Better Imaging Tools
NIH Institutes Share Expertise
BY KRYSSEN CARRERA, NIDDK

In 2011, two NIH institutes joined forces to share their expertise and sophisticated imaging tools to advance the understanding of cardiovascular disease, diabetes, and other challenging health conditions. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Biomedical Imaging and Biomedical Engineering (NIBIB) have been running a joint operation called the Biomedical and Metabolic Imaging Branch (BMIB) in the heart of the NIH Clinical Center (Building 10).

“Our multidisciplinary team includes imaging physicists, spectroscopists, and clinicians,” said NIDDK senior radiologist Ahmed Gharib, who manages the daily operations of the branch. BMIB’s high-quality imaging capabilities provide basic scientists and clinicians with a more accurate depiction of a developing disease, while low-quality images increase the likelihood of misdiagnosis.

For example, a low-resolution liver scan may leave important details—such as tiny tumors—blurry and difficult to identify. High-resolution scans, taken from many angles, however, provide clear and detailed images that enable researchers to pinpoint problems earlier in a disease. Advanced imaging techniques can also be used to examine multiple organs simultaneously, making it possible to understand, detect, and manage various systemic diseases.

CONTINUED ON PAGE 6

FAES Opens New Academic Center
Classrooms, Bookstore, Coffee Shop, and More
BY LAURA STEPHENSON CARTER

It’s been 10 years in the making, but the Foundation for Advanced Education in the Sciences (FAES) is about to open the doors of its new Academic Center in the Clinical Center (Building 10). As you walk along the corridor between the Masur Auditorium and the Clinical Center’s atrium, you may have noticed the large glass window and the spacious room that will soon house the FAES bookstore and a coffee bar. Behind the bookstore is a large skylighted terrace; downstairs are eight subdividable classrooms with state-of-the-art audiovisual equipment and Internet connections (both Wi-Fi and LAN).

“This is the first time there will be real classrooms and desks,” said former FAES president Edwin “Ted” Becker, who is overseeing the 20,000-square-foot renovation project. Becker, an NIDDK scientist emeritus, is a past director of the NIH Office of Research Services. Until now, “FAES classes used whatever space was available in the evenings.”

Classes range from introductory to advanced courses in the biomedical sciences and are taught by NIH scientists and fellows (Becker taught courses for 30 years). The intensive, hands-on Bio-Trac courses, which include both laboratory and lecture sections, are held in Building 60 and will eventually be moved to Building 10 when more space becomes available.

CONTINUED ON PAGE 10

CONTENTS
Many folks have been asking us recently about the roles of two foundations associated with the NIH: essentially, what they fund and how. These organizations—the Foundation for NIH (FNIH) and the Foundation for Advanced Education in the Sciences (FAES)—indeed have helped fund many priorities at NIH. They are important partners in improving the scientific and training environment because NIHers are not allowed to ask anyone outside the NIH for money.

**FNIH:** In 1990, the U.S. Congress created the FNIH as a 501(c)(3) nonprofit charitable organization and authorized it to raise private-sector funds in support of the mission and work of the NIH and facilitate public-private partnerships for biomedical research and training. FNIH, which began its work in 1996, has raised almost $700 million to support a broad portfolio of unique programs that complement and enhance NIH priorities and activities. Some FNIH-supported projects include:

- Grand Challenges for Global Health through the Bill and Melinda Gates Foundation to address issues of global health
- Medical Research Scholars Program (provides mentored research-training to medical, dental, and veterinary students at NIH)
- The Edmond J. Safra Family Lodge for families of patients taking part in clinical trials at NIH
- Biomarkers Consortium, a collaboration among NIH, pharmaceutical companies, and the FDA to support new drug development and enhance clinical care
- New procedures have recently been introduced that direct all “requests for collaboration” to proceed only with the approval of an institute or center (IC) director, endorsement by an NIH steering committee, and final consideration and approval by the FNIH Board of Directors. This process assures that the proposed collaborations support the mutual interests of both the NIH and the FNIH.

Maria Freire was recently appointed as the new FNIH executive director. She brings enthusiasm and excitement to the FNIH and is familiar with the NIH: She served as director of the Office of Technology Transfer from 1995 to 2001. She most recently was president of the esteemed Lasker Foundation in New York. FNIH’s board of directors is made up of talented and well-known academic, corporate, and philanthropic leaders from around the country.

**FAES:** The FAES was founded in 1959 by NIH scientists to serve selected needs of the NIH Intramural Research Program. In contrast to the FNIH, it lacks specific Congressional authorization and thus operates as an independent nonprofit organization in cooperation with FNIH. It does not solicit donations from outside sources but holds assets and conducts special programs that serve the intramural community.

NIH programs that wish to develop partnerships with FAES should create a memorandum of understanding, which must be reviewed by the originating IC and approved by the Office of Intramural Research before it can be sent to the FAES for consideration. FAES programs include:

- Graduate educational program that includes evening classes as well as specialized instruction in biotechniques (Bio-Trac)
- Health-insurance program for NIH fellows who are not eligible for federal employee benefits
- A bookstore, a chamber music series, housing opportunities, and more

FAES has funded the construction of an FAES Academic Center (FAC) that includes new classrooms, a graduate student lounge, a coffee shop and bookstore, and FAES administrative offices. The FAC is located in the former Visitor Information Center in the heart of Building 10. FAC, scheduled to open this summer, is expected to become a focal point for FAES classes, scientific lectures and conferences, and even the 2013 NIH Research Festival this fall. NIH is grateful to FAES for its generosity in creating this useful, attractive addition that will meet NIH needs for meeting and gathering space. (See story on page 1.)

FAES is a membership organization governed by a board of directors. The president is Earl Laurence (retired NIDDK executive officer) and the president-elect is Angela Gronenborn (former chief of structural biology at NIDDK and now at the University of Pittsburgh School of Medicine). FAES executive director is Christina Farias who was formerly at the Georgetown University Law School in Washington, D.C.

We welcome your comments and suggestions. For more information about FNIH and FAES, visit http://www.fnih.org and http://www.faes.org.
Scientists may be better able to study how heavy drinking damages the liver using a new mouse model of alcohol drinking and disease developed by researchers from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The model incorporates chronic and binge drinking patterns that more closely approximate alcoholic liver disease in humans than any existing method. A report of the new model appears in the March issue of the journal Nature Protocols (Nat Protoc 8:627–637, 2013).

