Meet the New Laskers
Investigating Sickle-Cell, Cancer, and Addiction
BY SARA LIOI, NINDS

Congratulations to the three new NIH Lasker Clinical Research Scholars: Hans Ackerman, Andrea Apolo, and Falk Lohoff.

Ackerman (National Heart, Lung, and Blood Institute) is studying how metabolic and genetic factors affect blood flow in people with sickle-cell disease, with a special emphasis on stroke and kidney injury in adults. He also is working with the Sickle Cell Research and Treatment Center in Bamako, Mali, to identify the major causes of death and disability in children with sickle-cell disease.

Apolo (National Cancer Institute) is developing and designing clinical trials to test novel agents for the treatment of urologic cancers. In particular, she is working to develop new bladder cancer–targeted therapies such as anti-angiogenesis compounds, inhibitors of the cellular Met receptors, and immunotherapeutic combinations.

Lohoff (National Institute of Alcohol Abuse and Alcoholism) is focusing on heritable and nonheritable genetic aspects that influence the onset, progression, and treatment of alcohol-use disorders and addictions. Findings from these studies are translated into human clinical studies using diverse approaches, including molecular biomarkers, pharmacogenetics, epigenetics, and functional-imaging genetics.

Scientific Ties Across the Pacific
NIH-Japan Collaboration in Biomedical Research
BY SOMA CHOWDHURY AND CHRISTOPHER WANJEK

Debris, rubble and damaged vehicles line the streets for several blocks in the fishing town of Ofunato, Japan, following the March 11, 2011, 9.0-magnitude earthquake and tsunami. Research facilities in Japan were damaged, too, and NIH, which has had a decades-long collaborative relationship with Japanese scientists, played a role in helping the displaced researchers get back to work. That collaboration continues with regularly scheduled symposia and other activities.

The earthquake was punishing enough, damaging more than a half-million buildings as far as 200 miles from the epicenter. But the magnitude 9.0 event on March 11, 2011, centered off the northeastern coast of Japan, will be most remembered for the harrowing tsunami that followed.

Within 30 minutes of the quake, a tsunami with waves towering as high as 130 feet made landfall, engulfing entire coastal towns in the Tohoku region north of Tokyo. Cars,
There are some 260 care providers employed by the NIH who have the professional designation of “Staff Clinician.” Most of the institutes’ and centers’ (ICs’) intramural programs and the Clinical Center employ staff clinicians, who play critical roles: They have important responsibilities in the conduct of NIH research; as parts of teams, they facilitate their own research and the research of other clinician-scientists; they are essential for the care of Clinical Center patients and consult on difficult clinical problems; and they lead the training of the next generation of clinician-scientists.

A subcommittee of the Advisory Board for Clinical Research—a Clinical Center oversight group consisting of NIH leadership and outside experts in clinical research, clinical care, and hospital management—recently completed a review of the Staff Clinician position and made three important recommendations that are currently being implemented.

The report’s three recommendations were:

1) Develop titles for all staff clinicians that appropriately reflect their work. Although “Staff Clinician” is the official intramural professional designation for clinicians with this varied group of responsibilities, each IC will develop more-appropriate titles to better define what they do as physician-scientists such as “Director of Training” or “Head, Division of Clinical Care” or “Chief, Diagnostic Development Unit.”

2) Each IC will organize a regular review of the activities of each staff clinician that are relevant to his or her roles and responsibilities. These reviews will reflect the needs of the intramural programs. In most cases they will include a Board of Scientific Counselors’ review of any independent research activities, as well as a review of patient care and mentoring and training activities by peers.

3) Ensure that the recruitment of Staff Clinicians is done with complete transparency: The nature of the work they will perform and their research resources will be accurately portrayed during the advertisement and recruitment process.

A town hall meeting was held on December 5, 2014, to discuss these recommendations with the community of staff clinicians. The meeting included presentations by Briggs; Holland; Richard Wyatt (Office of Intramural Research), and Steven Holland (a senior investigator in NIAID and deputy director for Intramural Clinical Research). The subcommittee’s report was presented to the Scientific and Institute Directors, by whom it was unanimously endorsed.

Gallin pointed out that staff clinicians are absolutely essential for NIH clinical-research activities and that there needs to be broad flexibility within this category of scientists for them to both facilitate NIH research and develop their own careers.

Liang suggested that a committee of staff clinicians be established to help develop further refinements of this position. The staff clinicians at the town hall welcomed this idea. There were recommendations for improved resources to help staff clinicians contribute to team science across the NIH institutes, and the expectation that positive reviews would result in greater appreciation of the quality and value of the work that they do at the NIH.

Most important moving forward is the creation of a LISTSERV to allow for the development of a community that can elect a staff clinician to represent their interests to the Medical Executive Committee and the Intramural Clinical Research Steering Committee. It is hoped that a staff-clinician community will allow better sharing of information across the NIH and lead to a more cohesive group of essential clinicians.

As always, please send me any comments you might have about how better to recognize the important contributions of our staff clinicians and how to enable the important work that they do.

To watch a videocast of the December 5, 2014, staff clinician town hall meeting, visit http://videocast.nih.gov/launch.asp?18763 (NIH and HHS only).
Beware of Predatory Publishers
Substandard Journals Exploit Open-Access Model
BY SUSAN BATES, NCI-CCR

The e-mail began, “Dr. Susan E. Bates, Hope you are doing well Doctor!” It was from a publishing group that “would really be grateful to you if you can assist us to successfully release the upcoming issue by your energetic and enthusiastic submission of manuscript which will be published under respective Journal for this wonderful year.”

That clumsily worded e-mail, from someone who used only an initial for his last name, invited the submission of any type of content within 10 days and was but one of many such e-mails that I had received from apparently new open-access (OA) journals. So I decided to investigate. I discovered that there are ongoing discussions in the scientific community about OA publishing and so-called “predatory publishers” that exploit the OA model.

The Open Access movement began in the 1990s as a worthy initiative to provide the public with unrestricted, free access to scholarly research publications. As journal subscription fees charged to libraries steadily increased and expensive download fees for individual articles became commonplace, access to scholarly research was becoming more limited for scientists, physicians, journalists, patients, and others.

OA journals, on the other hand, can be freely read on the Internet because the publishing is not funded solely through subscriptions. These journals allow for research data to be in the public domain where it can be easily accessed; can be more egalitarian than some established journals that, at times, seem to favor well-known or well-funded investigators; and provide a venue for the publication of negative data, which can be as important—if not more so—than positive data, but are often harder to publish.

In addition, it may be easier to get papers published in OA journals than in “high-impact-factor” journals. Some scientists consider more-established journals such as Nature, Cell, and Science to be more desirable to publish in because of their higher citation rates.

Unanticipated was the flood of OA journals that emerged as a result of the OA initiative. Unfortunately, some of those publishers have been labeled “predatory,” a term coined by academic librarian Jeffrey Beall at the University of Colorado in Denver (Nature 495:433–435, 2013). Predatory publishers produce journals of questionable quality, often simultaneously launch numerous journal titles on a wide range of topics, and seem to care more about profit than science. If they go out of business because they are not profitable, all traces of their published papers may disappear.

Some of the techniques that predatory publishers use to fool people into thinking they are scholarly publishing groups include:

• They maintain sophisticated Web sites, some similar to those of established journals, complete with links to other scholarly sites
• They have mission or vision statements that refer to the importance of open access.
• They note plans to index in PubMed regardless of whether PubMed has decided to accept the journal for indexing.
• They use names that appear to tie the journals to traditional journals or imply an association with academic institutions.

Clues that things are not as they appear:

• The Web address (URL) may link to an address that is obviously someone’s home or a small office.
• The Web site lacks a substantial archive of journal articles.
• The editorial board is made up of young scientists or editors who have no real control of content.
• The publishing group has launched numerous journals in disparate fields.
• The publishing group or journal has not met the rigorous standards to be indexed in PubMed.
• Impact factors are obtained from sources other than Journal Citation Reports.
• The Web site or journal contains typographical and grammatical errors.

Leaving aside the problem of predatory publishing, is there a real problem with the launch of hundreds of new journals? Some critics argue that there is little scientific rigor in the review of the articles that are submitted. That lack of rigor is a potentially serious problem, particularly in light of the recent focus on the lack of reproducible results in our high-impact journals.

I also worry about the competition for time from scientists already hard at work trying to fund their research endeavors. I am concerned that it will become more difficult to find original science if the number of journals continues to rise exponentially. Inevitably...
On a Thursday afternoon, the final bell rings at school, and I head to NIH in Bethesda. As I arrive on campus, excited to see how my cells are faring, I take a moment to gaze at the vast Clinical Center and wonder how many patients are being treated.

