THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

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A Lasker Award for CC Workers

NEWS FROM THE NIH CLINICAL CENTER

In September the Clinical Center was named the 2011 recipient of the Lasker–Bloomberg Public Service Award from the Albert and Mary Lasker Foundation, an organization that has recognized outstanding advances in medical research each year since 1945.

The award description recognizes the CC for spearheading major advances in a wide array of medical arenas, establishing an example for academic institutions across the country, and training thousands of investigators, many of whom now lead academic and research institutions across the world.

The award also acknowledges the CC's and the NIH's rich history of medical discovery through clinical research since the hospital opened in 1953. Since then, nearly half a million volunteers have participated in clinical research at the CC,and its mission has remained consistent—providing exceptional clinical care for research volunteers, an environment for innovative bench-to-bedside clinical research, and training for clinical researchers.

The Clinical Center's 58-year research portfolio has medical milestones including the development of chemotherapy for cancer; the first use of an immunotoxin to treat a malignancy (hairy cell leukemia); identification of the genes that cause kidney cancer, leading to the development of six new, targeted treatments for advanced kidney cancer; the demonstration that lithium helps depression; the first gene therapy;

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Systems Biology as Defined by NIH

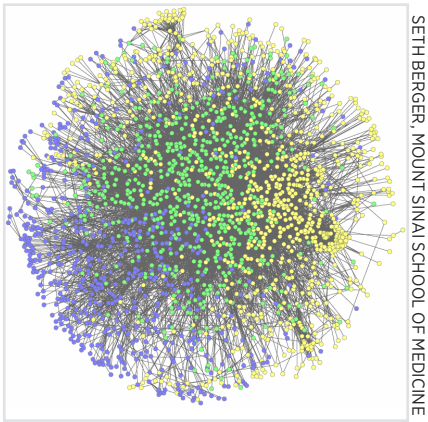
An Intellectual Resource for Integrative Biology

BY CHRISTOPHER WANJEK

Ask five different astrophysicists to define a black hole, the saying goes, and you'll get five different answers. But ask five biomedical researchers to define systems biology, and you'll get 10 different answers . . . or maybe more.

Systems biology is an approach in biomedical research to understanding the larger picture—be it at the level of the organism, tissue, or cell—by putting its pieces together. It's in stark contrast to decades of reductionist biology, which involves taking the pieces apart.

Yet with its complicated flow charts that can (in the words of T.S. Eliot) "follow like a tedious argument of insidious intent," systems biology has scared away more than a few researchers. Still others fail to fully appreciate its usefulness because it lacks a concise, unified definition.



SETH BERGER, MOUNT SINAI SCHOOL OF MEDICINE

It used to be as simple as "the knee bone connected to the thigh bone." Now scientists use systems biology approaches to understand the big picture of how all the pieces interact in an organism. The above illustration depicts an interactome, the whole set of molecular interactions in cells. The interactome is considered an essential systems biology resource.

"There [are] an endless number of definitions," said Ron Germain, chief of NIAID's new Laboratory of Systems Biology, NIH's first organized foray into systems biology, which has been nearly a decade in the making. "It's even worse than the elephant," that infamous elephant that stymies the attempts of blind men to describe it because each feels just one part.

"Some people think of it as bioinformatics, taking an enormous amount of information and processing it," Germain said. "The other school of thought thinks of it as computational biology, computing on how the systems work. You need both of these parts."

The new NIAID lab reflects an intellectual journey that Germain and some of his NIH colleagues embarked upon as the Human Genome Project was nearing completion.

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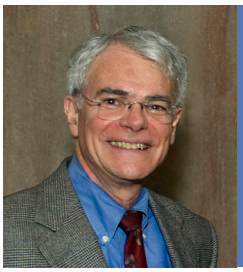


Valuing Diversity at NIH

BY MICHAEL GOTTESMAN, DDIR

NIH MAY SEEM LIKE A HIGHLY DIVERSE scientific community. After all, our intramural program is made up of male and female scientists who represent almost all races from around the world. But among our principal investigators and senior leaders, many groups are significantly under-represented. This problem is particularly apparent among African-American, Native American, and Hispanic investigators and in the relative under-representation of Asian–Pacific Islander scientists in senior leadership positions (see table below). The recent publication in *Science* of data showing that African–American scientists fare less well than other populations in the NIH extramural peer review process reinforces the urgency of developing strategies for improving diversity of the intramural scientific staff as well. (*Science* **19:**1015–1019 and 940–941, 2011)

We must, then, consider two critical questions for the intramural program: 1) Why are minorities so under-represented among our principal investigators and senior leaders? and 2) What can the intramural research program do to improve research and leadership opportunities for U.S. minority scientists?

The reasons for our lack of diversity are complex and rooted in history. At many levels, few people in the past recognized that a diverse scientific community has an enormous intrinsic value for a scientific program that prizes individual initiative, creative thinking, and team science. Limited diversity was the rule here, so NIH earned a reputation for being inhospitable to minority scientists. Many were reluctant to apply for positions. Furthermore—and this is an area of such sensitivity that we frequently shy away from discussing it publicly—we need to do much more to create an atmosphere of inclusiveness so minority scientists feel more welcome at NIH.

NIH Intramural Research Program Demographics

	Tenure Track	Senior Investigator	Lab/Branch Chief
Total	253	896	238
Females	33%	19%	16%
Males	67%	81%	84%
African–American	1.2%	1.1%	0.8%
Hispanic	3.2%	3.0%	2.9%
Native American	0%	0.1%	0%
Asian–Pacific Islander	26%	13%	5.9%
White	62%	83%	90%

Note: Only U.S. citizens and permanent residents are classified by race/ethnicity; therefore the percentages do not necessarily add up to 100%.

NIH has spent years developing diversity programs aimed at women and minorities, but those efforts have been largely unsuccessful in achieving fair representation for these groups. It's no wonder that NIH is still perceived as a place that is not uniformly accepting of diversity.

To address this issue with the urgency it demands, I established a Diversity Strike Force, co-chaired by Roland Owens, an assistant director in the OIR, and me. We have been conducting an analysis to understand why NIH has failed to recruit, retain, and promote women and minority investigators. Also, we have:

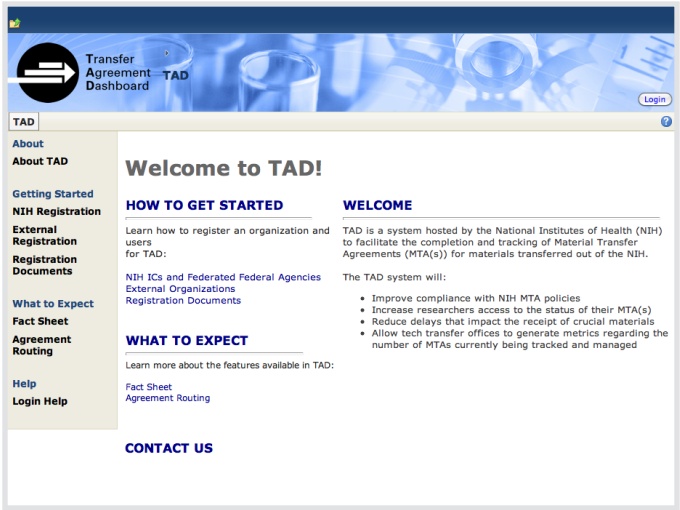
- added a module on diversity and inclusion of under-represented groups in biomedical research to a leadership course for new tenure-track investigators;
- modified criteria for tenure to better reflect the value we place on making sure that qualified persons from all groups are encouraged to apply for our training and PI positions;
- developed new recruiting materials to attract a diverse group of qualified applicants to our training and PI positions;
- increased advertisement of our intramural tenure-track investigator recruitments at diversity-focused science Web sites such as http://www.minoritypostdoc.org;
- developed a new training module for search committee chairs and modified the memo to PI search committees to encourage thinking broadly about who can contribute to the NIH mission (http://www.nih.gov/about/mission.htm).

The NIH Director has established a Diversity Task Force, which will make additional recommendations, but it is up to everyone at NIH to make sure we have the most hospitable, inclusive environment for all of our scientific staff and that we encourage our non-NIH colleagues to consider careers here. Expect more commentaries and articles on this important topic in future issues of *The NIH Catalyst*. ●

New Web-Based Material Transfer Agreements System

BY MICHAEL GOTTESMAN, DDIR

GOT MATERIALS? Before you share them, document them. NIH Material Transfer Agreements (MTAs) are agreements that govern the transfer of tangible research materials between two organizations when the recipient intends to use the material for his or her own research purposes.



The home page of the Transfer Agreement Dashboard for the new Web-based Material Transfer Agreement System: https://techtransferagreements.nih.gov.

Some examples of materials include unique reagents, cell lines, plasmids, chemical compounds, and vectors. MTAs also may be used for other types of research materials and resources, such as animal models and even some types of software.

Accurate data on NIH research materials transferred to other researchers has been very difficult to obtain across the NIH. But we need to be able to account—simply, quickly, and accurately—for all scientists' materials being shared. We need to ensure that there is appropriate documentation for all transferred material, too.

So, after many years of planning and with input from our scientists for a simple e-system, we recently deployed a centralized Web-based MTA system, called the Transfer Agreement Dashboard (TAD).

Material transfers between investigators are essential to the continued advancement of scientific research, and I believe the new NIH system will facilitate transfers, not hinder them. For starters, building on input from many NIH research and tech-transfer staff, the new system will be intuitive, less time-consuming, and nearly paperless. More important, the standardized workflow helps ensure compliance with requirements.

Initially, the TAD system will handle transfers of outbound NIH materials. Eventually the system will process inbound transfers of research materials to NIH researchers, allowing us to more easily access vital materials generated by the external research community and vice versa. Also, the TAD system will provide key metrics to help us better highlight NIH research and resources to Congress and the public.

The new enterprise-wide TAD system debuted in mid-October. Someone from your institute or center (IC) will be in touch to instruct you on its use. The TAD development team, along with CIT and other NIH ICs, offered demos of the new system at an exhibitor booth at the NIH Research Festival in October.

