Frederick National Lab

NCI-Frederick Gets a New Name
BY TANIA B. LOMBO, NCI

What’s in a name? If it is the Frederick National Laboratory (FNL), most recently known as NCI-Frederick, the name equates to a history—both as a portal to past accomplishments and as insight into NCI’s vision for the facility’s future.

While certain names and achievements in the Frederick labs might sound familiar—for example, Giorgio Trinchieri and his work on the complex crosstalk between inflammation and cancer in the NCI Laboratory of Experimental Immunology—some NIH Catalyst readers might not understand who does what in Frederick and how part of NCI wound up inside the gates of an army base.

This article highlights changes that have taken place at Frederick and offers a peek into the important intramural research and other collaborations now conducted in the NCI labs there.

The NCI has a 40-year relationship with the city of Frederick, Md., a Civil War-era mining and farming hub still surrounded by ample farmland some 35 miles north of the Bethesda campus NCI labs. In 1971, President Richard Nixon requested that approximately 70 acres and 60 buildings belonging to the U.S. Army at Fort Detrick be “converted into a leading center for cancer research” to be led by the NCI in partnership with the private sector.

The transfer met two of Nixon’s goals: the termination of research on offensive

CONTINUED ON PAGE 6

Details, Details, Details

Leaving the Bench, but Staying in Science
BY BEN PORTER, NINDS

Once you fall in love with science, you never really fall out of love with it. But what happens to a researcher who has lost that passion for conducting bench science and no longer wants to hold a test tube, write journal articles, or run a lab? To a postdoctoral fellow who has already devoted years to research, the loss of satisfaction with lab work can lead to feelings of guilt (for occupying a training position that could have gone to someone else) and confusion about what career path to pursue. Luckily, scientists can continue to play important roles in society whether they choose to stay at the bench or leave it.

“We desperately need a scientifically literate society,” said Sharon Milgram, director of the Office of Intramural Training and Education (OITE). “That requires scientists moving into many, many jobs away from the bench. That means public-service campaigns, people getting vaccinated, politicians making good decisions, inquiry-based decision making based on data. We need people who can communicate science to nonscientists.”

NIH is prepared to help postdocs explore non-bench careers with a mechanism called a detail. A detail is “when a student or a postdoc goes to a different work environment to

CONTINUED ON PAGE 10
This year the Clinical Center (CC) is celebrating its 60th anniversary, and the NIH is launching an exciting experiment using CC resources. We are opening our doors to investigators from academia and industry and providing them access to our special resources. The experiment provides, for the first time, a formal funding opportunity for new partnerships between outside and intramural investigators at the CC. The result should bring new intellectual excitement to the intramural program while enabling clinical research projects that might not otherwise occur.

This initiative came about as a result of the Congressionally mandated Scientific Management Review Board’s review in 2010. It recommended the CC’s vision be expanded to “serve as a state-of-the-art national resource, with resources optimally managed to enable both internal and external investigator use.” In response, NIH released a new Funding Opportunity Announcement called “Opportunities for Collaborative Research at the NIH Clinical Center” (http://grants.nih.gov/grants/guide/pa-files/PAR-13-029.html).

The new program, which will use the NIH U-01 grant mechanism, will support collaborative research that is aligned with NIH’s efforts to enhance the translation of basic biological discoveries into clinical applications that improve health. The program will provide renewable three-year awards and a stipend of up to $500,000 per year in direct costs. Research teams must have at least one extramural and one intramural co-principal investigator. Twelve institutes and centers (ICs) and two NIH offices have signed up to sponsor the new awards (NCI, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NLM, ORWH, and ODS). Institutes that have not signed on can participate next year.

The application process and key dates are described in detail on the Web site above. The applications will be batched annually with a single closing and due date (March 20) for each year. It’s strongly recommended, but not required, that applicants submit a letter of intent 30 days before the application is due so the CC and the proposed sponsoring IC can review it to determine resource availability and programmatic alignment.

Applications must be accompanied by letters from the CC and the sponsoring IC acknowledging the availability of resources and program alignment. Scientific reviews will be conducted by either institute-based or special study sections established by the NIH Center for Scientific Review. IC advisory councils will evaluate reviews in October.

Review criteria will include an assessment of whether the proposal has a well-defined collaborative plan with clearly identifiable responsibilities for the intramural and extramural investigators, a plan for management of the collaboration, descriptions of what each participant will provide, a clear statement of the advantage to bringing intramural and extramural investigators together, and a description of what unique CC research opportunities will be used. Award announcements are expected in November or December each year.

Grant funds will flow from the pool of extramural dollars to outside principal investigators, ICs will program intramural dollars to support the intramural investigators and CC costs. The funds needed for CC activities will be determined from resource templates submitted by investigators to the CC.

How will we measure success of this experiment? The intent is to enrich and not compromise the intramural environment. Investigator demographics, the portfolio of institutions applying for and receiving grants, the research studies associated with the grant, and the type of collaborations will be evaluated. The program will be reviewed for its ability to implement grants, develop new tools, and overcome barriers to the grant process. In addition, outcome measures such as the number and impact of resulting publications and the number of new drugs and devices will be monitored.

As the German writer and scientist Johann Wolfgang Von Goethe said in 1813, “Science and art belong to the whole world, and the barriers of nationality vanish before them.” If the NIH experiment works, we hope the barriers to intramural-extramural collaborations will vanish. What better way to celebrate the 60th anniversary of the CC than with the new vision of opening our doors?

For more information on the CC’s resources and potential partners as well as answers to frequently asked questions, visit http://www.cc.nih.gov/translational-research-resources. For other questions, e-mail ClinicalCtrPartner@mail.nih.gov or contact the Call Center at 301-496-4121.
The U.S. government is considering new regulations for mitigating the potential for harmful misuse of new research findings.

Almost 40 years ago, advances in recombinant DNA technology prompted the scientific community to confront public concerns about biosafety issues associated with the manipulation of genetic material. Biosafety risks include laboratory-acquired infections or accidental releases of microbes that could threaten public health or agriculture. In 1974, NIH established the NIH Recombinant DNA Advisory Committee to ensure the safety of recombinant DNA research.

The rapid advances in biomedical research stimulated the broadening of the government’s concerns to also include biosecurity risks, which include the intentional misuse of research products or information to threaten public health, the environment, agriculture, or other aspects of national security.


Those concerns were heightened by the terrorist attacks of September 11, 2001, and the deliberate distribution of anthrax spores in the U.S. mail shortly thereafter. In addition, the publication of certain types of research alarmed the government and the public. In the early 2000s, for example, the media reported that scientists had created viruses in test tubes and re-engineered a mousepox virus, a relative of the smallpox virus, to be so deadly to mice that antiviral drugs and vaccines couldn’t stop it.

A comprehensive consideration of the issues raised by such “dual-use” research findings—findings that advance technology and knowledge, but that could be misapplied to pose a threat to public health and safety—led to, in 2004, the landmark National Research Council report, “Biotechnology Research in an Age of Terrorism” (http://www.nap.edu/openbook. php?isbn=0309089778) and the establishment of the National Scientific Advisory Board for Biosecurity (NSABB). Although the NSABB published, for comment, a “Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information” in the Federal Register in June 2007, it did not trigger major new government oversight initiatives (http://oba. od.nih.gov/biosecurity/pdf/Framework%20 for%20transmittal%200807_sept07.pdf).

In the ensuing years, national and international meetings have been held to discuss dual-use research issues but it was not until 2011 that new research prompted further action. In that year, two groups described—and submitted papers for publication about—genetic modifications that broadened the host range for the H5N1 avian influenza to include mammals. Naturally occurring H5N1 infects chickens and other birds, and can infect humans—especially farmers and poultry workers—who are in close contact with infected birds. Alarming ly, 50-60 percent of those H5N1-infected humans die, yet they don’t transmit the virus to others.

It was scary that researchers could engineer a genetic mutation of H5N1 that could spread from mammal to mammal and conceivably from human to human. Scientists and non-scientists around the world engaged in an impassioned debate over the risks and benefits of such research. Some argued that the work should not be published because it might enable someone with ill intentions to create a mutated strain of H5N1 that could set off a catastrophic global pandemic. Others, including the scientists who created the mutant strains of H5N1, pointed out that influenza can mutate to virulent forms spontaneously and that it’s important to do research to understand the makeup of the virus and how it might become virulent naturally.