I have completed two summer internships and an independent research project at the NIH. In the summer between my sophomore and junior years of high school (2013), I was an intern at the National Center for Advancing Translational Sciences’ (NCATS’) National Chemical Genomics Center processing compounds for later testing. In my work within the analytical chemistry group—with Heather Baker, Madhu Lal, and Bill Leister—I gained valuable knowledge about lab techniques and how a laboratory operates on a professional level.

The next summer (2014), I began working in the National Institute of Dental and Craniofacial Research’s (NIDCR’s) Intracellular Membrane Trafficking Unit. I remember arriving on my first day, nervous and toting my bagged lunch, and hearing my name called out by my supervisor Panomwat “Walt” Amornphimoltham, a senior research fellow in Roberto Weigert’s lab.

Walt not only taught me how to perform complex procedures, but he also took the time to explain how each of them worked to prove something instrumental to the overall research. I learned how to approach research as a whole entity and not just as a set of random experiments. I helped plan and conduct experiments, but more importantly I knew why we were doing them and the role they would play in eventually helping a patient. I’m still working part time to finish my NIDCR project, which we hope to publish in mid-2015.

My most memorable experience, however, was conducting my own independent research at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) from 2013 to 2014. The Potomac School (McLean, Virginia), where I’m a senior, offers a Science and Engineering Research Curriculum that provides opportunities for students to work with outside mentors on in-depth projects.

I focused on tissue engineering. After reading the current literature and several papers by NIAMS’s Leon Nesti, I decided to pursue cartilage regeneration. I had read in his papers about how a novel type of mesenchymal progenitor cell (MPC) had many favorable qualities for wound healing; however, MPCs showed slightly impaired chondrogenic differentiation (into cartilage cells). How great it would be, I thought, if you could somehow assist those cells in their differentiation so they could be used to regenerate damaged cartilage.

I set out to find ways to increase the ability of these MPCs to turn into cartilage cells. I cultured them in a hyaluronic acid–infused fibrin hydrogel scaffold because I had read many papers about how that setup had boosted chondrogenesis in mesenchymal stem cells, which are closely related to MPCs. I sent a detailed proposal to Nesti and was soon ready to begin work.

This project gave me the opportunity to work independently while using many of NIH’s wonderful resources—minds as well as materials. With the help of Nesti, David Hall, and Youngmi Ji, I planned and conducted all of my own experiments and gathered my own results.

After about a year, we had gathered enough data to conclude that the experiments had worked. The hyaluronic acid did, in fact, increase chondrogenic differentiation in the MPCs. We are currently working to submit the research for publication and competitions.

I have learned much about the world of basic biological and translational research from my time at the NIH. I have also gained a lot of knowledge about how collaborative science works and how happy scientists are to share their knowledge and expertise. Throughout my time at NIH—whether working in my internships or on my project—I always witnessed enthusiasm and received many offers of help. At NCATS, Lal, Christopher Dextra, and Marc Ferrer let me use their advanced resources to start perfecting the fibrin hydrogel. At NIDCR, Walt provided advice and tutorials on equipment and even allowed me to use the fluorescence microscope to take three-dimensional images of the fibrin hydrogels.

My experiences at the NIH have influenced me more than anything else in my education and have inspired me to pursue research as a career. I hope that NIH continues to foster a sense of learning and exploration that allows students like me to have experiences such as these. I offer my thanks to the NIH and its scientists, and I can’t wait to impart the same knowledge and zeal of exploration to others.

Josh Tarplin is a senior at the Potomac School in McLean, Virginia. He heads to Yale University (New Haven, Connecticut) in the fall, where he hopes to study chemical engineering or molecular biology. He was recently named a 2015 Intel Science Talent Search semifinalist for his project with Nesti.
there will be duplication of research effort, and we may lose track of research published in obscure journals that were discontinued because they weren’t profitable enough.

But it’s the predatory journals that are of most concern. In 2012–2013, Science orchestrated a sting operation: It submitted a spoof paper—one that was obviously flawed, by a fake author at a nonexistent university—to some 300 open-access journals. More than half accepted the paper for publication (Science 342:60–65, 2013).

Meanwhile, Nature has reported on efforts by Beall, who maintains a Web site listing predatory publishers (http://scholarlyoa.com), as well as on the “Directory of Open Access Journals” (DOAJ) Web site (http://doaj.org), which indexes almost 10,000 open-access journals and plans to tighten its criteria to weed out substandard journals. DOAJ will require all of the publications it lists to reapply on the basis of stricter criteria; it estimates that 10 percent of the journals will not be able to pass the reapplication process (Nature 512:17, 2014).

There are certainly plenty of credible OA journals that have succeeded as scholarly endeavors. Still, we need to do some investigation before accepting an invitation to submit our papers for publication, write a review article, agree to perform peer review, or be on editorial boards. We should look carefully at each of those journals to be sure it is indexed in PubMed; has a track record; practices academic peer review; prominently displays its policy for authors’ fees; and has an active and involved editorial board, as well as that our papers will join other scholarly publications.

Don’t be fooled by logos on the site or quotes from prominent scientists that are meant to persuade you to submit your work for publication. Read the publisher’s Web site carefully, research the publisher, and ask for its track record or history of publications.

The National Institute of Allergy and Infectious Diseases (NIAID) has launched a new Web site, ClinRegs, to help researchers explore and compare country-specific clinical-research regulatory information.

The idea for ClinRegs originated under NIAID’s “Barriers to Clinical Research” project, which determined that finding and complying with regulations of other countries was a common challenge to launching and implementing clinical research abroad. Interviews with NIAID researchers revealed that NIAID-supported researchers would save time and resources if they had a centralized tool that could provide summaries of the regulatory requirements in multiple countries. “ClinRegs is another way we are supporting investigators to advance immunology, allergy, and infectious–disease research around the globe,” said NIAID Director Anthony S. Fauci.

The NIAID ClinRegs Web site provides an easy-to-use online database of country-specific clinical-research regulatory information that is designed to enable users to explore regulations within a country and compare requirements across countries. By providing well-documented, up-to-date regulatory information for multiple countries in a single place, ClinRegs serves as a central resource and time-saver for people who are planning and implementing international clinical research.

ClinRegs provides an overview of—and links to—country-specific regulations in the following topic areas: clinical-trial lifecycle, competent authority oversight, ethics committee review, informed consent, investigational products, specimens, and sponsorship.

“While researching and deciphering countries’ regulations is rather unglamorous, we knew our efforts had the potential to greatly benefit the clinical research efforts of NIAID and other stakeholders,” said ClinRegs Project Leader Jonathan Kagan, the assistant director for NIAID’s Division of Clinical Research. “The positive response we have received from the research community has confirmed the value of this project.”

The countries, based on priorities from within NIAID’s research portfolio, currently include Brazil, China, India, Kenya, Liberia, Malawi, Peru, South Africa, Sierra Leone, Tanzania, Thailand, Uganda, the United Kingdom, and the United States. The ClinRegs team plans to expand its country list in alignment with NIAID’s research priorities.

NIAID is striving to make ClinRegs a useful resource for all intramural researchers and welcomes comments, insights, and suggestions via a feedback survey on its Web site.

For more information including a user guide, visit http://clinregs.niaid.nih.gov.
NEW NAME FOR NCCAM

The National Center for Complementary and Alternative Medicine has a new name: the National Center for Complementary and Integrative Health (NCCIH). The revision was mandated as part of the omnibus budget measure signed by President Obama.

Integrative approaches to health and wellness have grown within care settings across the United States, including hospitals, hospices, and military health facilities.

“The intent of an integrative approach is to enhance overall health status, prevent disease, and alleviate debilitating symptoms such as pain and chemotherapy-induced nausea, among others. However, the scientific foundation for many complementary approaches is still being built,” said NCCIH Director Josephine P. Briggs. “The mission of NCCIH will remain unchanged. We will continue to focus on the study of the usefulness and safety of complementary and integrative interventions, and provide the public with research-based information to guide health-care decision-making.”

NCCIH’s intramural program focuses on pain perception and management integrated in the NIH neuroscience community. Catherine Bushnell, recruited from McGill University, is the scientific director. All this remains in place. Nothing, in fact, changes about NCCAM other than the name, the National Center for Complementary and Integrative Health.

The center’s research also encourages self-care methods that support healthier lifestyles and uncovers potential usefulness and safety issues of natural products. The practices and products studied by the center are prioritized by four guiding principles: scientific promise, amenability to be studied using the highest quality research methods, use by the American public, and the potential impact on public health.