“The NIAAA model represents a significant advance in understanding the progression of alcoholic liver disease, which in severe cases can lead to liver failure and death,” said Kenneth R. Warren, acting director of the NIAAA. “By replicating both chronic and binge drinking, we are able to simulate the natural drinking patterns of many alcoholic hepatitis patients and the resulting liver injury.”

The liver, which filters out harmful substances in the blood, plays a key role in breaking down alcohol. Alcoholic liver disease (ALD) refers to a broad range of liver injuries caused by drinking. Some forms are mild and reversible while others, such as cirrhosis, are life-threatening and irreversible. Fatty liver disease, an early form of ALD marked by a build-up of fat in liver cells, occurs in almost all heavy drinkers, but liver damage can usually be reversed if the individual stops drinking.

About 20–40 percent of heavy drinkers will develop more severe forms of ALD, including alcoholic hepatitis, which involves inflammation and swelling of the liver, and cirrhosis, which can lead to liver failure as scar tissue accumulates in the organ. Scientists do not completely understand why some people progress to more severe forms of ALD, although sex, obesity, genetic and dietary factors, and smoking may play a role.

“Many of the models for alcoholic liver disease currently used do not evoke the full range of symptoms or are expensive and technically difficult,” said senior author Bin Gao, chief of the NIAAA Laboratory of Liver Diseases.

In the most common model currently used, mice are allowed to feed for four to six weeks on a liquid diet that contains five percent ethanol. But this model doesn’t induce the kind of liver injury commonly caused by binge drinking; it only induces mild fat accumulation in liver cells, slightly elevated liver enzymes indicating damage, and little or no inflammation. Models that are better at replicating more severe forms of ALD involve infusing alcohol directly into the mouse’s stomach, which requires intensive medical care for the animals, high technical expertise, and costly equipment.

The NIAAA model, however, is simpler. It involves a 10-day feeding of an alcohol-containing liquid diet, followed by a single high-dose feeding of alcohol to approximate binge drinking. This results in a marked elevation of fatty liver and enzymes indicating liver injury.

“The NIAAA model is less costly, more time efficient, and easy to perform,” said Gao. “Importantly, it may more closely resemble the progression of human alcoholic hepatitis.” He noted that it may also be useful in studying damage to other organs caused by heavy drinking, including the heart, lungs, kidneys, pancreas, and central nervous system.
Ever met someone who is a forensic scientist, journal editor, patent officer, or grants administrator and wonder whether you could ever transition into one of those positions even though you’ve been doing bench work for years? Or are you interested in following the traditional academic route but wonder how you might go about doing that? Wonder no more: The Career Development Subcommittee can provide you with all kinds of information on career opportunities available to postdocs.

NIH hosts a multitude of fellows including more than 3,600 postdocs in research and clinical fields. FelCom’s Career Development Subcommittee is dedicated to providing postdocs with the tools they need to make a successful transition into their next career. The committee also organizes a yearlong seminar series to help postdocs explore career options.

Whether you are interested in pursuing positions in academia, industry, administration, or alternative careers, the Career Development Subcommittee is a one-stop shop for you. In 2013, the subcommittee has already hosted three seminars—one on careers in industry; a second on careers in government; and a third on careers in core facilities and service companies.

Each seminar includes experts who give short introductions about their backgrounds, describe what attracted them to their fields, and explain how they got their jobs. Postdocs can ask questions and then interact with each other and the experts at a social-networking event afterwards.

These seminars provide a wealth of information about traditional and not-so-traditional careers as well as ones you may not have known existed. Many postdocs have benefited from these seminars and gone on to make well-informed decisions about their next career move.

FelCom encourages you to visit the Career Development Subcommittee Web page (see below) for information on past and upcoming seminars. Check the Web site for details on the “Careers in Technology Transfer” seminar (June 17). Keep an eye out for e-mails about upcoming events, too.

For more information, visit the Subcommittee Web site: https://www.training.nih.gov/FelCom/CareerDevelopment

Summer is approaching, and the Office of Intramural Training and Education (OITE) is ready to welcome incoming summer students. For many scientists, summer research programs bring back fond memories: They represent a time of scientific exploration, intellectual challenge, and personal growth that may cement decisions to pursue careers in science. Every summer, NIH hosts hundreds of enthusiastic students from high schools, community and four-year colleges, as well as from professional and graduate schools.

OITE helps summer students and their mentors make the most out of their NIH experience. Besides having strong scientific credentials, to be successful, scientists must develop strong communication, leadership, and interpersonal skills. OITE encourages all trainees, including summer students, to develop professional competencies that are crucial for succeeding in scientific careers.

Throughout the summer, OITE offers science skill- and career-development workshops; the workshops complement the training activities offered by each institute or center. Some workshops focus on enhancing skills such as reading a scientific paper, creating dynamic posters, and delivering oral presentations. Others provide tools for career exploration and prepare students for applying to professional or graduate school.

Summer students who are stepping into the lab for the first time or have little previous research experience should consider the Science Skills Boot Camp, a daylong workshop that provides an introduction to the NIH research culture and to scientific communication and laboratory skills.

In addition, summer students may attend journal club sessions—led by postdoctoral fellows and graduate students—that cover a range of topics and promote scientific reading and critical-thinking skills. Finally, students will present posters that showcase their work on Thursday, August 8, 2013.

For more information, visit
https://www.training.nih.gov/for_staff/trainee_resources
https://www.training.nih.gov/for_summer_mentors
https://www.training.nih.gov
Free Stuff
For Science on a Shoestring Budget

Do you need to order equipment or supplies or get rid of items you no longer need? Before you do anything, check out the NIH FreeStuff Web site (http://stuff.nih.gov) to see what you can get for free or give away.

The NIH FreeStuff program was developed in 2011 by the National Institute of Allergy and Infectious Diseases (NIAID) and piloted by NIAID’s Division of Intramural Research. In 2012, it expanded to include all NIAID scientists and staff. And on April 2, 2013, the NIH FreeStuff program achieved its long-range goal: It became available to all of NIH.