On March 29, 2012, the federal government issued a policy that required its funding agencies to review funded life-sciences “dual-use research of concern” (DURC), and to establish criteria for the management of any research that is identified as DURC (http://oba.od.nih.gov/oba/biosecurity/PDF/United_States_Government_Policy_for_Oversight_of_DURC_FINAL_version_032812.pdf). The NSABB defines DURC as “research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment or materiel.”

Now the government is proposing that the institutions that conduct U.S. government-funded potential life-sciences DURC assume responsibility for overseeing such research themselves. The dual dilemma is how to develop procedures that will promote safety and security without discouraging investigators from pursuing potentially useful research.

To review the proposed “Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern” and instructions for submitting comments, go to http://www.phe.gov/s3/dualuse/Pages/default.aspx. Comments must be received by April 22, 2013.
Led by NEI Deputy Scientific Director Sarah Sohraby, the NEI intramural training program is helping research fellows balance work-life issues and become more competitive in the workplace.

Training programs offered by individual institutes and centers (ICs) “play a vital role in complementing efforts organized by the Office of Intramural Training and Education” (OITE), said Lori Conlan, director of OITE’s Office of Postdoctoral Services. The OITE hosts a curriculum of career-development topics aimed at scientists-in-training across NIH.

NIH hosts about 5,000 trainees, many of whom are from foreign countries. Getting lost in the shuffle is far too easy. About 120 trainees are at NEI, which also hosts about 30 interns each summer. “The NEI has built a very strong community within their training program,” Conlan said.

A community is what Sohraby envisioned when she took charge of the NEI training program in 2006. Sohraby, who’s from Belgium, was an NIH postdoc at the National Heart, Lung, and Blood Institute (NHLBI) in 1980-1983. She said she relied on her peers and mentors for career advice and felt fortunate to have landed in such a supportive environment. Some of her contemporaries had a harder time cultivating their careers.

She left NIH to continue her training and then spent 18 years in research and teaching positions in the medical and engineering schools at Belgium’s Université Libre de Bruxelles (Brussels). When she returned to NIH in 2006 as NEI’s deputy scientific director, she drew on her experiences as a postdoc as she began directing the institute’s intramural training program. She instituted entrance interviews to orient fellows when they arrived at NIH, as well as exit interviews when they left, to garner feedback about the strengths and weaknesses of the NEI’s training activities. Sohraby strongly encouraged fellows to take advantage of OITE services, too, including its weekly seminars on topics such as understanding workplace dynamics, test-taking skills, résumé writing, and job hunting.

“Tenure-track, and good research positions in general, are more difficult than ever to obtain,” said NEI Scientific Director Sheldon Miller. “Biomedical research is increasingly interdisciplinary, which means scientists who seek tenure-track research faculty positions must build critical communications skills earlier in their careers to compete in the workplace. Skills such as good speaking, writing, and networking are essential.”

Sohraby established quarterly group meetings for fellows to discuss important training-related issues and to help them practice presenting their research to their peers in a variety of formats, including talks without slides. And she established a two-day fellows retreat, Focus on Fellows, which has become an annual event that encourages fellows to gain perspective on their lives and careers as scientists. The event offers prizes for the best trainee presentations and features talks by noteworthy scientists who, in addition to presenting their research, are asked to reflect on their career journeys.

Trainees consider the retreat’s career development roundtables especially valuable. Scientists or professionals in science-related occupations facilitate discussions that engage fellows in issues ranging from improving grant submissions, to linking basic science research and clinical work, to transitioning to alternate career paths. Miller said he knows of several fellows who made critical career choices based on these round-table discussions.

In addition to planning and conducting training events, the NEI intramural training staff maintains an open-door policy to encourage trainees to seek guidance as issues arise.

“We see the fellows as part of a big family,” said NEI Scientific Program Administrator Cesar Perez-Gonzalez, who gladly offers guidance on challenging topics such as resolving disagreements in the workplace or more straightforward issues such as writing résumés and cover letters. He is currently exploring the feasibility of establishing career development plans for each trainee.

To learn more about NEI’s intramural training resources and opportunities, visit http://www.nei.nih.gov/training or contact Cesar Perez-Gonzalez at cesarp@nei.nih.gov. To learn more about OITE services, visit its Web site at https://www.training.nih.gov.
Research Training for Physician Scientists
A Proposal for a Structured Basic-Research Training Program

BY BOLANLE FAMAKIN, NINDS

Edward Korn’s letter about “Early Graduate Programs at NIH” in the September-October 2012 issue of the NIH Catalyst (http://irp.nih.gov/catalyst/v2015/commentary) rekindled my interest in advocating for a structured basic-research training program for physicians, like myself, who have completed medical training and want to become independent investigators engaged in basic research.

There is a precedent at NIH for such programs: the Associate Training Program (ATP), created in 1953. In 1956, the NIH Scientific Advisory committee proposed the formation of a “two-year [research associate] training program for people who have their M.D. degree and intend to go into medical research as a career.” Their training in the fundamentals of basic research and research methodology was through specialized didactic courses taught by experienced scientists.

The significance of the ATP program was highlighted in a study, published in Academic Medicine, which showed that participating physician-scientists have had more successful academic careers than physician-scientists who did not participate. Nine were later awarded Nobel prizes. Unfortunately, the ATP ended in 1992, coinciding with the national decline in the number of clinical investigators (Acad Med 86:502–508, 2011; Science 338:1033–1034, 2012).

The ATP program’s remarkable success is reason enough to call for establishing a similar program at NIH. Today’s avenues for physicians to obtain structured, advanced basic-research training are either too cumbersome or impractical. The typical M.D.-Ph.D. program involves continuous training for 16–20 years and is not attractive to many physicians who want to pursue basic science research.

Although NIH’s Graduate Partnerships Program (GPP) offers the M.D.-Ph.D. Partnership Training Program (http://mdphp.gpp.nih.gov), it is impractical for practicing physicians. It is full-time and inflexible and does not allow physicians to see patients on a part-time basis so they can maintain their clinical skills. Even the more flexible GPP—the NIH-Oxford Cambridge Scholars Program—is problematic because students must spend significant amounts of time outside the country.

I propose that NIH offer an advanced, structured, basic-research training program, for board-certified, eligible physicians who have completed residency and/or fellowship training. The elements would include:

• A competitive four- to five year-Ph.D. research fellowship offered by NIH and jointly administered by local universities;
• Coursework developed with the help of Ph.D.-granting universities to bridge the gap between medical training and bench research;
• The ability to see patients on a part-time basis to help foster the development of research questions from bench-to-bedside and from bedside-to-bench;
• Pay commensurate with pay for physicians who are just entering the workforce;
• The awarding of Ph.D. degrees, by partner institutions, upon successful completion of required coursework and thesis.

The NIH is the right organization to prepare the next generation of physician-scientists to tackle complex medical questions in biomedical and translational research.

Dr. Famakin, a stroke neurologist, was a clinical fellow in NINDS. She first wrote about this subject in the May-June 2008 NIH Catalyst (http://www.nih.gov/catalyst/2008/08.05.01/page4.html).

Response

Dr. Famakin’s proposal to provide coursework and formal research training for physicians who have completed their clinical training is intended to allow active clinicians to retain their clinical skills while they obtain a Ph.D. Training for physician-researchers is a timely topic as we try to improve the research-training experience for clinically trained scientists at NIH.

Her proposal is for NIH to not confer degrees but to take advantage of existing university programs through the Graduate Partnerships Program; students would do their thesis work at NIH and basic science coursework at a university that can confer degrees. NIH would pay. Paying students the proposed salary would be a reasonable investment because of the applicants' clinical credentials and their participation in patient-care rotations. It is easy to imagine a program in which clinical fellows would have the opportunity to get their Ph.D.s and become board eligible in a subspecialty. This possibility would be attractive to some early-career investigators and should attract the very best to NIH.

Extramural academic centers already provide such opportunities through support provided by NIH K12 awards. A more time-efficient alternative, which would more closely mimic the highly successful ATP program, would be to provide research coursework and rigorous research training in NIH laboratories without the need for the formal requirements (and the four-to-five year commitment) of a Ph.D. program. Some ICs, such as NCI, already provide this type of alternative for clinical fellows.

