Fostering Communication and Collaboration

The NIH Catalyst
A Publication for NIH Intramural Scientists

National Institutes of Health ■ Office of the Director ■ Volume 17, Issue 6 ■ December 2009

CHI

Spices Up NIH Research

By Stephanie Cooperstein

Finding strength in numbers, immunologists across the NIH campus are forming a new trans-NIH intitiative: the Center for Human Immunology, Autoimmunity, and Inflammation (CHI). The group hopes to help biomedical scientists and physicians translate research findings on the function and pathophysiology of the immune system to the clinic. CHI director Neal Young (NHLBI), provided and overview during the "Understanding Human Immunology" symposium at the 2009 Research Festival.

CHI will facilitate cooperative research by providing advanced technologies that are not usually available in individual laboratories: assays of immune cells and their products, based on flow cytometry and other emerging multiplexed techniques; high-throughput systems technologies—involving the use of new methods for large-scale examination of the genome, proteome, lipidome, and metabolome—and the application of advanced biostatical and computer modeling methods for mining these data; and protocol development.

NIH scientists Erica Lannan (NIEHS), Daniel Kastner (NIAMS), Bibi Bielekova (NINDS), Rodrigo Calado (NHLBI), and Ronald Germain (NIAID) discussed their latest research, including new imaging probes to examine tissues, a post-influenza database, and a module-based approach to illness.

CHI's ultimate goal is to determine how best to monitor the human immune system in real time. Ideally, CHI's work would better equip researchers and clinicians to identify progressive changes in immune system health and catch significant changes in the immune system in a shorter time.

For more information on the new Center for Human Immunology, Autoimmunity, and Inflammation, visit http://www.nhlbi.nih.gov/resources/chi. ■

Research Festival 2009

From the Rare to the All Too Common

By Sarah Freeman

From the bench to the bedside and back again, the 2009 Research Festival featured presentations on a variety of topics by all sorts of NIH basic researchers and clinical scientists. NIH Director Francis Collins got in on the act as well, kicking off the festival with an inspiring account of work from his own research lab.

NIH's own influenza team was on hand to describe their work on seasonal flu, the H1N1 flu virus, and flu vaccines. And more than 100 other scientists shared their findings at concurrent symposia (see pages 13-15); nearly 450 posters and exhibits were displayed (so many that there needed to be three separate poster sessions); and more than 400 exhibitors displayed state-of-the art research equipment and supplies at the Technical Sales Association tent show. The NIH Director's talk set the stage for the type of groundbreaking inspiring research commonplace at NIH.

NIH Director Francis Collins kicked off the 2009 Research Festival with an inspiring account of work he started in 2003 while director of NHGRI: the discovery of the genetic basis of progeria, a rare disorder that causes dramatic premature aging in one in four million children.

Progeria

In 2003 a multi-institution team led by then–NHGRI director Francis Collins discovered the genetic basis of progeria, a rare disorder that causes dramatic premature aging in one in four million children. As newborns, children with progeria usually appear normal. However, within a year, their growth rate slows and they soon are shorter and weigh much less than others their age. While possessing normal intelligence, affected children develop a distinctive appearance characterized by loss of hair, aged-looking skin, a pinched nose, and a small face and jaw relative to head size. They also often suffer from symptoms typically seen in much older people: stiffness of joints, hip dislocations, and severe, progressive cardiovascular disease.

The research team discovered that progeria is caused by a single-letter mutation in a single gene, known as *LMNA*. The defective gene produces an abnormal form of the lamin A protein that destabilizes the patient's cells.

"This project has been empowered by the capabilities of the intramural program," said Collins.

A clinical trial is now under way at Children's Hospital Boston to test the therapeutic effects of farnesyltransferase inhibitors (FTIs). Researchers in the Collins lab

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From the Deputy Director for Intramural Research

Clinical Research is a Team Sport

Michael Gottesman

*To facilitate translation of laboratory findings to new approaches to prevent and cure human diseases, the Intramural Research Program promotes interaction among laboratory, population-based and clinical scientists. The NIH Clinical Center is the largest facility in the world devoted purely to clinical research. The work at the Clinical Center emphasizes long-term, natural history studies of human disease, including rare diseases; "first-in-human" interventional clinical research; mechanism-based studies that maximize the scientific benefit of early-phase clinical trials; and studies, unencumbered by any perceived bias, that test existing hypotheses and treatments. (*NIH Intramural Research at the Threshold of a New Era*, http://www1.od.nih.gov/oir/sourcebook/ir-communictns/IRP_transition_booklet.pdf)*

The NIH Intramural Program has a proud history of developing new clinical paradigms and new treatments for human disease. We attribute much of our success to teams of talented individuals—collaborations among intramural scientists and between intramural and extramural colleagues. Even our tenure policy reflects the importance of teamwork in clinical research and other complex projects (see http://www1.od.nih.gov/oir/sourcebook/prof-desig/tenurecriteria.htm).

An increasing number of trans-NIH clinics are being developed to recruit and evaluate patients with diseases that are difficult to diagnose and manage. You are no doubt already aware of the Undiagnosed Diseases Program--a multi-institute effort led by NHGRI Clinical Director Bill Gahl—and the new Center for Human Immunology (CHI) led by Neal Young in NHLBI (see "CHI" on page 1). I would like to make you aware of several other trans-NIH clinics that are establishing NIH as the place to go for the evaluation of difficult clinical problems.

The Primary Immunodeficiency (PID) Clinic, developed by Steve Holland and Harry Malech of NIAID, is a national referral clinic for people with suspected or known immunodeficiencies. The PID Clinic draws on clinical expertise from across the NIH in allergy and immunology, infectious diseases, genetics, rheumatology, dermatology, gastroenterology, pulmonology, cardiology, otolaryngology, microbiology, nursing, and psychiatry. It is run by Gulbu Uzel and Sergio Rosenzweig, both of NIAID, with fellows from the allergy/immunology training program, a dedicated nursing staff, and consultants from throughout the NIH.

In addition to making new diagnoses of some rare, but previously described, immunodeficiency diseases, the PID has identified two new syndromes including humoral immunodeficiency with granulomatous lung disease and deficiency of the dedicator of cytokinesis 8 (DOCK8) protein (*NEJM* **361**:2046–2055, 2009). The PID Clinic is working with CHI to develop strategies to improve the efficiency of diagnoses that are based on the complete phenotyping of the human immune system.

A second clinic with an outstanding track record is the Chronic Graft-Versus-Host Disease (GVHD) Clinic initiated and led by Steve Pavletic (NCI). The NIH has world-class bone-marrow transplant efforts based in NCI, NHLBI, and NIAID. The clinic addresses complex chronic graft-versus-host conditions involving almost all organ systems. The clinic's recent contributions to a better understanding and improved management of GVHD include development and implementation of consensus clinical trial criteria and organ-system-specific interventional trials—topical thalidomide for oral GVHD, imatinib for sclerotic-type cutaneous GVHD, and montelukast for constrictive bronchitis induced by GVHD.

Finally, I would like to mention the Systemic Autoinflammatory Diseases Clinics that are based in NIAMS's Program for Translational Research. Dan Kastner, clinical director of NIAMS and NIH deputy director for intramural clinical research, maintains the Autoinflammatory Diseases Clinic, which is an international referral center for patients with hereditary periodic fever syndromes and other monogenic or undiagnosed autoinflammatory diseases. Pediatric rheumatologists Karyl Barron (NIAID) and Don Goldsmith (Drexel University, Philadelphia), general pediatrician Bob Lembo (CC), and pediatric hospitalist Debbie Stone (NIAMS) regularly participate in the clinic, which has evaluated more than 1,300 patients since its inception about 10 years ago.

More recently Raphaela Goldbach-Mansky (NIAMS), with help from intramural and extramural collaborators, established a second Autoinflammatory Disease Clinic for patients with neonatal-onset multisystem inflammatory disease, deficiency of the interleukin-1 receptor antagonist (DIRA), chronic recurrent multifocal osteomyelitis, and Behçet's disease.

NIH scientists have discovered several genetic disorders through these NIAMS clinics including familial Mediterranean fever, tumor necrosis factor receptor–associated periodic syndrome, neonatal-onset multisystem inflammatory disease, and more recently, as mentioned above, DIRA. The patients have also participated in a number of treatment protocols, have generously donated specimens for mechanistic studies in several NIAMS laboratories including the new Translational Immunology Section headed by Massimo Gadina, and have contributed to the education of a generation of rheumatology fellows and visiting clinical faculty.