RENEDEZVOUS WITH RAMÓN Y CAJAL

Want to see seven original neural-cell drawings by the father of modern neuroscience, Santiago Ramón y Cajal? Check out the exhibit in NIH’s Porter Neuroscience Research Center. These detailed diagrams of brain cells and his anatomical discoveries formed the basis of the Spanish scientist’s “neuron doctrine” and earned him the Nobel Prize in Physiology or Medicine in 1906, jointly with Camillo Golgi.

The drawings, which are on loan from the Cajal Institute in Madrid, not only honor Cajal’s legacy but are also a source of inspiration to neuroscientists at the NIH. Even former NIH artist-in-residence Rebecca Kamen is fascinated by the brain and its functions and uses Cajal’s illustrations as an inspiration to create bridges between art and science. Kamen, along with NINDS senior investigator Jeffrey Diamond and NINDS science writer Christopher Thomas, spearheaded the effort to bring Cajal’s work to NIH.

In 2012, the three Cajal enthusiasts visited the institute to study his works. Thomas facilitated the trip. Diamond gave a scientific talk. Kamen presented the institute with a miniature version of one of her creations, a sculpture representing Cajal’s illustration of the Purkinje cell. Diamond and Kamen knew they wanted to bring some of the drawings to NIH and were able to convince the Cajal Institute directors to share their national treasures. Hank Grasso of the Office of NIH History created an exhibit around the drawings. The institute’s vice director, Ricardo Martinez Murillo, was even on hand for the drawings’ NIH debut on November 7, 2014.

The drawings, which are on the south end of the first floor in Building 35, will remain on display through April 2015.

NEW SURGEON GENERAL

The U.S. Senate recently confirmed Vivek Murthy as the new surgeon general. He is an attending physician at Brigham and Women’s Hospital (Boston) and an instructor at Harvard Medical School (Boston), where he is an internal medicine hospitalist. He is also co-founder and president of Doctors for America, a grassroots organization of more than 15,000 doctors and medical students in 50 states who are working to build a high-quality, affordable health-care system for all Americans.

NURSING POSTCARDS

From angels to calendar girls to modern-day nurses, the image of nursing has changed over the past century. NIH’s National Library of Medicine (NLM) is hosting the exhibit “Pictures of Nursing: The Zwerdling Postcard Collection” to showcase changes in the public perception of nurses as depicted in a century’s worth of postcards. The library acquired a collection of 2,588 postcards from the American nurse and collector Michael Zwerdling. From these, around 50 historic postcards from 1893 to 2011 are displayed including many from the early 1900s, which was considered the “Golden Age” of postcards.

You can visit the exhibit in person at NLM’s History of Medicine Division through August 21, 2015, or explore the digital exhibit, which features more than 500 postcards, at http://www.nlm.nih.gov/exhibition/picturesofnursing/index.html.
Once upon a time, no one knew much about hepatitis C—except to call it non-A, non-B hepatitis. Hepatitis A, which is caused by the hepatitis A virus and spread through contact with an infected person’s stool, was discovered in 1973 by Albert Kapikian, Robert Purcell, and Steven Feinstone in the National Institute of Allergy and Infectious Diseases. Hepatitis B, which is caused by the hepatitis B virus and is spread via an infected person’s blood, semen, or other body fluids, was discovered in 1966 by then-NIH researcher Baruch Blumberg, who later went on to win the Nobel Prize in Physiology or Medicine in 1976.

But the non-A, non-B variety had researchers stumped until 1989, when the hepatitis C virus (HCV) was finally identified. (Harvey Alter, in the NIH Clinical Center’s Department of Transfusion Medicine, did work on non-A, non-B hepatitis that led to the discovery of HCV).

“Although hepatitis C was well characterized by the 1980s, there were continuing doubts about its underlying causes,” said viral hepatitis pioneer Jay Hoofnagle, the director of the Liver Disease Research Branch in the National Institute of Diabetes and Digestive and Kidney Diseases. “Despite the lack of serologic and therapeutics markers, therapy was attempted as a treatment option then.”

On Nov 12, 2014, Hoofnagle outlined the past and future therapies for hepatitis C at the annual Astute Clinician Lecture, part of the Wednesday Afternoon Lecture Series.

Hepatitis C is a contagious inflammatory liver disease—spread through contact with infected blood or through sex with an infected person—that leads to cirrhosis of the liver and sometimes liver cancer. An estimated 3.2 million people in the United State have a chronic HCV infection. Many of those infected may not have any symptoms for years.

Hoofnagle has been at the forefront of advancing hepatitis B and C therapeutics since coming to NIH in the 1970s. In the 1980s, he conducted the first clinical trial using interferon for chronic hepatitis B. He also used interferon to successfully treat a small group of people with non-A, non-B hepatitis. When those people were re-evaluated 10 years later, some had a sustained virologic response (SVR) and were still healthy. Achieving an SVR is an important endpoint in the treatment of hepatitis C.

A combined treatment with alpha-interferon and ribavirin (an antiviral drug) showed promising results, too.

Further advances were made to improve the efficacy of the drugs, but the variability of the HCV genotype interfered. For example, the response rates among African-Americans trailed behind those of Caucasians. Although higher doses of interferon were effective initially, chances of relapse increased once the treatment was stopped. Other drugs were tried: An HCV protease inhibitor such as boceprevir, telaprevir, or simeprevir, when given in combination with pegylated interferon and ribavirin, augmented the response rate. But even this combination therapy had limited success.

In recent months, a new treatment regimen has gained a lot of attention. An all-oral combination of ledipasvir and sofosbuvir with or without ribavirin given for 12 or 24 weeks has been highly effective in previously untreated patients who are infected with HCV genotype 1. In fact, ledipasvir-sofosbuvir is the first combination pill that has been approved by the FDA for treatment of chronic hepatitis C. But the new drug comes with a huge price tag of $1,125 a pill, or $94,500 for a 12-week course of treatment, Hoofnagle explained. “This is an enormous burden to an already overburdened medical-care system.” Another drug, with an even higher response rate in previously treated patients, is already in the pipeline.

There are vaccines against the hepatitis A and B viruses, but so far none for HCV.

Yet, thanks to scientists like Hoofnagle, liver disease research has come a long way. For Hoofnagle, “the Clinical Center at the NIH has been an ideal place for research” because it has given him the independence to pursue his goals, which “would not have been possible elsewhere.”

The Astute Clinician Lecture was established through a gift from Haruko and Robert W. Miller, M.D. It honors a U.S. scientist who has observed an unusual clinical occurrence and by investigating it, has opened an important new avenue of research. To see a videocast of Hoofnagle’s talk, “Past and Future Therapy of Hepatitis C,” go to http://videocast.nih.gov/launch.asp?18731.
Intramural Research Briefs

NIDDK, NIAID, CC, NICHID: INCREASED CORONARY-VESSEL WALL THICKNESS IN HIV-INFECTED YOUNG ADULTS

Individuals with long-term human immunodeficiency virus (HIV) infection are at risk for premature vasculopathy and cardiovascular disease (CVD), according to an NIH study: a prospective cross-sectional study of 35 young adults who acquired HIV in early life and 11 healthy control subjects, free of CVD. The researchers used time-resolved acquisition of phase-sensitive dual-inversion recovery (TRAPD) coronary vessel-wall magnetic resonance imaging to measure proximal right coronary artery (RCA) wall thickness. They found that the RCA vessel-wall thickness was significantly higher in HIV-infected patients than in control subjects. Increased duration of antiretroviral therapy, hyperlipidemia, and smoking contributed to the thickening of the coronary wall, independent of atherosclerotic plaque. These modifiable risk factors appear to influence early atherogenesis as measured by coronary wall thickness and may be important targets for CVD risk reduction. (NIH authors: K.Z. Abd-Elmoniem, A.B. Unsal, S. Eshera, J.R. Matta, N. Muldoon, D. McAreavey, J.B. Purdy, R. Hazra, C. Hadigan, and A.M. Gharib, Clin Infect Dis 15:1779–1786, 2014)

