found novel functions in zebrafish that we couldn't see in mice." Liu hopes that by understanding normal blood formation, his lab will be able to identify genes that are responsible for leukemia.

Liu isn't the only member of NHGRI working with these tiny fish. Shawn Burgess (no relation to Harold Burgess), head of the Developmental Genomics Section, is identifying novel genes involved in the development of the zebrafish ear and maintenance of inner ear stem-cell populations. He uses a retrovirus, or RNA virus, to create fish with mutated genes. These retroviruses allow his lab to use "reverse genetics" to

LEFT
Fluorescent dyes have been injected into the zebrafish to show the vascular system. This image shows a dorsal view of the head vessels in a 4.5-day-old zebrafish.

RIGHT
Zebrafish researcher Shawn Burgess, who is identifying novel genes involved in the development of the zebrafish ear, is checking his fish tanks.

MAGGIE BARTLETT, NHGRI

generate and identify mutations in genes and then screen those genes systematically for phenotypes. The functions of fewer than ten percent of the zebrafish's 25,000 genes have been documented so far.

Shawn Burgess is also building a coalition of zebrafish facilities that he hopes will identify phenotypes associated with mutated versions of every gene in the zebrafish genome. This comprehensive dataset will be available to researchers worldwide. His lab will serve as one of several screening sites that will coordinate efforts and provide resources not available in smaller labs.

"This is the kind of science NIH should be doing," he said. The new Shared Zebrafish Facility "is the largest [of its kind] in the country, maybe even the world. With unparalleled resources, this is an exciting place to learn about zebrafish."

The new facility in Building 6 is expected to reach full capacity—about 100,000 fish—in a few years. Some of the smaller zebrafish facilities will continue to operate, but NICHD and NHGRI investigators will move most of their research to the new space. With nearly 200,000 zebrafish on campus in the future, NIH may soon be known as the pre-eminent zebrafish research institution in the world. ●

LIFESTYLES OF THE FISH AND FAMOUS

Imagine moving from a cramped studio apartment in the city to a spacious estate in the country. There's excitement, nervousness, and anticipation. NICHD's and NHGRI's zebrafish researchers may not be moving to the country exactly, but they *are* relocating to spacious new quarters in the Shared Zebrafish Facility.

The new facility, nestled in the three lower levels of Building 6, comes in at 9,369 square feet. Compare that to the size of NIH's 10 existing zebrafish facilities, which range from 200 to 600 square feet. It's no wonder that people are eager to move. Even the celebrated zebrafish facility that opened in 1998 in Building 6B (part of the Building 6 complex) is only 495 square feet and houses a mere 2,754 tanks. The new facility will have more than 19,000 tanks and be able to accommodate upward of 100,000 of the minnow-sized striped fish. Eventually there will be twice as many zebrafish on campus as there are now. Some of the existing facilities, including the 1998 one, will continue to operate.

The new area must be conducive to zebrafish reproduction in order that thousands of progeny can be produced for the large-scale genetic screens. The temperature is kept at 82° Fahrenheit and special lights simulate a 24-hour day complete with dawn and dusk. Zebrafish spawn at dawn.

The fish live in six-liter, 1.8-liter, or 0.8-liter tanks, with a density of about five fish per liter of water. Most of the tanks are the 1.8-liter size. The fish are fed manually twice day by humans who sprinkle fish food into each tank. The diet varies based on the age of the fish but can include brine shrimp and dry crumble, which is similar to fish food from a pet store.

The tanks take up a little more than 40 percent of the facility's space. The rest is dedicated to a water-filtration system. More than 25,000 gallons of water are circulated and filtered continuously via mechanical, biological, and ultraviolet means. The water's temperature, pH level, conductivity, hardness, and the amount of dissolved oxygen, ammonia, nitrites, and nitrates are measured constantly.

Water is piped from the tanks to a mechanical filtration room, where debris, such as feces or excess food, is filtered out. Next, the water is pumped into a biofiltration room where there are four fluidized biofilter tanks, each containing 10,000 pounds of tightly packed silicon glass beads. Chemosynthetic bacteria, which are considered "good" bacteria, live on these beads and naturally purify the water by eating ammonia and nitrate as the water flows through. Finally, the water is pumped past ultraviolet lights that kill any remaining bacteria. Then the cleaned water is circulated once again to the fish tanks.

COURTESY T. SARGENT, NICHD

LEFT NIH's very first zebrafish facility, established in Building 6B in 1994, was tiny. It was cobbled together by postdocs from Igor Dawid's and Tom Sargent's labs. A bigger facility opened in 1998.

RIGHT As part of the new Shared Zebrafish Facility, this room in Building 6 can hold more than 19,000 fish tanks with the potential to house more than 100,000 fish.

COURTESY D. BARTLETT, NICHD

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career, which began with solving the genetic code for protein syntheses and led to understanding the normal function and disorders of the nervous system."

Marshall Nirenberg, who earned Nobel honors by cracking the genetic code, died in January 2010. He left behind an extraordinary and groundbreaking history of discovery. "There's perhaps nobody here at NIH who is not in some way dependent upon that legacy," NIH Director Francis Collins told the audience at the plenary session. Collins recalled the early days of Nirenberg's research, when Nirenberg's very small lab had trouble moving his research forward as quickly as the race to decipher codons required. But many of Nirenberg's colleagues put aside their own work to join the effort, making the Nobel prize–winning work possible. "That spirit of collaboration and team effort lives on today, in trans-NIH initiatives such as the Undiagnosed Diseases Program [and] the Therapeutics for Rare and Neglected Diseases Program," Collins continued.

MICHAEL SPENCER

ABOVE

Research Festival week festivities began and ended with events extolling the accomplishments of the late Marshall Nirenberg. Here NIH Director Francis Collins and Nirenberg's widow Myrna Weissman stand before a new exhibit honoring the Nobel laureate. The exhibit is located in Building 10 in a hallway near the Lipsett Amphitheater.

The two-year-old Undiagnosed Diseases Program (UDP) uses genetics and coordinates the efforts of many NIH researchers and specialists to help patients with puzzling medical conditions that have stumped physicians across the country. Out of some 3,000 inquiries that have poured into NIH so far, UDP has accepted nearly 300 cases. UDP director **William Gahl** (NHGRI) explained how the NHGRI Genomics Core does a genetic workup for UDP patients by using a technique called million-SNP (single nucleotide polymorphism) arrays—on tissue samples from the patients—to detect DNA deletions, duplications, copy-number variants, and regions of homozygosity (two identical stretches of nucleotide bases at a specific position in a gene, present on both chromosomes. He described a case in which researchers discovered a genetic defect that may be associated with a rare vascular calcification disorder. The defect causes an enzyme deficiency that ultimately leads to an increase in calcification along arteries and joint capsules. The deficient enzyme product may be a target for the treatment or prevention of the disease.