As we seek to accelerate cures of human disease and more efficiently use the resources available at the NIH, we will continue to establish multiple centers of excellence such as these multidisciplinary trans-NIH clinics. Some of these centers will include extramural colleagues who will bring their expertise and some will be part of a network of academic clinics throughout the United States. If you have ideas for additional clinics or are aware of others not mentioned here, please let us know. ■

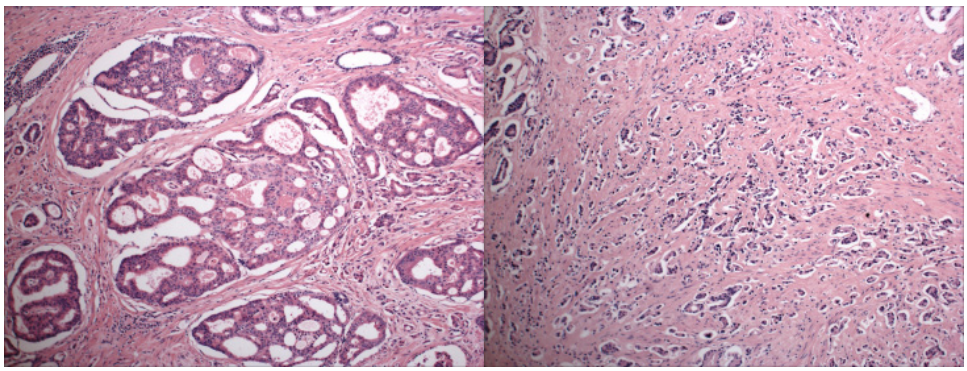
—Michael Gottesman, DDIR

Commentary

Why Pathology Is Important For Cancer Research

Pathology is the exact art and the subtle science of studying diseases by examining tissues, often under the microscope. The pathologist is a physician with the heart of a researcher, a proud heir to an eminent tradition of great masters, and someone who appreciates the value of applying biological research to the understanding of disease. By using ancient chemical staining techniques as well as novel molecular tools to interrogate cells under the microscope, she or he understands cells' behavior and can make them reveal their origin. And the pathologist can often predict a patient's future.

Pathology, a bridge between clinical medicine and basic science, shares its roots with the origins of medicine. In the third century B.C.E., Greek physicians at the Medical School of Alexandria were the first to perform autopsies to better understand human anatomy and disease.



These prostate cancer cells (100× magnification), on the left and right, depict different histological patterns, but are from the same patient. A clinical pathologist confirms a malignancy by examining the stained tissues and determining the histological grade. Investigators and pathologists try to understand the molecular changes and look for translational significance.

Almost a thousand years later, during the 12th century, the famous physician Ibn Zuhr (1091–1161), known in the Western world as Avenzoar, practiced autopsy as a tool for the study of disease. Modern pathology can be traced to 1761 when Giovanni Battista Morgagni (1618–1771) published a book entitled *De Sedibus et Causis Morborum per Anatomem Indagatis* (*The Seats and Causes of Diseases Investigated by Anatomy*), a collection of more than 600 case records that established the basis of the anatomical-clinical correlation.

Then Rudolf Virchow (1821–1902) revolutionized medicine when he applied the microscope to the study of human disease. He correlated the changes in the morphology of cells and tissues with gross anatomical alterations. In 1892 Virchow was awarded the Copley Medal—the most important scientific award at that time—for his investigations in pathology, pathological anatomy, and prehistoric archaeology. A few years later, Santiago Ramon y Cajal (1852–1934) and Camillo Golgi (1843–1926), both anatomic pathologists, were awarded the Nobel Prize in Physiology or Medicine in 1906 for their research revealing the structure of the nervous tissue.

During the 20th century, surgical pathology evolved as a separate discipline. This subspecialty applies pathology tools to the histological analysis of tissue samples obtained from patient biopsies for diagnostic, therapeutic, and prognostic purposes. Among the most important American pathologists who expanded the frontiers of surgical pathology and taught their craft to generations of new physicians are James Ewing (1866–1943), one of the founders of the American Association for Cancer Research (1907) and the American Cancer Society and a pioneer of the application of radiation therapy; Arthur Purdy Stout (1885–1967), a pioneer in surgical pathology; cancer pathologist Lauren Ackerman (1905–1993), who changed the character of anatomical pathology by directing the focus toward surgical pathology; and more recently Juan Rosai (1940–), a principal author and editor of a major textbook in the field of surgical pathology.

Researchers and physicians alike sometimes distrust the art of pathology because it seems to lack the numbers and equations that underlie the discipline of hard science. Yet pathology is a complex field, and its practitioners undergo years of rigorous training. The pathology diagnostic process integrates clinical science, demographic data, molecular biology, and histopathology. Successful pathologists undergo many years of training—ideally under the guidance of knowledgeable mentors—which continues far beyond residencies and fellowships. Even in the molecular era, the scientific art of evaluating stained tissue sections under the microscope continues to be the gold standard for the clinical diagnosis of cancer and many noncancerous diseases.

In cancer research, pathology is particularly valuable. Tumors show a wide range of histological patterns and the pathology report provides scientific data—which is translated into clinically useful information such as diagnosis and identification of prognostic and therapeutic markers—that will guide oncologists and surgeons as they develop therapies to treat cancer. Pathology information also augments the molecular analysis of tissues.

By integrating pathology into basic cancer research, biomedical scientists can enrich their projects with clinically valuable information and increase the translational value of their work. For example, a scientist studying breast cancer may want to use human tissue specimens to validate data obtained from experiments using cell lines. The scientist will quickly realize that tissues are far more complex than cell lines. Unlike pure cells arranged in the two dimensions of the Petri dish, tissues are organized in a three-dimensional framework composed of multiple cell populations and extracellular matrix components. Furthermore tumors can be highly heterogeneous and display diverse histotypes, which can be subdivided by histological grade and further subclassified by clinical and molecular markers. Pathologists can help basic scientists tease out the complexity of tissue specimens and incorporate the extracted information into valuable basic research findings.

Pathologists have long made contributions to the discovery, characterization, and classification of new medical conditions (some examples include Ewing's sarcoma, Rosai-Dorfman disease, and lymphomas). The fruitful interactions between basic scientists and pathologists have led to such remarkable advancements as the invention of laser capture microdissection—by NIH researchers in 1996 (*Science* **274**: 998–1001, 1996)—and the discovery of the bacterium *Helicobacter pylori* as a causal agent of gastric tumors by the Australian physician-scientists B.J. Marshall and J.R. Warren.

Incorporating the methods of pathology into basic biological studies will improve cooperation among physicians and scientists and enhance the translational potential of cancer research. Everyone benefits. Most of all the patient. ■

—Jaime Rodriguez-Canales, NCI

The Training Page

From the Office of Intramural Training and Education: Three NIH Scientists Recognized as Outstanding Mentors

By Stephanie Guzik, NHLBI

The more than 400 graduate students in the Graduate Partnership Program have access to unparalleled opportunities and resources as they conduct research on the NIH campus. Best of all they have willing, patient, and diligent mentors who help them navigate NIH's research labyrinth, gain the confidence they need to succeed, and learn to be compassionate toward future scientists.

Three of these mentors—W. Marston Linehan (NCI), Jennifer Lee (NHLBI), and Keir Neuman (NHLBI)—received Outstanding Mentor Awards recently. The Graduate Student Council selected the winners based on nomination letters submitted by students.

Linehan was nominated by Yukiko Hasumi, a second-year graduate student at Yokohama City University Graduate School of Medicine in Japan. Although Linehan has many obligations as chief of NCI's Urology Oncology Branch, he always kept his door open for trainees who needed guidance, Hasumi wrote. He "emphasize[d] that it is very important to connect basic research and clinical research [and] he encourage[d] us to use clinical samples, reminding [us] that our final goal is to overcome human disease [such as] cancer."

Lee was nominated by Candace Pfefferkorn, a fourth-year student in the biophysics program at the University of Maryland (College Park). Lee spent "countless hours [helping me] understand why and how things are best presented for publication" so that [I] could be independent and successful in [my] research," Pfefferkorn wrote. Lee encourages her students "to do things that will help [them] achieve [their] future professional goals."