The FreeStuff Web site is easy to use and the home page even includes two short instructional videos on how to post—and search for—such items as scientific equipment, lab supplies, office equipment and supplies, copy machines, printers, computers, and furniture. You simply post descriptions and photos of items you want to give away or search the site for things you need and submit requests to the people who posted those items.

When you exchange equipment and supplies this way rather than buying new or discarding the old—or immediately transferring them to the NIH Gaithersburg Distribution Center (GDC) warehouse—NIH saves money. From October 1, 2011, to January 15, 2013, 21 items were transferred within NIAID for a savings of nearly $57,000. Now that the program has become NIH-wide, even greater savings are expected.

The FreeStuff project team—which includes co-leaders Gwen Shinko and Claro Yu as well as members Jason Barnett and Shankar Somasekhar, all from NIAID—is exploring ways to coordinate with other NIH entities that also share or store unwanted equipment and supplies. For example, you can find surplus chemicals by calling the Division of Environmental Protection (in the Office of Research Facilities). And you can locate surplus furniture and equipment by looking through NBS reports or by going to the NIH Property Branch’s Surplus Yard on the Bethesda campus or GDC warehouse. The team hopes, however, that some of those items might be suitable for posting on the FreeStuff Web site. But remember, the site only works well if we all use it.

Note: NIH FreeStuff must be accessed from the NIH network. If prompted for a username and password, enter your NIH username starting with “NIH” and ending in your username. Then enter your current NIH password.
“Advances in imaging allow us to view parts of the body at a level of anatomic and functional detail and speed that had not been possible in the past,” said Gharib. BMIB researchers use a computed-tomography (CT) technique to capture crisp images of the heart’s blood vessels while the heart is beating. Imaging a moving heart is somewhat like photographing a fast-moving car—the more shots you take, the greater the likelihood that at least one will be clear. “We can now get a full cardiac CT in one to two heartbeats, compared [with] 16 [beats] just a decade ago,” Gharib explained. “This kind of development has made a big impact in translational biomedical research.”

The BMIB’s high-quality imaging capabilities provide basic scientists and clinicians with a more accurate depiction of a developing disease. Here, a Multidetector Computerized Tomography 3-D reconstructed image of the whole heart (center) is flanked by detailed images that were produced by a technique called multiplanar reformatting; the red arrows indicate non-calcified coronary plaques and the yellow arrows indicate calcified plaques: (right) right coronary artery; (left) left anterior descending coronary artery.

BMIB’s high-quality imaging capabilities provide basic scientists and clinicians with a more accurate depiction of a developing disease. Here, a Multidetector Computerized Tomography 3-D reconstructed image of the whole heart (center) is flanked by detailed images that were produced by a technique called multiplanar reformatting; the red arrows indicate non-calcified coronary plaques and the yellow arrows indicate calcified plaques: (right) right coronary artery; (left) left anterior descending coronary artery.

The work that we are doing in the branch holds tremendous promise for improved understanding of systemic disease and for early detection methods [especially for] atherosclerosis, which has long been the number one killer in much of the developed world,” said NIBIB Director Roderic Pettigrew. “We hope to see hospitals throughout the world one day using approaches based on this research.”

In keeping with NIH’s focus on collaboration, BMIB staff scientists Ronald Ouwerkerk and Khaled Abd-elmoniem and others work closely with other institutes—such as NICHD, NIAID, and NHLBI—that also depend on advanced imaging. For example, BMIB investigators have developed MRI and MRS techniques that can assess the metabolic composition of various organs and measure tissue stiffness. High-resolution coronary MRI provides a twofold improvement over conventional MRI in spatial resolution.

Additionally, improvements in temporal resolution allow researchers to view and measure the thickening of the coronary artery wall, the earliest stage of coronary artery disease. In the future, these new techniques may be used to monitor the effects of therapies and screen people at risk for coronary artery disease as well as metabolic and hepatic dysfunction.

“The collaborative infrastructure at NIH has enabled all of us to work together more efficiently,” said NIDDK Director Griffin P. Rodgers. “The Biomedical and Metabolic Imaging Branch is an excellent example of what can be accomplished through ongoing partnerships within NIH.”

The Perils of Nipah Virus and Ischemic Stroke

NIH’s Women Postdocs Are Tackling Challenging Diseases

BY MEGHAN MOTT, NIAAA

Nipah virus and stroke were featured at a recent seminar that recognized the achievements of two of NIH's female postdocs: Emmie de Wit and Zhifei Wang, who presented their research at the Women Scientist Advisors (WSA) Scholars Seminar on March 29, 2013.

Emmie de Wit studies virus pathogenesis and transmission in Heinz Feldmann's Laboratory of Virology at the National Institute of Allergy and Infectious Diseases' (NIAID’s) Rocky Mountain Labs in Hamilton, Montana. In 2012, she received a Fellows Award for Research Excellence (FARE) for her research on modeling the transmission cycle of the deadly Nipah virus.

Outbreaks of Nipah virus, which causes severe disease such as encephalitis, occur almost yearly in Bangladesh. The virus is thought to be transmitted from infected fruit bats to humans who consume the raw sap from a date palm tree that has been contaminated by bat urine or saliva. Humans can spread the virus to each other through close physical contact. There is no vaccine or treatment for Nipah virus, and, in Bangladesh, it kills up to 90 percent of the people who become infected, according to de Wit.

In her experiments, de Wit exposed Syrian hamsters to artificial date palm sap containing the virus. About 63 percent of the hamsters that drank the contaminated sap developed neurological disease and then transmitted the virus to eight percent of their uninfected cage mates (unpublished research).

“Understanding the Nipah virus transmission cycle is essential for mitigating Nipah virus outbreaks,” said de Wit. “The limited potential for medical intervention in resource-poor outbreak areas highlights the need for pre-emptive strategies focused on preventing transmission.”

De Wit earned her Ph.D. in 2006 from Erasmus University Rotterdam (Rotterdam, The Netherlands) and did her postdoctoral research at Erasmus Medical Center in Rotterdam, studying zoonotic and human-to-human transmission of the influenza A virus. She has published over 30 manuscripts in journals, including Science and the New England Journal of Medicine.