Karen Berman (NIMH) is as interested in neurogenetic mechanisms and neuroimaging as Nirenberg was. She presented her lab's neuroimaging studies of Williams syndrome (WS), a rare neuropsychiatric disorder characterized by mild to moderate mental retardation, impaired visuospatial abilities, and a unique personality that combines overfriendliness and high levels of empathy with anxiety. Berman's group found that a mutation in *LIMK1*—a gene involved in neuronal migration and maturation during brain development and known to be affected in WS—is associated with a structural irregularity in the brain's visual pathway where spatial information is processed. Berman believes that abnormalities in *LIMK1* and related genes may lead to the development of the visuospatial problems in WS.

Changsoo Kang (NIDCD), a winner of a Fellows Award for Research Excellence (FARE), is teasing out the genetic underpinnings of another neurological disorder—stuttering. He performed a genetic linkage study in Pakistani families with a high incidence of stuttering and discovered a mutation in a gene called *GNPTAB*. Further investigation showed that the same variation occurs in unrelated stutterers throughout Pakistan and India. *GNPTAB* encodes a subunit of an enzyme that shuttles other enzymes to the cell's lysosome for recycling. Kang also identified stuttering-related mutations in two other genes—*GNPTG* and *NAGPA*. His findings suggest that stuttering could be treated with drugs that replace the defective enzymes.

Scientists also examine nonhuman genomes as an indirect way of studying the genetic foundations of human disease. **Elaine Ostrander** (NHGRI) explores dog genetics to find and understand genes important for growth regulation in both canines and humans as well as disease-susceptibility and control of morphologic body plan. For example, her group has found genetic variations that are responsible for disproportionately short legs in certain dog breeds such as dachshunds, corgis, and basset hounds. After performing a genome-wide association that examined DNA samples from hundreds of dogs, the researchers discovered an extra, inserted, copy of the *FGF4* gene that was present only in short-legged dogs. This insert, called a retrogene (it was inserted into the dog genome after the ancestor of modern breeds diverged from wolves), does not contain the normal machinery necessary for it to be expressed. Surprisingly, however, it

overexpresses *FGF4*. Ostrander believes that when *FGF4* is overexpressed during development, the growth plates close prematurely so only short legs can develop. The unexpected discovery provides new clues about how physical differences may arise within species and may suggest new approaches to understanding a form of human dwarfism.

Diseases and disorders don't always arise from changes in DNA nucleotides. They may also be associated with epigenetic modifications—such as the addition or removal of methyl or acetyl groups—which may alter the way genes are expressed without changing the underlying DNA sequences. **Keji Zhao** (NHLBI) is mapping epigenetic modifications in T-cell-differentiation genes that determine the types of specialized immune cells the T cells will become. When the T-cell-differentiation process goes awry, autoimmune diseases can arise. He has generated data that will serve as a reference epigenome for scientists studying autoimmune diseases or other T-cell-related diseases.

The plenary session ended with **Christopher Austin**'s (NHGRI) presentation on translational therapeutic development for rare and neglected diseases. Austin, who's the director of the NIH Chemical Genomics Center (NCGC), described NCGC's method for developing small-molecule therapeutics. NCGC is one of the leading centers for high-throughput screening, chemical-probe development, and chemical genomics. He cited a trans-NIH collaboration in which an NCGC assay was used to identify several compounds that show promise as a more effective treatment for Gaucher disease, a rare inherited metabolic disorder marked by spleen and liver dysfunction and neurological impairments. The disease is caused by a genetic mutation that leads to an absence of an enzyme, thereby interfering with the lysosome's ability to break down and recycle unwanted cellular materials.

Austin also described a collaboration with a different NIH group that is trying to find potential treatments for Niemann-Pick disease type C, a progressive neurodegenerative disease associated with gene mutations that cause cholesterol to build up in lysosomes. NCGC screened its comprehensive collection of drugs already approved for other diseases to find one that could be repurposed to treat Niemann-Pick. One drug worked in patient cells as well as in animal models; clinical trials are set to begin in mid-2011. Austin urged NIH scientists interested in collaborating to contact him.

As the plenary session came to a close, hundreds of NIH researchers flocked to concurrent symposia sessions, eager to hear from other inspiring scientists and maybe even to find others to collaborate with. Some of those sessions are highlighted here.

Stress and Addiction

BY CATHERINE EVANS, NCI

Clinicians have long known that recovering addicts can relapse when they encounter stressors such as a bad day at work or turmoil in a relationship. What's not completely understood, however, is how stress interacts with neurochemical pathways in the brain to activate this vulnerability. Some NIH scientists are getting closer to the answer.

Corticotropin-releasing hormone (CRH), an excitatory neurotransmitter, is known to mediate stress responses in substance-dependent individuals. **Markus Heilig** (NIAAA) explained that compounds that block CRH from acting at its receptors can suppress stress-induced relapse in alcohol-dependent rats. **Marisela Morales** (NIDA) is zooming in on this CRH-dopamine interaction and has confirmed via electron microscopy that neurons containing CRH and glutamate form synapses on dopamine neurons; this synapse formation may be a way by which CRH activates the dopamine release associated with stress. Session organizer and chair **Roy Wise** (NIDA) reported that foot-shock stress in cocaine-dependent rats leads to the release of glutamate, which in turn causes dopamine to be released throughout the brain. The first clinical studies of CRH antagonists in humans with alcoholism are in the works.

It's known that stress-induced release of CRF can drive drug-dependent behaviors. **Antonello Bonci**'s lab (NIDA) has characterized cellular mechanisms underlying this effect; the lab demonstrated that in mice previously exposed to cocaine, CRF had an enhanced ability to regulate glutamate transmission onto ventral tegmental dopamine neurons. This finding represents a plausible cellular mechanism where drugs of abuse and stress could interact.

In exploring the consequences of drug abuse, FARE awardee **Britton Trabert** (NCI) found that frequent, long-term marijuana use is associated with increased risk of testicular germ-cell tumors. She speculated that marijuana use during puberty may result in altered levels of reproductive hormones.

Drug Repurposing

BY STEPHANIE COOPERSTEIN

NIH scientists are harnessing powerful molecular analysis and bioinformatics technologies to turn once-shelved drugs, as well as drugs approved for only one purpose, into new treatments for a variety of diseases. Severe depression is under attack by **Carlos Zarate** (NIMH), who reported that glutamatergic modulators such as ketamine (a general anesthetic used mainly by veterinarians) can produce antidepressant action within hours instead of weeks in patients with treatment-resistant depression. **Nigel Greig** (NIA) explained how the type 2 diabetes drug exendin-4 might be used to treat neurodegenerative disorders

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such as Alzheimer disease and Parkinson disease. They share several clinical and biochemical features with diabetes, including impaired insulin signaling and other pathogenic mechanisms that can be ameliorated by exendin-4.