Neuman was nominated by Ashley Hardin, a fourth-year student in the chemical physics program at the University of Maryland (College Park). Hardin, who had a physics background, only a rudimentary understanding of biology, and limited wet-lab experience, appreciated that Neuman was consistently "supportive, patient, and understanding." He had an open-door policy, making time for Hardin and his other trainees whenever they had "a question, concern, comment, or even just want to chat," Hardin wrote. Neuman encourages "[me,] as well as others in the lab, to disagree with him if we believe we are right."

The mentors were recognized during the Outstanding Mentor Award Ceremony at the Graduate Student Research Symposium, held on November 10, 2009, in Natcher Auditorium. The day-long symposium featured scientific presentations by the graduate students at NIH, a plenary address by Keith Yamamoto from the University of California at San Francisco, and a keynote speech by the current NIH Director, Francis Collins, who himself was awarded an NIH Outstanding Mentor Award in 2007. ■

From the Fellows Committee: Fellows Award for Research Excellence

By Aurelie Névéol, National Library of Medicine

More than 200 NIH intramural trainees were recognized recently for their outstanding scientific research, each receiving $1,000 to attend a scientific meeting of their choice. These intramural postdoctoral fellows, clinical fellows, and graduate students were winners of the Fellows Award for Research Excellence (FARE), an annual competition that has been ongoing since 1995.

Each year eligible intramural trainees are encouraged to be considered for FARE awards and are invited to submit abstracts describing their current NIH research. The FARE subcommittee oversees the submission process and ensures that all abstracts are reviewed fairly and equally. Abstracts are sorted into about 55 study sections—ranging from biochemistry to virology—and peer reviewed in a blind study section competition.

In each study section, a panel of seven volunteer judges composed of fellows and tenure-track and staff scientists evaluate anonymized FARE abstracts. Submissions are judged on scientific merit, originality, experimental design, and the overall quality of the presentation. Successful FARE abstracts are didactical and successfully convey the importance of the described research to a wide scientific audience.

In the 2010 FARE competition, 972 applications were submitted, and of those

Lori Conlan (OITE) highlighted the diversity of the science in the winning FARE abstracts.

232 (the top 25 percent of applicants in each study section) were chosen to receive awards. In addition to their travel awards, FARE winners were encouraged to present a poster at the 2009 NIH Research Festival. In addition, 18 of the awardees were invited to join other invited speakers in giving oral presentations of their work at Research Festival symposia.

At the FARE awards ceremony, held during Research Festival week in October 2009, Lori Conlan (Office of Intramural Training and Education) highlighted the diversity of the science represented in the winning abstracts. FARE co-chair Aurelie Névéol presented the FARE 2010 results. Vivian Pinn (director, Office of Research on Women's Health) and Michael Gottesman (deputy director for Intramural Research) congratulated the FARE awardees. Both expressed continued interest in supporting FARE and praised the quality of the science presented by FARE awardees. Afterwards, FARE awardees, principal investigators, judges, FARE subcommittee members, and others attended a reception.

Everyone looks forward to an equally exciting FARE 2011! For more information and a list of the 2010 winners, visit http://felcom.od.nih.gov/subCommittee/fare.aspx. ■

Jekyll and Hyde at NIH?
Report from the Anita B. Roberts Lecture Series

By Natalie Goldberger, NCI

Are Dr. Jekyll and Mr. Hyde lurking at NIH? Yes, according to Sharon Wahl (NIDCR), who is investigating a "Jekyll and Hyde" protein that both suppresses and promotes tumors. Like the doctor who transforms from his good self to his evil self on occasion, the SLPI (secretory leukocyte peptidase inhibitor, pronounced "slippy") protein transforms from good to bad sometimes. Wahl is trying to figure out what triggers its split personality.

SLPI's role in tumor development "appears increasingly complex, impacted by species, tumor location, endocrine effects, infectious agents, cell type, and stage of differentiation/progression," said Wahl in her presentation "Host Defense Gone Awry: From Inflammation to Cancer" at the Anita B. Roberts Lecture on October 15, 2009. The lecture series highlights outstanding research achievements of women scientists at NIH.

Wahl—who is the chief of the Oral Infection and Immunity Branch and chief of the Cellular and Clinical Immunology Section—investigates the biological mechanisms regulating inflammation and how their dysregulation contributes to the development of infectious and autoimmune diseases. For more than 15 years she has studied the enzyme SLPI, which plays a large role in immunity because of its antibacterial, antiviral, and antiproteolytic activities.

SLPI is secreted by epithelial cells to protect them from proteases and is found at high levels in saliva, seminal plasma, cervical mucus, and bronchial secretions. In the mid-1990s, Wahl and others demonstrated that SLPI attaches to the surface of monocytes and can block the AIDS virus from infecting human cells in vitro. Further experiments confirmed SLPI's antiviral activity and sparked interest in using SLPI as a microbicide to prevent HIV infection. This application is still being developed.

More recently Wahl has begun examining the link between inflammation and tumorigenesis. She has found that mice that have been genetically engineered to lack SLPI display aberrant wound healing as well as autoimmune, infectious, and allergic and asthmatic syndromes. Squamous cell carcinoma tumors in these mice exhibited increased invasion and metastasis to the lung. These findings suggest the absence of SLPI can shift the protease-inhibitor balance to promote metastasis. Wahl's lab is trying to better define how SLPI controls tumor progression, invasion, and metastasis in human head and neck squamous cell carcinoma.

Sharon Wahl is investigating an enzyme she's nicknamed Jekyll and Hyde for its ability to shift "personalities" and either prevent or promote tumors. Wahl spoke recently at the Anita B. Roberts Lecture series, which honors distinguished women scientists at NIH.

But, she pointed out, SLPI can have an opposite effect, too. Elise Kohn (NCI) has observed that when SLPI is overexpressed in ovarian carcinomas it enhances the progression of tumors. "A lot more work needs to be done to sort out the differential pathways of regulation," said Wahl.

Dr. Jekyll created a secret potion to turn himself into Mr. Hyde. Has SLPI created a secret potion, too? Perhaps one day Wahl and other NIH scientists will find out. ■

The Roberts Legacy: Anita B. Roberts spent 30 years at NCI before her death from gastric cancer in May 2006. She was chief of the Laboratory of Cell Regulation and Carcinogenesis and became well known for her groundbreaking work on transforming growth factor–beta and its role in the growth of epithelial and lymphoid cells. In 2003, Thomas Scientific's Science Watch listed her among the 50 most-cited scientists from 1982 to 2002, in a feature called "Twenty Years of Citation Superstars." The "Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH" honors the contributions Roberts and other successful female scientists have made to the NIH research community.

NIH ABBREVIATIONS

CC: NIH Clinical Center

CIT: Center for Information Technology

FAES: Foundation for Advanced Education in the Sciences

FelCom: Fellows Committee

NCCAM: National Center for Complementary and Alternative Medicine

NCI: National Cancer Institute

NCMHD: National Center on Minority Health and Health Disparities

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: 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

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

Champion of Science and Scientists: Ruth Kirschstein (1926–2009)

By Susan Chacko, CIT

Betsy Humphreys had been at NIH for only a few years when she first met Acting NIH Director Ruth Kirschstein. Humphreys was introducing herself at a meeting when Kirschstein said, "I know who you are." "She knew who all of us were," said Humphreys, now the deputy director of the National Library of Medicine. "She was keeping track of people and watching out for their careers."

Ruth Kirschstein, who died on October 6, 2009, at the NIH Clinical Center, was well known for her mentorship of NIH scientists and administrators, especially women and minorities. In a career spanning more than half a century at NIH, she became the first woman director of an NIH institute, headed NIGMS for 19 years, served as acting director of NIH twice, and was NIH deputy director for six years. She also led the search for a safer polio vaccine in the 1950s and the NIH response to the AIDS epidemic in the 1980s. Throughout it all, she valued the importance of a diverse scientific workforce and was the driving force behind programs to advance the careers of women and minorities in science.

Kirschstein was born in 1926 in Brooklyn, N.Y. She received a B.A. degree from Long Island University (Brookville, N.Y.) in 1947 and an M.D. degree from Tulane University School of Medicine (New Orleans, La.) in 1951. One of only 10 women in her medical school class of 110 students, she went on to do residencies in medicine and surgery at Kings County Hospital, Brooklyn, and in pathology at Providence Hospital, Detroit; Tulane University School of Medicine; and NIH's Clinical Center. In 1957 she became an experimental pathologist at the Division of Biologics Standards (now the Center for Biologics Evaluation and Research, Food and Drug Administration) on the NIH Bethesda campus.