Our recent experience suggests, however, that few fully trained M.D.s are interested in a sustained laboratory experience—whether it is structured as described by Dr. Famakin or is more flexible. Such a program would have to be made more attractive with competitive salaries and loan-repayment opportunities.

Michael Gottesman, M.D., DDIR
John Gallin, M.D., Director, NIH Clinical Center
biological weapons, which took place at Fort Detrick, and the campaign to eradicate cancer. Nixon wrote in a presidential statement in October 1971 that “some of the Nation’s most sophisticated scientific facilities” were at Fort Detrick and that they could be “converted so effectively and so inexpensively to an intensive program of cancer research.”

The U.S. Department of Health and Human Services (HHS) quickly established the National Cancer Research and Development Center with only a few dozen employees. By 1973 the burgeoning facility became the Frederick Cancer Research and Development Center. In 1975, the facility was designated as a Federally Funded Research and Development Center, analogous to the famed Los Alamos or Lawrence Livermore national labs. Such a center is a hybrid organization of federal workers and private enterprise. FNL is the only HHS-led national lab. FNL’s largest contractor is SAIC (formerly Science Applications International Corporation), which won its first contract from NCI in 1995.

The FNL has had several names through the years, such as Frederick Cancer Research Center dating to 1981, still seen in some signs around the campus, and the ever-colloquial NCI-Frederick. Yet the Frederick labs have always been more than the NCI contribution. So, in March 2012, NCI Director Harold Varmus announced that the organization and facilities formerly called NCI-Frederick would henceforth be known as the Frederick National Laboratory, reflecting the synergies offered by a national lab.

“This is a facility with a very broad mission, which is valuable to many people across the nation, and its activities are available for academic, industry, and other government agencies in the country and around the world,” said Craig Reynolds, NCI director of the Office of Scientific Operations at the FNL.

That mission includes biomedical research on cancer and on AIDS and other infectious diseases. Nearly 3,000 people work at the FNL. More than half of them are employed through SAIC under a single, long-term contract with the NCI, according to SAIC-Frederick CEO David Heimbrook.

To best understand the organization, think of FNL as an island campus within Fort Detrick. On that island are labs and offices belonging to the federally run NCI-CCR and privately owned SAIC-Frederick. (There are some smaller contractors on the island as well.) NCI-CCR has its base on the NIH Bethesda campus; SAIC-Frederick has facilities throughout the region, such as the new Advanced Technology Research Facility (ATRF) in Frederick.

Outside of contractual responsibilities, collaborations are encouraged. The ATRF, for example, is available for cooperative research and development projects with academia, government, and life-sciences industry partners to accelerate cancer and AIDS translational research.

And so, with that background, this article highlights the scientific programs located at FNL and some of the biomedical findings that are starting to give the Frederick National Laboratory its signature in the nation’s biomedical research arena.

FNL and the HIV Pandemic

In the 1980s, the human immunodeficiency virus (HIV) was identified as the cause of AIDS. But for pharmaceutical companies to develop a diagnostic test for HIV, large amounts of the virus needed to be grown quickly. Luckily, NCI’s Frederick National Laboratory already had a facility for producing retroviruses that cause cancer, and it refocused its efforts to produce large amounts of HIV instead. NCI partnered with five private companies and provided them HIV viruses, and within a year the effort produced an FDA-approved blood test to detect HIV. Use of these diagnostic tests to detect and discard blood from infected individuals resulted in the rapid decrease of blood transfusion–associated infections in the United States.

Cancer Treatment at the Nanoscale

FNL’s Nanotechnology Characterization Laboratory (NCL) serves as a national resource for cancer researchers to facilitate the regulatory review of nanotechnologies intended for cancer therapies and diagnostics. NCL performs preclinical efficacy and toxicity testing of nanoparticles; in addition, it characterizes nanoparticles’ physical attributes, their in vitro biological properties, and their in vivo compatibility using animal models. By providing the critical infrastructure and characterization services to nanomaterial providers, NCL accelerates the transition of basic nanoscale particles
and devices into clinical applications.

“This expensive service is free for the researchers in the field, and it is becoming a powerful tool to bring the nanomedicines into clinical trials,” said NCL scientist Jennifer Grossman. As of today, the NCL has evaluated more than 200 nanoparticles intended for medical applications. For more information, visit http://ncl.cancer.gov.

Biopharmaceutical Development

FNL’s Biopharmaceutical Development Program (BDP), established in 1993, supports the development of biopharmaceuticals and concentrates on products in early development. One of its early projects was producing monoclonal antibodies—when no pharmaceutical company would—to treat children with neuroblastoma, a common childhood cancer that grows in parts of the nervous system (http://www.cancer.gov/ncicancerbulletin/100510/page5). For more on the BDP, visit http://ncifrederick.cancer.gov/Programs/Science/BDP.

Molecular Targets Laboratory

The Molecular Targets Laboratory, which enables NCI investigators to pursue molecularly targeted drug discovery research, maintains the Natural Products Repository—a repository of natural product extracts that is the largest and most diverse in the world. These extracts, derived from terrestrial, marine and microbial organisms, constitute a unique source of chemical diversity for the discovery of compounds that can interact with molecular targets associated with human cancer. A number of “new drugs that have been approved in the last 10 years are natural products or chemical derivatives from them,” said NCI-CCR scientific director Robert Wiltrout. The program “is providing a tremendous chemical diversity that is not easily synthesized by using chemical libraries.”

FNL’s New Building

In 2012, FNL opened a new building—the Advanced Technology Research Facility (ATRF)—that consolidates labs and operations that had been scattered among more than 30 buildings at the FNL’s Fort Detrick campus. The ATRF houses laboratories of the Advanced Technology Program and the Biopharmaceutical Development Program and also dedicates space to accommodate co-location partnerships. For more information, visit http://atp.ncifcrf.gov/atpi/atrf.

Read more about the Frederick National Lab at the NIH Catalyst online: http://irp.nih.gov/catalyst/v21i2/frederick-national-laboratory.
Intramural Research Briefs

**NICHID: EARLY STAGES IN MUSCLE FORMATION AND REGENERATION DISCOVERED**

NICHID scientists have identified proteins that allow muscle cells in mice to form from the fusion of the early-stage cells that give rise to the muscle cells. The findings have implications for understanding how to repair and regenerate muscle tissue and processes involving cell fusion, such as when a sperm fertilizes an egg, viruses infect cells, or specialized cells called osteoclasts dissolve and assimilate bone tissue in order to repair and maintain bones.

Muscle cells originate from precursor cells known as myoblasts, which fuse to form a single long, tubular cell called a myocyte. The fusion of myoblasts into muscle fibers takes place early in fetal development. With exercise and throughout a person’s life, the process is repeated to form new muscle mass and repair old or damaged muscle.

The researchers identified the two distinct stages of cell fusion and the essential proteins that facilitate them. In the first stage, two myoblasts meet, and proteins on cell-surface membranes cause the membranes to meld. In the second stage, a pore opens between the cells and their contents merge. This second step is guided by proteins inside the cells.

The work identifies two cell-surface proteins that belong to a large family of proteins called annexins, which are known to play a role in membrane repair and in inflammation. The researchers also identified the protein dynamin, found inside the cell, as essential to the second stage of the cell-fusion process. Dynamin also has an unexplained link to certain rare and poorly understood myopathies—disorders characterized by underdeveloped muscles. The researchers hope that further examination of the role of dynamin in cell fusion will lead to a greater understanding of these conditions. (NICHID authors: E. Leikina, K. Melikov, S. Sanyal, S.K. Verma, B. Eun, C. Gebert, K. Pfeifer, V.A. Lizunov, and L. V. Chernomordik; J Cell Biol 200:109–123, 2013)

**NIAAA: ADVANCING THE UNDERSTANDING OF MOVEMENT CONTROL**

Voluntary movements involve the coordinated activation of two brain pathways that connect parts of deep brain structures called the basal ganglia, according to a study in mice by NIAAA researchers. The findings challenge the classical view of basal ganglia function that proposes that direct and indirect pathways originating in the striatum have opposing effects on movement. It is thought that neuron activity in the direct pathway promotes movement, while activity in the indirect pathway inhibits movement. Newer models suggest that co-activation of these pathways is necessary to synchronize basal ganglia circuits during movement, but until now it’s been difficult to test them.