Amanda Law (NIMH) summarized her work showing that therapies for schizophrenia may lie in scientists' ability to regulate the PI3-kinase pathway downstream of the *ERBB4* gene, which is mutated in cancer as well as in schizophrenia.

Certain novel cancer treatment drugs may also modify this pathway. FARE Award winner **George Lountos** (NCI) is using X-ray crystallography and structure-based drug-design methods to optimize checkpoint kinase 2 inhibitors that may be beneficial in dual-therapy use with chemotherapy and radiation for cancer treatment. And **Noel Southall** (NHGRI) encouraged researchers interested in drug repurposing studies to consider using resources offered by the new NIH Center for Translational Therapeutics, TRND (which stands for Therapeutics for Rare and Neglected Diseases), and the NIH Chemical Genomics Center.

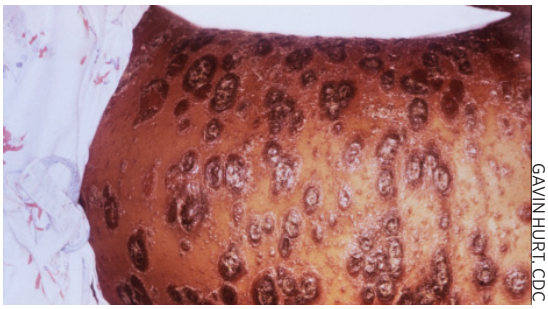
This symposium was organized and co-chaired by **Craig Thomas** (NHGRI) and **Minkyung (Min) Song** (NCI).

Commensal Bacteria in Health and Disease

BY DOMINIC FRANCESE, NCI

Whole industries have sprung up to ensure that our bodies and environments stay as sterile as possible. What is often forgotten, however, is that the commensal bacteria living on and in us keep us healthy. In a session organized and co-chaired by **Yasmine Belkaid** (NIAID) and **Brian Kelsall** (NIAID), several NIH researchers explored the relationship between commensal bacteria and their hosts.

Julie Segre (NHGRI) is looking at the diversity of skin microbiota and its relationship to health and disease. Her lab sequences the DNA of bacteria on human skin as part of its investigation into how changes in the bacterial community contribute to chronic skin disorders such as eczema and psoriasis. One cause of immune system activation in chronic human immunodeficiency virus infections is the translocation of microbial products from the gastrointestinal tract lumen into peripheral circulation, according to **Jason Brenchley** (NIAID), who is studying simian immunodeficiency virus infection in Asian macaque monkeys.



GAVIN HURT, CDC

ABOVE Julie Segre, who is interested in the diversity of skin microbiota, is sequencing the DNA of bacteria on human skin as part of an investigation into how changes in the bacterial community contribute to chronic skin disorders such as psoriasis.

FARE awardee **Audrey Chong** (NIAID) found that the surface protein DipA is essential to the intracellular survival of the infectious bacterium *Francisella tularensis*, which causes tularemia in rodents and other mammals, including humans.

Different populations of gastrointestinal tract macrophages and dendritic cells may play discrete roles in regulating immune system responses to commensal bacteria, reported **Aymeric Rivollier** (NIAID). But in some instances the gut flora itself can become a liability. **Warren Strober** (NIAID) described how polymorphisms in the gene that encodes for nucleotide oligomerization domain (NOD) proteins are susceptibility factors in Crohn disease, a condition marked by excessive inflammatory responses to normal bacterial flora.

The Cognitive Complexities of Complex Behaviors

BY SARAH RHODES, NIMH

A myriad of cognitive processes underlie emotional, social, and choice behaviors in human and nonhuman primates. Deciphering the associated neural mechanisms is key to understanding various neurological and psychiatric disorders.

Session chair **Betsy Murray** (NIMH) and **Okihide Hikosaka** (NEI) discussed the role of different brain regions in decision making. Murray explained how our choices are guided by cues that signal the greatest reward and adapt to current needs. Hikosaka outlined the importance of corticobasal ganglia networks when switching between controlled and automatic behavior.

Christina Barr (NIAAA) and **Ellen Leibenluft** (NIMH) described what happens when such complex cognitive processes go awry. Leibenluft is investigating the neural circuitry of irritability in youth, which in some cases can be associated with bipolar disorder or other severe mood disorders.

Dysregulation of attention-emotion interactions can be a contributing factor. Barr explained how, in monkeys, environmental conditions interact with the genetic makeup to affect the development of different behaviors. For example, certain variants of the gene for the neurotransmitter corticotropin-releasing hormone increase the risk of stress reactivity and alcohol consumption in early stress-exposed monkeys.

FARE winner **Nitzan Censor** (NINDS) is interested in how the human brain modifies existing motor memories and described how primary cortical processing during memory reactivation enables the modification of existing motor memories. His findings may have important future clinical applications for stroke victims.

Molecular Signatures

BY ERIKA GINSBURG, NCI

Recent advances in genomics, proteomics, and metabolomics have helped researchers identify clinically relevant molecular profiles and biomarkers. **David Goldstein** (NINDS) and **Minkyung (Min) Song** (NCI) organized and chaired a session that highlighted how scientists now have a better understanding of the mechanisms underlying diseases and variable responses to therapies.

Goldstein, who is especially interested in Parkinson disease (PD), conducts research on disorders of brain regulation of the cardiovascular system. Recent imaging studies revealed that most patients with PD have cardiac sympathetic denervation (interruption of nerves to the heart), which can be caused by a mutation in the alpha-synuclein gene. Loss of cardiac sympathetic nerves may be a biomarker of presymptomatic PD.

Adrenal carcinomas are rare malignant cancers, and most don't come to the attention of physicians until the tumors have already metastasized. **Electron Kebebew** (NCI) has turned to profiling the transcriptome to identify targets for novel therapies that may help increase survival. Head and neck squamous cell carcinoma is another cancer that is usually malignant by the time it's diagnosed. **Zhong Chen** (NIDCD), who wants to find less debilitating therapies than surgery or radiation, discovered that the epidermal growth factor receptor is aberrantly turned on in 90 percent of these cancers.