For more information, visit https://techtransferagreements.nih.gov or e-mail NIHTADSupport@mail.nih.gov. ●

Benefits of the Web-Based MTA

More than 6,000 intramural researchers at NIH laboratories along with 325,000 scientists and research personnel at more than 3,000 institutions nationwide drive the research and discovery process. Material transfers between investigators, laboratories, and organizations are essential to the continued advancement of scientific research.

Material Transfer Agreements (MTAs) govern the transfer of tangible research materials between organizations when the recipient intends to use the material for his or her own research purposes. The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives.

The new Web-based MTA system:

Is less time consuming

- Expect shorter turn-around time related to materials requests.
- Spend less time dealing with MTAs and more time on research.
- Electronic signatures enables fast, paperless execution of MTAs.

Is intuitive and easy

- Standardized workflow makes compliance with requirements easy.
- Key steps are less likely to be omitted.
- Online forms have built-in validation and provide instant notification of possible compliance or accuracy issues.

Provides better access to MTA data

- Have 24/7 access to the status of in-process MTAs.
- Track the number and types of outbound MTAs at an enterprise level across ICs.

Lets researchers leverage lessons learned

- Quickly search for MTAs that have been successfully implemented.
- View comments and history of the full transaction process.

FROM THE FELLOWS COMMITTEE

SOS: Service With a Scientific Twist

BY SARAH RHODES, NIMH

Felcom's role is to serve the fellows' community here at NIH; each subcommittee is tasked with enriching different aspects of our NIH training. However, during one Felcom meeting in fall 2010, members decided it was time for Felcom to reach out and help others. So the Service and Outreach Subcommittee (SOS) was formed.

SOS aims to find new and inventive ways to give back to the NIH and greater Washington, D.C., communities. In addition, SOS presents an opportunity for team building as we work collectively toward a common goal.

Our first SOS-organized event this past spring was a food drive for the NIH Safra Family Lodge, which offers a home away from home for families and loved ones of adult patients who are receiving care at the Clinical Center. NIH does not provide meals for these families so they must eat in the cafeterias, dine at local restaurants, or cook for themselves at the lodge. Because families arrive at the lodge at all hours, they are often unable to immediately stock up on food. We thought we could stock the pantry for them.

From late March through early April we collected nonperishable food items ranging from canned goods to dried pasta and donated them to the lodge. You probably saw and perhaps dropped off donations at one of our collection boxes around the NIH campus. The inaugural food drive was a huge success, and Felcom received a letter of thanks from Safra Lodge Operations Manager Margo Bradford. Of course, we hope to outdo ourselves when we run the event again next year.

Over the next few months we are planning several activities including tree planting in Washington, D.C., and food packing at the Capital Area Food Bank. If these activities are successful, we hope more fellows will participate in outreach activities. SOS may be starting small, but we are thinking big. We are always seeking new ways for fellows to be involved in outreach opportunities such as judging at science fairs or helping with high school science clubs.

If you have suggestions for SOS activities or would like to join the committee, contact either of the co-chairs, Shu Hui Chen (chensh2@mail.nih.gov) or Julien Senac (senacjs@mail.nih.gov). For more information on Felcom or SOS, go to the new home of the Felcom Web site: https://www.training.nih.gov/felcom. ●

SPECIAL: FROM THE NICHD TRAINING OFFICE

Two Students Chosen for NICHD's Scholars Program

BY ROBERT BOCK, NICHD

Two students have been selected from the NIH Academy to participate in the NICHD Scholars Program. The academy is a research program for recent college graduates interested in health disparities among populations in the United States.

Carla Lopez and Chinedu Anyaeji are the first participants in the NICHD Scholars Program. Lopez was a pre-med major and is a graduate of Wellesley College (Wellesley, Mass.). Anyaeji majored in engineering and is a graduate of the University of Texas at Austin.

"The NICHD Scholars Program provides extensive career counseling and guidance . . . as well as help in preparing for graduate and professional school interviews," said Brenda Hanning, head of NICHD's Office of Education.

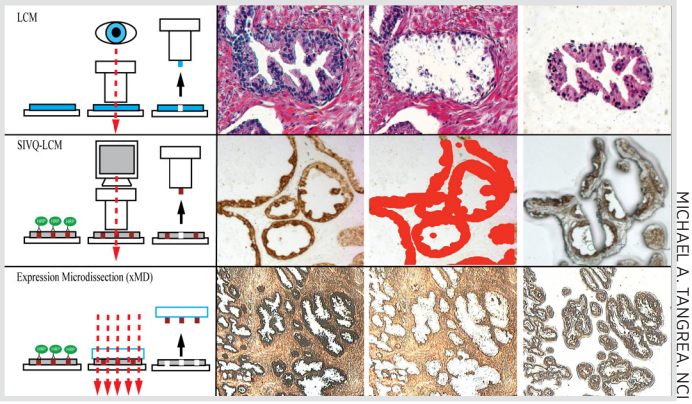
Anyaeji will work in the laboratory of Peter Basser, director of the NICHD Program on Pediatric Imaging and Tissue Sciences. Anyaeji will take part in the effort to develop new polymer phantoms—substances with properties of living tissues, used to calibrate diffusion-tension magnetic-resonance imaging equipment. Specifically, he will formulate and test various physical and nuclear-magnetic-imaging-resonance properties of candidate polymers. He will also help test a new device for gastrointestinal imaging that the group is developing.

Lopez will work with Chris McBain, head of the Program in Developmental Neuroscience and chief of NICHD'S Section on Cellular and Synaptic Physiology. She will be involved in a project to chart the migration, development, and location of interneurons, which are brain cells in the central nervous system. She will help track the migration of embryonic interneurons from their original location toward the rear of the fetal brain to their ultimate locations in the cortex and hippocampus.

NIH trains physicians and scientists at the postdoctoral and clinical levels, graduate and medical students, post-baccalaureate fellows, and summer students. For more information, visit http://irp.nih.gov/research-training. ●

Laser Capture Micro-Dissection Gets Automated

BY CHRISTOPHER WANJEK



MICHAEL A. TANGREA, NCI

NIH researchers use three different types of laser-capture microdissection (LCM) technologies to dissect tissue such as the human prostate gland shown here. From top, the traditional LCM and the more automated systems—spatially invariant vector quantization (SIVQ)–LCM and expression microdissection (xMD).

You'd think it would be hard to top laser-capture microdissection, or LCM. This technique, developed at the NIH in the 1990s, uses lasers and other specialized instruments to carve out sections of tissue as small as a few cells from across a complex specimen and then lift them away almost magically, undamaged, for further analysis.

For the operator, it's like playing a video game, zapping and lifting with trigger buttons, guided by microscopic visualization.

LCM instruments are in pathology labs across the globe and have generated close to 3,000 scientific publications and hundreds of millions of dollars in sales, licensed through Arcturus Engineering/Life Technologies and other companies. The inventors include NCI's Michael Emmert-Buck, NICHD physicist Robert Bonner, CIT engineer Tom Pohida, and Lance Liotta, former deputy director for intramural research.

But manual laser slicing is so old school. Now, NIHers are further automating the process, developing parallel technologies that employ immunohistochemistry and image-analysis software to make the microdissection process nearly operator-independent.

Their goal, said Emmert-Buck, is to bring laser dissection to the clinic to help precipitate the era of personalized medicine. The new techniques are ideal for studies requiring large amounts of material, such as proteomics and genomic assays. For example, to understand how a drug will interact with a specific patient's tumor, one often needs thousands of precisely dissected cells. Automated methods can dissect cells much faster than the manual-based traditional LCM.

"They are trying to replace me," laments Jaime Rodriguez-Canales, a molecular pathologist in the NCI Laboratory of Pathology's LCM Core, which has assisted with dissections for countless NIH labs over the past decade.

Although sounding like a modern-day John Henry—the American folk hero who proved he could hammer rocks faster than a steam-powered hammer—Rodriguez-Canales is being facetious. Yes, it is true that his steam-hammer-wielding colleague, biomedical engineer Jeffrey Hanson, was slicing out dozens of cancer cells. But expert molecular pathologists will be needed more than ever to prep specimens for dissection and then discern the meaning of the data that comes out.

One new dissection method is expression microdissection (xMD), which uses a targeting probe for cell procurement in place of the operator-based, cell-by-cell LCM selection process. This technology recently was adapted for commercially available LCMs, enabling investigators outside of the NIH to use it. The xMD method might allow subcellular dissections, a notable advance for the field.

The other new method is spatially invariant vector quantization (SIVQ)-LCM, an image-based dissection technology developed by the NIHers and University of Michigan School of Medicine (Ann Arbor, Mich.). SIVQ uses mathematical modeling and image processing to locate phenotypically similar cells across entire tissue sections.

The complementary LCM, xMD, and SIVQ-LCM technologies can be applied widely in research and clinical settings. For example, a pathologist analyzing a patient biopsy to provide a standard histopathological diagnosis can select a molecular target panel to be studied using the optimal technique—SIVQ–LCM, xMD, or standard LCM—for harvesting cells.

The pathologist then can provide information to clinicians on clinical diagnosis and status of biological markers, useful for determining patient prognosis and selecting the most efficacious treatment. The NIH Clinical Center is evaluating such a workflow.

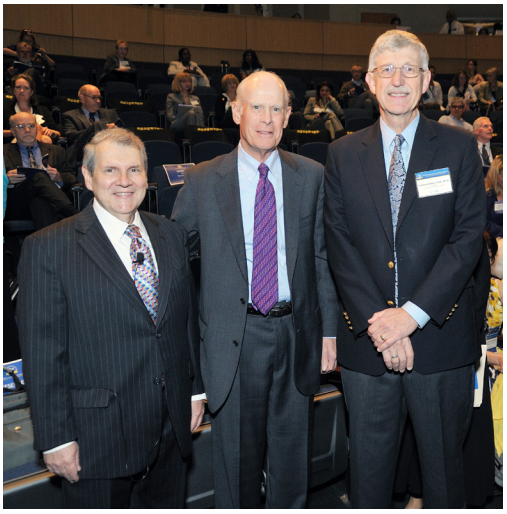
The NIH intramural program is an ideal incubator for these technologies because of the confluence of clinicians, engineers, pathologists, and molecular biologists, said Emmert-Buck. Although both xMD and SIVQ–LCM are still in the early commercialization stage, he welcomes NIH collaborators to beta-test the new methods.