In the 1950s, a pharmaceutical company in California produced several batches of the Salk polio vaccine that unintentionally contained live polio virus. The

Ruth Kirschstein was beloved throughout NIH. The first woman director of NIGMS and acting director of NIH twice, she played key roles in the development of a safety test for polio vaccines and in the fight against AIDS. In a career spanning half a century, she was well known for her mentorship of NIH scientists and administrators, especially women and minorities.

contaminated vaccine caused 10 deaths and more than 200 cases of paralysis and made tens of thousands of children seriously ill. Kirschstein led the development of a safety test for polio vaccines, which ensured the safety of the Salk vaccine and enabled the worldwide use of the Sabin oral vaccine.

Kirschstein was director of NIGMS when the AIDS public-health crisis emerged in the 1980s. She assembled a team of researchers to investigate the epidemic and organized funding for AIDS research and drug development in spite of strong opposition from conservative lawmakers and lobbyists.

Under her directorship at NIGMS, the Genbank nucleic acid sequence database was established in 1982 and has been a critical research tool for biomedical researchers ever since. In 1993, she was the acting director of NIH and then served as deputy director under NIH Director Harold Varmus for six years. She was acting director again from 2000 to 2002.

"Dr. Kirschstein was very proud of the NIH intramural program," said Yvonne Maddox, who was Kirschstein's acting deputy director during that period. "She would not hesitate to make personal contact with an intramural investigator to inquire on a new discovery or a recent publication or to congratulate them when she had read an article that they authored. Her 'take home' folder most evenings included the e-clips and articles that came out of our laboratories."

After 2003, Kirschstein was a senior advisor to the NIH director and was actively involved in NIH until her final illness. "Last week, in fact, I was on a conference call with her," said NIH Director Francis Collins on October 7. "Her insightful contribution made it clear she had not missed a beat."

In all of her roles at the NIH, Kirschstein was exceptionally supportive of women and minorities in science. "When I got the job as director of NIGMS, I had to see that we changed the culture. That we thought about women for jobs, and we thought about minorities for jobs," she said in an interview in 2007. "People said 'Well, you're going to hire only women.' I said, 'No, I'm going to give women an equal opportunity to men.'"

She had a great interest in the careers of postdoctoral fellows, and her efforts to improve salaries and working conditions for postdocs led to the Inaugural Distinguished Service Award that the National Postdoctoral Association awarded her in 2004 for "profound and sustained contribution to improving the postdoctoral experience." In 2002, Congress renamed the National Research Service Awards (NRSA) for postdocs as the Ruth L. Kirschstein NRSA program.

Among her many honors were the U.S. Public Health Superior Service Award (1978), the Presidential Meritorious Executive Rank Award (1980), election to the Institute of Medicine (1982), the Public Health Service Special Recognition Award and the Presidential Distinguished Executive Rank Award (1985), and the Women of Achievement Award from the Jewish Anti-Defamation League (2000).

She is survived by her husband, Alan Rabson, deputy director of NCI, and their son Arnold Rabson, a molecular biologist. ■

An Inspiration to Many . . .

Ruth embodied the spirit of NIH. She was an icon. She was loved and admired by so many at the NIH, across the medical research community, among hundreds of members of Congress, and around the world. Knowing Ruth, she would cringe if she heard us praise her—modesty was one of her strongest suits.

—Francis Collins, Director, NIH
in an e-mail message to NIH staff

Dr. Kirschstein truly represented the best of NIH—public service, wisdom, and deep knowledge and analysis of important problems.

—Jeremy Berg, Director of NIGMS

For many of us, Dr. K (as she was fondly called) was bigger than life. Her passion for NIH and its many employees was always evident, from those she tutored to become leaders to those she encouraged by her recognition of them in the halls or on the grounds. She served as a wise counselor for so many people who knew her (and even some who didn't know her).

—Yvonne Maddox, Deputy Director, NICHD

She was responsible for the career development of countless NIH scientists and administrators, including me. She was warm and very strong at the same time; she worked at least 24 hours a day and was up-to-date on any issue about which she had responsibility or interest.

—Michael Gottesman, Deputy Director for Intramural Research, NIH

She was an avid promoter of research that was innovative and worked to ensure that young investigators would be funded. She had major concerns that the pipeline would not dry up and worked on mechanisms to fund and train younger scientists. She wanted to create an environment where young talented scientists would not get discouraged.

—Nora Volkow, Director, NIDA

As the NIH deputy director during my tenure as director, she provided a rich knowledge of NIH history, a perceptive analysis of the people who worked there, a willingness to take on thankless tasks that were often assigned to the director's office, and an indefatigable, cheerful appetite for work. My job would have been much less enjoyable and NIH would have been less successful during that exciting era without her remarkable efforts.

—Harold Varmus, Director, NIH (1993–1999)

I feel honored to hold an award named after her.

—Postdoc recipient of the Ruth L. Kirschstein NRSA award, on an NIGMS bulletin board

Ruth was a valued mentor to me here at NIH. I can say without any hesitancy that I would not be where I am without her support (on a bad day, I once joked to her that I still valued and respected her in spite of that!). It was an honor to be selected to follow her as the NIH Deputy Director—she was a tough act to follow.

—Raynard Kington, Deputy Director, NIH

I wanted to be a doctor from a very young age—even before I went to high school. I'm not sure exactly what motivated me. I had a father who was a chemist. I had a mother who was extremely ill through most of my childhood, and spent a long time in the hospital. It may have been that, that motivated me partly as well. When I applied for medical school women were not very commonly applying for school—I actually applied to every medical school in the United States. At least one of them wrote me and said, "We only take men." And that sort of was not a very good thing, and it didn't make me very happy. Today, over 50 percent of each medical school class are women.

—Ruth Kirschstein (2007)

Other NIH Deaths

Carl G. Baker (November 27, 1920–February 11, 2009) was the director of the NCI and one of the premier architects of the United States' "War on Cancer" in the early 1970s.

John N. Brady (1952–April 27, 2009) was chief of NCI's Virus Tumor Biology Section and tackled cell-virus interactions that influence viral gene regulation, viral pathogenesis, and oncogenic transformation.

Robert B. Bradley (died on November 19, 2009, at 88) was a physicist who worked for the federal government including NIH from 1957 to 1977.

Robert A. Cohen (1909–October 9, 2009) was one of the founders of NIMH's intramural program.

Erminio (Mimo) Costa (1924–November 28, 2009), a neuropsychopharmacologist in the National Heart Institute (now NHLBI), was known for his pioneering studies on serotonin in the human brain (1958) that established the neurotransmitter as a target for the action of antidepressant and antipsychotic drugs.

David Derse (December 22, 1949–October 9, 2009) was the head of NCI's Retrovirus Gene Expression Section of the HIV Drug Resistance Program.

Louis Stanley "Buddy" Diamond (1920–September 6, 2009) was renowned for his studies of the biology of *Entamoeba histolytica*, a leading cause of infectious dysentery in humans.

Charles J. Donnelly (died on April 11, 2009, at 88) worked at what is now NIDCR as chief of research grants, chief of dental caries and hard tissues, and chief of epidemiology.

Zelda Janus (died on November 2, 2009, at 91) was a biostatistician at NCI and contributed to the landmark 1964 Surgeon General's report on smoking and health.

Seymour Kaufman (March 13, 1924–June 23, 2009, at 85) was a scientist in NIMH whose work helped lay the groundwork for understanding genetic disorders such as phenylketonuria.

Annie Le (July 3, 1985–September 8, 2009), an Undergraduate Scholarship Program Scholar from 2005 to 2007 in NIAMS, was murdered in her lab at Yale University (New Haven, Conn.), allegedly by a co-worker.

Constantine "Dean" Londos (died on December 6, 2009) was an NIDDK researcher whose pioneering studies led to a penetrating vision of adipose tissue as a novel regulatory organ and of lipid droplets as unique, dynamic organelles.

Lawrence E. Shulman (July 25, 1919–October 10, 2009) became the founding director of NIAMS in 1986, a post he held until 1994.

Ichiji Tasaki (October 21, 1910–January 4, 2009) set a record as the oldest scientist to retire from NIH—in September 2008 at the age of 97. His research in NIMH included the groundbreaking discovery that neuronal impulses jump from gap to gap in myelinated axons via saltatory conduction.