Zhifei Wang, a postdoc in De-Maw Chuang's laboratory in the National Institute of Mental Health (NIMH), does research on novel therapeutic applications of mood-stabilizing drugs to treat ischemic stroke. She received a FARE award in 2012 for her work showing that treatment with valproate (VPA) enhances post-ischemic angiogenesis in a rat model of ischemic stroke (Stroke 43:2430–2436, 2012). VPA is an FDA-approved product used to treat seizures and bipolar disorder.

Stroke is the second leading cause of death worldwide; 87 percent of strokes are ischemic and caused by a clot in a vessel that supplies blood to the brain. Angiogenesis, the formation of new blood vessels, is known to promote recovery after a stroke. Wang's work demonstrated that in a rat model of middle cerebral artery occlusion, post-ischemic VPA treatment enhances angiogenesis and also improves coordinated locomotor performance, reduces brain infarction, enhances microvessel density, facilitates endothelial cell proliferation, and increases cerebral blood flow in part of the cortex.

“Combined with its long history of safe use in humans to treat bipolar disorder,” said Wang, “these findings may pave the way for clinical trials using valproate to treat stroke.”

After receiving her Ph.D. in 2007 from Shanghai Institute of Materia Medica, Chinese Academy of Sciences (Shanghai), Wang began her postdoctoral training at NIMH. She has published over 20 manuscripts in journals, including Stroke and Journal of Cerebral Blood Flow and Metabolism.

The NIH WSA Scholars Seminar was sponsored by WSA and the NIH Office of Research on Women’s Health. The WSA committee, aims to advance the scientific careers and scientific contributions of women at NIH. Each year, the WSA selects two awardees from the pool of female FARE winners for this special recognition and gives them the opportunity to present their research to the NIH community. To learn more about the history and activities of the WSA, visit http://sigs.nih.gov/WSA/Pages/default.aspx.
Intramural Research Briefs

NIDA: RESETTING THE ADDICTED BRAIN
Could drug addiction treatment of the future be as simple as an on-off switch in the brain? A study in rats has found that stimulating a key part of the brain reduces compulsive cocaine-seeking behavior and suggests the possibility of changing addictive behavior generally. NIDA researchers used an animal model of cocaine addiction in which some rats exhibited addictive behavior by pushing levers to get cocaine even when followed by a mild electric shock to the foot. Other rats did not exhibit addictive responses.

The NIDA scientists compared nerve-cell firing patterns in both groups of rats by examining cells from the prefrontal cortex. They determined that cocaine produced greater functional brain deficits in the addicted rats. The researchers then used optogenetic techniques on both groups of rats—essentially, shining a light onto modified cells to increase or lessen activity in that part of the brain. In the addicted rats, activating the brain cells (thereby removing the deficits) reduced cocaine-seeking behavior. In the nonaddicted rats, deactivating the brain cells (thereby creating the deficits) increased compulsive cocaine seeking.

This is the first study to show a cause-and-effect relationship between cocaine-induced brain deficits in the prefrontal cortex and compulsive cocaine seeking. The results provide evidence for a cocaine-induced deficit within a brain region that is involved in disorders characterized by poor impulse control, including addiction. The researchers hope that the findings can lead to treatments that would reduce compulsive cocaine seeking and craving in patients. (NIH authors: B.T. Chen, H.-J. Yau, C. Hatch, I. Kusumoto-Yoshida, A. Bonci; Nature 496:359–362, 2013)

NICHD, NINDS, NCI: NEW SYNDROME LINKED TO A SOMATIC HIF2A MUTATION
A team of NIH researchers, in collaboration with scientists from the University of Utah (Salt Lake City) and Tufts Medical Center (Boston), have identified a new syndrome involving two rare neuroendocrine tumors and a rare blood disease. The syndrome was observed in four female patients who had multiple paraganglioma and somatostatinoma tumors and the blood disease polycythemia.

Somatic mutations in the gene that encodes hypoxia-inducible factor-2-alpha (HIF2A) cause increased production of erythropoietin, which leads to increased red blood cell production called polycythemia. The mutations increase HIF2A stability and enhance its functional capacity by extending its half-life. Symptoms of the new syndrome include high blood pressure, heart palpitations, headaches, and anxiety. Polycythemia in the four women was found either at birth or in early childhood. All developed tumors later in life (the paragangliomas were in the abdomen and somatostatinomas in the duodenum). It is not clear whether the syndrome also exists in men.

Increasing HIF expression has been shown in many tumors, but HIF mutations have never been reported in tumors. The research is the first to provide direct evidence of HIF involvement in tumorigenesis and suggests that inhibiting HIF2A may be a way to treat the disease. The team is currently exploring that avenue. (NICHD authors: K. Pacak, I. Jochmanova, T. Prodanov; NCI authors: M. Merino, T. Fojo; NINDS authors: Z. Zhuang, C. Yang; J Clin Oncol 31:1690–1698 2013)

NIEHS: DISCOVERY OF MUTATED GENE IN NEURODEGENERATIVE DISEASE
An international research team that included several NIEHS scientists has identified a novel factor that removes poly(adenosine diphosphate (ADP)-ribose) chains from proteins. Originally called C6orf130, the scientists renamed this gene TARG1 and its protein terminal ADP-ribose protein glycohydrolase (TARG1) because it cuts off ADP-ribose and poly(ADP-ribose) units that are directly attached to proteins. Individuals who inherit two defective copies of the TARG1 gene suffer from a progressive neurodegenerative disease characterized by seizures, lack of tendon reflex, and a weakened swallowing reflex.

The tagging of ADP-ribose chains to proteins controls gene expression, cell death, and cellular responses to DNA damage. Using X-ray crystallography and cell biological and biochemical approaches, the research team demonstrated that TARG1, a member of a large class of macrodomain proteins, homes in on and erases ADP-ribose tags. The work shows that this TARG1 action is critical for cells to coordinate normal DNA repair processes in support of proper cellular function. Future work is required to gain a better understanding of when and where TARG1 acts to regulate cellular functions. (NIEHS authors: C.D. Appel, M.J. Schellenberg, J.G. Williams, J. Krahn, R.S. Williams; EMBO J 32:1225–1237, 2013)

NIDDK: ACTIVITATING THE BETA CELL PATHWAY TO PROTECT AGAINST DIABETES
In type 2 diabetes (T2D), pancreatic beta cells fail to release enough insulin to maintain blood glucose concentrations within a normal range. So scientists are trying to develop therapeutic strategies that would improve the function of defective pancreatic beta cells.