Terrance O'Hanlon (NIEHS) studies plasma proteomic profiles comparing identical twins and unrelated matched control subjects to determine why there is an increased prevalence of autoimmune diseases in certain families and ethnicities. **Christina Annunziata** (NCI) is designing clinical studies that build on her finding that ovarian cancer as well as multiple myelomas depend on the nuclear factor kappa-light-chain-enhancer of activated B cells (more commonly known as NF-kappa B) pathway for survival. FARE Award winner **Yi-Ping Fu**'s (NCI) work expands upon rs11249433, a single nucleotide polymorphism recently identified as a genetic risk factor for breast cancer; she proposes that nearby gene *NOTCH2* is a potential candidate for breast cancer susceptibility.

Asthma: From Bench to Bedside

BY ANGEL DAVEY, NIAID

Several basic and translational researchers talked about their efforts to better define the link between the immune system and asthma in a symposium organized and co-chaired by **Darryl Zeldin** (NIEHS) and **Stewart Levine** (NHLBI).

Thomas Wynn (NIAID) is studying the molecular and immunological mechanisms of fibrosis in schistosomiasis and other chronic fibrotic diseases including severe asthma. He explained that blocking interleukin-13, which is a mediator of allergic inflammation, inhibits liver fibrosis in a schistosomiasis infection and suppresses chronic airway inflammation and hyperresponsiveness in rodents. **Stavros Garantziotis** (NIEHS) and **Michael Fessler** (NIEHS) are busy identifying additional targets that may mediate asthma-associated airway inflammation. Garantziotis has demonstrated that in mice with ozone-induced airway disease elevated hyaluronan levels contribute to airway hyperreactivity (AHR). And Fessler explained that increased serum levels of low-density lipoprotein cholesterol suppress neutrophil trafficking to the lungs of *Klebsiella pneumoniae*–infected mice and correlate with decreased asthma in humans.

Further, **Stewart Levine** (NHLBI) has identified an endogenous apolipoprotein E (apoE) low-density lipoprotein receptor pathway in the lung as a negative regulator of AHR and airway remodeling, as well as a role for apoE mimetic peptides to treat asthma. **Eva Mezey** (NIDCR) is exploring the use of bone marrow stromal cells to treat asthma and other allergic conditions. In trying to learn more about the mechanisms of T helper 2 (Th2) cells in allergic asthma, FARE Award winner **Hideki Nakano** (NIEHS) found that certain lung dendritic cells induce Th2 differentiation, take up low amounts of antigen in vivo, and produce high concentrations of Th2-associated cytokines.

Obesity and the Liver

BY ANA DEPINA, NIA

In a session co-chaired by **Bin Gao** (NIAAA) and **Snorri Thorgeirsson** (NCI), NIH intramural scientists presented exciting findings about the factors, pathways, and mechanisms by which obesity adversely affects the liver. **Bernard Miller** (NIDDK) presented data showing how low-fat and low-carbohydrate weight-loss diets modify lipid and lipoprotein metabolism in obese people with type 2 diabetes. Although low-carbohydrate diets are better at reducing serum triglyceride concentration—an independent risk factor for cardiovascular disease—they can increase free fatty acid concentration, which is associated with insulin resistance. More research is needed, Miller explained, to weigh the pros and cons of these diets and their effects on metabolism.

George Kunos (NIAAA) presented recent findings on the association of obesity with the hyperactivation of the endocannabinoid system (which mediates appetite and other physiological processes) and discussed the therapeutic potential of peripheral endocannabinoid antagonists in treating fatty liver disease and metabolic syndrome. **Chuxia Deng** (NIDDK) has uncovered additional factors contributing to fatty liver disease and showed that *SIRT6* plays an important role in regulating glucose metabolism, fatty liver, and liver cancer.

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SIRT6 is a member of the sirtuin gene family, which regulates longevity and cell repair.

Yingzi Yang (NHGRI) has identified several signaling pathways that control liver regeneration and size. She found, for example, that the Hippo signaling pathway is a potent suppressor of liver tumor formation; the loss of Hippo signaling led to an enlarged liver and liver tumors. **Jens Marquardt** (NCI) underlined the importance of specifically targeting cancer stem cells for effective treatment of liver cancer.

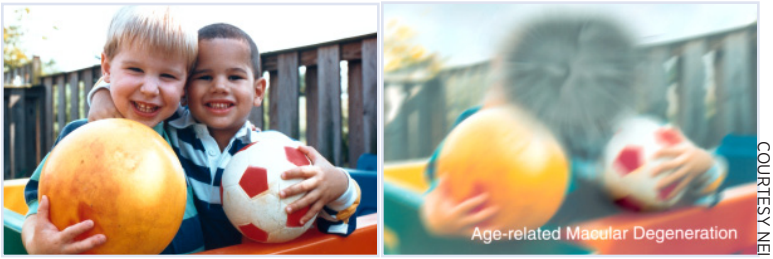
And FARE Award winner **Sailu Yellaboina** (NIEHS) elucidated novel regulators that are essential for the maintenance of embryonic stem cells and show potential for advancing therapies involving tissue regeneration.

Ears and Eyes

BY MICHELE COX, NIMH

Diseases of the eye and ear are sometimes due to developmental processes that have gone awry. NIDCD's **Doris Wu** and **Bechara Kachar** organized and co-chaired a session that brought together several researchers to talk about their work.

Wu's lab is identifying the molecular mechanisms underlying the formation of the inner ear and has shown, in experiments with mouse and chicken embryos, that retinoic acid is a key signaling molecule in establishing the anterior-posterior axis of the inner ear. Another unique feature of the inner ear is the stereocilia, which convert sound pressure into electrical signals for the hair cells that in turn stimulate the auditory nerve. Studies on protein turnover in the Kachar lab showed that stereocilia undergo continuous renewal and dynamic shape regulation. These studies, together with the identification of stereocilia myosins and their actin regulatory cargos, provide new insights into the stereocilia's long-term maintenance mechanisms as well as the molecular and structural basis for their mechanosensitivity.



COURTESY NEI

ABOVE A scene as it might be viewed by someone with normal vision (left) compared with how it might be viewed by a person with age-related macular degeneration. NEI researcher Ignacio Rodriguez has identified a molecule that may cause the disease.

In the eye-centered portion of the symposium, researchers presented findings on photoreceptor differentiation and how the four types—low-light-sensitive rods and three types of color-sensitive cones—differentiate from their precursor. **Douglas Forrest** (NIDDK) proposes a stepwise process of transcription control that also involves an important role for thyroid hormone and endocrine signaling in determining how the different types of photoreceptors are formed. FARE Award winner **Jerome Roger** (NEI) discussed a novel mouse retinal mutant that arose spontaneously; it presented a unique phenotype with only immature conelike photoreceptors.