NIAID: NIAID-GSK EXPERIMENTAL EBOLA VACCINE STIMULATES IMMUNE RESPONSE

An experimental vaccine to prevent Ebola virus disease was well-tolerated and produced immune system responses in all 20 healthy adults who received it in a phase 1 clinical trial conducted by NIH researchers. The candidate vaccine, which was co-developed by NIAID’s Vaccine Research Center (VRC) and GlaxoSmithKline (GSK), was tested at the Clinical Center. The investigators also analyzed the research participants’ blood to learn whether the vaccine prompted the production of T cells. A recent study, published in Nature Medicine, by VRC scientist Nancy J. Sullivan and colleagues, showed that nonhuman primates inoculated with the candidate NIAID-GSK vaccine developed both antibody and T-cell responses, and that these responses were sufficient to protect vaccinated animals from disease when they were later exposed to high amounts of Ebola virus. In the clinical trial, the experimental NIAID-GSK vaccine induced a T-cell response in many of the volunteers, including production of CD8 T cells, which may be an important part of immune protection against Ebola viruses. Four weeks after vaccination, CD8 T cells were detected in two volunteers who had received the lower-dose vaccine and in seven of those who had received the higher dose. There were no serious adverse effects observed in any of the volunteers, although two people who received the higher-dose vaccine did develop a brief fever within a day of vaccination. Additional details about this trial, VRC 207, are available at http://www.clinicaltrials.gov using the identifier NCT02231866. For more information about early-stage Ebola vaccine clinical trials, see http://www.niaid.nih.gov/news/ QA/Pages/EbolaVaxResultsQA.aspx. (Clinical trial: VRC/NIAID authors: J. E. Ledgerwood et al., N Engl J Med DOI:10.1056/NEJMoa1410863; Sullivan study: VRC authors: D.A. Stanley, N.J. Sullivan, et al., Nat Med 20:1126–1129, 2014)

Read more online at http://irp.nih.gov/catalyst/v23i1/research-briefs.

NIDA: NIDA RESEARCHERS CONFIRM IMPORTANT BRAIN-REWARD PATHWAY

NIH: NIH SCIENTISTS DETERMINE HOW ENVIRONMENT CONTRIBUTES TO SEVERAL HUMAN DISEASES

NICHID: CHRONIC HIGH BLOOD GLUCOSE MAY BE DETRIMENTAL TO THE DEVELOPING BRAIN OF YOUNG CHILDREN
Defeating a Devastating Neuromuscular Disorder

Bryan Traynor’s Search for Genetic Links to ALS

BY SOMA CHOWDHURY

It didn’t take last summer’s Ice Bucket Challenge to get NIH scientist Bryan Traynor fired up about amyotrophic lateral sclerosis (ALS). He has been excited about the possibility of finding a cure for this devastating neuromuscular disease since the 1990s when as a young medical student—at University College Dublin in Ireland—he attended a memorable lecture on the subject.

He also remembers being surprised to learn that several famous people, including his favorite British actor—David Niven—had ALS. In 1981, Traynor and other television viewers grew alarmed when they noticed Niven slurring his speech on a live television talk show. They wondered whether he was drunk or had suffered a stroke. It was neither—he was diagnosed with ALS later that year and died in 1983 at the age of 73.

Today, Traynor—who is a senior investigator in the National Institute of Aging (NIA) and head of its Laboratory of Neurogenetics—is best known for his work on understanding the genetic causes of ALS. He and staff clinician Camilo Toro (National Human Genome Research Institute) presented their work on ALS at the September 3 Clinical Center Grand Rounds. Toro described the etiology, nature, and background of the disease and told how the first cases of ALS were described and diagnosed by the French neurologist Jean-Martin Charcot in the 1860s. (Charcot didn’t coin the term ALS until 1874.)

Toro explained how the term “amyotrophic lateral sclerosis” is descriptive of what happens during the progressive degeneration of motor nerve cells: amyotrophy means “muscle wasting”; “lateral” refers to the lateral parts of the spinal cord that are affected; and “sclerosis” refers to the scarring of the nerve cells.

Typically, ALS strikes people between the ages of 40 and 70. It occurs worldwide and affects as many as 30,000 people in the United States. Most patients die from respiratory failure within three to five years after the onset of symptoms, but 10 percent survive for 10 years or more.

Traynor’s laboratory published the first genome-wide association study of ALS (2007); was the first to identify (in 2010) an association signal for ALS on the short arm of chromosome 9 in the Finnish founder population (Finland has the highest ALS incidence in the world); and discovered that mutations in the VCP gene are responsible for a significant fraction of familial (inherited) ALS (2010). In 2011, he led the international consortium that identified a pathogenic hexanucleotide repeat expansion in the C9ORF72 gene as the underlying mutation in a large proportion of cases of familial ALS and frontotemporal dementia (FTD) as well as in cases of the more common, sporadic forms of both neurodegenerative diseases.

“From the clinical perspective, knowing the gene is only the starting point,” he explained at the Grand Rounds. One of the starting points was in 1993, when a research group from the Northwestern University Medical School (Chicago) was the first to identify an ALS-associated gene—SOD1. In 2006, researchers from Massachusetts General Hospital and Harvard Medical School found that a small locus (9p21) on the short arm of chromosome 9 accounted for a large percentage of familial ALS and familial frontotemporal dementia cases (FTD). Despite considerable efforts in many leading laboratories around the world, the underlying mutation was proving difficult to find.

When Traynor’s group was the first to identify a significant mutation called C9orf72 in 2011, he was surprised and excited to see the result because it was “really, really common as a cause of ALS.” The mutation occurred in 40 percent of familial ALS, eight percent of sporadic ALS, and in FTD.

Several other NIH scientists are revealing more pieces of the ALS puzzle. National Institute of Neurological Disorders and Stroke (NINDS) Clinical Director Avindra Nath’s studies of the pathophysiology of retroviral infections in the nervous system might shed some light on the immunological aspect of ALS. Freya Kamel, in the National Institute of Environmental Health Sciences, is finding genetic and environmental contributors to ALS. NINDS senior clinician Mary Kay Floeter has established a clinic that will recruit 60 people with the C9orf72 mutation for a clinical study, follow their illness for three years, and collect samples and data. Traynor hopes that this study, on which he works with Floeter, will improve the understanding of the disease and identify a biomarker for ALS.

Traynor is optimistic that in the next few years, all these efforts will help us understand the entire “genetic etiology of ALS”…and move us closer to finding a cure.

buses, and whole houses flowed like slurry through once-active streets; smartphone videos captured scenes of panicked people desperately trying to escape the deluge. Nearly 16,000 people were swept up and perished.

But the horror didn’t end there.

Approximately 50 minutes after the quake, the torrent slammed into the Fukushima Daiichi Nuclear Power Plant, a complex of six nuclear reactors. Waves 46 feet high breached the plant's 33-foot-high seawall. Although the reactors had been shut off as a precaution, the flooding overwhelmed the cooling systems and the reactors began overheating. By the next morning, the plant was leaking substantial amounts of radioactivity, and in the days that followed, the Japanese government relocated more than 200,000 residents to ever-expanding evacuation zones.

The earthquake and tsunami also destroyed research facilities at Tohoku University (Sendai) and other universities in the affected areas and displaced many scientists. NIH stepped up to help in several ways. It created the NIH Japanese Scientists Association (NJSA)—a volunteer organization of NIH and FDA researchers from Japan—that arranged for surplus research equipment to be sent to Japan and for Japanese scientists to temporarily relocate their work to the NIH. In addition, NIH and Tohoku University are taking turns hosting a symposium every 18 months to stimulate the recovery process and highlight the work of Japanese and NIH scientists. The latest symposium took place at NIH in October 2014.

But NIH and Japanese scientists were collaborating long before the earthquake hit. Since 1950, thousands of Japanese scientists have conducted research and been trained in NIH laboratories. NIH's first formal proposal for collaborative health-related research with Japan was made in 1965 by the National Institute of Allergy and Infectious Diseases.

"Many young Japanese scientists came to NIH as research trainees," said Yoshihiko Yamada, who helped organize the 2014 symposium. He was a postdoc himself when he came to the National Cancer Institute (NCI) in 1978 and is now a senior investigator at the National Institute of Dental and Craniofacial Research. "Now many of them are the leaders in their own fields."

In fact, for many years, Japanese researchers constituted the largest contingent of foreign researchers at NIH. (Today, only China and India have more postdoctoral visiting fellows at NIH.)

NIH also has a long-standing collaborative relationship with Tohoku University, where many of the Japanese NIH alumni are now faculty members. That relationship prompted the Japanese scientists at NIH to schedule a meeting within a week of the disaster and discuss ways to help their colleagues at Tohoku University and other affected areas.

A newly established Web site (http://www.nihjsa.org) enabled NIHers to communicate with Japanese biomedical researchers quickly and effectively. And the Foundation for Advanced Education in the Sciences helped NJSA to establish a fund to support the Japanese researchers who traveled to NIH in the aftermath of the earthquake.