The researchers devised a new approach that uses fiber-optic probes implanted in the mouse brain striatum to measure light emissions from neurons engineered to glow when activated. The researchers detected neural activity in both the direct and indirect pathways when mice performed a bar-pressing task.

A better understanding of how the basal ganglia control movements may lead to treatments for disorders in which these circuits are disrupted such as Parkinson disease, Huntington disease, and addiction. In addition, the new technique will be useful for studying other brain regions. (NIAAA authors: G. Cui, X. Jin, M.D. Pham, S.S. Vogel, D.M. Lovinger, R.M. Costa; Nature 494:238–242, 2013)

**NIEHS: HINI FLU SHOTS ARE SAFE FOR PREGNANT WOMEN**

Norwegian pregnant women who received a vaccine against the 2009 HINI influenza virus showed no increased risk of pregnancy loss, whereas pregnant women who experienced influenza during pregnancy had two-fold risk of miscarriages and stillbirths, according to a study by NIEHS researchers in collaboration with scientists in Norway. (NIEHS authors: S. Haberg and A. Wilcox; N Engl J Med 368:333–340, 2013)

**NCI: INCREASES IN RISK OF CERTAIN LEUKEMIAS RELATED TO TREATMENT**

A new NCI study describes the pattern of risk for one form of cancer, acute myeloid leukemia (AML), that has risen over the past three decades for adults who have previously been treated with chemotherapy for other forms of cancer, notably non-Hodgkin lymphoma (NHL). The increased risk among NHL survivors could be due to prolonged survival in recent years for some lymphoma subtypes that are associated with multiple courses of chemotherapy. The findings are based on data from NCI’s Surveillance Epidemiology and End Results cancer registries to evaluate the risk of leukemia in more than 426,000 adults who had been diagnosed with cancer between 1975 and 2008 and who had received chemotherapy as part of their initial cancer treatment. Among these patients, the authors identified 801 people who subsequently developed AML.

Over the study time period, the researchers observed declining risk among patients treated for ovarian cancer, myeloma, and possibly lung cancer. The decreased risk among patients with ovarian cancer is consistent with a shift from use of a certain alkylating agent—associated with the risk of developing leukemia—to platinum-based chemotherapy in the early 1980s. The authors also found evidence that the risk of treatment-related AML has increased since 2000 among patients treated for esophageal, prostate, and cervical cancer and since the 1990s among patients treated for cancers of the bones and joints and of the endometrium.

Future studies are needed to gather information on the risks associated with specific chemotherapy agents, which could not be obtained from this study. (NCI authors: L.M. Morton, G.M. Dores, M.A. Tucker, C.J. Kim, E.S. Gilbert, J.F. Fraumeni, Jr., and R.E. Curtis; Blood DOI:10.1182/blood-2012-08-448068)
Andrew Singleton: Treating Rare Diseases from Bench to Bedside

BY KRISTINA MCLINDEN, NINDS

In 2010, a grieving mother whose two young children had died from a rare neurological disorder was determined to see that no other family would suffer as hers had. She turned to NIH, sure that its scientists could decipher the genetic causes of Brown-Vialetto–Van Laere syndrome (BVVL), a disorder characterized by deafness, paralysis, and respiratory failure. Neurogeneticist Andrew Singleton at the National Institute on Aging (NIA) accepted the challenge. After all, he and his colleagues had discovered the genetic mutations responsible for a similar, albeit more common, neurodegenerative disorder—Parkinson disease (PD). PD affects seven to 10 million people worldwide, but since the beginning of recorded medical history only 58 patients have been diagnosed with BVVL.

“I recognized BVVL as a tractable problem,” Singleton explained. “I was able to sequence the genome of two families afflicted with it and narrow the list of possible targets down to five genes.”

At about the same time, a researcher at Kings College in London discovered that one of those genes encoded an intestinal riboflavin (vitamin B2) transporter protein; a mutation in the gene causes BVVL and an extreme deficiency in vitamin B2.

“We were beaten to the punch there,” said Singleton. “But then we showed that mutations in another riboflavin transporter caused an overlapping disorder.”

He has also been collaborating with clinicians in Europe who are now providing high-dose riboflavin treatment to young patients with BVVL. Results of the treatment are promising so far, but it is unclear whether it can halt or reverse the disease.

Singleton’s skill in solving puzzles began when he was a boy growing up on the small Channel Island of Guernsey in the United Kingdom. He obtained a B.S. in physiology from the University of Sunderland (Sunderland, England) and a Ph.D. in neuroscience from the University of Newcastle (Newcastle upon Tyne, England), where he studied Alzheimer disease (AD) and other dementias. He continued studying neurological disorders during a postdoctoral fellowship at the Mayo Clinic (Jacksonville, Fla.) and as a research scientist at Johns Hopkins University (Baltimore).

In 2002, he was drawn to NIH, nicknamed by a colleague a “Disneyland for doctors” because it was chock full of resources for medical research. It wasn’t long before he became a tenured senior investigator and branch chief of NIA’s Molecular Genetics Section and the Laboratory of Neurogenetics.

“NIH allows me the flexibility to follow my ideas and interests from day to day,” he said. “If I want to investigate a potentially risky hunch, I can do the experiment that same week rather than write a grant and wait six months to see if it gets funded or not.”

Singleton is perhaps best known for his contribution to the discovery that mutations in the SNCA (encodes alpha-synuclein) and LRRK2 genes are associated with early-onset and familial PD. The mutated proteins are involved in the death of neurons in the substantia nigra, a brain region responsible for movement. Understanding the genetics of what initiates PD—and other neurological disorders—is a crucial first step in slowing it down or stopping its onset.

“Although the sequencing of the human genome has led to few cures, I believe that genetics is the best foundation for ultimately solving these problems,” said Singleton. “What is required now is funding, acquiring sample tissue, and simply doing the work.”

While Singleton has been busy solving the puzzles underlying the genetic basis of and environmental contributors to neurodegenerative disorders, advises scientists to collaborate as much as they can.


NIA neurogeneticist Andrew Singleton, who solves puzzles underlying the genetic basis of and environmental contributors to neurodegenerative disorders, advises scientists to collaborate as much as they can.
gain experience, typically in a job unrelated to bench science,” Milgram explained. “It really is an internship to get your foot in the door, to gain insight, to gain experience, and to build a network.”

Detail assignments can take place within any government agency—or even outside of government—and can include science administration, science policy, science writing, technology transfer, and animal use. At NIH, details can be part-time or full-time and can range from doing a “sabbatical” in another lab to learn a new technique, to going on patient rounds in the Clinical Center, to working in an office where scientific knowledge can be integrated with new skills. Arrangements can be informal with only verbal agreements or very formal with a memorandum of understanding that involves the postdoc’s PI and institute as well as the hosting office. Specifics about the detail, such as the hours and the length, are arranged among the PI, detail host, and the trainee. Usually the PI’s lab continues to pay the salary during the detail.

Not everyone knows that NIH policy has a specific reference to details: “A rotation in a science policy office, generally only one rotation of three months or less, is permitted when such activity can be justified as an integral part of the NIH research experience” (NIH Policy Manual’s chapters on the Intramural Research Training Award, http://oma.od.nih.gov/manualchapters/person/2300-320-7/2300-320-7.pdf) and the Visiting Fellow Program (http://oma.od.nih.gov/manualchapters/person/2300-320-3).

Still a detail is “not a right, not an entitlement,” pointed out Lori Conlan, director of Postdoctoral Services and Career Services in OITE. It’s “something you carve out to build the skill sets that you need.”

Finding the right detail can take time. The OITE posts some opportunities. Most are found, however, through connections that trainees make by networking and conducting informational interviews with people in their fields of interest. Once you’ve found a potential detail, you need to talk to your PI about it.

“Be direct,” advised NCI PI Stan Lipkowitz, who allowed one of his postdocs to do a detail. “Go to the PI and say, ‘I would like to do a detail in XYZ because it will be beneficial to my career development.’ [The postdoc] also should be prepared to address specifics such as how much time and for how long, and how their lab work will continue to move forward.”

“There’s an aspect of mentoring and career support and advocacy for people’s career development that is essential as a base to allow the details to take place,” said Deputy Director for Intramural Research Michael Gottesman.