Next, two presenters focused on molecules that affect retinal health. **Preeti Subramanian** (NEI) described the discovery of pigment epithelium–derived factor's ability to stimulate the phospholipase activity of its receptor, possibly leading to a cellular signal that increases cell longevity. **Ignacio Rodriguez** (NEI) identified 7-ketocholesterol (7KCh) as a molecule that may cause wet age-related macular degeneration (AMD). The 7KCh causes a chronic immune response as it accumulates in oxidized lipoprotein deposits that result from aging and oxidative stress; the retinal pigment epithelial cells release cytokines, including vascular endothelial growth factor, that are associated with wet AMD.

Brain Microcircuits and Behavior

BY CAROLYN GRAYBEAL, NIAAA

Heather Cameron (NIMH) organized and chaired a session in which researchers described how they are unraveling the intricacies of neural circuits that mediate behaviors. Their insights may lead to a better understanding of and possible treatments for cognitive disorders.

Using optogenetics, **Alexei Morozov** (NIMH) has determined how inhibitory synaptic transmission influences plasticity in cortical pathways that converge in the amygdala, a brain region that is critical for the learned association between neutral and aversive stimuli. **Thomas Jhou** (NIDA) discussed lesion, electrophysiological, and pharmacological experiments that characterized the rostromedial tegmental nucleus (RMTg) in the midbrain dopaminergic reward circuit. Dysfunction in RMTg may contribute to the pathology of bipolar disorder.

Disruptions in the normal development of neural circuits can have significant effects on behavior. **Michael Ashby** (NINDS) used computational modeling and electrophysiology to demonstrate how early life experiences influence the development of functional circuits in the mouse cortex. When newborn mice are deprived of sensory input, normal interconnectivity fails to develop and neuronal synapses are nonfunctional.

Kazu Nakazawa (NIMH) reported that genetically induced hypofunction of *N*-methyl-D-aspartate (NMDA) receptors models the behavioral pathology seen in

neuropsychiatric disorders. In mice, when functional NMDA receptors are missing from neurons that mediate inhibitory signaling, schizophrenia-like symptoms appear: increased stress-induced anxiety and sensitivity to psychostimulants as well as memory impairments. FARE awardee **Jonathan Brigman** (NIAAA) used pharmacology and genetics to determine that, in mice, a subunit of an NMDA receptor was critical in learning to adjust previously learned behavior.

Noncoding RNA Elements and Their Mechanisms of Action

BY NATALIE GOLDBERGER, NCI

Proper messenger RNA (mRNA) stability, expression, and regulation are important for preventing disease. Noncoding RNA elements such as microRNAs (miRNAs) can control gene expression through splicing, translational efficiency, and turnover. Some mRNA elements are targeted for regulation by miRNAs. In this session, which was organized and co-chaired by **Richard Maraia** (NICHD) and **Yun-xing Wang** (NCI), four of the six talks focused on miRNA research.

Joseph Zigelbauer (NCI) is studying how miRNAs expressed by Kaposi's sarcoma–associated Herpesvirus target the tumor necrosis factor TNFRSF12A to inhibit apoptosis and suppress an inflammatory response. **Myriam Gorospe** (NIA), who is using cellular senescence to study aging, has shown that overexpressing a combination of miR-15b, miR-24, miR-25, and miR-141 in human fibroblasts decreases concentrations of the kinase MKK4 and promotes a "young cell" phenotype.

Zhi-Ming Zheng (NCI) has demonstrated that the expression of tumor-suppressive *miR-34a* is reduced by viral oncoprotein *E6* in cervical cancer tissues and cervical cancer–derived cell lines that contain an oncogenic human papillomavirus. And FARE Award winner **Praveen Sethupathy** (NHGRI) revealed that the human miRNA *miR-27* may be a master regulator of cholesterol metabolism because it targets the gene *HMGCR*, which codes for a rate-limiting enzyme for cholesterol synthesis.

The other two presenters described their work on mRNA expression and regulation. **Shuibang Wang** (CC) talked about how certain mitogen-activated protein kinases regulate the stability of mRNA. **Laura Elnitski** (NHGRI) detects genomic sequence variants that cause exon skipping. Her lab developed a publicly accessible Web-based tool called Skippy that detects splice-modulating exonic variants.

Judith Stoffer; NIGMS

Several NIH scientists described their work with mitochondria, organelles involved in cellular processes such as energetics, survival, and signal transduction.

Mitochondrial Energetics

BY ANA DEPINA, NIA

Mitochondria are organelles involved in cellular processes such as energetics, survival, and signal transduction. **Mark Stevens** (NHLBI) and **Steven Zullo** (CSR) organized and co-chaired an energetic session about advances in mitochondrial proteomics.

FARE Award winner **Jaime Ross** (NIDA) presented exciting findings showing that high levels of mitochondrial DNA (mtDNA) mutations cause premature aging in mice. She described how high brain lactate concentrations may predict aging and suggested the use of lactate measurements as a way to track the aging process.

In "A Tale of Two Tissues, the Heart and the Liver," **Robert Balaban** (NHLBI) told how metabolic homeostasis is maintained in the mitochondria. He explained that tissue-specific mitochondrial protein programming occurs, with the heart having more proteins present at reduced activity, and proposed that post-translational modifications likely regulate the metabolic steady state. **Youn Wook Chung** (NHLBI), who is characterizing the complex of signaling molecules responsible for cardioprotection, found that targeted disruption of a cyclic nucleotide phosphodiesterase protects rodent hearts from ischemia-reperfusion, an injury associated with disruption of mitochondrial morphology and function.

Matthew Longley (NIEHS) explained how defects in mtDNA helicase (a DNA unwinding enzyme) contribute to ophthalmoplegia (the paralysis of muscles that control eye movement) and other disorders. Palmitoylation (reaction with palmitic fatty acid) of a membrane protein may play a role in mitochondrial targeting of the transmembrane lipid transporter phospholipid scramblase–3, according to **Michael Fessler** (NIEHS). Using proteomics, **Michael Sack**'s group (NHLBI) has identified and characterized sirtuin mitochondrial acetylated protein targets; he reported that *sirtuin 3* (*SIRT3*) knockout mice are resistant to acetaminophen-induced liver damage. *SIRT3* is a member of the sirtuin gene family, which regulates longevity and cell repair. **B.J. Song** (NIAAA) described a novel method of tagging cysteine residues with biotin to identify oxidized proteins that accumulate when mitochondrial function is disrupted long before organ damage occurs. This method was used to study the underlying mechanisms of mitochondrial dysfunction in such pathophysiological states as alcohol- and drug-mediated organ damage.