Robert Wenthold (June 20, 1948–Oct 30, 2009) was the scientific director of NIDCD and recognized for his work on glutamate receptors.

Herman Ziffer (died on November 6, 2009), worked in what is now NIDDK, published on photochemistry, enzymatic synthesis, neurotoxins, and antimalarial drugs and discovered, in now-classic studies, a new type of asymmetric synthesis. ■

The SIG Beat:
News from and about the NIH Scientific Interest Groups

NEW SIG: Probiotic and Prebiotic Working Group

The Probiotic and Prebiotic Working Group (PPWG) is a trans-NIH effort that was formed in 2006 to identify gaps and challenges in prebiotic and probiotic research. The group's goals include facilitating interactions and collaborations among research scientists in the field of probiotics and prebiotics; advancing prebiotic and probiotic research; and understanding the role of gut microbiota and the use of prebiotics and probiotics in health and disease.

To achieve these goals, the working group strives to promote constructive interactions across NIH institutes, centers, and offices. It disseminates real-time information to keep PPWG members abreast of current and future activities occurring in the fields of probiotics and prebiotics. The group meets as needed to form allied partnerships and collaborate on various pre- and probiotic activities. PPWG sponsors and co-funds workshops and conferences geared toward topics related to pre- and probiotics.

PPWG is delighted to add new members who plan to play an active role within the group; however, membership is limited to NIH employees. Please e-mail group coordinator Crystal McDade-Ngutter at mcdadengutterc@niddk.nih.gov if you are interested in joining the PPWG. The website is at http://sigs.nih.gov/ppwg.

NEW SIG: TGF-Beta Superfamily Interest Group

The transforming growth factor–beta (TGF-beta) superfamily occupies a central position in the signaling circuits that control cell growth, differentiation, and death. Seminal work has resulted in a deeper appreciation of the integration of TGF-beta pathways into signaling networks at large and their disruption in a wide variety of human disorders. Although TGF-beta remains elusive in terms of our complete understanding of its multifunctional modes of action, its potential as a therapeutic target in many pathological settings is promising.

The TGF-beta Superfamily Interest Group keeps abreast of advances in the field of TGF-beta superfamily research and in our understanding of the global ramifications when TGF-beta signaling goes awry in diseases such as cancer, diabetes, obesity, immunological disorders, and pathological fibrosis. This group also serves as a platform for dissemination of TGF-beta-related reagents and expertise on campus. The group's moderators are Lalage Wakefield (NCI) and Sushil Rane (NIDDK). They invite all investigators interested in TGF-beta research to join. The website is at http://sigs.nih.gov/TGF-beta. ■

News You Can Use: AAHRPP

The Office of Human Subjects Research is ramping up for the Association for the Accreditation of Human Research Protection Programs (AAHRPP) accreditation process.

That's pronounced "a-harp." Some of you, expressing your anxiety, are inserting too much "ahhhhh" in AAHRPP. But this is not the kind of accreditation that's do or die, pass or fail.

Accreditation is not a goal in and of itself, but rather is about creating an integrated and shared human-research protection program that has good facilities, is user-friendly and efficient, and puts the minimum burden on investigators and institutional review boards (IRBs).

Jeffrey Cohen, a consultant based in New York City who has shepherded several organizations through AAHRPP accreditation, presented an overview at a joint meeting of clinical and scientific directors in November. We are hiring him to help with our Human Research Protections Program accreditation. He explained how consistency is essential in human research to advance treatments and cures while protecting human subjects of research.

Someone in the audience asked, quite reasonably, how uniformity is possible or even desired at the NIH, given the number of diverse IRBs.

Cohen conceded that decentralization and the diversity of IRBs can be a pitfall for accreditation but that consistency does not mean uniformity. That is, there can be consistency with flexibility to allow the kinds of research we do here.

And this mix gets to the heart of the question of efficiency, particularly as we move to improve and increase clinical research with more multi-institute participation.

In seeking this accreditation, we are conducting a comprehensive review of our human-research protection programs to identify and address any weaknesses and to enhance our strengths. This process, regardless of whether it carries the AAHRPP brand, is long overdue.

In the coming months those of you involved with clinical research will hear from Charlotte Holden, the acting director of the Office of Human Subjects Research, and two others in her office recently recruited: Leody Bojanowski, the accreditation team leader, and Mo Elsafy. Like you, they hope to conduct their work as noninvasively as possible.

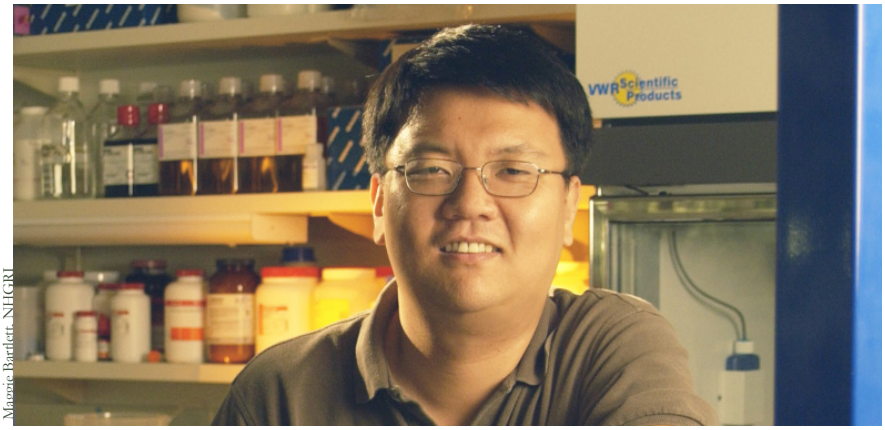
We have started with the self-evaluation and preparation of materials, and we plan to submit an application next spring. This will ultimately lead to the AAHRPP site visit next fall.

Can we continue with business as usual without the accreditation? To remain a world leader in translational and clinical research, we really don't have that luxury.

—Michael Gottesman, DDIR

Colleagues

Recently Tenured



Maggie Bartlett, NHGRI

Kyungjae (KJ) Myung, NHGRI

Working at NIH is the best environment for a young investigator, says **Kyungjae (KJ) Myung,** *who's a recently tenured senior investigator in NHGRI. There's "lots of collaboration and lots of learning." Myung came to NIH in 2002 after completing a postdoctoral fellowship at the Ludwig Institute for Cancer Research, University of California at San Diego. He earned a masters degree in molecular biology from Seoul National University (Seoul, South Korea) in 1993 and a Ph.D. in molecular, cell biology, and biochemistry from Brown University (Providence, R.I.) in 1999. Myung heads the Genome Instability Section in NHGRI's Genetics and Molecular Biology Branch. When he's not working, he enjoys playing the piano and playing tennis with some of his colleagues.*

The long-term goal of my lab's research is to understand the mechanisms of the genome instability frequently found in many genetic disorders including cancer. We are investigating DNA repair, replication, and recombination mechanisms and their roles in the production and suppression of gross chromosomal rearrangements (GCRs). Using a whole-genome screening method that we developed, our laboratory is studying some of the pathways that maintain genome stability and, when perturbed, contribute to the occurrence of GCRs. Recently, in a genome-wide screen of yeast, we identified 10 more genes that encode proteins that suppress GCRs.

We have focused on post-replication repair (PRR) pathways in yeast. There are two PRR mechanisms: a template-switching mechanism regulated through proliferating cell nuclear antigen (PCNA) poly-ubiquitination and a trans-lesion synthesis mechanism regulated through PCNA mono-ubiquitination. RAD5 ubiquitin ligase functions in the center of the template-switching mechanism. We discovered its human homologs—two mammalian RAD5 genes, called *SHPRH* and *HLTF*—that the scientific community had been trying to find for 20 years. These two genes have been implicated as tumor-suppressor genes, suggesting we have linked the tumor-suppressor roles of *SHPRH* and *HLTF* (the proteins SNF2 histone linker PHD RING helicase and helicase-like transcription factor) to their mechanism in DNA repair.

We also identified *ELG1*, a novel gene that suppresses genomic instability through its interaction with PCNA. In studies of higher mammals, we found that *ELG1* regulates the level of ubiquitinated PCNA and functions as a tumor suppressor.