Details are short—usually only a few months out of several years of productive research—compared with the overall time that a trainee spends as a postdoc, Lipkowitz pointed out. And the labs don’t lose out completely. Postdocs doing part-time details continue working in the lab, too.

Still, PIs may be reluctant to give permission. Postdocs were “hired” to do work in the lab, and participating in a detail takes time away from the research. This concern is underscored by NIH’s flat budgets, the increasing costs of conducting biomedical research, and the potential budget cuts that lie ahead.

There are resources to help trainees, however. It helps to “have an ally who can help encourage the PI on your behalf,” advised a former postdoc who struggled to convince her PI to give her permission to do a detail. These allies can be colleagues, IC training officers, and the folks at OITE.

Institute training officers can remind the PIs and lab chiefs about the importance of providing postdocs with career-exploration opportunities, said NEI training director Sarah Sohraby. OITE can also help prepare trainees to talk to their PIs and can provide advice for handling difficult negotiations. In the end, however, it’s up to the PI whether to allow the detail.

If doing a detail isn’t possible, then the trainee may be able to participate in what Gottesman calls “intellectual details.” These include activities outside the normal lab hours that do not require working in a separate office, such as being a volunteer writer for the NIH Catalyst.

“There are a lot of reasons why [doing a detail] is a good idea,” said Gottesman. “It has a lot to do with training someone to become prepared for whatever life will offer them.”

Following are edited interviews with six NIH postdocs and former postdocs who have done details. Read the full interviews online at http://irp.nih.gov/catalyst/v21i2/details-details-details.

For more information on details, contact OITE (https://www.training.nih.gov/home) or your institute’s training office.

Ben Porter, a postdoctoral fellow at NINDS, is on detail to the Office of Extramural Research in the Office of the Director, NIH. To read his article on the Klebsiella mystery, which appeared in the November-December 2012 issue of the NIH Catalyst, visit http://irp.nih.gov/catalyst/v20i6/intramural-detectives.
Meet the Detailees

ANGEL DAVEY, PH.D.
Interviewed by Sarah Naylor, NIMH
Came to NIH: In 2009 as a postdoc in NIAID
Details
• Office of Technology Development, NIAID (four hours/week, Nov 2010–April 2011)
• Office of Extramural Research, OD (12 hours/week, June 2012-August 2012)
Current position: Science Officer (grants manager), Congressionally Directed Medical Research Programs, Department of Defense (February 2013–present)

How did you first hear about details?
At a training workshop hosted by OITE.

Describe your details.
Technology Development: Reviewed and edited agreements; attended meetings and a training workshop.
Extramural Research: Development, oversight, and improvement of NIH peer-review policies, analyzed data, and more.

How did you approach your PI?
My PI was willing to provide training opportunities outside the lab. When I started working there I was honest with her about my interests, so she was not surprised when I asked about doing a detail.

What’s next for you?
I am pursuing a career in science administration where I can focus on the big picture of science research and work with groups of people.

LESLEY EARL, PH.D.
Interviewed by Meghan Mott, NIAAA
Came to NIH: In 2010 as a postdoc in NIDCR
Detail: Writer for NIH Research Matters and NIH News in Health (full time, December 2011–March 2012)
Current position: Postdoctoral fellow, Biophysics Section, Laboratory of Cell Biology, NCI; doing writing and science communications (March 2012–present)

How did you first hear about details?
At an Association for Women in Science event on campus.

How did you find your detail?
By networking. I talked to lots of people who suggested places where I could do science writing.

Was there anything surprising?
Writing came easily. Being in a place where I loved what I was doing was shocking.

How was the detail beneficial to your career?
Learning how to interview people, delve into unfamiliar topics, and write for the public prepared me for what I’m doing now.

Any advice?
If you want to get away from the bench and gain new skills, then do a detail. Approach your PI before setting one up.

Do you think you’ll return to the bench?
No. One thing I like about my current job is that I get to see the real data, as they come out, and talk to people about their science.

HELEN HUANG, PH.D.
Interviewed by Nicole Acciavatti, NHLBI
Came to NIH: In 2009 as a postdoc in NICHD
Details:
• Scientific Review Branch, NICHD (five days/week, January–June 2011)
• Office of Postdoctoral Services, Office of Intramural Training and Education (one day/week, August 2010–January 2011)
Current position: Scientific Review Specialist, Scientific Review Branch, NICHD (July 2011–present)

How did you first hear about details?
From Lori Conlan in OITE.

Why did you decide to do details?
To explore other career paths.

Describe your details.
OITE: I developed career-track seminars.
NICHD: I helped set up the initial peer-review meetings. It dawned on me that I had finally found my niche.

What would you have done differently?
I would start thinking about different career paths earlier, talk to more people, and even do more details if possible.

What was surprising?
I did not know I could do something I had no experience in and that so many people would be willing to help me.

Anything you’d like to add?
I am grateful for all those who helped me and I’d like to help others who want to try a non-bench career.

http://irp.nih.gov/catalyst 11
SARAH RHODES, PH.D.
Interviewed by Kristina McLinden, NINDS
Came to NIH: In 2007 as a postdoc in NIMH
Detail: Policy analyst, Office of Autism Research Coordination, NIMH (16–20 hours/week in 2009–2010; four days/week in 2012)
Current position: Policy analyst, Office of Autism Research Coordination, NIMH (2012–present)

How did you first hear about details? At science-policy career symposium in 2009. I spoke with one of the panelists, the NINDS director of science policy, who suggested that I do a detail.

Describe your detail. I prepared, coded, and analyzed autism research-funding data; planned meetings and workshops; prepared materials for briefings and testimonies by NIH and HHS leadership; and prepared responses to information requests.

How did you approach your PI? I was lucky my PI was very approachable and supportive, but she did set limits: The detail couldn’t be full-time because I still needed to run my experiments in the lab.

What were the best and worst parts? The best part was sinking my teeth into what policy work is about. The worst part was feeling as if I was working two jobs.

Was there anything surprising? I was surprised and impressed by the variety of work and that I was allowed to really do it!

How was the detail beneficial to your career? It gave me the opportunity to prove myself and build connections.

Would you like to go back to the bench? Doing a detail confirmed that policy was what I wanted to do. I did go back to the bench, temporarily, to finish my projects.

PHILIP RYAN, PH.D.
Interviewed by Lesley Earl, NCI
Came to NIH: In 2003 as graduate student and worked in NCI; in 2008 became a postdoc and worked in the same lab
Detail: Intern, OITE (two days/week, November 2010–August 2011)
Current position: Director of Student Services at NIH Graduate Partnerships Program, OITE (June 2012–present)

How did you first hear about details? When I was involved with the graduate student council here, I heard rumors that students spent time away from the lab working in other fields doing “details.”

Describe your detail. I helped create a series of Web tutorials for young scientists and I managed the Intra-mural AIDS Research Fellowship.

How did you find your detail? I did informational interviews with most everybody in OITE.

How did you approach your PI? I had a unique relationship with my PI. He was a mentor and a personal friend. He said, “All right, what do you want to do, and how do we get you there?”

How was the detail beneficial? I got a job doing exactly what I want to do. Through the detail I proved that I could do the job well.

Is there anything you’d like to add? I think even if you do a detail and you hate it, then at least you realize it’s a job that you don’t want to do.

TYRONE SPADY, PH.D.
Interviewed by Laura S. Carter
Came to NIH: In 2006 as postdoc in NHGRI
Detail: Office of Public Affairs, Federation of American Societies for Experimental Biology (FASEB) (12 hours/week, March–June 2009)

Describe your detail. FASEB had just launched an NIH advocacy clearinghouse and I proposed working on it as my project.
How did you first hear about details?
From the staff of the NIH Office of Science Policy.

How did you find yours?
I was e-introduced to FASEB’s Director of Public Affairs. I arranged an informational interview and asked whether he knew of opportunities that might allow me to gain policy experience.

How did you approach your PI?
I waited until I had worked out the general terms of my detail before approaching my PI. I laid the groundwork well in advance by stating my intention to gain science-policy experience.

What were the best and worst parts?
The best part was knowing that I was making progress toward transitioning into policy. The most challenging aspect was committing to leaving the bench.