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Molecular Imaging: Biology, Physics, and Chemistry

BY ANGEL DAVEY, NIAID

Molecular imaging not only makes noninvasive characterization of cellular and molecular biological processes possible, but also recent innovations have led to more precise diagnosis and improved treatment of various diseases. In a session organized and chaired by **Xiaoyuan (Shawn) Chen** (NBIB, CC), several NIH scientists described their work.

Gary Griffiths (NHLBI) and workers at the Imaging Probe Development Center synthesize various imaging agents, including optical and photoactivatable probes, metal chelate agents, halogen radionuclide probes, nanoparticles, and other multifunctional probes for numerous NIH collaborators. **William Kreisl** (NIMH) uses positron emission tomography (PET) imaging of a radiolabeled substrate for p-glycoprotein, which protects the brain from exogenous toxins, to elucidate the role of the blood brain barrier when human immunodficiency virus–infected monkeys and humans are treated with protease inhibitors. **Gang Niu** (CC, NIBIB) and colleagues are doing small animal studies to better understand the mechanisms underlying common diagnostic and therapeutic methods. They are using bioluminescent imaging of luciferase reporter genes encoding tumor growth-associated proteins and PET imaging of a radiolabeled monoclonal antibody against epidermal growth factor receptor, which promotes tumor progression in solid cancers.

David Bluemke (NIBIB, CC) and **Peter Choyke** (NCI) reviewed some key molecular imaging probes used in cardiovascular disease and cancer diagnosis. They touched on the legal, regulatory, and economic challenges of developing and bringing to the clinic such molecular imaging agents and noted the great diagnostic potential of combined PET–computed tomography or PET–magnetic resonance imaging approaches, which provide both metabolic and anatomic information. And **Barbara Croft** (NCI) offered advice on applying for extramural research grants from the Cancer Imaging Program that fellows who may one day leave NIH might find useful.

Epigenetics, Chromatin, and Gene Regulation

BY STEPHANIE COOPERSTEIN

In a symposium organized and co-chaired by **Raja Jothi** (NIEHS) and **Elissa Lei** (NIDDK), several intramural scientists discussed how chromatin structure (the complex of DNA and proteins within the cell nucleus) and epigenetic markers (chemical modifications to DNA and proteins that control gene activity without causing a change in DNA sequence) regulate gene expression during cell development and cell differentiation. **Paul Wade** (NIEHS) reviewed his research on the epigenetics of a human immune response. The epigenetics of skeletal myogenesis intrigues **Vittorio Sartorelli** (NIAMS); he discussed his studies on the protein MyoD, which plays a key role in regulating muscle differentiation.

Judith Kassis (NICHD) studies Drosophila to understand the recruitment of the Polycomb group proteins, which can silence certain genes. **Raja Jothi** (NIEHS) has explored the master regulations of signaling pathways and epigenetic mechanisms (chromatin remodeling and histone modifications) in embryonic stem cells. **Gordon Hager** (NCI), who spoke about access to regulatory elements in chromatin, described how local disruptions in nucleosome structure (monitored as DNaseI hypersensitive sites) control the access of tissue-specific transcription factors to regulatory elements. ●

If you are interested in writing for *The NIH Catalyst*, please e-mail Managing Editor Laura Carter (carterls@od.nih.gov) for details.

Obituaries

CONTINUED FROM PAGE 3

Elaine Sloand (died on December 5, 2010) was a principal investigator on many NHLBI Hematology Branch protocols for bone-marrow failure. She first arrived at NIH in 1986.

Thomas R. Sweeney (died on June 14, 2010, at 95) began his career at NIH as a research chemist in the 1940s and stayed until 1959. He later led efforts to develop an antimalarial drug.

Hiroshi Taniuchi (died on March 25, 2010, at 80) was a protein chemist and section head in the Laboratory of Chemical Biology (now called the Molecular Medicine Branch) in NIDDK until he retired about 10 years ago.

Jonathan Vogel (died on October 30, 2010, at 56) was a senior investigator in the NCI Center for Cancer Research Dermatology Branch. He joined the NCI in the 1980s and focused his research on skin gene therapy and keratinocyte stem cells.

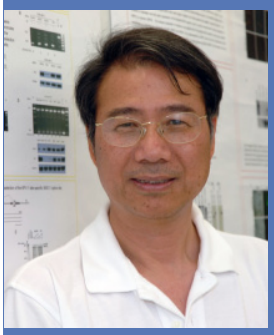
Xiuwen Wang (died on October 7, 2010, at 28) was a graduate student from China and predoctoral visiting fellow in NIBIB. She died after being struck by a car.

James T. Winslow (died on November 17, 2010), who was head of NIMH's Neurobiology Non-Human Primate Core, arrived at NIMH nearly 25 years ago. His wife is Katherine Egan, head of NIMH's communications office.

Bernhard Witkop (died on Nov. 22, 2010, at 93) became chief of the Laboratory of Chemistry at the National Institute of Arthritis and Metabolic Diseases in 1957, a position he maintained through the various transitions of NIDDK until his retirement in 1987.

Seymour H. (Sy) Wollman (died on June 6, 2010, at 92) was one of the first scientists to arrive at the then-new NIH campus in the late 1940s. He came to NCI's Laboratory of Physiology in 1948 and spent a long and productive scientific career on numerous aspects of thyroid gland function until he retired in 1985. ●

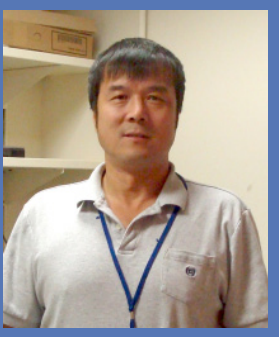
Recently Tenured



Zhi-Ming Zheng, NCI

Brigitte Widemann, NCI

Shmuel Muallem, NIDCR



Tian Jin, NIAID

William Dahut, NCI

ZHI-MING ZHENG, M.D., PH.D., NCI

Senior Investigator and Head, Tumor Virus RNA Biology Section, HIV and AIDS Malignancy Branch, Center for Cancer Research, NCI

Education: Wuhan University School of Medicine, Hubei, China (M.D.); University of South Florida School of Medicine, Tampa, Fla. (Ph.D. in microbiology and immunology)

Training: Postdoctoral training at Yale University School of Medicine (New Haven, Conn.) and Laboratory of Tumor Virus Biology, NCI

Before coming to NIH: Associate professor of virology and chief, Clinical Virology Laboratory, and deputy director and acting director of the Virus Research Institute, at the Wuhan University School of Medicine (Hubei, China)

Came to NIH: In 1994 as a fellow in NCI; became senior staff in 1997 and tenure–track investigator in 2000

Outside interests: Listening to classical and country music, playing the Chinese erhu (Chinese violin), walking and running, and playing ping-pong

Research interests: My research interests center on the RNA processing and tumorigenesis of papillomaviruses, which can lead to cervical and anal cancers, and Kaposi's sarcoma–associated herpesvirus (KSHV), which can lead to the AIDS-related Kaposi's sarcoma and lymphoma. In particular, our lab aims to understand protein-RNA and RNA-RNA interplays in RNA splicing and small regulatory RNA function in regulation of viral and cellular gene expression during oncogenic virus infection. Our long-term goal is to develop a series of RNA-based therapeutic approaches to control viral or cellular gene expression and to identify some biomarkers for clinical diagnosis and prognosis.