NIDDK researchers recently demonstrated that stimulating a specific type of cell-surface receptor activated a novel beta cell–signaling pathway that had multiple metabolic benefits in mice. The mice were protected against experimentally induced diabetes and glucose intolerance that had been provoked by either streptozotocin (a toxin that selectively destroys beta cells) or an energy-rich, high-fat diet. The findings provide a rational basis for the development of anti-diabetic drugs targeting this class of receptors. (NIDDK authors: S. Jain, I. Ruiz de Azua, H. Lu, J.-M. Guettier, J. Wess; J Clin Invest 123:1750–1762, 2013) ●

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Neal Young: Conquering Aplastic Anemia

BY KATHERINE BRICENO, NINDS

FORTY YEARS AGO, A DIAGNOSIS OF severe aplastic anemia meant almost certain death. The bone marrow would suddenly stop producing new blood cells—red blood cells, white blood cells, and platelets. Today, however, thanks to the work of NIH scientist Neal Young and others, the survival rate for this rare disease is above 80 percent.

Young first encountered patients with severe aplastic anemia as a medical student at Johns Hopkins (Baltimore) in the 1970s. He found it especially painful to care for these patients because they were young and previously healthy. There was little anyone could do for them medically.

After completing his residency, Young went to NIH to learn protein biochemistry in the laboratory of Nobel laureate Christian Anfinsen; then went to the Barnes Hospital of Washington University School of Medicine (St. Louis) to do a fellowship in hematology; and returned to NIH for a second postdoctoral fellowship in molecular biology under Arthur Nienhuis in the National Heart, Lung, and Blood Institute (NHLBI).

In 1981, Young became a senior investigator and established a section to study the pathogenesis and treatment of human bone-marrow failure. He is the chief of NHLBI’s Hematology Branch and director of the trans-NIH Center for Human Immunology, Autoimmunity, and Inflammation. His outpatient department may be the largest bone-marrow-failure clinic in the world.

There’s a better understanding of what causes aplastic anemia now than when Young was in training. It’s long been linked to a group of environmental factors and other associated diseases: toxins such as pesticides, arsenic, and benzene; radiation and chemotherapy; some medicines; and even some infectious diseases and autoimmune disorders. For acquired aplastic anemia, regardless of the presumed inciting cause, the immune system does the damage by destroying bone-marrow stem and progenitor cells. Depending on the severity of the disease, follow-up can range from observation, to treatment with blood transfusions and medications, to bone-marrow transplant or immunosuppressive therapy.

Young is credited with developing an immunosuppressive regimen that has become the standard treatment for aplastic anemia. Early in his career, he came across European studies that showed the immune system—suppressing biologic called antithymocyte globulin (ATG) could help. Although others were skeptical, he decided to test ATG in a clinical trial in the United States. Patients responded favorably and most became free of the need for transfusion and no longer were susceptible to serious infections. Later he added cyclosporine, a drug used to prevent the rejection of transplanted organs, and the success rate rose from 50 to 70 percent. Today, Young is testing novel therapies to increase the response rate.

In one of his current clinical trials, he is treating aplastic anemia patients with a pill—a synthetic molecule that stimulates hematopoietic stem cells in the bone marrow. He is optimistic that by combining immunosuppression and stem-cell stimulation, aplastic anemia may one day be successfully treated without resorting to bone-marrow transplants.

Young’s research started with patients but it has diverse laboratory components, too. Early on, he used flow cytometry and molecular biology methods, then new to the clinic, to characterize the aberrant immune response in aplastic anemia. He has found that many of the immune abnormalities resemble those seen with viral infection. This interest in viruses led him to examine a newly discovered virus called B19 parvovirus. B19 could cause one type of anemia due to marrow failure. He elucidated the virus’s cellular and molecular biology and developed a vaccine that is now in clinical trials.

Recently, his group discovered genetic defects in patients with aplastic anemia as well as in patients with liver cirrhosis, lung fibrosis, and leukemia. The mutated genes regulate the repair of telomeres (DNA sequences that cap chromosome ends). Telomeres loss and repair are now an important part of Young’s research. He is studying the effects of male sex hormones on the length of telomeres and testing whether androgen therapy can repair or stabilize telomeres.

Young appreciates how NIH has allowed him flexibility and has enjoyed training fellows who now lead groups of their own. Most important is being able to stay close to the patients who have sought out diagnosis and treatment at NIH. The sustained efforts of his laboratory and clinic have had a profound impact on the lives of those patients and others with aplastic anemia.

To read more about Neal Young, visit http://irp.nih.gov/pi/Neal-Young.
Academic Center on Old Georgetown Road; and cultural escapes such as the Manchester String Quartet, which plays eight concerts a year in the Masur Auditorium (Building 10).

But wait, there’s more. FAES administrative offices (most are now in Building 60) and a new graduate student lounge are being constructed along the north corridor that leads to the NIH Blood Bank. The lounge will be a gathering place for the 500 students in the Graduate Partnerships Program (https://www.training.nih.gov/programs/gpp) who are scattered in intramural labs throughout the NIH campus.

And on the second floor, in the old medical boardroom near the cafeteria, there will be a small dining room that will have a small catering kitchen and accommodate up to 40 people.

FAES was launched in 1959 with a mission to “foster and encourage scientific research and education . . . by whatever means may be practicable.” Today, the foundation offers nearly 200 graduate and undergraduate courses a year; a health-insurance program for fellows who are not eligible for federal employee benefits; a bookstore (now on level B1 of Building 10); reception facilities at the Social and

NIH donated space for the construction; FAES funded it out of its financial reserves. Gilbane, Inc., is the builder; McKissack and McKissack is the project manager. The renovation will be completed in 2013 except...
for the relocation of the Bio-Trac teaching laboratory. FAES will present the new center to NIH during the 2013 Research Festival (October 7–11).