Three scientists took shelter at NIH temporarily: Wataru Sakamoto from Fukushima Medical University, who joined Jürgen Wess’s laboratory at the National Institute of Diabetes and Digestive and Kidney Diseases; researcher Misako Sato, who was working in Lalage Wakefield’s lab when the quake hit, received permission to extend her work and postpone her scheduled move to Sendai, Japan; and Keiichi Itoi from Tohoku University, who was in Greti Anguilera’s laboratory at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). It was Itoi’s relationship with NIH that spurred the idea of regularly scheduled symposia as a way to continue the scientific cooperation between the two countries.

To commemorate the second anniversary of the earthquake, the Japan Society for the Promotion of Science (JSPS) and Tohoku University—with the help of Keiko Ozato, a senior investigator at NICHD and president of NJSA—organized a
symposium at Tohoku University in May 2013. Nine senior scientists from NIH including Deputy Director for Intramural Research Michael Gottesman were invited and attended. Gottesman and Tohoku University President Susumu Satomi signed an “Expression of Intent” to strengthen the collaboration between their institutions.

This year’s symposium—“Highlights from the Frontiers of Biomedical Science from NIH and Japan,” which took place at NIH October 23–24, 2014—featured NIH’s and Japan’s cutting-edge biomedical research and promoted the career development of younger scientists. On the first day, prominent NIH and Japanese scientists made presentations that covered a variety of topics including disease metabolism, stem-cell regeneration, and host immunity to microbes. And young scientists from Japan and NIH presented posters that focused on cancer biology, neuroscience, developmental biology, and immunology.

The second day featured updates on the “Recovery from the Great Tohoku Earthquake and Fukushima Nuclear Plant Disaster”—moderated by Reiko Toyama (NICHD), co-chaired by Kiyohiko Mabuchi (NCI) and Hitoshi Oshitani (Tohoku University)—and subsequent concurrent workshops on cutting-edge research in various fields at NIH and Tohoku University. Itoi’s presentation at one of the workshops was on “Neural and Humoral Mechanisms for the Regulation of Corticotropin-releasing Factor Neurons in the Hypothalamus.” The day included career development of younger scientists. On the first day, prominent NIH and Japanese scientists made presentations that covered a variety of topics including disease metabolism, stem-cell regeneration, and host immunity to microbes. And young scientists from Japan and NIH presented posters that focused on cancer biology, neuroscience, developmental biology, and immunology.

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Amid the chaos of the March 11, 2011, earthquake, tsunami, and Fukushima Daiichi Nuclear Power Plant disaster, the United States Department of Health and Human Services (HHS)—at the request of the U.S. ambassador to Japan—deployed a five-person team from the NIH, CDC, and FDA to Tokyo. They arrived on March 21 and 22. The two NIHers were Norman Coleman and Steven L. Simon, both from the National Cancer Institute (NCI).

Initially, this response was intended to provide the U.S. Embassy in Tokyo with accurate information to relay to the 150,000 Americans living in Japan; approximately half were in Tokyo, about 150 miles from the damaged nuclear reactors. How substantial and how far the radiation could travel was the topic of much speculation. The HHS team quickly earned the respect of the Japanese government and assisted these colleagues in their own official assessment of the disaster.

According to Simon, head of the Dosimetry Unit in NCI’s Division of Cancer Epidemiology and Genetics, little authoritative information about the extent and meaning of radioactive contamination to human health was available at the time through the American and Japanese news media. General fear of radiation coupled with uncertainty and outright mistrust of the information being relayed had gripped the local American community, he said.

The HHS team monitored real-time data from radiation detection devices set up by the U.S. Navy and provided guidance on radiation dose and cancer risk, including an assessment of food and water contamination and the necessity of distributing potassium iodide. The team provided information to the embassy and directly to the U.S. community, striving to put the radiation risk they faced into a perspective they could understand. The team stayed in Japan for three weeks and remained involved with the radiation assessment for many more weeks after its return to the United States.

The team’s assessment was that those living in and around Tokyo were at low risk of the ill effects of Fukushima’s radiation via food, air, or water.

While pleased to be of assistance, Coleman, head of the Experimental Therapeutics Section in NCI’s Center for Cancer Research, was particularly impressed by the Japanese response. “Japan is a stunningly capable country, and [it] showed,” said Coleman, who also is the assistant secretary of preparedness and response in the HHS Office of Preparedness and Emergency Operations.

Responding to public-health emergencies is one of five key elements of the mission of the NIH intramural-research program. As such, in an effort to relay lessons learned from the Fukushima disaster response, Coleman, Simon, and their colleagues have summarized their experience in three published articles:

The Lasker program, now in its fourth year, is a collaborative initiative of the NIH and the Albert and Mary Lasker Foundation that will nurture the next generation of clinician-scientists. Talented early-stage clinical researchers are selected to do independent research for five to seven years at the NIH. After completing their initial term, scholars will either remain at NIH as independent investigators, or join the faculty of an extramural research institution where they can receive up to five more years of NIH financial support. NIH funds the research and provides the scholars access to the resources of the NIH Clinical Center. The Lasker Foundation provides the opportunity for the scholars to attend its annual awards luncheon, where they can present their results and interact with senior colleagues.

The following is a lightly edited version of interviews with Ackerman, Apolo, and Lohoff.

**HANS ACKERMAN, M.D., D.PHIL., M.SC.**
Lasker Clinical Research Scholar; Chief, Physiology Section, Sickle Cell Branch, National Heart, Lung, and Blood Institute

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**Education:** William and Mary, Williamsburg, Va. (B.S. in biology); University of Oxford, Oxford, England (M.Sc. in human biology; D.Phil. in human genetics); Harvard Medical School, Boston (M.D.)

**Training:** Residency in internal medicine at Massachusetts General Hospital (Boston); fellowship in critical-care medicine at NIH Clinical Center; research fellowship in NIAID's Laboratory of Malaria and Vector Research

**Came to NIH:** In 2007 for subspecialty training in critical-care medicine and to begin research on endothelial biology in malaria and sickle-cell disease; in 2011 became assistant clinical investigator in NIAID's Laboratory of Malaria and Vector Research

**Outside interests:** Working creatively with his hands—cooking, painting, landscaping, gardening, home remodeling, and restoring old cars; playing sports (especially soccer and cycling) with his three sons; enjoying music, good food, and travel with his wonderful wife

**How did you get interested in your field?**
When I was growing up, my family lived in rural central and western Africa. I think that experience is an ever-present reminder of how many families in the world (including in the United States) live: without a steady source of income, adequate nutrition, or protection from disease. I've chosen to focus on sickle-cell disease and malaria because there is not only an urgent need to improve access to screening, education, and preventive measures, but also a tremendous opportunity to make a difference with improved treatments developed through scientific discovery.

**What's your current research at NIH?**
I am continuing my studies of sickle-cell disease and malaria, focusing on their similarities. Sickle-cell disease became common in areas of the world where malaria is prevalent because carriers of the sickle-cell trait are protected from complications of malaria and are more likely to survive. Sickle-cell disease and malaria have an evolutionary link and many of the same disease-causing mechanisms. Both are diseases of red-blood cells and cause them to become stiffer, stickier, and more fragile.

In order to understand the mechanisms underlying vascular dysfunction in sickle-cell disease and malaria, we will also study how naturally occurring genetic differences in healthy people change nitric-oxide signaling and vasodilation responses in blood-vessel walls. Once we understand how these common genetic changes affect blood-flow regulation, we will examine how they affect the severity and outcome of patients' sickle-cell disease. Ultimately, we hope to develop drugs that mimic vascular-protective genetic factors; these drugs could potentially prevent or treat the vascular complications of sickle-cell disease or malaria.

**What made you decide to come to NIH?**
NIH provides an unparalleled opportunity to link basic-science discovery with clinical and translational studies to help the patients I care about.
What is most exciting about your work?
I'm always learning something new from my patients or my fellows.

Is there anything you can look back on now and realize it was significant?
I worked really hard to get into a great immunology laboratory as an undergraduate student. However, I had no idea how much time it took to do science well; I had to drop my honors thesis and thought I would never be able to do basic-science research again. I settled into a one-year anthropology program instead of beginning doctoral studies, but six months later I found myself back in the laboratory sequencing genes and looking for genetic factors of severe malaria. As a graduate student, I learned how exciting research can be—not just the excitement of discovery but of dreaming up a hypothesis and pursuing it. These experiences guide me when I am working with students and fellows here at NIH. I also recognize how much fun science can be and what a privilege it is to pursue.