For example, in our recent work on human papillomavirus infection and viral gene expression, we have developed several small interfering RNAs (siRNAs) to selectively silence the expression of each viral oncogene based on RNA structure and alternative splicing of viral oncogenes *E6* and *E7*.

We further demonstrated that aberrant expression of oncogenic and tumor-suppressive microRNAs in cervical cancer is required for cancer cell growth and viral oncoproteins are partially responsible for this deregulation. In our KSHV work, we are exploring the mechanisms that regulate the expression of viral and cellular genes.

We have identified *KSHV ORF57* as an essential viral gene responsible for productive KSHV infection, viral RNA splicing, and expression of both viral and human IL6, a cytokine involved in inflammation.

BRIGITTE WIDEMANN, M.D., NCI

Section Head, Pharmacology and Experimental Therapeutics Section and Genetic Tumor Predisposition Program

Education: University of Cologne, Germany (M.D.)

Training: Residency in pediatrics at the Children's Hospital, University of Cologne (Cologne, Germany); fellowship in pediatric hematology and oncology at NCI

Came to NIH: In 1992 as a fellow in pediatric hematology and oncology in NCI's Pediatric Branch. In 1993 joined the Pharmacology and Experimental Therapeutics Section; in 2000 became clinical tenure track investigator

Other professional activities: Assistant Professor, Department of Oncology and Department of Pediatrics, Johns Hopkins Medicine (Baltimore)

Outside interests: Spending time with family; traveling; enjoying outdoor activities

Research interests: Our research focuses on developing more effective treatments for children and young adults with cancers. Our early clinical trials target children with refractory cancers for whom no effective treatment exists. In addition, we have established a program for neurofibromatosis type 1 (NF1)–related tumor and non-tumor manifestations. NF1 is a genetic disorder, characterized by the

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development of neurofibromas and other tumors along the nerves in the skin, brain, and other organs.

We developed novel imaging methods and pioneered the development of early-phase drug treatments for NF1-related plexiform neurofibromas. We are also interested in rare genetic endocrine disorders such as multiple endocrine neoplasia types 2A and 2B, which lead to the development of medullary thyroid cancer in children. Surgically removing the thyroid is the only standard treatment, but must be performed when the tumor is confined to the thyroid gland. Traditional chemotherapy is not effective. We recently started a phase 1/2 clinical trial using the targeted agent vandetanib for children and young adults with this cancer.

SHMUEL MUALLEM, PH.D., NIDCR

Senior Investigator and Chief, Epithelial Signaling and Transport Section, Molecular Physiology and Therapeutics Branch

Education: Ben Gurion University, Beersheeba, Israel (M.S. in biochemistry); Weizmann Institute of Science, Rehovot, Israel (Ph.D. in biochemistry and physiology)

Training: University of Cambridge, England; University of California, Los Angeles

Before coming to NIH: Professor of physiology at the University of Texas Southwestern Medical Center, Dallas, Texas

Came to NIH: In July 2010

Other professional activities: Editor-in-chief, *Cell Calcium*; editorial board of several journals

Outside interests: Reading history

Research interests: My lab is interested in epithelial transport, especially in the area of exocrine physiology and the regulation of enzymes and fluid and electrolyte secretion by epithelial cells. We are studying calcium (Ca) ion signaling in pancreatic and salivary gland acinar cells that secrete fluid and digestive enzymes. In particular we are focusing on the gating mechanism governing the opening and closing of Ca^{2+} influx channels and their role in inflammatory autoimmune diseases such as acute pancreatitis, which can lead to multisystem failure, and Sjögren's syndrome, a disorder that affects the exocrine glands that produce saliva and tears.

We are also investigating bicarbonate (HCO_3^-) transporters in ductal HCO_3^- secretion, which is vital for the function and health of all secretory glands. Defective regulation of HCO_3^- secretion occurs in many epithelial diseases including cystic fibrosis. HCO_3^- facilitates solubilization of macromolecules in secreted fluids to prevent clogging of the ducts. We combine electrophysiological and imaging techniques with molecular and biochemical approaches to study the organization of Ca^{2+} signaling complexes in cellular microdomains and the coordination of ductal HCO_3^- secretion.

TIAN JIN, PH.D., NIAID

Senior Investigator and Chief, Chemotaxis Signal Section, Laboratory of Immunogenetics

Education: Beijing University, China (B.S. in biology); Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, N.J. (Ph.D. in biochemistry)

Training: Postdoctoral training at Johns Hopkins University School of Medicine (Baltimore)

Before coming to NIH: Instructor in the Department of Cell Biology and Anatomy at Johns Hopkins University School of Medicine

Came to NIH: In July 2001

Outside interests: Playing tennis, basketball, and soccer

Research Interests: My research is focused on understanding the molecular mechanisms underlying three biological processes, namely, chemotaxis, phagocytosis, and the chemokine-receptor-mediated HIV infection of immune cells. My group has developed cutting-edge, live-cell imaging techniques, such as fluorescence resonance energy transfer, fluorescence recovery after photobleaching, and single molecule imaging, to reveal the dynamic nature of signaling molecules in space and time and enable us to construct computational models that simulate dynamics and offer testable predictions to refine the signaling networks at a systems level. We use a combination of molecular, genetic, and biochemical approaches to investigate the molecular details of these processes.

Understanding these fundamental biological functions is likely to help us reveal novel targets for therapeutic development.

WILLIAM L. DAHUT, M.D., NCI

Principal Investigator; Clinical Director, Center for Cancer Research; Chief, Genitourinary Clinical Research Section, Medical Oncology Branch

Education: Georgetown University, Washington, D.C. (B.S. in psychology; M.D.)

Training: Residency in internal medicine, National Naval Medical Center (Bethesda, Md.); fellowship in hematology and medical oncology, National Naval Medical Center and the Medicine Branch of the NCI.