The new FAES subdividable classrooms have state-of-the-art audiovisual equipment and Internet connections (both Wi-Fi and LAN). Here, four classrooms are shown with their connecting walls partly retracted.

Read more about FAES (and about the Foundation for NIH) in the essay on page 2. In addition, you can learn more about FAES at http://www.faes.org.

This computer rendering shows the new FAES dining room, which will have a small catering kitchen and be able to accommodate up to 40 people.

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CDC: Centers for Disease Control and Prevention
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
DOE: Department of Energy
FAES: Foundation for Advanced Education in the Sciences
FelCom: Fellows Committee
FDA: Food and Drug Administration
FNL: Frederick National Laboratory
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCATS: National Center for Advancing Translational Sciences
NCCAM: National Center for Complementary and Alternative Medicine
NCBI: National Center for Biotechnology Information
NCI: National Cancer Institute
NEI: National Eye Institute
NHGRI: National Human Genome Research Institute
NHLBI: National Heart, Lung, and Blood Institute
NIA: National Institute on Aging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAID: National Institute of Allergy and Infectious Diseases
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB: National Institute of Biomedical Imaging and Bioengineering
NICHHD: 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
NIEMS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIIMH: National Institute of Mental Health
NIIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
OD: Office of the Director
ODS: Office of Dietary Supplements
OITE: Office of Intramural Training & Education
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women’s Health
OTT: Office of Technology Transfer
Lin Asks Why
Genetic Mechanisms of Hematopoiesis: An Interview with Paul Liu
BY LIN WANJEK-YASUTAKE, SPECIAL TO THE NIH CATALYST

Five-year-old reporter Lin Wan- jek-Yasutake grilled NHGRI researcher Paul Liu, M.D., Ph.D., over lunch last month to learn how chance got him to study leukemia and how, 20 years onward, he is in pre-clinical experiments. The interview has been lightly edited.

Lin Wanjek-Yasutake: What are you doing?
Paul Liu: I’m studying the genetic mechanisms of hematopoiesis. One particular research direction is leukemia, specifically acute myeloid leukemia (AML), which I’ve been working on for about 20 years.

Lin: Why?
Paul: Leukemia is an example of hematopoiesis gone wrong. About 15 to 20 percent of patients with AML have a certain mutation that I found.

Lin: Why?
Paul: That’s the major question. We aren’t sure why the mutation does what it does. But once we learn more, we can better understand other kinds of blood disorders. My lab has many things ongoing. We have animal models. We are doing patient sequencing. And we are developing new treatments for leukemia, which to me is the most exciting part.

Lin: Why?
Paul: It’s coming full circle in my life. We found the initial mutation; studied it; and now hopefully we can target that mutation and help patients. It was by chance that I entered into this research area. Twenty years ago genetic studies were based not on disease but on chromosomes, because it was so hard to study a whole genome. Even a whole chromosome was a big deal. We were concentrating on chromosome 16. We were building YAC [yeast artificial chromosome] libraries, cosmid libraries. All of this research was aided by the Los Alamos National Laboratory in New Mexico, believe it or not.

Lin: Why?
Paul: Well, at that time, funding was abundant, and you could do whatever you wanted. Luckily, we found a probe just near the break point. And we found that the inversion generates a fusion gene between the core binding factor beta gene, or CBFβ, and MYH11, the gene encoding smooth muscle myosin. So over the years we’ve been trying to understand how this fusion gene contributes to leukemia.

Lin: Why?
Paul: Scientifically, to us, what’s interesting is what this gene does. About 15 to 20 percent of patients with AML have this inversion. And when they have this inversion, they always have a fusion protein, CBFβ-SMMHC. The fusion gene blocks normal hematopoiesis through its fusion gene. So what we did was design a fluorescence in situ hybridization procedure to detect the fusion gene. We have a patent for this diagnosis tool that’s used for all leukemia patients with AML.

Lin: Why?
Paul: Because if they have the fusion gene, it will predict how the prognosis will be. When doctors see it, they will give the patients certain chemotherapy known to help with this
kind of leukemia subtype. There are 10,000 to 15,000 cases of AML annually in the United States. Those who have this particular mutation number only about 2,000 to 3,000. So pharmaceutical companies are not interested in developing a targeted treatment. But obviously there is still a sizeable population that could benefit from a target treatment.

Lin: Why?
Paul: Good question. I see where you are leading. The interesting thing is that this fusion protein binds to another protein called RUNX1. RUNX1 itself is the target of several chromosome rearrangements seen in leukemia. This suggests this whole pathway is important. So now we are studying these proteins together.

Lin: Why?
Paul: Well, I’m not a hematologist. One reason I went into this field was because of my interest in chromosome 16. But since then I’ve seen how this problem provides a fascinating way to understand normal hematopoiesis. It is scientifically and clinically important. In this regard, I’ve benefited from being at the NIH.

Lin: Why?
Paul: We had to create many different mouse models. It’s difficult in the outside world to get funding for such a long-term project. There were many approaches to take and we tried several. We eventually succeeded with a technology called homologous recombination.

Lin: Why?
Paul: This fusion gene is paradoxical. If it’s overexpressed too much, it’s toxic to cells. But with only a subtle change, it can lead to leukemia. It will change the differentiation of blood cells, changes their survival and proliferation. Our mice with the fusion gene will eventually get AML, very similar to human AML. And we were able to show what it does in the pre-leukemia stage.

Lin: Why?
Paul: Because once you get leukemia, you don’t know what went wrong. You need more than one mutated gene to get leukemia. It takes time to develop. If you are unlucky, you get AML earlier. If I can anticipate your next question, the mice don’t have leukemia at birth. We have many ways to demonstrate this finding. You can do random mutagenesis; you can zap them with radiation. The key difference is that if you treat the wild-type mice without the fusion gene with high-dose radiation or a mutagen, they don’t get AML. Maybe they get a thymus tumor. But the mice with the fusion gene will get AML faster than without the mutagen. So we could show how the fusion gene is a contributing factor and a potential drug target.