ANDREA B. APOLO, M.D.
Lasker Clinical Research Scholar; Chief, Bladder Cancer Section, Genitourinary Malignancies Branch, National Cancer Institute—Center for Cancer Research

Training: Residency in internal medicine at New York–Presbyterian Hospital/Weill Cornell Medical Center (New York); fellowship in medical oncology at Memorial Sloan-Kettering Cancer Center (New York)
Before coming to NIH: Clinical research fellowship in genitourinary oncology at Memorial Sloan-Kettering Cancer Center (2006–2009)
Came to NIH: In January 2010 as an assistant clinical investigator in NCI’s Medical Oncology Branch
Outside interests: Running and spending time with her family
Web site: http://irp.nih.gov/pi/andrea-apolo

How did you get interested in your field?
I worked with a community medical oncologist in the Bronx while completing a summer preceptorship in my freshman year of college. There for the first time I saw the great struggle cancer patients face with their therapies, and I realized the critical need to find more-effective therapies with less toxicity. When I was awarded a scholarship to come to the NIH the following summer under the Undergraduate Scholarship Program (UGSP), I chose to work at the NCI to learn more about the research being conducted in tumor biology.

What was your work before NIH?
I was fortunate to work with one of the world leaders in bladder cancer research while at Memorial Sloan–Kettering Cancer Center in New York. There I learned how to write protocols and to conduct clinical trials and understand the important issues that need to be addressed in studying and treating this disease. My research focused on developing genetic biomarker signatures for tumor surveillance and on incorporating new imaging modalities in clinical trials for new potential treatments. I was also involved in the development of the first clinical trials looking at targeted anti-angiogenic agents in patients with bladder cancer.

What’s the research you are doing at NIH?
I am interested in improving the treatment and survival of patients with genitourinary tumors. My research involves designing clinical trials to test novel agents for the treatment of urologic cancers. My primary research interest is in bladder cancer (urothelial carcinoma). In particular, I am working to develop new bladder-cancer therapies that use targeted agents including anti-angiogenesis compounds and inhibitors of Met receptors. I am planning to test these targeted compounds individually or in combination with immunotherapies. We are also working on developing predictive and prognostic biomarkers in muscle-invasive and metastatic disease.

What made you decide to come to NIH?
I came to the NIH to fulfill a service commitment from the UGSP scholarship. I stayed at the NIH because there is no other place like it in the world to conduct translational and clinical research. I also stayed because of the people: My colleagues at the NIH are so committed to scientific research that it makes the NIH a great environment in which to work.

What is most exciting about your work?
I get to take part in the evolution of cancer therapy. I don’t just treat patients with standard anticancer therapies—I am involved in finding more-effective, “smarter” therapies that may improve outcomes and change the standards of care.
FALK W. LOHOFF, M.D.
Lasker Clinical Research Scholar; Chief, Section on Clinical Genomics and Experimental Therapeutics, Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism

Did your view of psychiatry change after beginning your studies?
I entered into psychiatry training with enthusiasm only to later appreciate how complex psychiatric phenotypes really are and how complex human molecular genetics are. Ultimately, I was surprised to learn how little we know so far about the underlying neurobiology of psychiatric disorders.

What was your work before NIH?
After completing my residency training in psychiatry and a fellowship in neuropsychopharmacology at the University of Pennsylvania, I stayed on as faculty and started my own lab. My interest was in genetics, psychopharmacology, and personalized medicine for the evaluation, diagnosis, and treatment of psychiatric disorders and addictions. I wanted my work to span bench to bedside, so I provided care for patients with mood and anxiety disorders, involved myself in clinical trials testing new treatments for these disorders, and collected biospecimens and DNA samples for molecular analyses.

What’s the research you are doing at NIH?
My research is focused on translational medicine and spans areas of molecular genetics, epigenetics, imaging genetics, pharmacogenetics, and clinical experimental trials. I oversee preclinical studies and translational clinical studies that focus on genomics and epigenetics related to the pathophysiology and treatment of alcohol-use disorders and addictions. In our preclinical work, we are using a wide array of methods (including human population genetics, genome-wide genotyping approaches, next-generation DNA and RNA sequencing, and epigenetic-proteomic profiling) to identify molecular mechanisms that are involved in addictions. We translate the findings into human clinical studies using molecular biomarkers as well as pharmacogenetic, epigenetic, and functional-imaging genetic approaches. Our clinical studies include early phase 1 and phase 2 proof-of-concept studies of experimental novel therapeutics guided by molecular-biomarker profiling.

What made you decide to come to NIH?
The Lasker Clinical Research Scholars Program is a fantastic opportunity for me to carry out meaningful human research focused in the area of experimental medicine. The program provides unparalleled resources and an outstanding environment at the NIH Clinical Center.

What is most exciting about your work?
My vision over the next several years is to expand our current understanding of the underlying neurobiology of drug addiction by using personalized genomic and translational approaches. Given the substantial variability in phenotype, even within a single addiction diagnosis and substantial comorbidities, new approaches are needed to dissect the neurobiology of addiction. This work will, on the one hand, include large-scale interrogation of the genome and epigenome, but also require carefully designed prospective clinical trials of individuals with known functional genetic risk profiles that are then assessed with regards to circuitry variation, pharmacological response, and clinical outcomes. With my background—in clinical psychiatry, basic science, pharmacogenetics, and experimental clinical trials—I hope to bridge these areas and facilitate translational collaborations.

To read about NIH’s first NIH Lasker Clinical Research Scholars—Nehal Mehta (National Heart, Lung, and Blood Institute) and Jessica Gill (National Institute of Nursing Research)—in the January-February 2013 issue of the NIH Catalyst, go to http://irp.nih.gov/catalyst/v21i1/nih-lasker-scholars.
NCCIH’S 6TH ANNUAL STEPHEN E. STRAUS DISTINGUISHED LECTURE
January 26, 2015, 10:00–11:00 a.m.
Masur Auditorium (Building 10)
For information: http://nccam.nih.gov/news/events/lectures/
The husband-wife team of Jerome Groopman, M.D. (Harvard Medical School), and Pamela Hartzband, M.D. (Harvard Medical School), will present “When Experts Disagree: The Art of Medical Decision Making.” In their talk, they will weave vivid narratives from real patient experiences with insights from recent cognitive research to demonstrate how to arrive at choices that serve the individual best. The event will be videocast live on the Web. For questions, contact Prachi Patel (prachi.patel@patelpa.com or 301-275-4769).

FIRST ANNUAL ASSAY GUIDANCE MANUAL WORKSHOP
Friday, Feb. 6, 2015, 9:00 a.m.–4:30 p.m.
Building B, Room 377
9800 Medical Center Drive, Rockville
Assay development for a high-throughput screen or lead optimization can be a challenging, but rewarding, endeavor. The editors of the Assay Guidance Manual (http://www.ncbi.nlm.nih.gov/books/NBK53196/), an e-book that shares the best practices in quantitative biology and the development of robust assay methods throughout the drug-discovery community, will hold this workshop for NIH intramural researchers. To register, e-mail NCATS_AGM_Editors@mail.nih.gov.

THE 11TH JEFFREY M. TRENT LECTURE IN CANCER RESEARCH
Wednesday, Feb. 11, 2015, 1:00–2:00 p.m.
Masur Auditorium (Building 10)
Stephen J. Chanock, M.D., director of NCI’s Division of Cancer Epidemiology and Genetics, will present “The Complexity of Genetic Susceptibility to Cancer.” Chanock is a leading expert in the discovery and characterization of cancer-susceptibility regions in the human genome. Sign-language interpreters will be provided. Individuals with disabilities who need reasonable accommodation to participate in this event should contact Nora Miralieva (nora.miralieva@nih.gov or 301-443-4404).

INDIAN HERBS IN BRAIN HEALTH AND NEURODEGENERATIVE DISEASES
Tuesday, March 3, 2015, 10:00 a.m.–noon
Building 40, Room 1201/1203
A talk by Lal Hingorani, Ph.D. (Pharmanza Herbal Pvt Ltd, Ahmadabad, Gujarat). For information, contact Harish Pant (panth@ninds.nih.gov or 301-402-2124).

NEUROSCIENCE LECTURE SERIES
Monday, March 9, 2015, noon–1:00 p.m.
Room 620/630
Porter Neuroscience Research Center (Building 35A)
Deanna Barch, Ph.D. (Washington University, St. Louis), will present “Neurobiological Mechanisms of Emotion Processing and Regulation in Preschool Onset Depression.” The event will be videocast (http://videocast.nih.gov). For more information, contact Dana Camak (dana.camak@nih.gov or 301-435-2232).

HISTORY OF MEDICINE LECTURES FOR 2015
2:00–3:00 p.m. (unless otherwise noted)
Lister Hill Auditorium (Building 38A)
The lecture series of the NLM History of Medicine Division promotes awareness and use of NLM and other historical collections for research, education, and public service in biomedicine, the social sciences, and the humanities. Lectures are free and open to the public.
Wednesday, February 18: “The History of Race in Randomized Controlled Trials: Ethical and Policy Considerations,” Laura Bothwell, Harvard Medical School
Tuesday, March 17, 2015: Special Program, “A Tribute to Marshall Nirenberg.” Special two-hour program, 1:00–3:00 p.m.