In an effort to find genes that promote genomic instability in yeast we identified Mph1, which is a yeast homolog of the Fanconi anemia M protein. Fanconi anemia is a rare genetic blood disorder that involves a defect in the repair of cross-linking DNA damage. We demonstrated that Mph1 functions in the repair of cross-linking DNA damage, and we have started to dissect the mechanisms of how yeast repair cross-linking DNA damage and to extend the conserved role of Mph1 in mammals. ■

A year after earning his Ph.D. in biochemistry from the University of Arizona (Tucson) in 1995, **Jesus Valenzuela** *joined the Laboratory of Parasitic Diseases in NIAID. Today he's the chief of the Vector Molecular Biology Section in NIAID's Laboratory of Malaria and Vector Research. He recently received a Gates Foundation exploration grant for testing salivary-based vaccines in Rhesus macaques using a natural model of transmission. "I have found at NIH a great environment to perform science at the highest level," he says. "The infrastructure, the critical mass of renowned scientists, the flow of ideas and discussions, [and] the exposure to the different basic and clinical research areas makes this institute a unique place to do research."*

Jesus Valenzuela, NIAID

I work on something that is a bit unfamiliar to most investigators at NIH—the saliva and gut proteins from insects that transmit pathogens. I am very much interested in understanding the repertoire of molecules in the saliva and guts of sandflies (insects that transmit the parasitic disease leishmaniasis to animals and humans) and how immunity to these molecules can protect against a parasitic disease. Leishmaniasis takes several different forms, including the most common cutaneous leishmaniasis, which causes skin sores, and the more severe visceral leishmaniasis, which affects internal organs such as the spleen, liver, and bone marrow.

We hypothesize that immunity to a specific sandfly salivary protein creates an environment that accelerates a protective immunity against the Leishmania parasite and that a salivary protein may be an important

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Recently Tenured

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component of an anti-Leishmania vaccine. We also discovered novel salivary molecules with powerful activities such an anti-complement, a serotonin-binding molecule, an anticoagulant, and a very powerful anti-inflammatory protein that may be relevant in pathogen transmission.

Another focus of my lab is the study of the molecular interactions between sandfly gut proteins and the Leishmania parasite. We found that this parasite alters the expression profile of some insect gut molecules and that antibodies to one of these molecules blocked the development of the parasite inside the sandfly. This discovery is quite exciting because this protein may represent a powerful transmission-blocking vaccine that can be used in the field to interrupt the development of the parasite inside the sandfly and prevent the transmission of leishmaniasis from animal reservoirs—such as dogs—to humans.

I am quite fortunate to be working with a very dynamic team of researchers who find the excitement to move the frontiers of science for the benefit of human health. ■

Calling All Recently Tenured

If you are an NIH intramural scientist or clinician and have been tenured within the past year or so, we invite you to write about your work in the "Recently Tenured" section of *The NIH Catalyst*. Scientists whose work has been profiled in previous issues have told us that being featured in the *Catalyst* increased campus-wide interest in their research.

All you have to do is either respond to our invitation or take the initiative and get in touch with us first. It's easy. You provide your CV and a photo, answer a few basic questions, and then write a brief (200-word) description of your work.

To find out more, please contact Laura Carter, managing editor of the *Catalyst,* at carterls@od.nih.gov or 301-402-1449. Or just say "Yes" when you get that invite in the e-mail.

—Laura Stephenson Carter, Managing Editor

Mark Creighton-Gutteridge

Daniel McVicar, NCI

One-time sailing instructor. Former head of a kitchen in a seafood restaurant. Now a senior investigator at NCI. Daniel McVicar sailed into a career as a scientist when he joined NIH as a postdoctoral fellow in 1990 after completing his Ph.D. training at the Medical College of Virginia, Virginia Commonwealth University (Richmond, Va.). He started out as a postdoc in the Laboratory of Experimental Immunology in NCI's Biological Response Modifiers Program. There, his observation that natural killer (NK) cells had high levels of protein tyrosine phosphorylation sent him on a search for novel tyrosine kinases. He discovered two novel kinases including Janus kinase 3 (JAK3), which is critical for the development and function of lymphocytes. Inhibitors of JAK3 are being tested as immune suppressants in clinical trials. In 1995 he became a senior staff fellow and by 1998 he was a principal investigator. Today he works in the Cancer and Inflammation Program, Center for Cancer Research. "The work environment at NIH is fantastic! People are supportive and eager to help," McVicar says. "The scientific flexibility that NIH provides permits the study of avenues that would otherwise have been ignored."

The immune system is unique in its requirement for rapid expansion upon exposure to a pathogen followed by an ordered contraction back to steady state once the danger has been cleared. Inappropriate immune activation can lead to autoimmunity or promote the development of cancer. Innate immune cells are often the first to encounter a pathogen, and they not only begin to clear the offending agent, but also are critical in orchestrating subsequent responses.

Since arriving at NIH I have been unraveling signal-transduction cascades used by innate immune cells as they respond to pathogenic insult. Much of my work has focused on the signaling of the receptor chain known as DAP12. This signaling chain was first thought to be critical in the regulation of natural killer (NK) cell responses only, but it has quickly become apparent that almost every innate immune cell expresses receptors that signal via DAP12. In addition to being expressed on many cell types, new data suggest DAP12-mediated signals can integrate with several other signaling pathways including those involved in pathogen recognition by the Toll receptors, cellular adhesion, cytokine responses, and even signaling from proto-oncogenes.

We recently demonstrated that a platelet-specific gene we discovered within a cluster of DAP12-coupled receptors, although DAP12-independent, is involved in the regulation of platelet function during inflammatory conditions such as sepsis.

Our finding shows that this gene cluster regulates multiple facets of an inflammatory response—from the response of leukocytes to pathogenic signals to the control of vascular integrity at the infection site. Understanding the intricacies of DAP12 signaling and how these pathways integrate and modulate other signaling pathways is likely to lead to significant understanding of the role of innate immune cells in control of inflammation and cancer and provide novel targets for therapeutic intervention. ■

ANNOUNCEMENTS

NIH Management Intern Program

Are you looking to apply your intramural experience toward a new career and climb the career ladder in administrative management? The NIH Management Intern Program has a history of developing exceptional administrative managers through training, rotations, and mentoring by senior NIH leadership. Interns are exposed to managerial career tracks in budget, grants management, contracts, information technology, human resources management, program and management analysis, and general administration. The vacancy announcement will open on February 12, 2010, and close on March 12, 2010. Candidates are encouraged to attend information sessions on February 5, 10, 17, 23, or March 2. For more information, visit http://www.jobs.nih.gov/intern/about.html or e-mail mi_info@od.nih.gov.

Seventh Annual Jeffrey M. Trent Lectureship in Cancer Research Tuesday, January 19, 2010 1:00–2:00 p.m. Masur Auditorium (Building 10) (Overflow in Lipsett Auditorium)

Nobel Laureate Carol Greider, Ph.D., will present "Telomerase and the Consequences of Telomere Dysfunction." Greider, a professor at Johns Hopkins University School of Medicine in Baltimore, shared the 2009 Nobel Prize in Physiology or Medicine with two others "for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase."

"I Am Intramural" We Are Listening . . .

What are the reasons your coworkers like working for the Intramural Program? Follow "I Am Intramural" on Twitter, where you'll receive updates of the latest stories and opinions of NIH intramural employees at http://twitter.com/i_am_intramural. Share your comments at http://iamintramural.nih.gov and your input might be one of the stories we tweet about!

—Natalie Giannosa, NCI

NIH Research Matters

Research Matters is a review of NIH research, gathered and presented by the Office of Communications and Public Liaison. Every two weeks recent intramural and extramural NIH research is highlighted in digestible nuggets with images and links, usually in doses of three. To find out more, visit http://www.nih.gov/researchmatters.

Wednesday Afternoon Lecture Series Update 3:00–4:00 p.m. Masur Auditorium (Building 10)

Wednesday, January 20, 2010: Cancelled

Thursday, March 11, 2010: Nobel prize winner Dr. Mario Capecchi will present a Director's Lecture.

Thursday, May 20, 2010: Carol Robinson, a professor of the Royal Society at the University of Oxford, England, will present "From Rare Gases to Ribosomes." (rescheduled from January 20, 2010)

Frontiers in Intravital Microscopy February 8–9, 2010 8:30 a.m.–4:15 p.m. each day Natcher Auditorium (Building 45)

This two-day symposium, organized by NIDCR, will complement a hands-on course scheduled for February 10–12 (registration required for that). The symposium will focus on the state of the art in intravital microscopy in different areas of biomedical sciences such as cell biology, immunology, neuroscience, stem cells, and tumor biology. The goal is to educate investigators within the NIH intramural community about this technique and its potential applicability to their work. Top scientists in the field will be the featured speakers. No registration is required. For more information, visit http://www.nidcr.nih.gov/Research/NIDCRLaboratories/OralPharyngeal/IntravitalMicroscopy.htm or contact Roberto Weigert at weigertr@mail.nih.gov.