Lin: Why?
Paul: Well, let me backtrack: We discovered the gene in 1993; we had the mouse model in 1996. Then we were doing basic research studies. But a big breakthrough was the NIH Chemical Genomics Center (NCGC), which didn’t come until about five years ago. The NCGC allows you to test many compounds quickly. This wasn’t very feasible before. So now we can use zebrafish to...

Lin: Zebra are fish?
Paul: No, no. Zebrafish are small fish with zebra-like stripes. We generated them to contain the fusion gene; they are born with the mutation. If we treat the embryos with various compounds, we can quickly look for the specific defects that we know are induced by the mutation.

Lin: Why?
Paul: The nice thing about zebrafish is that you can easily do high-throughput experiments. You just put a male and female fish together, and they give you hundreds of eggs. And you can make transgenic fluorescent embryos and label specific cell lineages with bright green or bright red color, so you can score them relatively easily. On 96-well plates, you can put five or six embryos per well so we can test hundreds of compounds quite efficiently. We are collaborating with TRND [Therapeutics for Rare and Neglected Diseases] in NCATS [National Center for Advancing Translational Sciences] to do preclinical studies and hopefully move to clinical trials.

Lin: Why?
Paul: This is my first try with preclinical work. I’ve been content with basic research, but I’ve always wanted to do something to improve treatment. The treatments today are usually chemotherapy or bone marrow transplants. Chemo has improved quite a bit. The initial effect is pretty good, but many patients come back. And once they relapse, it’s very hard to treat. A bone marrow transplant isn’t always available. Regardless, many patients still die from leukemia even with the best treatment options. Therefore new and better treatments are clearly needed. A drug might not be optimal, but it can slow the disease. Or it to reduce the dose of chemotherapy. Current chemotherapy is very toxic, especially in elderly patients. Basically, we need many ways—a multiprong attack—to treat AML.

Lin: Oh, ok.
Paul: Nice talking with you.
Research interests: Early in my scientific career, I was interested in the hypothalamic regulation of the pituitary and endocrine organs. Later I turned my focus to neuronal regeneration and examined the ability of circulating blood cells to enter the brain and participate in its regeneration in health and disease. I demonstrated the presence of bone marrow–derived neural cells in the central nervous system of mice as well as in humans. In humans, we used post-mortem brain samples of female patients who had previously received bone marrow transplants from male donors, and we used the Y chromosome as the donor-specific marker.

Later I became interested in learning how bone marrow–derived stromal cells (BMSCs) affect the host immune system. We showed that intravenously injected BMSCs significantly improved the survival of mice with sepsis. Clinical trials have recently been initiated in Canada to test whether human sepsis could also be treated using BMSCs.

We were the first group to suggest that this beneficial effect in mice might be due to reprogramming macrophages from a pro-inflammatory into an anti-inflammatory phenotype producing large amounts of the anti-inflammatory cytokine interleukin-10. We also asked whether BMSCs could rebalance the immune system in an allergic environment. In a ragweed–induced allergy model, BMSCs protect mice from most asthma-specific pathological changes. Our studies suggest that BMSCs respond to the local environment where they are injected.

Research interests: I lead a translational research group that addresses the kidney disease focal segmental glomerulosclerosis (FSGS), a disease that causes scar tissue to form in the kidneys’ glomeruli. Podocytes are specialized glomerular cells that are implicated in FSGS. Variants in the gene APOL1 are associated with FSGS and related diseases, but only in individuals of African descent. We are determining how APOL1 genetic variation contributes to microvascular kidney disease that usually, but possibly erroneously, is attributed to hypertension; whether APOL1 risk alleles are associated with a shorter renal allograft survival and/or worse renal donor outcomes; and the cellular mechanisms by which APOL1 risk alleles confer susceptibility to glomerular disease.

We are conducting two open-label, single-arm, trials for treatment of FSGS: One examines the efficacy of rituximab combined with cyclosporine (for 48 weeks); the other examines the efficacy of isotretinoin (over 24 to 48 weeks). We are also running a multicenter randomized controlled trial that examines the efficacy of fresolimumab, an antibody that neutralizes transforming growth factor–beta-1, a scarring cytokine. We are also examining the use of cyclophosphamide plus plasma exchange for recurrent FSGS after renal transplant and assessing the role of cardiotrophin-like cytokine 1 as a candidate permeability factor.

Recently Tenured

JEFFREY B. KOPP, M.D., NIDDK
Principal Investigator, Kidney Disease Section, Kidney Diseases Branch
Education: Harvard University, Cambridge, Mass. (B.A. in social studies); University of Pennsylvania School of Medicine, Philadelphia (M.D.)
Training: Residency in Internal Medicine and Nephrology at the University of Washington (Seattle)
Came to NIH: In 1987 as a staff fellow in NIDCR; joined NIDDK in 1995
Selected professional activities: Consulting nephrologist at the CC; commissioned officer (captain) with the U.S. Public Health Service
Outside interests: Hiking; backpacking

Research interests: I lead a translational research group that addresses the kidney disease focal segmental glomerulosclerosis (FSGS), a disease that causes scar tissue to form in the kidneys’ glomeruli. Podocytes are specialized glomerular cells that are implicated in FSGS. Variants in the gene APOL1 are associated with FSGS and related diseases, but only in individuals of African descent. We are determining how APOL1 genetic variation contributes to microvascular kidney disease that usually, but possibly erroneously, is attributed to hypertension; whether APOL1 risk alleles are associated with a shorter renal allograft survival and/or worse renal donor outcomes; and the cellular mechanisms by which APOL1 risk alleles confer susceptibility to glomerular disease.