As for the good-natured joking about John Henry, Emmert-Buck reassured Rodriguez-Canales: "A good pathologist with a good tool is just going to be better," he said. "The history of science shows that new technologies lead to new discoveries that benefit everyone." ●

NIAMS Celebrates Turning 25

BY RACHEL WELLER

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) marked its 25th anniversary with a scientific symposium to commemorate a quarter-century of research, training, and information dissemination in disease areas that affect nearly every home in America. NIH Director Francis Collins, NIAMS Director Stephen Katz, Research!America Chairman John Edward Porter, and panels of patients, scientists, and clinicians reminisced about NIAMS to a packed Lipsett Amphitheater in June.



ERNIE BRANSON

NIAMS Director Stephen Katz (left), Research!America Chair John Porter (center), and NIH Director Francis Collins helped NIAMS celebrate its 25th anniversary.

In his opening remarks, Katz reminded everyone that the seeds of the institute were planted 60 years ago as an arthritis program in the National Institute of Arthritis and Metabolic Diseases. Reorganizations led to the Division of Arthritis, Musculoskeletal, and Skin Diseases within the Institute of Arthritis, Diabetes, and Digestive, and Kidney Diseases, until, Katz joked, "We broke them off from us in 1986. They are still thriving today as the NIDDK."

Collins praised NIAMS for making strides in developing treatments and understanding the pathophysiology and genetics of so many chronic and crippling diseases.

"We now know the molecular bases of about 4,000 diseases," he noted. "We knew only a few dozen back when NIAMS was getting started. But of those 4,000 [diseases], we currently have effective treatments only for about 200." He added, "We have the chance to focus even more intentionally now on taking the deluge of basic science discoveries pouring out of laboratories across all of the diseases that are in NIAMS' portfolio and making sure that we apply those as quickly as possible in the translational arena."

Both Porter, who served two decades in the U.S. House of Representative representing Illinois, and Collins emphasized that researchers today need to share the compelling stories coming out of their labs.

During the panel sessions, NIH intramural program scientists credited the NIH culture—which promotes collegiality, intellectual rigor, and the flexibility to pursue one's interests—with stimulating the discoveries flowing today from intramural laboratories.

NIAMS Scientific Director John O'Shea called NIH a place where "people come from around the world and give their heart and soul to tough problems." He recalled cloning the gene for the tyrosine kinase Jak3 in the mid-1990s: "It was actually really hard to clone a gene then," he said. "I literally read every base pair, base pair by base pair. . . . Now, of course, it takes just a few seconds."

But that slow-going work paid off. In recent years, O'Shea's team has collaborated with Pfizer to develop a Jak3 inhibitor, one of a new class of immunosuppressants that effectively blocks transplant rejection.

Daniel Kastner, formerly of NIAMS and now the scientific director of NHGRI, likewise recalled "the wonderful opportunities" that NIH afforded a young scientist. "I started in this area of research back in late '85, when I saw a young man of Armenian ancestry with a lifelong history of episodes of arthritis that would last a week at a time, roughly once a month," he said. "It was familial Mediterranean fever, at that time known simply to be a genetic disorder caused by a single recessive gene. But nobody knew what that gene was, or what it did, or even what chromosome it was on. But this was back at that wonderful time, the dawn of the Human Genome Project, when with positional cloning—that method in which if you could recruit a group of families, if you knew it was a single-gene disease—you could discover the gene, even if you didn't know anything about it. Seeing the dramatic inflammatory phenotype that this man had, I thought: That's for me! . . . The adventure was on."

An evening dinner program, "Bringing Medicine and Science to the Public," brought a twist with Katz interviewing National Public Radio's own consummate interviewer Diane Rehm. They discussed her views on the public's perception of medical research and her journey with the voice disorder spasmodic dysphonia.

Katz concluded the daylong event by thanking the Foundation for the NIH and the other organizations that made the symposium possible. "We believe in leveraging our resources with the other ICs, as well as with outside organizations and agencies," he said. "In many ways, this is a celebration of their contributions also. We are really all celebrating because we've been in this together." ●

NINR also celebrated its 25th anniversary this year. The NIH Catalyst will report on NINR research advances in an upcoming issue.

Medical Research Scholars Program

BY ALAN SMITHEE

"Medical discoveries of tomorrow depend on the students we train today," said NIH Director Francis Collins. In September 2012, a new NIH Medical Research Scholars Program "will help ensure that there is a steady pipeline of scientists conducting the full range of biomedical research."

The new program, which offers a comprehensive yearlong research experience for medical, osteopathic, dental, and veterinary students, will begin on NIH's Bethesda campus in September 2012. Scholars will engage in mentored research experiences with NIH intramural investigators in basic science laboratories and in clinical and translational research conducted at the Clinical Center.

The Medical Research Scholars Program builds on a long partnership established with Howard Hughes Medical Institute in 1985 that provided laboratory research training to top students in medical, dental, and recently veterinary schools. The new program blends the bench-focused HHMI–NIH program and the more clinically focused NIH Clinical Research Training Programa (CRTP). CRTP participants engage in clinical and translational research.

Basic, clinical, and translational research will be part of the new Medical Research Scholars Program. The program is made possible through a partnership with the Foundation for the National Institutes of Health; it is supported by a grant from Pfizer Inc and contributions from HHMI.

"Pfizer has a long tradition of supporting medical education and is proud to support the NIH Clinical Center, one of the most important teaching and research hospitals in the world," said Freda Lewis-Hall, Pfizer's executive vice president and chief medical officer. "Those who benefit from the Medical Research Scholars Program will gain special insight into many conditions [for which] further research and greater medical understanding are urgently needed."

Program applications will be accepted from October 1, 2011, through January 17, 2012. At least 40 students are expected to be admitted during the program's first year. The goal is to accept up to 70 students as the program grows.

Support for students selected for the program includes a stipend and resources for educational enrichment, such as travel to scientific meetings. There will be a curriculum in clinical protocol development and the conduct of human subjects research; seminars focusing on basic and laboratory studies and their translation into clinical protocols; and a component on the development of leadership skills.

"HHMI is pleased to have an ongoing role in this important NIH initiative," said HHMI president Robert Tjian. "Our support will enable NIH to continue a long-running seminar series that brings these clinician-scientists into contact with leading researchers from around the nation. These opportunities—coupled with the experience of working in an NIH lab—can inspire a lifelong commitment to research."

This is now one program, one application, and one review process offering medical, osteopathic, dental, and veterinary students a broader spectrum of opportunities all housed within the CC's Office of Clinical Research Training and Medical Education, which is directed by Fred Ognibene. ●

For more information and to apply, visit http://clinicalcenter.nih.gov/training/mrsp.

Medical Residents Visit NIH

BY ELLEN CROWN, CC

A dozen second-year residents—in pediatrics, internal medicine, and neurology—from regional academic medical centers—visited the NIH Clinical Center recently at NIH's first Resident Research Career Day, held on October 17.

"It's an opportunity to come to the NIH campus to see both the physical plant and to experience the Clinical Center, a 240-bed hospital totally dedicated to clinical research," said Fred Ognibene, director of the CC's Office of Clinical Research Training and Medical Education, which organized the event.

"When we go out to academic medical centers [and] they find out that [the Clinical Center] is actually a hospital and that it is a state-of-the-art institution, the eyes get wider and the questions start," said Robert Lembo, executive director of the CC's Graduate Medical Education. "Then we're able to tell them more about the research [and] training opportunities, which often come as big news to them." ●

ELLEN CROWN, CC

Janice Hobbs, chief resident in pediatrics at Saint Christopher's Hospital for Children in Philadelphia, discusses a poster with an NIH fellow during Resident Research Career Day, October 17, at the Clinical Center.

Research Briefs

NIAID: PRIMING WITH DNA VACCINE MAKES AVIAN FLU VACCINE WORK BETTER

The immune response to an H5N1 avian influenza vaccine was greatly enhanced in healthy adults if they were first primed with a DNA vaccine expressing a gene for a key H5N1 protein, according to a NIAID study that described results from two clinical studies. Most study volunteers who received the DNA vaccine 24 weeks before receiving a booster vaccine made from whole, inactivated H5N1 virus produced high concentrations of antibodies thought to be protective against the globular head region of the protein hemagglutinin (HA).

Traditional seasonal influenza vaccines are designed to elicit antibodies to the head region of HA, but it changes each year and so vaccines must be repeated annually to maintain immunity. In some volunteers, the prime-boost vaccine regimen also spurred production of broadly neutralizing antibodies aimed at the HA stem, a region that is relatively constant across many strains of influenza viruses. (NIAID authors: J.E. Ledgerwood, C. Wei, Z. Hu, I.J. Gordon, M.E. Enama, C.S. Hendel, P.M. McTamney, H.M. Yassine, J.C. Boyington, R. Bailer, T.M. Tumpey, R.A. Koup, J.R. Mascola, G.J. Nabel, B.S. Graham, VRC 306 Study Team; *Lancet Infect Dis* DOI: 10.1016/S1473-3099(11)70240-7)

NHGRI, CC, NINDS: UNDIAGNOSED DISEASES PROGRAM IS CLINIC OF LAST RESORT

After its first two years of work, NIH's Undiagnosed Diseases Program (UDP) is citing successes in patients whose cases have stumped specialists at leading medical institutions around the country. UDP diagnosed siblings whose calcium-riddled blood vessels made it excruciatingly painful to walk, a woman with life-threatening protein deposits in her muscles, and a 20-year-old whose diagnosis makes him the oldest survivor of his previously undiagnosed muscle and lung disorder. The report focuses on 160 patients of the total 326 cases accepted into the program. More than half of the accepted patients had undiagnosed neurological problems. Other prominent disorder categories include gastrointestinal disease; fibromyalgia and chronic fatigue syndrome; immune-mediated and rheumatic illnesses; psychiatric conditions; pain; dermatologic disorders; and cardiovascular disease. (NIH authors: W.A. Gahl, T.C. Markello, C. Toro, K. Fuentes Fajardo, M. Sincan, F. Gill, H. Carlson-Donohoe, A. Gropman, T.M. Pierson, G. Golas, L. Wolfe, C. Groden, R. Godfrey, M. Nehrebecky, C. Wahl, D.M.D. Landis, S. Yang, A. Madeo, J.C. Mullikin, C.F. Boerkoel, C.J. Tifft, D. Adams; *Genet Med* DOI: 10.1097/GIM.0b013e318232a005)

NIEHS: CAN EXERCISE PREVENT BRAIN DAMAGE CAUSED BY ALZHEIMER DISEASE?