STADTMAN SEMINARS
Schedule: https://ccrod.cancer.gov/confluence/display/NIHStadt
The Earl Stadtman Investigator search will be hosting public seminars featuring its top candidates in 21 areas, from aging to virology. Check the Web site for schedule and locations.

ENHANCING THE TRANSPARENCY OF CLINICAL TRIAL RESULTS

OFFICE OF DIETARY SUPPLEMENTS RESEARCH SCHOLARS PROGRAM
Letters of Intent due May 4, 2015
Full applications due June 23, 2015
For information: http://ods.od.nih.gov/Research/Scholars.aspx
The Office of Dietary Supplements announces its 2015 Research Scholars Program for NIH intramural early-career scientists. The program is a one-year competitive scholarship opportunity to study the role of dietary supplements in health promotion and disease prevention. Projects can request up to $100,000 in funds, which can be spent in fiscal year 2015 or 2016. For additional information contact Dr. Cindy Davis (davisci@od.nih.gov or 301-496-0168).

Read more online at http://irp.nih.gov/catalyst/v23i1/announcements.
AVINASH BHANDOOLA, PH.D., NCI-CCR
Senior Investigator; Head T-Cell Biology and Development Section, Laboratory of Genome Integrity, National Cancer Institute–Center for Cancer Research

Education: Grant Medical College, Bombay, India (M.B., B.S. in medicine); University of Pennsylvania, Philadelphia (Ph.D. in immunology)

Training: Postdoctoral fellowship in pathology and laboratory medicine, University of Pennsylvania; postdoctoral fellowship, NCI’s Experimental Immunology Branch (EIB)

Before coming to NIH: Professor, University of Pennsylvania

Came to NIH: From 1995 to 2000 for training in NCI’s EIB; returned in 2014 to join NCI’s Laboratory of Genome Integrity

Selected professional activities: Enjoys reviewing interesting manuscripts (editorial board member, PLoS Biology; section editor, Journal of Immunology) and teaching; teaches T-cell development for the American Association of Immunologists Advanced Courses in Immunology

Outside interests: Fishing (fresh and salt water), especially in the nearby Potomac River

Web site: https://ccr.cancer.gov/avinash-bhandoola

Research interests: I have always wanted to understand the rules that underlie the development and deployment of a functional immune system. In my lab at Penn we initially focused on early T-cell development. We eventually realized that the transcriptional mechanisms we worked on were shared by precursors of adaptive T cells and precursors of innate lymphocytes. Innate lymphocytes and T cells have very similar effector functions, and one attractive idea is that the factors we’ve worked on somehow program this ability of innate lymphocytes and T cells to access these effector functions. Our long-term goal is to understand the shared as well as the unique features and functions of these apparently closely related cell lineages.

A new area of interest is the epithelial cells that make up the thymus and that support T-cell development. Our knowledge about these cells lags greatly behind our knowledge of T cells. Thymic epithelial cells make the chemokines that attract blood-cell progenitors to the thymus, and they also attract many other signaling molecules that are essential for almost every subsequent step of T-cell development and T-cell quality control. Their numbers reduce with aging (age-related thymic involution), and they are damaged by irradiation and other conditioning regimens used in cancer treatments and in bone-marrow transplantation. Perhaps for this reason, many bone-marrow transplant patients have poor T-cell reconstitution. We would like to understand how these epithelial thymic cells develop and how their numbers and function are maintained through life.
In order to study these events in live organisms, we have developed subcellular intravital microscopy, a series of light-microscopy-based techniques that enable the real-time observation of intracellular processes in live animals.

Our studies have underscored the importance of the tissue environment in regulating cellular events. We have shown that several processes cannot be recapitulated in reductionist model systems. We have unraveled novel roles of the actin cytoskeleton during regulated exocytosis, invasion, and metastasis in head-and-neck cancer. We also unraveled a novel modality of mitochondrial metabolism in vivo.

In our current research, we are further exploring the principles that regulate the temporal and spatial coordination among cell signaling, actin cytoskeleton, and cellular bioenergetics and their relation to modifications of the composition and biophysical properties of membranes. We envision that our work will provide novel insights into the cell biology of secretory systems and provide valuable information for the treatment of various diseases of the oral cavity.

**CUILIN ZHANG, M.D., M.P.H., PH.D, NICHD**

**Senior Investigator, Epidemiology Branch, Division of Intramural Population Health Research, National Institute of Child Health and Human Development**

**Education:** Beijing Medical University, Beijing, China (M.D.); University of Washington School of Public Health, Seattle (M.P.H. and Ph.D. in epidemiology)

**Training:** Research associate in genetic and nutritional epidemiology, Harvard University School of Public Health (Boston)

**Before coming to NIH:** Research scientist, Harvard University School of Public Health

**Came to NIH:** In 2007 as a tenure-track investigator in NICHD

**Selected professional activities:** Associate editorial board, International Journal of Molecular Epidemiology and Genetics; academic editor, PLoS ONE; grant reviewer for the Health Research Council of New Zealand, Research Grants Council of Hong Kong, the Royal Society of New Zealand, and the Medical Research Council of UK

**Outside interests:** Playing the guqin (an ancient stringed instrument); playing sports (running, hiking, tennis); and cooking

**Web site:** http://1.usa.gov/14uk9V9

**Research interests:** My research focuses on the determinants and health consequences of diabetes and obesity. My group and I are trying to determine how pregnancy complications, such as gestational diabetes, may be understood in the context of pre- and peri-conceptional factors and linked with later-onset diseases, and what the health implications for “exposed” offspring are. Our research group determined that prepregnancy risk factors are critical for the development of gestational diabetes. Collectively, our findings suggest that a large percentage of cases of gestational diabetes could be prevented through prepregnancy lifestyle modifications. Importantly, these findings apply to both normal-weight and obese or overweight women.

In addition, our research group is seeking to identify novel biomarkers based on both targeted and nontargeted approaches, such as nontargeted metabolomics, that may enhance our capacity for understanding etiology and improving prediction, screening, and diagnostic protocols of diabetes in pregnancy.

Our research also goes beyond the pregnancy time window. I am leading the Diabetes and Women’s Health Study (http://www.dwhstudy.org), which applies a hybrid design among approximately 4,000 women—from the United States and Denmark—who had diabetes in pregnancy. The study is focusing on the identification of determinants (medical, lifestyle, and genetic factors and their interactions) for the progression from gestational diabetes to type 2 diabetes and its complications and the investigation of biochemical markers that may predict these complications among the high-risk population.

Moreover, we are planning to establish a cohort of offspring aged from early childhood through reproductive age to investigate the short-term and long-term trans-generational impact of diabetes and obesity and to decipher underlying mechanisms. The ultimate goal of our research is to improve maternal and child health at multiple critical times of human development and to disrupt the vicious cycle of diabetes-begetting-diabetes.

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**Read this section in upcoming issues of the NIH Catalyst to learn about other recently tenured colleagues, including:**

- Swee Lay Thein (NHLBI)
- Janet Hall (NIEHS)
- Michele K. Evans (NIA)
- Ivan Ovcharenko (NLM)
- Xiaohong (Rose) Yang (NCI)
- Daphne Bell (NHGRI)
- Lisa Cunningham (NIDCD)
- Jon Lorsch (NIGMS)
- Elissa Lei (NIDDK)
- Francesco DeMayo (NIEHS)
- Ludmila Prokunina-Olsson (NCI)
- Rajeshwari Sundaram (NICHD)
- Hannah Valentine (NHLBI)

http://irp.nih.gov/catalyst
In 2013

R. Wayne Albers (died on September 28, 2013, at 85) was a world-recognized neuroscientist noted for his research in the field of membrane cation transport and neuronal excitability in the nervous system. He was a former chief of the Section on Enzyme Chemistry in the NINDS Laboratory of Neurochemistry.

John Milner (died on December 31, 2013, at 66), well known for his broad understanding of nutrition and its role in cancer prevention, was chief of the Nutritional Science Research Group in NCI’s Division of Cancer Prevention.

In 2014

George Gilbert “Gil” Ashwell (died on June 27, 2014, at 97) was chief of the Laboratory of Biochemistry and Metabolism in the National Institute of Arthritis and Metabolic Diseases, and held that position (through the institute’s name changes) through most of his NIH career. He was a pioneer in the field of glycobiology and world-renowned for co-discovering the “Ashwell-Morrell” receptor in the liver, perhaps the first receptor ever described.