What was surprising about the detail?
I hadn’t anticipated how much more formalized, hierarchical, and rigidly stratified working in an office could be.

Would you like to go back to the bench?
I’ve found policy and legislative affairs to be a better fit for me. I get to think about big-picture issues, meet lots of interesting people, and translate compelling stories from the bench to nonscientists. It’s the best of both worlds.

Anything you’d like to add?
Network! Don’t hesitate to reach out to anyone. You never know where you’ll find your first break.

To read the full interviews online, visit http://irp.nih.gov/catalyst/v21i2/details-details-details.

ADVICE TO WOULD-BE DETAILEES
BY KRISTOFOR LANGLAIS, OD

As a postdoctoral fellow at NIH in the Washington, D.C., area, you are in a unique position to arrange a high-exposure detail and experience a wide range of work behind the scenes: program, policy, writing, advocacy, budget, and more. Detailing in an office will allow you to see whether you like work away from the bench and you’ll gain invaluable perspective and experience that will likely be key in successfully taking the next step in your career.

• Look for opportunities posted by OITE, network, and do informational interviews.
• Consider doing a detail beyond NIH such as at the National Academies, Federation of American Societies for Experimental Biology, Congressional committees, and more.
• Choosing the right office for a detail is important. As you do informational interviews, you can shop around and talk to others about their experiences.
• Doing a detail in an office that is committed to mentoring you is far more important than landing in a high-profile office.
• Don’t worry if you feel you are going beyond your expertise—you are doing the detail to gain new skills and experiences.
• An understaffed and busy office can provide opportunities, but there may be pressure, too.
• If possible, the detail should give you a “real” position and allow you to do real work.
• The detail should be long enough to be beneficial to both you and the host and provide you with the necessary experience to prepare you to enter that field.
• In some cases, the detail works best if it’s full-time for up to three months; in other cases, a part-time assignment may be appropriate.
• Keep in mind that the detail office must invest time in you and you will have to learn the ropes before you have an impact and gain the experience you are looking for.
• Communicate what your expectations are; know what your supervisor expects of you.
• Writing for a variety of audiences is one of the most important skills you’ll learn.
• When asking permission to do a detail, be direct with your PI and explain how it would be beneficial for your career development. Be prepared to address other specifics such as how long the detail would be and how your lab work will continue to move forward.
• If it’s difficult to convince your PI, contact your institute’s training office and OITE for help.
• The timing is important. Asking a PI to go on a detail too soon after joining the lab is not a good idea. A trainee should also be sensitive to other things going on in the lab. For instance, avoid approaching the PI right before a Board of Scientific Counselors review.
• If it’s not possible to do a detail, you can gain writing and communications skills by volunteering to write for the NIH Catalyst and other campus publications.

Kristofor Langlais, a former postdoc in NICHD who did a three-month detail as an international health analyst at the office of Global Affairs in the Department of Health and Human Services, is now a health-science policy analyst in the Office of Biotechnology Activities, Office of the Director. His previous articles for the NIH Catalyst include one on malaria research (March-April 2011 at http://www.nih.gov/catalyst/2011/11.04.01/catalyst_v19i2.pdf) and on the dbGaP database (May-June 2012 at http://irp.nih.gov/catalyst/v20i3/news-you-can-use).
LAURA ELNITSKI, PH.D., NHGRI
Senior Investigator; Head, Genomic Functional Analysis Section
Education: Pennsylvania State University, University Park, Pa. (B.S. in molecular biology; Ph.D. in biochemistry and molecular biology)
Training: Ruth L. Kirschstein National Research Service Award recipient, Department of Computer Science, Pennsylvania State University
Before coming to NIH: Research associate, Department of Computer Science, Pennsylvania State University
Came to NIH: In 2005
Selected professional activities: Member of Encyclopedia of DNA Elements (ENCODE) Rat, Mouse, Chicken, and Bovine Genome Sequencing Consortium
Outside interests: Long-distance competitive horseback riding; personal fitness; restoring a 1967 Ford Mustang
Research interests: As a molecular and computational biologist, I integrate bioinformatic and experimental approaches to study noncoding functional elements in vertebrate genomes. Functional sequences, which encode proteins, make up less than two percent of the human genome. The remaining 98 percent is made up of non-coding functional sequences of regulatory regions (containing promoters, enhancers, silencers, and RNA-splicing elements). It is essential to identify and characterize these noncoding sequences, especially because mutations in them can cause disease.

We apply computational approaches to zero in on sequences that are functionally important, predict detrimental mutations in regulatory sequences, and interpret the role of mutations identified in genome-wide association studies of disease. In one project, my group is investigating elusive functional elements in the human genome known as exonic splicing enhancers (ESEs). When DNA mutations fall within ESE-containing sequences, unnatural exon skipping can result. For example, exon skipping is caused by genetic mutations in the breast cancer BRCA1 gene and the cystic fibrosis CFTR gene. We have built probabilistic models and implemented them in a Web server known as Skippy to allow high-throughput screening for genomic sequence mutations that disrupt ESE sequences and normal RNA splicing. This tool is one of many that facilitate the interpretation of DNA sequence variants identified in whole-exome and whole-genome sequencing projects.

My group is also identifying, characterizing, and mapping a specific type of functional region—bidirectional promoters—that directs transcription in the human genome. Bidirectional promoters are often associated with DNA repair genes and genes that are implicated in somatic cancers. They may also play a role in the evolution of the human genome.

Finally, I have been involved in NHGRI’s ENCODE project since its inception.

CAROLINE FOX, M.D., M.P.H, NHLBI
Education: University of Michigan, Ann Arbor (B.A. in English and M.P.H. in epidemiology); Perelman School of Medicine at the University of Pennsylvania, Philadelphia (M.D.)
Training: Residency in internal medicine and fellowship in endocrinology at Brigham and Women’s Hospital (Boston)
Came to NIH: In 2002
Selected professional activities: Associate editor, Circulation; associate clinical professor of medicine at Harvard Medical School (Boston); appointment in Brigham and Women’s Hospital Department of Endocrinology (Boston)
Outside interests: Enjoys outdoor activities; reading; baking; playing with her children
Research interests: My research is focused on the epidemiologic and genetic aspects of chronic kidney disease (CKD) and metabolic factors associated with heart disease, including obesity and diabetes. I use the traditional tools of epidemiology and population science as well as high-throughput biomarkers, genetics and genomics, and imaging to better understand the risk factors and outcomes related to metabolism and heart disease. I run CKDGen, a consortium that consists of more than 50 studies and is dedicated to uncovering genes for renal function. We have uncovered nearly 50 genetic loci for kidney function and related traits.

I also convene a consortium dedicated to uncovering genes for ectopic fat depots. We have shown that there are unique genetic loci for ectopic fat (fat that accumulates in the abdominal region, liver, and heart and is associated with insulin resistance and type 2 diabetes), above and beyond associations with generalized adiposity. The genetic studies are a vehicle for translational discovery and help inform my nongenetics work.

I am dedicated to training the next generation of physician-scientists and actively mentor several individuals in my laboratory.
Distinguished Investigator, University of South Alabama’s Mitchell Cancer Institute (Mobile, Ala.)

**Recently Tenured**

**SHARON A. SAVAGE, M.D., NCI-DCEG**

Senior Investigator, Division of Cancer Epidemiology and Genetics, Clinical Genetics Branch

**Education:** Worcester Polytechnic Institute, Worcester, Mass. (B.S. in biochemistry); University of Vermont College of Medicine, Burlington, Vt. (M.D.)

**Training:** Residency in pediatrics at Children’s National Medical Center (Washington, D.C.); fellowship in pediatric hematology/oncology at the NCI Pediatric Oncology Branch and Johns Hopkins University (Baltimore)

**Came to NIH:** In 2000 for training; became tenure-track investigator in 2006

**Selected professional activities:** NCI liaison to the Council on Environmental Health of the American Academy of Pediatrics; member of the Medical Advisory Board for Dyskeratosis Congenita Outreach

**Outside interests:** Enjoys family-related activities; traveling; playing tennis with her son; horseback riding with her daughter; dog agility training

**Research interests:** My current lab-based work is focused on DNA damage and repair as it relates to anticancer chemotherapy. We recently published on the molecular connection between chemotherapy-related DNA repair and the Hedgehog pathway. The Hedgehog pathway is critically important in the development of drug resistance in cancer cells. We showed that when the Hedgehog pathway is blocked in cancer cells at the molecular level, these cells become much more sensitive to anticancer chemotherapy.