Exercise allows the brain to rapidly produce chemicals that prevent damaging inflammation and could help develop a therapeutic approach for early intervention in preventing damage to the brain, according to NIEHS researchers. Their study showed that mice that exercised regularly prior to exposure to a chemical that destroys the hippocampus—the part of the brain that controls learning and memory—produced interleukin-6, which seemed to protect the hippocampus from inflammation and damage. This research may provide clues as to how exercise could be used to affect the path of human neurodevelopmental disorders and neurodegenerative diseases. (NIEHS authors: J.A. Funk, A.D. Kraft, C.A. McPherson, J.B. Collins, J. Harry; *Brain Behav Immun* **25**:1063–1077, 2011)

NIAAA: DOCTORS MISS MANY ALCOHOL-SCREENING OPPORTUNITIES

In the United States, excessive alcohol use is the third leading preventable cause of death and also a significant cause of disability, yet physicians often fail to counsel their young adult patients about excessive alcohol use. In a recent study, NIAAA and colleagues at Boston University School of Public Health and Boston Medical Center conducted a random survey of more than 4,000 people between the ages of 18 and 39 and asked them about their drinking habits and whether they had been seen by a doctor during the past year.

Of respondents whose drinking exceeded NIAAA guidelines, only 49 percent recalled being asked about their drinking, and only 14 percent were counseled about it. Young adults between ages 18 and 25 were the most likely to report drinking in excess of NIAAA guidelines, and only 34 percent of them were asked about drinking by their doctors compared with 54 percent of adults ages 26 to 39. (NIAAA author: R.W. Hingson; *J Gen Intern Med* DOI: 10.1007/s11606-011-1851-1)

NICHD: ANTI-HIV DRUG BLOCKS HERPES VIRUS

The anti-HIV drug tenofovir may be an anti-herpes drug, too, according to researchers at NICHD and other institutions. The drug stops the spread of the genital herpes virus by disabling a key DNA enzyme of the herpes virus. The findings explain the results of a recent clinical trial (http://www.ncbi.nlm.nih.gov/pubmed/20643915) showing that tenofovir, when it is formulated as a vaginal gel, could reduce the risk of herpes simplex virus (HSV) infections—as well as HIV infections—in women. Tenofovir taken orally inhibits reproduction of HIV, but had not been known to block the genital herpes virus. The researchers examined cells infected with HSV and found that high concentrations of tenofovir prevent the ability of this virus to reproduce. The vaginal gel has higher concentrations of tenofovir than the oral form does. (NICHD authors: A. Lisco, C. Vanpouille, A. Introini, L. Margolis; *Cell Host Microbe* **10**:379–389, 2011) ●

Mapping Translocations

New Technique Identifies First Events in Tumor Development

NIAMS AND NCI RESEARCH NEWS

A novel technique that enables scientists to measure and document tumor-inducing changes in DNA is providing new insights into the earliest events involved in the formation of leukemias, lymphomas, and sarcomas and could potentially lead to the discovery of ways to stop those events.

A team of researchers at NIAMS, NCI, and Rockefeller University (New York) developed a high-throughput technique—called translocation capture sequencing (TC-Seq)—to document chromosomal rearrangements, or translocations, in primary cells. They reported their findings recently in the journal *Cell* (*Cell* DOI 10.1016/j.cell.2011.07.048).

Translocations occur when a broken strand of DNA from one chromosome is erroneously joined with that of another. Such irregularities can be beneficial—they may enable the immune system to respond to a vast number of microorganisms and viruses—but they can result in tumors. Translocations can take place during the course of normal cell division when each chromosome is copied verbatim to provide genetic information for the daughter cells.

"The cell expresses specific enzymes whose primary purpose is to repair such lesions effectively, but when the enzymes mistakenly join pieces of two different chromosomes, the cell's genetic information is changed," said Rafael Casellas, senior investigator in the NIAMS's Genomics and Immunity Section.

Casellas likens the phenomenon to breaking two sentences and then rejoining them incorrectly. For example, "The boy completed his homework" and "The dog went to the vet" might become "The dog completed his homework" and "The boy went to the vet." When a cell gets nonsensical information such as this, it can become deregulated and even malignant.

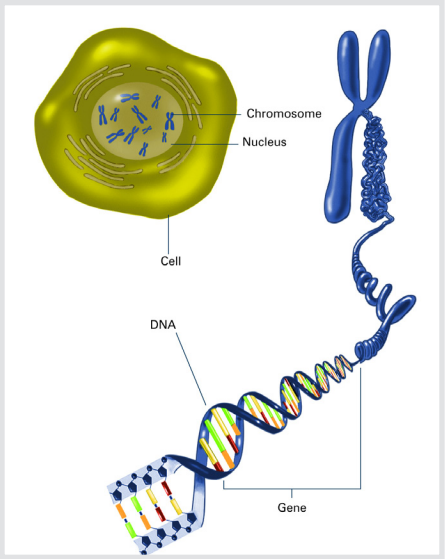
Scientists have known since the 1960s that recurrent translocations play a critical role in cancer. What was unclear was how these genetic abnormalities are created, since very few of them were studied, and only within the context of tumors, said Casellas. To better understand the nature of these tumor-inducing rearrangements, the authors created a system to visualize their appearance in normal, nontransformed cells.

Using the TC-Seq system they created, the scientists investigated how oncogenic rearrangements occur. First, they introduced enzymes that recognize and cause damage at a particular sequence in the DNA into cells from mice, thereby constructing a genome in which a unique site is broken continuously.

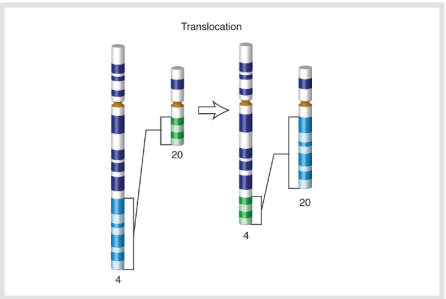
Next, they used polymerase chain reaction—a technique to quickly amplify short sequences of DNA—to check all of the sites in the genome that would get translocated to this particular break. The researchers examined more than 180,000 chromosomal rearrangements from 400 million B cells.

Based on this large data set, the scientists made several important observations about the translocation process. They learned that most of the translocations involve gene domains rather than the space on the DNA between the genes.

They also found that most translocations target active genes, with a clear bias for the beginning of the gene, as opposed to its middle or end. The team also showed that a particular enzyme that normally creates DNA breaks in B cells dramatically increases the incidence of translocations during the immune response.



NIGMS



NHGRI

The long, stringy DNA that makes up genes is spooled within chromosomes inside the nucleus of a cell. (Note that a gene would actually be a much longer stretch of DNA than what is shown here.)

Translocations occur when a broken strand of DNA from one chromosome is erroneously joined with that of another chromosome. Translocations can result in tumors.

This feature explains the long-standing observation that more than 95 percent of human lymphomas and leukemias are of B-cell origin.

This molecular understanding of translocation hot spots "is allowing us to understand how tumors are initiated," said Casellas. "It is the kind of information that in the near future, might help us prevent the development of cancer." ●


Ron Germain

LEFT If the NIAID Systems Biology Laboratory were a symphony orchestra, lab chief Ron Germain would be its conductor-musician. As conductor, Germain provides the necessary structure for tempo and harmony. As musician, he provides the immunology base, essentially the study of macrophages. He has recruited "orchestra" members for the lab who have the skills to work on their own but are also able to work together in the name of systems biology.

At that time, circa 2001, biology was rich in genomic data; proteomics had come of age; and immunologists had identified many cellular and even molecular components of the immune system. Yet predicting immune system behavior remained as elusive as ever.

Whether a systems biology lab could tease out answers was far from clear. But despite the risk, NIAID Director Anthony Fauci and Scientific Director Kathy Zoon committed a steady stream of resources. Together with Germain, they hoped for, and threw their energy into, a new approach to understanding the immune system that would better embrace experimental and computational techniques to explore connections in all their intricate glory.

The new lab, formed in early 2011 from the Program in Systems Immunology and Infectious Disease Modeling (PSIIM), comprises Martin Meier-Schellersheim, head of the Computational Biology Unit; Iain Fraser, head of the Signaling Systems Unit; Aleksandra Nita-Lazar, head of the Cellular Networks Proteomics Unit; John Tsang, head of the Systems Genomics and Bioinformatics Unit; and Germain, chief of NIAID's Lymphocyte Biology Section, providing the immunology base to this operation.

Independently, the unit heads interact with labs at NIH and beyond to establish and incorporate systems biology methods. In true team spirit, they work together to attack the most basic elements of immunology such as a response to an infection or vaccination.

Ironically, to best understand this new lab, we should take a reductionist approach to defining its parts. The system, it seems, is more than the sum of its parts.

Start with Computational Modeling

Sophisticated computational models and simulations represent integral parts of systems biology. In immunology, they are needed to understand the complex biochemical networks that regulate the interactions among the immune system's cells and between these cells and infectious organisms.

Enter Martin Meier-Schellersheim, a physicist by training. He was the first to join NIAID's venture in 2001, even before the launch of PSIIM. He has been most successful in empowering non–computational biologists to do computational biology. Indeed, he has helped foster the very team concept that underlies the new lab; his software brings advanced computational capacity to a broad range of biologists.

This willing involvement of biologists is paramount because models need solid experimental data as input and as a reference to ensure reality checks. Otherwise the biological models are likely to be oversimplified either for lack of data or because their development suffers from poor communication between experimentalists and theorists.

Meier-Schellersheim's primary software tool, called Simmune, facilitates the construction and simulation of realistic multiscale biological processes. He is also involved in the ongoing development of a systems biology markup language, SBML3, that can encode advanced models of cellular signaling pathways.

Add Some Cell Biology

Iain Fraser, a biochemist and molecular biologist interested in the mechanisms of cell signaling, arrived at NIH in 2008. As the lead high-throughput member of the lab, he has several powerful tools on hand to generate key data sets. These data sets ultimately feed into Meier-Schellersheim's software to produce quantitative models.