Demystifying Medicine Is Back

This course consists of presentations about patients, pathology, diagnosis, and therapy in the context of major disease problems and current research. Primarily directed toward Ph.D. students, fellows, and staff, the course is also of interest to medical students and clinicians and is designed to help bridge the gap between advances in biology and their application to major human diseases.

Each session includes clinical and basic science components, which are presented by NIH staff and outside invitees. Those seeking academic credit may register with FAES. Those not seeking academic credit should register through the course e-mail list. For details visit http://demystifyingmedicine.od.nih.gov or contact Win Arias at ariasi@mail.nih.gov. (See lecture dates and topics in column to right.)

Demystifying Medicine 2010 Tuesdays 4:00–6:00 p.m. Ground Floor Auditorium Building 50

Jan. 12: "Tuberculosis: The Great White Plague"; Steven Holland (CC), Clifton Barry (NIAID)

Jan. 19: "Hepatitis C: A Global Time Bomb"; Harvey Alter (CC), Patrizia Farci (NAID)

Jan. 26: "HIV: Getting Better and Worse"; John Coffin (NCI), Henry Masur (CC)

Feb. 2: "Swine and Other Flus: An Epidemic/Pandemic?"; Jeffrey Taubenberger (NIAID, Gary Nabel (NIAID)

Feb. 9: "Diarrheal Diseases: Global Killers at All Ages"; Roger Glass (FC), John Robbins (NICHD)

Feb. 16: "Horror Autoinflammaticus: Expanding Spectrum of Inherited Disorders of Inflammation"; Daniel Kastner (NIAMS), Ivona Aksentijevich (NIAMS)

Feb. 23: "Schizophrenia in the Genomic Age"; Daniel Weinberger (NIMH), Joseph Apud (NIMH)

March 2: "Drug Addiction: Marihuana and Stronger Stuff"; Nora Volkow (NIDA), George Kunos (NIAAA)

March 9: "Friederich's Ataxia: An Iron Link"; Kenneth Fischbeck (NINDS), Tracey Rouault (NICHD)

March 16: "Natural Products: Keys to Treating Cancer and Infection"; Carole Bewley (NIDDK), David Newman (NCI)

March 23: "Inflammatory Bowel Disease: Crohn's Disease and Ulcerative Colitis"; Warren Strober (NIDDK), Michael Yao (NIDDK)

April 6: "Prostate Cancer: Mechanisms, Epidemic, Treatment"; Kathleen Kelly (NCI), William Dahut (NCI)

April 13: "Breast Cancer: Genetic and Other Mechanisms"; Lawrence Brody (NHGRI), Kathleen Calzone (NCI)

April 20: "Diabetes: Autoimmunity and Therapeutic Challenges"; Abner Louis Notkins (NIDCR), Jean-Marc Guettier (NIDDK)

April 27: "Stem Cells: Where Do We Stand?"; Ronald Mckay (NINDS), Cynthia Dunbar (NHLBI)

May 4: "Autism: What Do We Know?"; Tom Insel (NIMH) And TBN

May 11: "FINALE: What Does The Future Hold for Ph.D.s?"; Michael Gottesman (OD), Jonathan Yewdell (NIAID), William Galey (HHMI), Win Arias (NICHD)

Research Festival

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showed that FTIs, originally developed for cancer, can reverse the dramatic cell-structure abnormalities present in progeria.

Although it is still too early to tell whether the clinical trial will show the FTIs to be effective in treating progeria, Collins indicated that an increase in physical growth would be one method to measure success.

Still, Collins is pleased with the progress made so far. "To go from a condition that was essentially a death sentence six years ago with no knowledge of its cause, to now having essentially all the progeria kids that can be identified in the world enrolled in a clinical trial is a pretty amazing consequence," he said.

Nearly 450 posters and exhibits were displayed at the 2009 NIH Research Festival.

Influenza A: Pathogenesis and Pandemics

NIH is leading the attack on flu on all fronts as they investigate how new strains emerge—including pandemic flu such as the 2009 H1N1 strain—and evade the immune system. They are also exploring the development of new vaccines.

The 2009 H1N1 virus, which began to spread in Mexico and the United States in the spring of 2009 and spread all over the world, returned to the Northern Hemisphere this fall.

"The virus is causing [the] most severe disease in children and young adults," said Jeffery Taubenberger, senior investigator in NIAID. "Mortality, while lower than [in] past pandemics, has been associated with a younger age group than typically seen in seasonal influenza."

Normally the spread of seasonal flu is prevented or slowed when portions of the population have been immunized against or have had prior exposure to the strain that is circulating. When vast numbers of the population do not have any pre-existing immunity to a new influenza A strain, mass vaccination is the only weapon to fight a pandemic.

"There is no question that the best way to curtail an impending pandemic is by global vaccination," said Hana Golding, a scientist in the Food and Drug Administration's Laboratory of Retroviruses. She's helping to develop new molecular tools to evaluate responses to flu vaccines. "Our concerted efforts right now are to try and provide enough doses to vaccinate most of the susceptible, high-risk population both in the United States and [around] the world."

Influenza A occurs annually in all types of warm-blooded animals, including humans, with new virus strains emerging each year, Taubenberger explained. As the virus strains mutate, infection can occur in individuals who have no pre-existing immunity.

Sometimes animals or humans can become infected simultaneously with two different strains of the influenza A virus. As the strains exchange genes in a re-assortment process, an entirely new strain, or daughter virus, emerges. Such new strains can lead to flu pandemics because no one has immunity to the new virus.

That's what happened with H1N1. It is known that two separate H1N1 flu strains had been evolving simultaneously, but separately, explained Taubenberger. It's unclear "why these two [H1N1] viruses—which had each circulated for decades [in swine] and occasionally caused human infection—did not cause a pandemic until a re-assortment event occurred that led to a fully transmissible human virus."

Uncertainties as to why H1N1 caused an epidemic now, compounded by influenza A's annual antigenic drift, make this virus a constantly evolving enemy.

"Antigenic drift is the reason we have to make new flu vaccines each year," said Scott Hensley, a researcher in NIAID's Laboratory of Viral Diseases. "When we pick a flu stock for the vaccine, often the virus drifts so much that vaccine stock is no longer effective."

NIH scientists compare the new virus's lineage, or genetic relationship to past pandemic and seasonal flu strains, to better understand how to fight the flu. Because this year's H1N1 strain shares genes with the 1976 swine flu, "prior exposure to antigenically related H1N1 viruses of swine origin by prior infection or receipt of the swine flu vaccine of 1976 will likely provide some protective immunity against the 2009 pandemic H1N1 virus," said Kanta Subbarao, NIAID senior investigator. "These vaccines represent a strain change, not new vaccines."

NIAID flu investigator Jeffery Taubenberger was one of several NIH flu experts who talked about research aimed at developing a better understanding of seasonal and pandemic flu and efforts to create a universal flu vaccine.

It's been recommended that people with chronic health disorders or compromised immune systems receive the H1N1 vaccine because they may face potentially fatal complications if they become infected. In fact more than 90 percent of H1N1-related deaths occur in patients with serious underlying medical issues. To better understand the severity of the disease, Taubenberger and his colleagues worked with New York City medical examiner James Gill to study 34 fatal cases of H1N1. Those who died had a median age of 41 years, and most had serious underlying medical issues, such as congestive heart failure, asthma, cancer, and AIDS. And 70 percent of people who died were obese.

Even seasonal flu can be fatal. Each year in the United States seasonal influenza kills more than 36,000 people and hospitalizes 200,000 more. A universal flu vaccine would help prevent seasonal as well as pandemic flu. Developing a universal flu vaccine may be possible in the future once there's a better understanding of the structure and genetics of the flu virus and if the potency and breadth of a new vaccine could be achieved, explained NIAID vaccine research scientist Gary Nabel. "If we're able to develop a vaccine that could hit the pandemic strains, that's not enough," said Nabel. "We need to be able to hit the circulating seasonal flu strains."