In my clinical trials at the University of South Alabama, I conducted studies in ovarian cancer and advanced-stage prostate cancer. I plan to continue my focus on advanced-stage prostate cancer at the NIH in collaboration with William Dahut (NCI).

As clinical director, I will oversee a combination of studies including outpatient, inpatient, epidemiological, clinical, and laboratory-based investigations. I will help build a multi- and interdisciplinary research program geared to translating basic research into clinical trials and interventions. In addition I will lead the NIMHD effort in enhancing the recruitment and retention of minorities and other underserved populations in clinical trials.

A major goal of my research program is to advance the understanding of genetic contributions to pediatric cancer etiology. Our studies focus on osteosarcoma, the most common primary malignant bone tumor, which typically occurs during the adolescent growth spurt. We have discovered novel genetic variants that are associated with this cancer type. We plan to follow up on these findings through fine-mapping studies and other genetic analyses.

We are also trying to expand the understanding of the underlying biology of inherited cancer predisposition syndromes in order to improve clinical management. We have developed a new clinical, genetic, and epidemiologic study of Li-Fraumeni syndrome (LFS), a hereditary cancer-susceptibility syndrome associated with a wide range of cancer types that occur at younger-than-expected ages. We have helped establish partnerships—an international research consortium of LFS families and a LFS family support group—that have enabled us to design studies to define the cumulative cancer risk in individuals with LFS, as well as evaluate the psychological and social effects of LFS on the entire family.

**JYOTI MISRA SEN, M.SC., PH.D., NIA**

Senior Investigator, Immune Cells and Inflammation Section

**Education:** Maharaja Sayajirao University, Baroda, India (B.Sc. in chemistry, physics, and zoology); Indian Institute of Technology, Kanpur, India (M.Sc. in chemistry); Columbia University, New York (Ph.D. in biological sciences)

**Training:** David Abraham Fellow at Dana Farber Cancer Institute (Boston)

**Before coming to NIH:** Claudia Adams Barr Investigator with faculty appointments at Dana Farber Cancer Institute and Harvard Medical School (Boston)
Adjunct faculty at the School of Medicine Immunology Graduate Program, Johns Hopkins University (Baltimore)
Selected professional activities: Adjunct faculty at the School of Medicine Immunology Graduate Program, Johns Hopkins University (Baltimore)
Outside interests: Enjoys music and art; reading; cooking

Research interests: I am interested in studying the mechanisms that mediate the development and function of immune cells and control age-associated systemic inflammation. I am exploring the molecular basis for immune cell development and the age-related decline in the immune system. The renewal of the mammalian immune system from bone marrow–derived hematopoietic stem cells throughout life is orchestrated by events that are robust in young individuals but decline with age. As a result, older people may have poor outcomes for vaccinations and medical interventions and experience chronic systemic inflammation.

My laboratory’s recent work has focused on the transcription factor T-cell factor–1 (TCF-1) and its co-factors beta-catenin and Groucho. We have demonstrated that TCF-1 and beta-catenin have critical roles in T-cell development and selection in the thymus. In addition to confirming the well-accepted role of TCF-1 downstream of the Wnt signaling pathway, our studies demonstrate that the T-cell receptor (TCR) and pre-TCR activate TCF-1 and beta-catenin function in developing thymocytes and T cells. Interestingly, the Wnt signaling pathway also regulates thymic epithelial and thymocyte cross talk that controls age-associated shrinking of the thymus. These observations have implications for restoring thymic function in the elderly.

In addition, our studies show that TCF-1 and beta-catenin contribute to immune function by controlling T helper cell differentiation upon encounter with pathogens. TCF-1 and beta-catenin promote differentiation of T helper type 2 cells, which are involved in allergy and asthma, while inhibiting inflammatory T helper responses. These observations will aid our ability to modulate immune responses by pharmacologic manipulation of TCF-1 and beta-catenin expression and function.

We anticipate that our work to understand the mechanisms by which the immune system protects against invading pathogens without triggering autoimmune responses will lead to insights that may help improve the quality of life of the elderly.

AFONSO C. SILVA, PH.D., NINDS
Senior Investigator; Head, Cerebral Microcirculation Section
Education: Universidade Federal de Pernambuco, Recife, Brazil (B.S. and M.S. in electrical engineering); Carnegie Mellon University, Pittsburgh (Ph.D. in biomedical engineering)
Training: Postdoctoral training at the University of Minnesota’s Center for Magnetic Resonance Research (Minneapolis)

Came to NIH: In 1999 as a staff scientist; in 2004, became a tenure-track investigator and head of the Cerebral Microcirculation Unit

Selected professional activities: Member of the editorial boards for Journal of Cerebral Blood Flow and Metabolism, Neuroimage, and NMR in Biomedicine; member of the International Society for Cerebral Blood Flow and Metabolism, the International Society for Magnetic Resonance in Medicine, and the Society for Neuroscience

Outside interests: Swimming; fitness; running; raising tropical fish

Research interests: We are trying to understand the mechanisms of neurovascular coupling, which is the tight relationship between neuronal activity and the regulation of cerebral blood flow (CBF) in the brain. These mechanisms are crucial to maintaining the homeostasis of the delicate cellular environment of the brain. Their disruption causes brain dysfunction and disease. We are exploring what drives the changes in CBF in response to neural activity; the primary signaling and molecular pathways that translate a change in brain activity into a vascular response; how the cerebral microvasculature organizes to optimally support focal changes in neural activity; and how alterations in neurovascular coupling lead to brain dysfunction.

To understand how CBF is regulated during normal brain activity and in pathological brain states (for example, hypertension and stroke), my laboratory is using rodents and small nonhuman primates as models of localized functional brain activation in combination with neuroimaging techniques such as functional magnetic resonance imaging and two-photon optical microscopy. More information about our research can be found in our laboratory’s Web page at http://www.lfmi.ninds.nih.gov/cmu-main.html.
Maryland’s U.S. Senators Visit NIH
Senators Ben Cardin and Barbara Mikulski Talk About Sequestration

BY JOSEPH P. TIANO, NIDDK

The Senator and NIH Director Francis Collins then fielded about a dozen questions from the audience, including:

What is the most effective way that federal employees can protest the budget cuts?
The Senator suggested that NIHers “put a face on the issue. [You’re] real people, [you] have real lives.” He said to personalize our jobs and NIH achievements and point out that we are on the front lines of public service. He stressed that “the reason why the federal workforce is attacked is because it’s an attack on government. It’s not an attack on what [you] do.”

How will sequestration affect NIH?
The Senator said that if sequestration happens and Congress does not correct it within “a matter of weeks and it goes on for months, then administrative heads must produce the [required] savings.” For NIH that could mean cutting back on grant funding and furloughs without pay. (To see the videocast, visit http://videocast.nih.gov/launch.asp?17795.)

At the February 20 press conference held at NIH, Senator Mikulski talked about the impact that sequestration and its automatic spending cuts would have on NIH. “We talk a lot about threats to the United States,” she warned. But sequestration is “a self-inflicted wound.”

U.S. Senator Ben Cardin toured NIH and appeared at an NIH Town Hall Meeting on February 8, to express his support for NIH and its mission, to talk about the state of the federal budget and his hope that sequestration—which took effect on March 1—could be avoided, and to field questions from the audience.

Sequestration requires mandatory across-the-board budget cuts to all government agencies that would equal $1.2 trillion over 10 years. NIH is required to cut its spending by at least five percent in the remaining seven months of FY2013, or about $1.6 billion.

In his opening remarks, Senator Cardin praised and thanked NIH and its employees for the “world-class” research that has led to treatments for disease. He presented a general but optimistic description of what NIH employees can expect from Congress in the coming months. He said sequestration could cost our economy thousands of jobs and that “these across-the-board cuts were never intended to take effect.”