Fraser's tools include in-house genome-wide RNAi screens to characterize signaling network relationships in hematopoietic cells. Such screens are beginning to identify key components in innate immune pathogen-sensing networks. He interacts closely with the NIH-wide RNAi screening group at the NIH Chemical Genomics Center and also with the RNAi Global consortium.

Fraser said immune-system signaling networks can be unraveled by using proper systematic approaches to interpret complex data sets. He offers the example of Toll-like receptors (TLRs), which trigger an intricate cellular response that activates multiple intracellular signaling pathways.

Excessive activation can lead to chronic inflammatory disorders; insufficient activation can render the host susceptible to infection. Unbiased screening approaches can help identify the components that allow the immune system to maintain a homeostatic balance in the face of microbial challenges.

One of Fraser's early successes, using a systems biology approach, was demonstrating how a single protein kinase can mediate the anti-inflammatory effects of cyclic adenosine monophosphate in its crosstalk with TLR4.

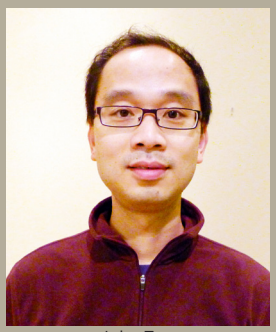
Fraser sums up his time at NIH as establishing "the screening infrastructure for dissecting the response of the macrophage to a broad range of pathogenic stimuli."

RIGHT The "orchestra" members for NIAID's new Systems Biology Laboratory include Martin Meier-Schellersheim, head of the Computational Biology Unit; Iain Fraser, head of the Signaling Systems Unit; Aleksandra Nita-Lazar, head of the Cellular Networks Proteomics Unit; and John Tsang, head of the Systems Genomics and Bioinformatics Unit.


Martin Meier-Schellersheim


Iain Fraser


Aleksandra Nita-Lazar


John Tsang

One Generous Serving of Proteomics

Aleksandra Nita-Lazar is developing new methods to obtain quantitative data that improve our understanding of cell biology and also funnel key information into model building. Her domain is the system-wide analysis of the proteome, which has fallen behind DNA analysis partly for want of the necessary tools.

The difference stems from the accommodating nature of DNA. DNA is easily recognized, replicable, and relatively stable, whereas the folded structure of proteins can't be amplified. Yet protein studies are essential in developing useful models for many reasons, Nita-Lazar said. Such studies can reveal the molecular constituents of a cell; provide information about the biochemical state of the proteins; and determine catalytic rates and the association and disassociation rates for molecular pairs.

Nita-Lazar uses mass spectrometry to investigate protein phosphorylation, the process of binding with a phosphate group, one of the most common modes of protein-function regulation. She can use the same protocols that Fraser helped develop, and the same cell types, to determine which proteins are phosphorylated in response to a particular stimulus, when they are phosphorylated, and how those data fit into what is known about the transcriptional response.

Nita-Lazar's group, with Fraser's group, has been harvesting from these screens the key components required for the signal to flow through a pathway and also for the induction of the inflammatory cytokine messenger RNAs that arise. "This kind of approach used to be dismissed as a fishing expedition," said Nita-Lazar. The goal is not to catch that one big tuna, however nice that would be, but rather to see the whole school of fish, the entire ecosystem.

Mix Well with Genomics

The enormous amount of data being collected requires processing and analysis—computational tools plus genetics and genomics "to build things from the top down," Germain said.

Enter John Tsang, the most recent member of Germain's lab and the element that transformed the PSIIM into a full-fledged systems biology lab.

On the genomics side, Tsang collects and analyzes data on gene expression, miRNAs, epigenetic modifications, and commensal microbes, and he conducts experiments to connect signaling to gene expression. On the bioinformatics side, he develops and applies statistical tools for large and diverse data sets, such as data from microarrays and high-throughput screenings, with an eye toward network models that involve genes, proteins, miRNAs, and epigenetic states.

Tsang also heads bioinformatics at the trans-NIH Center for Human Immunology (CHI), using similar integrative genomics approaches to study the human immune system, such as immune reactions to the flu vaccine in patients.

A core theme for building network models is capitalizing on systematic perturbations and -omics technologies to measure genome-wide responses. From the TLR stimulations that Fraser studies to vaccinations and natural genetic variations in humans, "all are valuable perturbations to help us figure out the wiring and function of the underlying system," said Tsang.

Oh, Right, Immunology Too

"So, what am I doing in all of this aside from raising money and pontificating?" Germain joked.

If the NIAID Systems Biology Laboratory could be considered a symphony orchestra, Germain would be its conductor-musician. As conductor, he provides the necessary structure for tempo and harmony. As the musician, he provides the immunology base, essentially the study of macrophages.

Germain has seen systems biology labs in which collaborations are more opportunistic than routine, the shortsighted result of building a building, adding smart people, and hoping it all works out. His strategy instead has been to recruit individuals with the necessary skill sets to work on their own but also to work together in the name of systems biology.

"We all have slightly different interests, but there is enough overlap between those interests for us to develop those core projects and for us to be invested in them," said Fraser.

All Together Now

To understand the response to infection or vaccination at an integrated level, the lab is studying the intersection of innate and adaptive receptor-dependent pathways and their control of gene networks. The researchers have bottom-up projects to understand and model the signaling within specific cell types at a fine-grained level.

CONTINUED ON PAGE 12

Systems Biology

CONTINUED FROM PAGE 11

And they have a top-down approach that uses inferences from perturbation analyses to probe the large-scale structure of the interactions not only at the cellular level, but also at the tissue and even the organism level.

To accomplish this grand goal, Germain said, the lab works in digestible chunks, focusing on pathogen sensing in key innate cells, such as macrophages, and the intersection of signaling by antigen receptors, cytokines, and TLRs in determining whether B cells become memory cells or long-lived plasma cells.

This process is critical for vaccine development. At the top-down level, the lab uses host genetics and microbiota variation to explore how the immune system's set point is determined for responses to infections and vaccines.

This early into the chase, the lab has not yet published results on these pursuits, although a paper is pending on the lab's work with CHI and the flu.

Towards a Trans-NIH Approach

Germain hopes the Laboratory of Systems Biology will serve "as an intellectual resource for people who are thinking in the systems mode and have their hands on these technologies [and want] to see how they could be applied to their work."

He named the lab the Laboratory of Systems Biology with no mention of immunology or host-pathogen interaction to designate its raison d'être. Inspired by NIAID's efforts, NCI and NHLBI are actively recruiting researchers to establish systems biology programs. NHLBI has just named Keji Zhao, senior investigator, as director of its new Systems Biology Center.

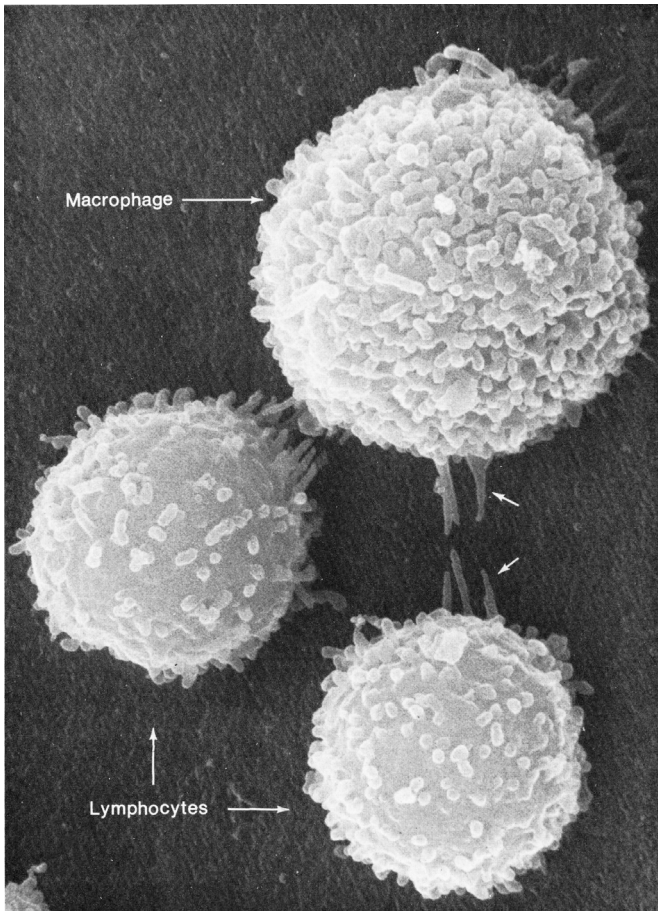
Meanwhile, the trans-NIH effort for a Center for Systems Biology is not dead. A search for a very senior systems biologist to develop and lead the center came up dry, and now the budgetary stresses have put the search on hold. But most NIH researchers understand that purely reductionist approaches to biology are no longer enough to solve complex biological problems and that integrated approaches are needed. David Levens (NCI), Dan Camerini (NIDDK), and Alan Michelson (NHLBI), along with Germain, continue to lead efforts for this trans-NIH initiative.

NIAID's Laboratory of Systems Biology is "a smaller model of what the larger enterprise could be," Germain said. The new lab "is very good for the NIH. We are getting applicants from top universities who want to come to the lab as fellows."

And the NIH intramural research program is well suited for systems biology, with a long-term perspective and a retrospective review process that doesn't require grant writing.

Germain helped change the NIH tenure process, too, to be sure that team science, and not necessarily a steady stream of published papers, is recognized and rewarded.

"Nothing happens if you don't put work into it," he added. ●



DON W. FAWCETT, EMMA SHELTON

Macrophages and lymphocytes, the two types of immune cells pictured above, interact with their surroundings in complicated ways. NIH researchers are using systems biology approaches to understand the totality of such interactions.

Reporter's note:

Ron Germain does have his own definition of systems biology that he's sticking to: a scientific approach that combines the principles of engineering, mathematics, physics, and computer science with extensive experimental data to develop a quantitative as well as a deep conceptual understanding of biological phenomena, permitting prediction and accurate simulation of complex (emergent) biological behaviors.

For more information about the Laboratory of Systems Biology, visit http://www.niaid.nih.gov/labsandresources/labs/aboutlabs/lsb/Pages/default.aspx.