First came to NIH: In July 1990 for fellowship at NCI

Other Non-NIH positions: Faculty, Lombardi Cancer Center at Georgetown University Medical Center

Returned to NIH: In 1998 as head of NCI's prostate cancer clinic

Outside interests: Spending time with two teenage daughters and their athletic activities (soccer and swimming); cycling; biking from Pittsburgh to Gaithersburg, Md., annually to raise funds for injured veterans

Research interests: My research focuses on prostate cancer, the most common non-dermatologic malignancy in American men and the second leading cause of cancer-related death. We need new therapies to prevent the progression of the cancer from early stage to advanced

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Recently Tenured

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metastatic disease and we need to further improve the survival of patients with castration-resistant prostate cancer. I led clinical trials that combined vaccine therapy with hormonal therapy, radiotherapy, chemotherapy, and more recently an experimental monoclonal antibody. Based on the trials' demonstration of an immune response, other scientists have launched a large phase-3 trial that combines vaccines with chemotherapy. I also conducted trials that were the first to combine agents directed against different targets in the angiogenic (formation of new blood vessels) pathway. My studies combining angiogenic inhibitors with chemotherapy have the highest published response rate of any therapy in patients with metastatic castration–resistant prostate cancer.

I have had a longtime interest in how the prostate-specific antigen (PSA) is used as a biomarker for prostate cancer. In 1999 I organized the initial PSA Working Group, which developed guidelines for PSA screening. Later, my research suggested that PSA is not always a good biomarker due to the possibility of discordant PSA and radiographic responses. We were the first to show that in some patients treated with oral tyrosine kinase inhibitors that the PSA would increase dramatically while there was tumor shrinkage demonstrated on computed tomography scans. This finding was replicated by others and led to an update of the PSA Working Group Criteria, which eliminated PSA as a primary measure of progression. I recently organized a smaller meeting to delineate similar criteria for PSA doubling time, another progression indicator. ●

If you were tenured in the past year or so, *The NIH Catalyst* would like to include an article about you and your work in this section. We will contact you within the next few months.

ANNOUNCEMENTS

PROSTHETIC HEART VALVES EXHIBIT OPENING SOON

A new exhibition that features significant contributions made to the development of replacement heart valves by NIH surgeons, researchers, and investigators in the late 1960s and early 1970s will soon greet visitors to the South Lobby of the Clinical Center (Building 10). The extraordinary collection is from the NIH Office of History Stetten Museum and includes heart valves that were sent to NIH for evaluation after the Clinical Center's surgical wing opened in 1963. NIH was one of a very few sources for objective data comparing the performance of the numerous heart valve models available at the time.

2011 FARE COMPETITION

APPLICATION PERIOD: February 22–March 22

NIH intramural trainees are invited to submit applications for the annual Fellows Award for Research Excellence (FARE) competition. Winners will each receive a $1,000 stipend* to attend a scientific meeting, present their work at the 2011 NIH Research Festival, and serve as judges for the next FARE competition. Application and abstracts must be submitted online between February 22 and March 22. Winners will be notified by June 30, 2011. For more information, visit http://felcom.od.nih.gov/subCommittee/fare.aspx.

*NHLBI Fellows do not receive the stipend, but will be acknowledged as FARE awardees, if selected. NHLBI fellows are allowed to attend a sufficient number of conferences independent of the stipend. Contact Herbert Geller or Robert Balaban with any NHLBI questions.

NATIONAL POSTDOCTORAL ASSOCIATION 2011 ANNUAL MEETING

Friday, March 25–Sunday, March 27, 2011

REGISTRATION DEADLINES: February 18, 2011 (early); March 11, 2011 (regular)

Natcher Conference Center (Building 45)

Don't miss the 9th Annual National Postdoctoral Association (NPA) Meeting, sponsored by the NIH Office of Intramural Training and Education. The NPA is the national voice for postdoctoral fellows and believes that postdoctoral fellows make invaluable contributions to the research enterprise and share personal responsibility for the progression and outcomes of their careers. Each NPA Annual Meeting is highly engaging and productive for postdoctoral scholars, administrators, and other individuals working to enhance the postdoctoral experience. More information about the NPA can be found at http://www.nationalpostdoc.org. To register for the 2011 Annual Meeting, visit https://www.nationalpostdoc.org/annual-meeting.

NIH MANAGEMENT INTERN PROGRAM RECRUITING NOW!

The NIH Training Center is pleased to announce its recruitment season for Management Interns. The Management Intern Program has been developing highly motivated NIH employees for more than 50 years! This two-year career development program gives employees the opportunity to take rotations of three to four months in various career tracks in NIH public service. Graduates of this program move into new career paths, and many former interns have gone on to hold high-level managerial positions at NIH. Management interns gain valuable experience and insight into the inner workings of the NIH in career tracks in budget and finance, program and management analysis, grants management, contracts and procurement, information technology, human resources, and general administration as well as other electives such as science policy and communications. Management Interns come from both the administrative and scientific fields, from travel planners to biologists. The MI Program job vacancy announcement opens on February 25, 2011, and closes on March 25, 2011. Current GS-7 through GS-12 NIH employees are invited to apply. For other details and to register for one of the upcoming information sessions, visit http://www.jobs.nih.gov/intern/mi.html.

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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.

IN FUTURE ISSUES:

- MALARIA RESEARCH
- HISTORY OF HEART VALVES
- SHARED RESOURCES

LABORATORY CONFESSIONS

Is Plain Language Discriminatory?

BY NAME WITHHELD

I'm all in favor of communicating in a common language, but the emphasis on plain language is shortsighted. Perhaps you have seen the e-mail messages encouraging you to use plain language in all of your correspondences. In October, President Obama signed the Plain Writing Act of 2010. And here at the NIH, there's a plain language award program.

The gist, as far as I can tell, is that plain language is touted as being synonymous with clear communication. Yet if you ever visited the Plains and tried ordering a soda at a restaurant, you'll know that plain language is not the lingua franca of the United States. These people use the word "pop" instead.

This mandate to use plain language will mean our nutrition campaigns will offer the advice to not "piece around" (snack) between meals. Our scientific rebuttals and letters to the editor will be colored with "I don't rightly know 'bout that," "who's ta say," and "uff da." Better get the flu shot or the flu will "beat you like a rented mule."

Being from Providence, R.I., I know the meaning of "Hey, next time you cut through my garden, you walk around." Quite clear. But I don't expect the people from the Plains to follow.

We should be striving for standard American English, not any particular dialect, and certainly nothing from the Plains. I suggest we adopt something all of us understand, like Philadelphian.

What'a yous think?

EDITOR'S NOTE: HAVE A LATE-NIGHT LABORATORY CONFESSION? WE MIGHT PRINT IT IF IT IS INDECENT ENOUGH.

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

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