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EVA MEZEY, M.D., PH.D., NIDCR
Senior Investigator; Chief, Adult Stem Cell Section
Education: Semmelweis University Medical School in Budapest, Hungary (M.D.); Hungarian Academy of Sciences in Budapest (Ph.D. in neuroendocrinology); Hungarian Academy of Sciences in Budapest (D.Sc. in stem cells)
Training: Postdoctoral training at Utrecht University (Utrecht, The Netherlands) and in the Laboratory of Cell Biology, NIMH
Came to NIH: In 1982 for training; left in 1985 to work at Semmelweis Medical School; returned to NIH in 1987 as a visiting scientist; in 1996 became head of the In Situ Hybridization Facility, NINDS; in 2004 transferred to NIDCR
Selected professional activities: Editor for PLOSOne; editorial board for Oral Diseases
Outside interests: Spending time with family; reading, watching soccer; playing Ping-Pong

If you have been recently tenured, the NIH Catalyst will be contacting you soon about including you on these pages.
THE NIH DIRECTOR’S AWARDS CEREMONY  
Wednesday, June 12, 2013, 2:00 p.m.
Natcher Kirschstein Auditorium  
Natcher Building (Building 45)

All employees are invited to attend the 2013 NIH Director’s Awards Ceremony. Each year, we come together to honor NIH employees for the outstanding way they support the mission of the NIH. Awards will be presented in six categories: Director’s Awards (Scientific/Medical, Administrative, and Technical/Clerical/Support); Common Fund Leadership Awards; Ruth L. Kirschstein Mentoring Awards; Alan S. Rabson Award for Clinical Care; Commissioned Corps Awards; and Equal Employment Opportunity Awards. A reception will be held after the ceremony in the Natcher dining room. Sign language interpreters will be provided. Individuals with disabilities who need reasonable accommodations to participate in the event should contact Moniqua Roberts at 301-496-6211 or nihawards@od.nih.gov. To watch the live video cast, visit http://videocast.nih.gov.

NIH GRADUATE AND PROFESSIONAL SCHOOL FAIR  
Wednesday, July 17, 2013  
9:00 a.m.–3:00 p.m.
Natcher Conference Center (Building 45)

The fair provides an opportunity for NIH summer interns (especially those in college) and postbaccs, as well as other college students in the D.C. area, to prepare for the next step in their careers by exploring educational programs leading to the Ph.D., M.D., D.D.S., M.D.-Ph.D., and other graduate and professional degrees. More than 100 outstanding colleges and universities from across the United States will be sending representatives of their graduate schools, medical and dental schools, schools of public health, and other biomedicine-related programs to the fair in hopes of recruiting NIH trainees. The day will also include workshops on getting to graduate and professional school, M.D.-Ph.D. programs, interviewing, and careers in public health, psychology, and dentistry. Exhibits will be open from 10:00 a.m. to 1:45 p.m. A list of participating institutions planning to attend and registration information can be found at https://www.training.nih.gov/gp_fair.

REMINDER: TAKE THE SECURITY AND PRIVACY REFRESHER TRAINING!

All NIH staff must complete the FY13 annual “Information Security and Privacy Awareness Training” refresher courses, which were launched in April. Completion of the courses will provide you with valuable information about your responsibilities to secure NIH resources and protect all forms of personal information, whether it belongs to you, members of the public, grant applicants, research study participants, or patients of the NIH Clinical Center. To meet your annual training requirement, visit http://irtsectraining.nih.gov.

AWARDS
Harvey Alter Wins 2013 Gairdner Award

Harvey Alter, chief of clinical studies and associate director of research in the Clinical Center’s Department of Transfusion Medicine, has been selected to receive the 2013 prestigious Canada Gairdner International Award at the conclusion of the Gairdner National Program events on October 24, 2013, in Toronto. Alter will share the award with Daniel Bradley, a consultant at the Centers for Disease Control and Prevention, and Michael Houghton, a researcher and professor at the University of Alberta (Edmonton, Canada) in recognition of their critical contributions to the discovery and isolation of the hepatitis C virus, which has led to development of new diagnostic and therapeutic agents. The announcement was made on March 20, 2013.

Thirty years ago, about a third of transfused people received tainted blood, which later inflamed their livers, producing hepatitis (also called viral hepatitis), the leading cause of cirrhosis and liver cancer and the most common reason for liver transplantation. Alter was the principal investigator on studies that identified non-A, non-B hepatitis, now called hepatitis C. Alter’s work was instrumental in providing the scientific basis for instituting blood-donor screening programs, which have decreased the incidence of transfusion-transmitted hepatitis to near zero. To view a video of Alter describing his work in hepatitis research, visit the NIH YouTube channel at http://www.youtube.com/watch?v=R2GBXuSYnWk. The Canada Gairdner International Award is given to individuals who have demonstrated outstanding leadership in medicine and medical science and whose work has contributed significantly to improving the quality of human life. To date there have been 313 awardees, of whom 80 have gone on to win a Nobel prize in physiology or medicine.

Louis Staudt and Wei Yang Elected to NAS

Lou Staudt and Wei Yang have been elected into the National Academy of Sciences (NAS), according to an announcement on April 30, 2013. They are among 84 new members. Members are elected to the NAS in recognition of their distinguished and continuing achievements in original research. Yang is the section chief of NIDDK’s Laboratory of Molecular Biology. Her lab studies mismatch repair, a process that corrects replication errors, and translesion DNA synthesis, which completes DNA replication when normal polymerases are stalled by damaged bases and V(D)J recombination.

Staudt is deputy chief of NCI CCR’s Metabolism Branch. His laboratory studies the molecular pathogenesis of human lymphoid malignancies and has three primary goals: to establish a new molecular diagnosis of human lymphoid malignancies using gene-expression profiling, to elucidate the oncogenic pathways that result in malignant transformation of normal B lymphocytes, and to identify molecular targets for development of novel therapeutics for these cancers.

http://irp.nih.gov/catalyst
The Office of NIH History (http://history.nih.gov) came across a box with these instruments in it recently and is trying to determine whether they have anything to do with a project that former NIH scientist Roderic E. Steele was developing in the 1980s. Steele was in the Laboratory of Technical Development in NHLBI from 1975 to 1988. He had received his Ph.D. from Stanford University (Stanford, Calif.) and done work in the Radiology Department there with Robert Kallman. At NIH, he worked closely with Joseph S. Handler in NHLBI’s Laboratory of Kidney and Electrolyte Metabolism. The box also contained letters, dated 1983 to 1984, between Steele and Becton Dickinson representatives about a porous membrane for cell-culture experiments. It is unclear whether these instruments are those mentioned in the letters or whether the project ever came to fruition. If you can shed any light on this mystery, please contact the NIH Catalyst at catalyst@nih.gov or 301-402-1449.

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

Also, we welcome “letters to the editor” for publication and your reactions to anything on the NIH Catalyst pages.