Lasker Award

CONTINUED FROM PAGE 1

the first treatment of AIDS (with AZT); and the development of tests to detect AIDS and human immunodeficiency virus and hepatitis viruses in blood, which led to a safer blood supply.

"The Clinical Center's work has always depended on patients and healthy individuals from around the world who volunteer for clinical research here," said CC Director John Gallin. "Our patients include those with rare diseases, common disorders, and undiagnosed conditions. There are about 1,500 clinical research studies under way today, and the patients and healthy volunteers who participate in them are true partners in research."

Advancements through clinical research also depend on having a cadre of investigators trained to do it, Gallin added. "Students in the health sciences and clinicians come here to learn how to conduct clinical research by working closely with NIH investigators. Since 1995, more than 22,000 students around the world have participated in the Clinical Center's clinical research training curriculum offered through distance-learning programs."

The original hospital, the Warren Grant Magnuson Clinical Center, opened in 1953. A new research hospital, the 240-bed Mark O. Hatfield Clinical Research Center, opened in 2004. Most of NIH's 27 institutes and centers conduct clinical research at the Clinical Center through their programs on the NIH campus in Bethesda, Md. NIH plans to open the facility for use by external researchers, based on the 2010 recommendations from the Scientific Management Review Board, established under the NIH Reform Act of 2006, which will allow the Clinical Center to facilitate clinical research on a broader scale. ●

To learn about the 30 other NIH Lasker winners, visit http://irp.nih.gov/about-us/honors/lasker-award. To see their photos, stroll through the hallway connecting the old and new sections of Building 10.

NIH Welcomes Google Scholars

Three Teens Are Wowed by NIH Science

BY LAURA STEPHENSON CARTER

After a whirlwind tour of Washington, D.C., and a private meeting with President Barack Obama, three Google Internet Science Fair winners were welcomed and wowed by scientists at NIH in Bethesda.

The winners were among 10,000 students from 91 countries who participated in Google's first science fair, held in partnership with *Scientific American*, CERN, LEGO, and *National Geographic*. Fifteen finalists, aged 13 to 18, were invited to Google headquarters in Mountain View, Calif., and had their projects judged by a panel of experts. And three teenage girls were selected as grand prize winners and awarded scholarships, LEGO-based trophies, and a trip to our nation's capitol—and to NIH.

ERNIE BRANSON

Left to right: Google Scholars (a.k.a. Science Fair winners) Lauren Hodge (winner of the 13- to 14-years-old category), Shree Bose (winner of 17- to 18-years-old category), and Naomi Shah (winner of the 15- to 16-years-old category) were impressed with the scientists and labs at NIH and long for the day when they will be full-fledged scientists, too.

The winning students were Lauren Hodge (14), from York, Pa., who determined which marinades produce fewer carcinogens in grilled food; Naomi Shah (16), from Portland, Ore., who analyzed the effect of indoor air quality on asthma symptoms; and Shree Bose (17), from Fort Worth, Texas, who discovered a way to improve ovarian cancer treatments for people who have built up a resistance to cisplatin.

At NIH, the students met with several scientists and talked eagerly about their plans to earn advanced degrees and to one day become scientists themselves. The students impressed the NIH scientists and vice versa. NIH Deputy Director for Intramural Research Michael Gottesman encouraged the teens to consider a career at NIH, too. "We try to identify talent as early as we can and recruit them back here."

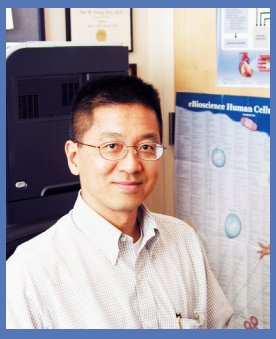
The teens were whisked off to visit the labs of intramural scientists Sriram Subramaniam, a senior investigator in NCI's Laboratory of Cell Biology, and Pamela Robey, Chief of NIDCR's Craniofacial and Skeletal Diseases Branch.

"The campus was spectacular, the labs were first class, and the people just seemed so genuinely enthusiastic to meet with us," said Bose who, as grand prize winner, will get an all-expense-paid trip to the Galapagos Islands. "I definitely walked away from the entire experience even more certain of the fact that I want to go into medical research and biology and someday have the opportunity to return to NIH." ●

Recently Tenured


ALEXEI BAGROV, NIA


RAFAEL CASELLAS, NIAMS


PAUL HWANG, NHLBI


LAURA KOEHLY, NHGRI


RUSSELL LONSER, NINDS

ALEXEI BAGROV, M.D., PH.D., NIA

Senior Investigator and Head, Hypertension Unit, Cardiac Function Section, Laboratory of Cardiovascular Science

Education: Saint Petersburg State I.P. Pavlov Medical University, Saint Petersburg, Russia (M.D.); I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, St. Petersburg (Ph.D. in pharmacology)

Training: Residency in cardiology (St. Petersburg)

Before coming to NIH: Senior scientist at Sechenov Institute of Evolutionary Physiology and Biochemistry

Came to NIH: From 1992 to 1994 as a visiting associate in NIA; in October 2001 as investigator and head of NIA's Hypertension Unit in the Laboratory of Cardiovascular Science

Outside interests: Reading fiction and history books; traveling

Research interests: Hypertension affects about 25 percent of adults and is a major risk factor for cardiovascular disease. High dietary intake of sodium chloride is an important contributor to the genesis of hypertension; cardiotonic steroids (CTS) link high salt intake and high blood pressure. CTS are also important in the pathogenesis of and targets for intervention in chronic kidney disease and preeclampsia (high blood pressure in pregnancy), a major cause of maternal and fetal mortality and morbidity. We are studying how CTS interact with the sodium-potassium pump (sodium-potassium adenosine triphosphatase, or Na/K-ATPase) and lead to the development of hypertension.

Our goals are to define cause-and-effect relationships between CTS and hypertensive phenotypes; investigate how CTS contribute synergistically with other vasoconstrictors to cardiovascular remodeling; study signaling pathways that underlie the effects of CTS; and elaborate novel approaches that counteract the deleterious effects of CTS. We are focusing on translational research and exploring how the immunoneutralization of CTS and disruption of CTS-Na/K-ATPase interactions could be used for pharmacological interventions in renal failure and preeclampsia.

If you have been tenured in the last year or so, *The NIH Catalyst* will be in touch soon to include you on these pages.

RAFAEL CASELLAS, PH.D., NIAMS

Senior Investigator; Acting Chief of Genomics and Immunity Section, Molecular Immunology and Inflammation Branch; Adjunct Investigator at NCI-CCR

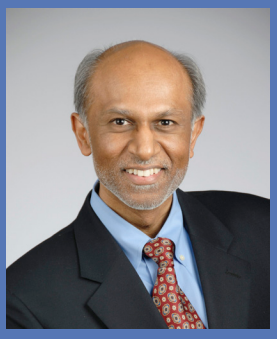
Education: Brigham Young University, Provo, Utah (B.S. in chemistry); Rockefeller University, New York (Ph.D. in molecular immunology)

Training: Postdoctoral training with Nobel Laureate David Baltimore at California Institute of Technology (Pasadena, Calif.)

Came to NIH: In January 2004

Outside interests: Playing classical guitar; reading French, English, and Spanish literature

Research interests: Our laboratory studies the molecular mechanisms by which the immune system can modify genes and generate a vast diversity of antibody binding sites. Unfortunately, because the enzymes that can accomplish these functions may modify non-immune-system-related genes, they can lead to the generation of tumors. We are trying to understand the mechanisms that minimize this side effect. By combining molecular biology and gene-targeting techniques with genomic and bioinformatic tools, we are uncovering diverse details of B-cell ontogeny such



AVINDRA NATH, NINDS

THEODORE PIERSON, NIAID

THIS COULD BE YOU IF YOU WERE TENURED WITHIN THE PAST YEAR AND YOU ANSWER THE CALL FROM *THE NIH CATALYST* WHEN YOU'RE INVITED TO HAVE YOUR STORY INCLUDED IN AN UPCOMING ISSUE. IT'S A GREAT WAY FOR COLLEAGUES TO LEARN ABOUT YOUR WORK.

as a new pathway that shuts down transcription in response to DNA damage and the microRNA landscape that regulates bone marrow and peripheral development.

We are also interested in the processes that assemble, diversify, and provide effector functions to antibody receptors. The mistargeting of non-immunoglobulin genes (including oncogenes) results in widespread genomic instability, the formation of chromosomal translocations, and tumor development. Our goal is to understand how these activities are regulated to ensure a healthy immune response while avoiding malignant transformation.

PAUL HWANG, M.D., PH.D., NHLBI

Principal Investigator, Laboratory of Cardiovascular and Cancer Genetics

Education: University of Kansas, Lawrence, Kan. (B.A. in biochemistry and chemistry); The Johns Hopkins University School of Medicine, Baltimore (M.D.; Ph.D. in neuroscience)

Training: Residency in internal medicine at the University of California at San Francisco School of Medicine (San Francisco); clinical fellowship in cardiology at Johns Hopkins Hospital (Baltimore); Howard Hughes postdoctoral fellowship for physicians at The Johns Hopkins University School of Medicine

Came to NIH: In July 2001

Outside interests: Spending time with family and friends; would love to do more traveling and outdoor activities

Research interests: There is a strong inverse relationship between cardiorespiratory fitness and cancer incidence in large population studies. We are investigating a specific metabolic determinant of exercise capacity that could influence the formation of cancers.

We previously showed that tumor suppressor protein p53 (which is encoded by the gene *TP53*, one of the most commonly mutated genes in human cancers) can regulate aerobic metabolism and determine exercise capacity. This role also appears to protect against DNA damage and has implications for cancer prevention.

We are expanding on these basic observations using genetic knockouts in human somatic cell lines and mouse models. We are also investigating whether observations made in our model systems are applicable to humans through translational clinical studies. We hope what we learn about aerobic metabolism will help us develop new preventive and therapeutic strategies against cancer and cardiovascular diseases.