James Bahre (died on October 2, 2014, at 73) provided scientific instruments for NIH medical researchers, working first for Beckman Instruments and then Fuji Corporation. In 1987, he was honored with the NIH Director’s Award for his contributions to the advancement of science, the only non-NIH person to ever receive this prestigious award.

Alessandra Margherita Bini (died on February 26, 2014, at 63) was a highly accomplished scientist and a program director at NCI.

Willy Burgdorfer (died on November 17, 2014, at 89) was a medical entomologist at NIAID’s Rocky Mountain Laboratories (Hamilton, Montana). He gained international acclaim for identifying the cause of Lyme disease—the Lyme spirochete that was later named for him (Borrelia burgdorferi).

William G. Coleman Jr. (died on August 18, 2014, at 72) was a distinguished researcher at NIH for 40 years and became the first permanent African-American scientific director in the history of the NIH Intramural Research Program when he was appointed to direct NIMHD’s intramural research program in 2011.

Morris F. Colien (died on September 27, 2014, at 100), a valued advisor to the NLM, was a medical-computing pioneer and was known around the world as “Mr. Medical Informatics.” As an NLM scholar-in-residence (1987–1993), he wrote a highly regarded history of the medical applications of the computer.

Robert E. Cooke (died on February 2, 2014, at 93), a pediatrician, was a member of President John F. Kennedy’s presidential task force that laid the groundwork for the founding of the Eunice Kennedy Shriver National Institute of Child Health and Human Development in 1962.

Roselyn Epps (died on September 29, 2014, at 84), an expert in NCI’s Public Health Applications Branch, spread knowledge about research results on smoking prevention and cessation. She was the first African-American to be the national president of the American Medical Women’s Association.

Nancy McCartney Francis (died on January 24, 2014, at 63), an immunologist in NIDCR, helped demonstrate that transforming growth factor-beta (TGF-beta) is an extremely potent chemoattractant.

William Galey (died on May 17, 2014, at 71) oversaw the Howard Hughes Medical Institute–NIH Research Scholars Program, which gave outstanding students at U.S. medical schools the opportunity to receive NIH research training.

Mark Garfield (died on September 1, 2014, at 61) was a chemist in NIAID who specialized in Edman sequencing, a method of sequencing N-terminal amino acids. Although many experiments that once used Edman sequencing now rely on mass spectrometry, N-terminal sequencing still occupies a very important niche in biomedical research.

Steven Goldberg (died on November 25, 2014, at 73), chief of the NIDA’s Pre-clinical Pharmacology Section, made outstanding contributions to our understanding of the behavioral and neuropharmacological mechanisms triggered by drugs of abuse.

Claire Hall (died on May 28, 2014, at 83) was a research chemist at the National Institute of Arthritis and Metabolic Diseases (now NIDDK) for 40 years before retiring in 1999.

Mary Ruth Cailey Hartman (died May 9, 2014, at 92) was chief of the special events section in the Clinical Center.

Terrell Leslie Hill (died on January 23, 2014, at 96), a physical chemist and molecular biologist, was chief of NIDDK’s Section on Theoretical Molecular Biology. He was among the first to emphasize the need for interdisciplinary research across chemistry, biology, and physics.

Albert Z. Kapikian (died on February 24, 2014, at 83) was a pioneering virologist at NIAID who discovered the norovirus (initially called the Norwalk virus) and led a decades-long effort that resulted in the first licensed rotavirus vaccine. He was the chief of the epidemiology section of NIAID’s Laboratory of Infectious Diseases, a position he held for 45 years. Kapikian often was called the father of human gastroenteritis virus research for his work on improving the understanding and prevention of viral diseases that affect the gastrointestinal tract. In 1973, Kapikian and his colleagues identified the hepatitis A virus.

Hector Lopez (died June 21, 2014, at 66) was a scientist with expertise in medical ultrasound imaging and a program director in NIBIB.
Donald Morton (died on Jan 10, 2014, at 79), who did a fellowship at NCI, gained renown as a cancer surgeon (at UCLA) for developing the sentinel lymph node biopsy, which was adapted for breast cancer and melanoma. His technique involved first testing the lymph nodes nearest the tumor—if they had no malignant cells, then there was no need to remove any other nodes.

S. Harvey Mudd (died January 21, 2014, at 86) was a physician and researcher at NIMH. His discoveries led to the routine screening of newborn infants for metabolic irregularities. His research led to the practice of putting folic acid in the flour supply to help prevent birth defects.

J. Frederic Mushinski (died on December 18, 2014, at 76) was head of the Molecular Genetics Section in the NCI Laboratory of Genetics and the Laboratory of Cancer Biology and Genetics.

Eddie Reed (died on May 28, 2014, at 60), NIMHD’s clinical director, was a giant in the fields of cancer pharmacology and health disparities. He studied DNA damage and repair in cancer cells in response to anticancer agents.

Martin John Rogers (died in September 2014 at 54), a biologist in NIAID’s Parasitology and International Programs Branch, specialized in tropical diseases, particularly malaria.

S. Stephen Schiaffino (died on April 3, 2014, at 86) was the director of the Division of Research Grants and senior science advisor to NIH Director James Wyngaarden.

Sherry S. Sherman (died October 21, 2014, at 66) was the former director of clinical endocrinology and osteoporosis research at NIA.

Albert Sjoerdsma (died on February 27, 2014, at 89), chief of NHLBI’s Laboratory of Clinical Biochemistry, diagnosed and defined the carcinoid syndrome, an unusual cancer characterized by serotonin-filled tumors; established the mechanism of action of the first antidepressants, monoamine oxidase inhibitors.

Jesse Steinfeld (died on August 5, 2014, at 87) was surgeon general (1969–1973) under President Richard Nixon. Before that he was a deputy director in NCI. As surgeon general, he fought tobacco: He issued a report on the dangers of second-hand smoke; proposed a Non-Smoker’s Bill of Rights; strengthened warnings on cigarette packages; and issued the first ban on smoking in certain government buildings.

Ellen Lee Simon Stover (died on March 16, 2014, at 63) was following in the footsteps of her father, Ralph Simon (NIMH), when she began work as a psychologist at NIMH. Beginning in 1983, she pioneered the NIMH initiative for research on AIDS and later became the director of the Division on AIDS Research.

John H. Weisburger (died February 17, 2014, at 92), head of NCI’s Carcinogen Screening Section and later director of the Bioassay Carcinogenesis Programs, studied the effects of environmental chemicals on the alteration of the structure and function of DNA, contributing pioneering work on the mechanism of the carcinogen 2-acetylaminofluorene.

Mitchel Mitsuo Yokoyama (died January 9, 2014, at 86), who worked in the NIH Blood Bank (1959 to 1964), made significant contributions in the areas of blood typing, forensic medicine, and immunology. Novelist Erle Stanley Gardner based some of his Perry Mason stories on cases from Yokoyama’s early forensic career.

Robert W. Zwanzig (died on May 15, 2014, at 86), former chief of NIDDK’s Section on Theoretical Biophysics, was a brilliant theoretical chemist and biophysicist. Well known for his ability to describe a wide variety of physical phenomena using very sophisticated model systems of his own invention, he produced fundamental works on the theory of rate processes, including protein folding. ●

Read expanded versions online at http://irp.nih.gov/catalyst/v23i1/obituaries.

NIH ABBREVIATIONS
CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CDC: Centers for Disease Control and Prevention
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
FAES: Foundation for Advanced Education in the Sciences
FARE: Fellows Award for Research Excellence
FelCom: Fellows Committee
FDA: Food and Drug Administration
FNL: Frederick National Laboratory
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCATS: National Center for Advancing Translational Sciences
NCBI: National Center for Biotechnology Information
NCCIH: National Center for Complementary and Integrative Health
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
NIEMS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
OD: Office of the Director
OITE: Office of Intramural Training and Education
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women’s Health
OTT: Office of Technology Transfer
President Barack Obama visited the NIH on December 2, 2014, to thank NIH for its continuing work on the Ebola virus. “One of the things that has always marked us as exceptional is our leadership in science and education research,” he said in an address to a packed Masur Auditorium. “Here at NIH, you have always been at the forefront of groundbreaking innovations.” He also visited two of NIAID’s Vaccine Research Center labs—Mario Roederer’s and Nancy Sullivan’s—that led the successful Ebola vaccine trial (see “Intramural Research Briefs” on page 8). From left: NIAID Director Anthony Fauci, HHS Secretary Sylvia Burwell, President Obama, and Nancy Sullivan.

**Surprise Visit from the President**

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