New SIGs:
Pathology Informatics

Pathology informatics is an emerging field of cutting-edge pathology that incorporates various types of pathology data: digital images, laboratory information and molecular data. Investigators from disparate fields (computer science, engineering, mathematics and pathology) can contribute significantly. The group aims to create a collegial environment, drawing from professional expertise within NIH as well as from the Greater Washington D.C.-Baltimore corridor to explore digital pathology, image analysis and information technology aspects of pathology informatics. Meetings are planned for once a month, with invited speakers and SIG member presentations. Networking opportunities and LISTSERV-based communication (BELTWAY-PATHOLOGY-INFORMATICS@LIST.NIH.GOV) will serve as a primary mechanism for collaborative discussions and brainstorming. Contact Jason Hipp (jason. hipp@nih.gov) or Avi Rosenberg (avi.rosenberg@nih.gov) for more information.

Optogenetics

Optogenetics is the integration of optics and genetics to control events within cells, such as driving or inhibiting the firing of neurons with pulses of light. Optogenetics has revolutionized neuroscience research and led to breakthroughs in understanding of anxiety, depression, Parkinson disease, and other neurological disorders. In 2010, optogenetics was chosen as the Method of the Year across all fields of science and engineering by the interdisciplinary research journal Nature Methods. The new Optogenetics SIG will meet monthly to discuss new technical advances and applications as well as help other scientists at the NIH start using this powerful method. Contact Alexxai Kravitz at (alexxai.kravitz@nih.gov) for more information.

The complete list of Scientific Interest Groups (SIGs), a.k.a. NIH Inter-institute Interest Groups, is at http://www.nih.gov/sigs.
CLINICAL RESEARCH DAY 2013
Wednesday, April 10; begins at 8:30 a.m.
Lipsett Amphitheater (Building 10)
Registration deadline: March 31
This event will highlight the Clinical Center’s expanded engagement with extramural investigators as well as opportunities for clinical and translational research. Included: remarks by NIH Director Francis Collins; scientific presentations from NIH clinician-scientists; overviews on the Clinical Center and research opportunities; and informal meetings with NIH clinical and translational researchers. Registration is free; for more information, visit http://irp.nih.gov/clinicalresearchday.htm.

FARE IS BACK FOR FY2014!
Application deadline: March 20, 2013
NIH intramural trainees may submit applications for the annual Fellows Award for Research Excellence competition. Winners will receive a $1,000 travel award to attend a scientific meeting, present their work at the 2013 NIH Research Festival, and serve as judges for the next FARE competition. (NHLBI fellows do not receive the travel grant.) For information, visit https://www.training.nih.gov/felcom/fare.

MOLECULAR MECHANISMS REGULATING MAMMALIAN AGING
Thursday, March 28, 2013
12:00–1:00 p.m.
Lipsett Amphitheater (Building 10)
Toren Finkel (chief, NHLBI’s Center for Molecular Medicine), will discuss his work at this Geno-science Interest Group seminar, which will be videocast at http://videocast.nih.gov and archived. For information, go to http://calendar.nih.gov/app/MCalInfoView.aspx.

ANNUAL NIH WSA SCHOLARS SEMINAR
Friday, March 29, 2013; 12–1:00 p.m.
Wilson Hall (Building 1)
Two Women Scientists Advisors (WSA) Scholar Award winners will give presentations: Emmie de Wit (NIAID) on the Nipah Virus; Zhifei Wang (NIMH) on stroke treatment in animal models.

COURSES ON STEM-CELL RESEARCH
Check Web site for dates
FAES and the NIH Center for Regenerative Medicine (CRM) will be hosting three Bio-Trac courses that will provide hands-on training for critical applications for stem-cell research. TRAC CRM47: “iPSC II: Human Induced Pluripotent Stem Cells (hiPSC); Differentiation to Neural Lineages.” TRAC CRM48: “Using TALENs for Genome Engineering.” TRAC CRM 49: “Making iPSC from Blood.” Registration is limited. To register, go to http://www.biotrac.com. For more information, contact Mark Nadone (nardonem@faes.od.nih.gov).

BEDSIDE-TO-BENCH APPLICATIONS
Letters of intent due April 3
The Bedside-to-Bench (B2B) Award funds research teams seeking to translate basic scientific findings into therapeutic interventions or to increase understanding of important disease processes. Up to $135,000 per year in direct costs for two years is available to support clinical-research intramural-extramural partnerships. Both intramural and extramural NIH investigators may initiate applications for B2B research projects. For more information, go to http://www.cc.nih.gov/ccc/btb/awards.shtml or e-mail BedsidetoBench@mail.nih.gov.

CANCER IMMUNOTHERAPY CLINICAL TRIALS: CONCEPTS AND CHALLENGES
April 4–5, 2013; 8:00 a.m.–5:00 p.m.
Masur Auditorium (Building 10)
Hotel reservations deadline: March 27
Registration (required) deadline: March 28
This Society for Immunotherapy of Cancer workshop will outline challenges in developing therapeutic trials in immunotherapy: preclinical testing requirements; clinical-trial design; patient selection; end-point determination; developing combination therapies to improve long-term disease management and survival; and accelerating the development, validation, and approval of anticancer agents. Free to government employees. To register, visit http://www.sitcancer.org/sitc-meetings/cict13.

NIHLM BI MITOCHONDRIAL BIOLOGY SYMPOSIUM 2013
May 6–7, 2013
9:00 a.m.–5:00 p.m. (to 12:00 p.m. on May 7)
Natcher Conference Center (Building 45)
Abstract deadline: March 29, 2013
The 2013 "NHLBI Mitochondrial Biology Symposium: Mitochondrial Genetics in Health and Disease" is the third in a series of biennial conferences and will feature leading mitochondrial genetics researchers. To submit an abstract, register, or get more information, visit http://www.nhlbimitochondrialbiology.com.

FAES STEM-CELL INDUSTRY SYMPOSIUM
May 29, 2013; 8:00 a.m.–6:00 p.m.
Building 31 (6th floor, C wing)
Come to the Stem-Cell Industry Symposium—organized by FAES and the NIH Center for Regenerative Medicine—to learn about advances in the field. Last year’s event featured 17 companies and led to major discounts. To register, go to http://citfm.cit.nih.gov/bio/registration.html. For questions, contact Joshua Hunsberger (hunsbergerj@mail.nih.gov).

STEM-CELL RESEARCH SYMPOSIUM
May 30–31, 2013; 8:00 a.m.–6:00 p.m.
Lister Hill (Building 38A)
NIH’s Center for Regenerative Medicine is building the infrastructure to enable the advance of regenerative medicine. This event will showcase the Center’s pilot award program projects as well as other stem-cell projects with translational potential; provide investigators with the opportunity to provide critical updates on their work; foster the sharing of resources including new protocols and cell lines developed by NIH CRM–funded investigators; encourage the development of collaborations; and address the roadblocks to clinical translation. To register, go to http://citfm.cit.nih.gov/ncrm-scig/symposium.html. For other questions, contact Joshua Hunsberger (hunsbergerj@mail.nih.gov).

ONLINE: Read more (http://irp.nih.gov/catalyst/v21i2/announcements).
Kuan-Teh Jeang, an accomplished virologist and chief of the Molecular Virology Section of the NIAID Laboratory of Molecular Microbiology, died suddenly on January 27, at age 54. He had worked at NIH since 1985. Jeang’s research focused on the gene regulation of the human immunodeficiency virus (HIV) and how human T-cell lymphotropic virus type 1 (HTLV-1) causes leukemia. He was a prolific scientist who authored or co-authored more than 300 publications. He cofounded and served as editor-in-chief of the online journal *Retrovirology*. In this position, he helped establish an award to recognize midcareer scientists and advocated passionately for open access to scientific information.

“Teh was a talented researcher who believed strongly in the equal and global distribution of scientific knowledge,” said NIAID Director Anthony S. Fauci. “He made many important contributions to our understanding of HIV and HTLV-1, leaving a lasting legacy here at NIH and beyond. We will miss him deeply.”

From 2010 to 2011, Jeang served as president of the Society of Chinese Bioscientists in America, where he sought greater representation in leadership positions for Asian-American scientists. His recent awards include the International Retrovirology Association’s Dale McFarlin Award in 2011, Biomed Central’s Open Access “Editor of the Year” award in 2010, and research support from the Bill & Melinda Gates Foundation in 2011, 2012, and 2013.

Jeang leaves behind his wife and three children, as well as an NIH community profoundly saddened by his passing. (Read more online at http://irp.nih.gov/catalyst/v21i2/obituaries.)