LAURA KOEHLY, PH.D., NHGRI

Principal Investigator, Social and Behavioral Research Branch; Head, Social Network Methods Section

Education: University of California, Davis (B.S. in psychology); University of Illinois, Urbana-Champaign (A.M. and Ph.D. in quantitative psychology; M.S. in statistics)

Training: Postdoctoral training in the Department of Behavioral Sciences, Division of Cancer Prevention, at the University of Texas MD Anderson Cancer Center (Houston)

Before coming to NIH: Assistant professor of psychology at Texas A&M University (College Station, Texas)

Came to NIH: In June 2005

Selected professional activities: Member of the board of directors of the International Network of Social Network Analysis

Outside interests: Duckpin bowling; gardening; cooking and baking

Research interests: Families coping with cancer do better when there is an interconnected system of communication, emotional support, and behavioral encouragement. My recent work investigates how families at genetic risk of cancer, such as inherited forms of colorectal, breast, and ovarian cancer, communicate about and cope with their increased risk of cancer. I have shown that risk communication can lead to cooperative, family-centered approaches for reducing distress and improving health-promoting behaviors. Results from this research are being translated into interventions that motivate families to discuss their genetic risk of disease and mobilize related social-support resources to enhance health-promoting behaviors.

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Recently Tenured

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One such effort, Project RAMA (Risk Assessment in Mexican Americans), provides members of multigenerational Mexican-American households with family history based on feedback about common health conditions such as diabetes. We have found that compared with an individual-level approach, a family-based approach in providing risk information motivates more risk communication and behavioral encouragement among family members, which in turn leads to improved health behaviors. In a new project, we will evaluate whether a family genomics health educator is just as effective as a family-based approach in educating family members about their disease risk and motivating them to engage in health-promoting behaviors.

In the future, I will investigate whether patterns of communication, support, and encouragement are common across diseases and vary across families from different ethnic and racial backgrounds.

RUSSELL LONSER, M.D., NINDS

Senior Investigator, Neurosurgical Biology and Therapeutics Section; Chief of the Surgical Neurology Branch

Education: Andrews University, Berrien Springs, Mich. (B.A. in economics); Loma Linda University Medical School, Loma Linda, Calif. (M.D.)

Training: Residency in neurological surgery at the University of Utah (Salt Lake City)

Came to NIH: In August 2001

Selected professional activities: Program Director, NINDS Neurological Surgery Residency Training Program

Research interests: My laboratory studies drug delivery for the treatment of neurologic disorders and investigates tumor biology and treatment. We have several clinical trials under way. In one, we are doing a prospective natural history study of patients with von Hippel–Lindau disease, a rare genetic multisystem disorder characterized by the abnormal growth of tumors in the central nervous system and elsewhere.

We are determining what factors (pregnancy, puberty, menopause, blood proteins, etc.) affect tumor growth. Surgical removal of brain and spinal cord tumors is currently the treatment of choice when these lesions cause neurological problems. A better understanding of which tumors are likely to grow and which will remain stable may guide physicians in treatment decisions and avoid unnecessary procedures.

In another trial, we are evaluating patients with a variety of neurological disorders that may require surgery. The study is designed to help us learn more about changes that cause nervous system disorders; train physicians in the evaluation and treatment of these disorders; and establish a pool of patients who may be eligible for other NINDS protocols.

AVINDRA NATH, M.D., NINDS

Clinical Director; Director of the Translational Neuroscience Center; Chief of the Section of Infections of the Nervous System

Education: Christian Medical College in Ludhiana, India (M.D.)

Training: Residency in neurology and fellowship in multiple sclerosis and neurovirology at the University of Texas Health Science Center (Houston); fellowship in neuro-AIDS at NINDS

Before coming to NIH: Faculty positions at the University of Manitoba (Winnipeg, Manitoba, Canada) and the University of Kentucky (Lexington, Ky.); Professor of Neurology and Director of the Division of Neuroimmunology and Neurological Infections at The Johns Hopkins University (Baltimore)

Came to NIH: In February 2011

Selected professional activities: Vice president, International Society of NeuroVirology; chair, Section of Neuro-Infectious Diseases of the American Academy of Neurology

Outside interests: Playing golf; gardening; bicycle riding

Research interests: We are trying to understand the pathophysiology of and develop new diagnostic and therapeutic approaches for retroviral infections of the nervous system. In particular, we study how human immunodeficiency virus (HIV) can establish a reservoir in the brain and mechanisms by which viral proteins can cause immune activation and neurodegeneration. A similar approach is being used to study endogenous retroviruses and their role in the pathophysiology of neurological diseases.

Our laboratory made a key observation that complete viral replication is not necessary, but rather some of the nonstructural proteins can be released extracellularly and cause widespread neuronal injury. Using cutting-edge technology in proteomics, stem cell biology, and genomics, we have developed experimental models to identify common mechanisms of neuronal injury in these diseases.

We work with well-defined clinical cohorts and use clinical samples from patients to confirm in vitro findings, develop surrogate markers for diagnosis and prognosis, and generate hypotheses that may be tested using experimental systems. To facilitate this bench-to-bedside approach, we are establishing a translational neuroscience center that will assist in preclinical drug development and provide an infrastructure for conducting clinical trials.

THEODORE PIERSON, PH.D., NIAID

Senior Investigator; Chief, Viral Pathogenesis Section, Laboratory of Viral Diseases

Education: Eckerd College, St. Petersburg, Fla. (B.S. in marine science); The Johns Hopkins School of Medicine, Baltimore (Ph.D. in immunology)

Training: Postdoctoral training in the Department of Microbiology, University of Pennsylvania School of Medicine (Philadelphia)

Came to NIH: In March 2005

Selected professional activities: Adjunct professor, University of Maryland, Department of Cell Biology and Molecular Genetics; editorial board member, *Journal of Virology*

Outside interests: Spending time with his wife and two-year-old son; trying to keep up with the marine science field, especially anything to do with the deep-sea-dwelling giant squid (genus: Architeuthis); following Indianapolis Colts football

Research interests: Flaviviruses—a group of RNA viruses that can cause dengue fever, West Nile virus–related illnesses, and other diseases—are responsible for considerable morbidity and mortality worldwide. Vaccines being developed against flaviviruses rely on eliciting a protective humoral immune response. But under some circumstances, the antibodies that develop after a natural infection or vaccination have the potential to make the disease worse. Using West Nile and dengue viruses as models, we are defining factors that govern the potency of neutralizing antibodies, their mechanism of action, and their potential for the antibody-dependent enhancement of infection thought to contribute to severe manifestations of dengue infection.

Much of our work has focused on developing quantitative models of neutralization that have provided a foundation from which to explore the genetic and biochemical complexity of factors that modulate antibody function.

We have been applying the principles identified using the reductionist approaches described above toward the study of the humoral response to flavivirus infection and vaccination. Our goal is to deconstruct human polyclonal antibody responses in order to identify the significant components.

We are developing functional approaches to map the composition and dynamics of the polyclonal response to flavivirus infection with the goal of identifying epitopes (the parts of antigens recognized by antibodies) that are important for neutralization and protection. ●

The NIH Catalyst is planning to include stories about NIH intramural researcher alumni in the near future. Alums are researchers who trained and/or worked at NIH. If you have suggestions for stories, please e-mail Laura Carter at carterls@od.nih.gov.

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DOE: Department of Energy
FAES: Foundation for Advanced Education in the Sciences
FelCom: Fellows Committee
FDA: Food and Drug Administration
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCCAM: National Center for Complementary and Alternative Medicine
NCBI: National Center for Biotechnology Information
NCI: National Cancer Institute
NEI: National Eye Institute
NHGRI: National Human Genome Research Institute
NHLBI: National Heart, Lung, and Blood Institute
NIA: National Institute on Aging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAID: National Institute of Allergy and Infectious Diseases
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB: National Institute of Biomedical Imaging and Bioengineering
NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDA: National Institute on Drug Abuse
NIDCD: National Institute on Deafness and Other Communication Disorders
NIDCR: National Institute of Dental and Craniofacial Research
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
OD: Office of the Director
OITE: Office of Intramural Training and Education
OIR: Office of Intramural Research
ORS: Office of Research Services

THE ANNUAL KINYOUN LECTURE
"A PUBLIC HEALTH APPROACH TO INFECTIOUS DISEASE PREVENTION AND CONTROL FOR THE 21ST CENTURY"
Thursday, November 17, 2011
2:00–3:00 p.m.
Lipsett Amphitheater (Building 10)
Thomas R. Frieden, Director, Centers for Disease Control and Prevention, will deliver the talk. For more about him, visit http://www.cdc.gov/about/leadership/director.htm. The event will be videocast live on the Web, http://videocast.nih.gov. For more information about the event contact Julie Marquardt (marquarj@mail.nih.gov or 301-443-8147).

THE NIH TELEWORK FESTIVAL
Tuesday, November 22, 2011
9:00 a.m.–1:00 p.m.
Natcher Conference Center (Building 45)
Support scientific discovery from offsite locations. Learn how teleworking can be part of the solution to help NIH support employee work-life balance; improve NIH's ability to retain high-quality staff; maintain NIH performance during emergencies without reducing productivity; decrease traffic congestion; and meet DHHS and NIH sustainability goals. Hear from senior scientific and business leaders on how they have integrated telework into their operations. Participate in interactive telework technology demonstrations by CIT, NIA, and NIMH. Show your creativity and enter the Telework Poster Contest. Salute the NIH winners of the HHS Green Champion awards. Visit exhibitors from OHR, ORS/ORF, and other telework-related organizations. For more information and to register visit http://meetings.nigms.nih.gov/meetings/Telework Festival or view via videocast at http://videocast.nih.gov. Onsite registration is available.

HAVE YOU . . .
Checked out the new online face for the NIH Intramural Research Program? Visit the Web site at http://www.irp.nih.gov.

NINDS GRAND ROUNDS
"THE ROLE OF RETROVIRUSES IN NEUROLOGICAL DISEASES AND HUMAN EVOLUTION"
Tuesday, November 22, 2011
10:30 a.m.–12:00 p.m.
Lipsett Amphitheater (Building 10)
NINDS Clinical Director Avindra Nath will be the presenter. For more information, contact Wanda Haddaway (haddawayw@ninds.nih.gov or 301-496-4393).

HHS MENTORING PROGRAM
Permanent federal employees interested in serving as mentors and mentees across the NIH community may be interested in a program that emphasizes building confidential, interactive relationships and focuses on developing leadership and management competencies at various levels. The HHS Mentoring Program does not supplant the NIH scientific mentoring and customized leadership mentoring programs that are available to employees in some institutes and centers. Instead, it fills an existing need and enables NIH-wide relationships. For more information, including links to online registration and upcoming information sessions, visit the NIH-HHS Mentoring Program Web site at http://trainingcenter.nih.gov/hhs_mentoring.html.

NIH DIRECTOR'S SEMINAR SERIES
Wilson Hall (Building One)
12:00–1:00 p.m. (Fridays)
November 18: Craig Blackstone (NINDS), "Out of Shape: Endoplasmic Reticulum Morphology Defects in the Hereditary Spastic Paraplegias"
December 16: Katherine Roche (NINDS), "Molecular Mechanisms Regulating Excitatory Synapses"
January 20: Jesús Valenzuela (NIAID), "Basic and Translational Research on Saliva from Insect Vectors of Neglected Diseases: From Pharmacology to Biomarkers and Vaccines"
February 17: Matthew Hoffman (NIDCR), "Epithelial-Progenitor Cell-Neuronal Communication: Implications for Tissue Regeneration"
March 16: Adrian Ferré-D'Amaré (NHLBI), "Catalytic and Gene Regulatory RNAs: Structural Biology, Physiology and Evolution"
April 20: Ola Landgren (NCI-CCR), "Multiple Myeloma and Its Precursor Disease: The Future Is Already Here"
May 18: Serena Dudek (NIEHS), "New Insights Into Regulating Synaptic Plasticity from an Unexpected Place"

GENOMICS IN MEDICINE LECTURE SERIES
First Fridays, December 2, 2011–June 1, 2012
8:00–9:00 a.m.
Lower level auditorium
Suburban Hospital, Bethesda, Md.
This Grand Rounds lecture series, a collaboration of NHGRI with Suburban Hospital and The Johns Hopkins University School of Medicine, will highlight the intersection of genomics and medicine. Advance registration is not required; those requesting continuing medical education credit can sign in on site. The lectures will be recorded via GenomeTV, NHGRI's YouTube channel. For information, contact Alice Bailey (NHGRI) at baileyali@mail.ni.gov or Susan Laine (Suburban Hospital) at slaine@suburbanhospital.org.
December 2, 2011: David Valle (The Johns Hopkins University School of Medicine), "The Human Genome and Individualized Medicine"
January 6, 2012: Lawrence Brody (NHGRI), "An Introduction to Genomics: Breast Cancer Genes, Risk Assessment and Screening"
February 3: Stanley Lipkowitz (NCI), "An Introduction to Genomics: Breast Cancer Diagnosis and Treatment"
March 2: Jonathan Zenilman (Johns Hopkins, Bayview Medical Center), "What's Bugging You? The Intersection of Genomics and Infectious Disease"
April 13: Les Biesecker (NHGRI), "The Heart of the Matter: Genomics and Cardiovascular Disease"
May 4: Hal Dietz, M.D. (Johns Hopkins), "Rational Therapeutics For Genetic Conditions"
June 1: Barbara Biesecker (NHGRI), "Genomics In Maternal Child Health"

WALS 2011–2012

Most Wednesdays
3:00–4:00 p.m. (reception follows)
Masur Auditorium (Building 10)

November 16: Jonathan Weissman (University of California at San Francisco): "New Strategies for Decoding Genomes"

November 30: Diane E. Griffin (The Johns Hopkins School of Public Health), "Virus Clearance: It Isn't Easy"

December 7: Gerald W. Hart (Johns Hopkins), "Bittersweet Roles of *O*-GlcNAcylation in Diabetes, Alzheimer Disease and Cancer"

December 14: Victor Corces (Emory), "Throwing Transcription for a Loop: The Role of Chromatin Insulators in the 3D Nucleus"

January 4: David Botstein (Princeton), "Evolution and Cancer"

January 11: Gary H. Gibbons (Morehouse School of Medicine), "Cardiovascular Health Disparities: Integrating Genomic and Social Determinants"

January 23 (Monday): Jacques Banchereau (Roche USA), "Will Dendritic Cell Subsets Help Us Address the Challenges of Cancer, Autoimmunity, and Chronic Viral Diseases?"

January 25: Anthony Atala (Wake Forest School of Medicine), "Regenerative Medicine: Current Concepts and Changing Trends"

February 1: Bonnie Berger (Massachusetts Institute of Technology), "Computational Biology in the 21st Century: Making Sense out of Massive Data"

February 8: Karen Guillemin (University of Oregon), "Molecular Dialogues with the Microbiota: Insights from the Zebrafish Intestine"

February 15: Lewis H. Kuller (University of Pittsburgh), "The Obesity Epidemic: Why Have We Failed?"

February 22: Wei Yang (NIDDK), "Genome Integrity and Cancer Prevention: Molecular Mechanisms of DNA Repair"

Lectures continue through June 20, 2012. For more information, visit http://wals.od.nih.gov. Lectures are available via live videocast at http://videocast.nih.gov and are archived one week after each lecture.

DEMYSTIFYING MEDICINE 2012

Tuesdays, starting January 10, 2012
4:00–5:30 p.m.
Building 50 Conference Room (unless otherwise noted)

The 16-week "DeMystifying Medicine" course bridges the gap between advances in biology and their application to major human diseases. The course, sponsored by FAES/CC/OD, includes presentations about patients, pathology, diagnosis, and therapy in the context of major disease problems and current research. Although it's primarily directed toward Ph.D. students, fellows, and staff, the course is also of interest to medical students and clinicians. For details visit http://demystifyingmedicine.od.nih.gov or contact Win Arias at ariasi@mail.nih.gov. Register through the course e-mail list (to subscribe to that list, visit https://list.nih.gov/cgi-bin/wa.exe?A0=demystifyingmed). If you would like a DVD of the 2011 sessions, e-mail your request and mailing address to Priyanka Basa at basap@faes.od.nih.gov.

January 10, 2012: Anthony Fauci (NIAID) and John Coffin (NCI), "Global Infections: The Great Challenge"

January 17: Mahendra Rao (ICRM) and Ronald Gress (NCI), "Stem Cells: The New Frontier in Biology and Medicine"

January 24: Codrin Lungu (NINDS) and Edward Giniger (NINDS), "Parkinson's Disease and the Fly"

January 31: Eric Green (NHGRI) and William Gahl (NHGRI), "Genomics and Undiagnosed Disease"

February 7 (Masur Auditorium, Building 10): Dennis Drayna (NINDS), Penny Friedman (CC), and Donna Krasnewich (NIGMS), "Stuttering: A Medical Disease?"

February 14: Matthias Machner (NICHD) and Tara Palmore (NIAID), "Legionella: More Than Only Veterans"

February 21: Nicholas Ryba (NIDCR) and colleague TBN, "Taste: Good and Bad"

February 28: No lecture

March 6: Toren Finkel (NHLBI) and Luigi Ferrucci (NIA), "Aging Gracefully"

March 13: Jean Pierre Gillet (NCI), Itzhak Avital (NCI), and Win Arias (NICHD), "Hepatocellular Cancer: A Global Disease"

March 20: Silvio Gutkind (NIDCR) and Carter Van Waes (NCI), "Head and Neck Cancer: New Paradigms and Treatment"

March 27: Warren Strober (NIAID) and Michael Yao (NIAID), "Inflammatory Bowel Disease: New Biologic and Therapeutic Players"

April 3: Nora Volkow (NIDA) and David Goldman (NIAAA), "Addictions: Are They All the Same?"

April 10: Roger Glass (FIC) and Mark Donowitz (Johns Hopkins), "Diarrheal Diseases: Deadly Events"

April 17: Thomas Insel (NIMH), "Autism: Progress Continues"

April 24: Bana Jabri (Univiersity of Chicago) and Irwin Rosenberg (Tufts), "Gluten Enteropathy: An Expanding Disease"

May 1: Finale: "Present and Future Status for Careers in Biomedical Research"

NIH LIBRARY CLASSES

Let the NIH Library help you improve your searching and reference-management skills. Classes are free, hands-on, open to NIH and HHS staff, and held in the Training Room on the first floor of the NIH Library. The NIH Library is located near the South Entrance of Building 10. Registration is required for all classes. For a list of classes and to register, visit http://nihlibrary.nih.gov/Pages/default.aspx.

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CATALYTIC REACTIONS?

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

Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

WE HAVE NOT YET IDENTIFIED THE MASKED SURGEON. SEE HTTP://IRP.NIH.GOV/CATALYST/V19I5/LABORATORY-CONFESSIONS.

LABORATORY CONFESSIONS

Medicated Lab Chief

BY NAME WITHHELD

I confess that I like my lab chief better on painkillers. I'm not entirely sure what he's taking. I think it is Vicodin or some hydrocodone-based drug to relieve his periodic back pain. He's lucid, of course, and in fact as sharp as ever. Under his leadership, our lab still continues to pump out papers in high-quality journals, including those coveted journals with single-word titles. Nothing at all changes in terms of productivity, and we certainly aren't publishing papers with psychedelic titles along the lines of "Lucy in the Lab with *c*-Jun *N*-Terminal Kinases." It's just that being in the lab is more pleasant when he is medicated.

For example, his aggressive personality—which some here euphemize as gregarious—has mellowed considerably. Questions such as "How's the assay coming along?" might now be heard only once a day, as opposed to once every eight minutes. I don't feel his aggressive, excuse me, gregarious presence hovering over my back like a boulder just a raindrop away from crashing down the slope. And I can take lunch without fear of 20 "friendly e-mail reminders" from him about a pending publication deadline.

I'd never wish back pain on anyone and certainly not on my lab chief, whom I truly love dearly, medicated or not. I can only urge other lab chiefs to treat their trainees and staff lovingly with trust. The work will get done without nagging. Trust your skills in recruitment and take a "chill pill". . . or do yoga or meditation or maybe drink just two fewer cups of coffee each day.

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

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

Address correspondence to:
Building 1, Room 333, NIH
Bethesda, MD 20892
Ph: 301-402-1449
Fax: 301-402-4303
e-mail: catalyst@nih.gov

The NIH Catalyst online:
http://irp.nih.gov/catalyst