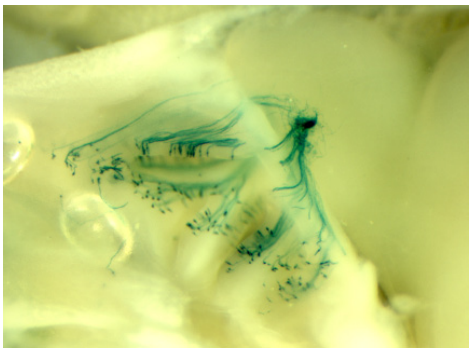
It may be a while before we see a universal vaccine. In the meantime, NIH scientists remain vigilant in their fight against seasonal and pandemic flu. ■

(All photos: Bill Branson)

Research Festival Highlights:
Selected Symposia (A Stroll Through the Festival)

From Cell Fate to Neural Circuitry

To paraphrase Cassius in Shakespeare's *Julius Caesar*, "neurons at some time are masters of their fates." Nowhere was Cassius more right than at the neurogenesis symposium, where presenters discussed their efforts to understand how cells master their own fates in the developing nervous system.



Olfactory sensory neurons in newborn mice. Leonardo Belluscio (NINDS) has shown that changing an olfactory receptor alters the function of the olfactory neuron, causes it to project its axons on a different part of the olfactory bulb. (photo by Kai Cheng, NINDS)

The olfactory system provides one exciting playground for researchers trying to understand how cells' fates are determined. Cells in the nasal epithelium, the first locus in odor detection, regenerate continuously from stem cells so that the olfactory system is constantly rewiring itself. This process gives researchers such as **Leonardo Belluscio** (NINDS) a chance to examine the interdependence of the sensory neuron cell's molecular identity, function, and neural circuitry. Each olfactory sensory neuron expresses just one odorant receptor—out of more than 1,000 possibilities—which allows it to detect specific odor molecules. The type of receptor determines where the neuron projects its axons on the olfactory bulb (an area of the brain that processes odor information).

Belluscio's group and others have shown that changing an olfactory receptor (either by swapping receptors that normally occur in other locations or by modifying the genetic coding) alters the function of the olfactory neuron, causes it to project its axons on a different part of the olfactory bulb, and even affects the subsequent connections deeper in the olfactory bulb.

Debra Silver (NHGRI) works with a mouse model to understand the genetics of microcephaly (abnormally small head and brain. Her mice have a defect in a gene that is involved in the division of neural stem cells. In the healthy developing brain the gene allows for stem cells to divide into either two new stem cells or a stem cell and a neuron; in microcephalic mice, stem cells divide disproportionately into neurons, which failed to keep up the stem cell populations.

The symposium also featured **Edward Giniger** (NINDS), whose work with fruit flies helps to explain how segments of the nerve cord connect to each other, **Mihaela Serpe** (NICHD), who explores the fine-tuning of signaling gradients, also in fruit flies, and **Thomas Brody** (NINDS), who uses an EvoPrinter (a multigenomic comparative tool for rapid identification of functionally important DNA) and other DNA analysis programs to compare enhancers in—you guessed it—fruit flies.

—Eric Schaffer

Regulation of the Immune Response

The immune system affects tissue and vice versa, explained NIH scientists whose research into how different tissues interact with the immune system may result in future therapies for cancer and other diseases.

On the cancer front, **Andy Hurwitz** (NCI-Frederick) is looking at the connection between autoimmune disease and tumor immunity using a mouse model of prostate cancer. He and colleagues have discovered that prostate tumors in mice can cause immune cells known as CD8+ T cells to change their function from antitumor activity to suppression of immune responses. This finding has important implications for the design of immune-based therapies for cancer and may help explain why some cancer patients' initial response to immune-based therapy is promising but fails with time.

NIH research may also lead to better treatments for people with asthma. Postdoctoral fellow **Karin Fredriksson** (NHLBI), who is investigating airway inflammation and hyperreactivity in allergic asthma, is determining how exosomes (complete sets of exons, which contain genetic information needed to produce proteins), derived from antigen-pulsed immature dendritic cells, inhibit airway hyperreactivity in mice with asthma.

NIH researchers are focusing on other immune diseases, too. NEI researchers **Reiko Horai** and **Rachel Caspi** are using a new mouse model of uveitis (inflammation of the eye) to understand the special relationship between the immune system and the eye and to design novel strategies for immunotherapy that may also help with other tissue-specific autoimmune diseases.

Ethan Shevach (NIAID) talked about his work with natural and adaptive regulatory T cells that control immune responses in the skin, stomach, and central nervous system. And **Yasmine Belkaid** (NIAID) talked about her discovery that the DNA of beneficial, or commensal, bacteria in the intestines defends the body against infections. An immune response to beneficial bacteria in the gut causes problems such as Crohn's disease. She hopes that one day beneficial bacteria may be used as targets for oral therapies against infections or autoimmune diseases.

—Angel Davey, NIAID

Large-scale RNAi Screening

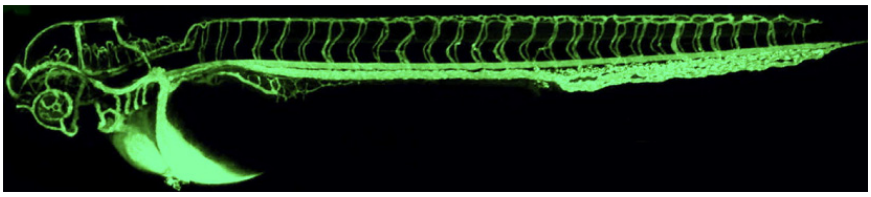
A fully automated, genome-wide RNA-mediated interference (RNAi) screening facility, which will soon be available, will enable NIH researchers to process cell-based screens of more than 100,000 microplate wells quickly and uniformly. The facility is scheduled to open in 2010 and will be housed in NIH's Chemical Genomics Center (NCGC), explained NCGC director **Christopher Austin** and RNAi screening team leader **Scott Martin**. RNAi is a gene-silencing process in which double-stranded RNAs trigger the destruction of specific RNAs.

Austin and symposium co-chair **Natasha Caplen** (NCI) described existing RNAi work on campus and pointed out the high-throughput screening facility's potential benefits, which include limiting potential bias in identifying genes of interest, accelerating the screening timeline, and offering a better and more comprehensive understanding of gene function, gene-related drug activity, pathway analysis, and molecular targets.

Information gathered from RNAi screenings can help researchers pinpoint disease-specific genes. **Louis Staudt** (NCI) discussed the potential for RNAi screenings to better identify the essential genes of cancer, target drugs to these specific genes, and lead, he hopes, to different therapeutic approaches for patients and cancers.

Cancer researchers aren't the only scientists who can benefit from this screening facility. **Liping Zhang** (NIDCR) is using RNAi in Drosophila cell cultures to understand the cellular interactions that take place during development and hopes that the knowledge gained will also shed light on glycosylation of proteins in mammalian systems. **Iain Fraser** (NIAID) emphasized that high-throughput screenings allow researchers to rely on data sets that are more comprehensive because they represent complex cell input and stimuli. Echoing these potential implications, **Brian Oliver** (NIDDK) explained that a better understanding of cell mechanism and function through an RNAi screen will help researchers answer the question, "What are these genes doing?"

—Sarah Freeman



Green fluorescent microspheres, intravascularly injected into a 2.5 day old zebrafish larva, allow high-resolution visualization of the entire vascular system. (Confocal microscopy image courtesy Brant Weinstein, NICHD)

Organ Morphogenesis

It's a good thing that NIH scientists aren't fazed by the adage "a watched pot never boils" when it comes to watching how organs evolve. Several of these patient observers of organ morphogenesis enthusiastically reported on their research at the 2009 Research Festival. Organ morphogenesis is an essential developmental process during which an organ takes or changes its shape. Morphogenesis occurs in embryos, in mature organisms, and inside tumors. Understanding the molecular, cellular, and extracellular mechanisms and multitissue interactions of these developmental processes can help scientists gain insights into tumor growth as well as develop tools for regenerative medicine.

By observing how limbs develop in mice, **Susan Mackem** (NCI) aims to understand how normal transcription programs regulate normal skeletal morphogenesis during development during development. She plans to apply what she's learned to deciphering abnormal gene-expression patterns in tumors and to devising new strategies to intercept cellular targets that are driving tumor-cell behavior.

Kenneth Yamada (NIDCR) studies embryonic tissues to determine the mechanisms of tissue assembly and regeneration. He has found that epithelial cells in the mouse submandibular gland self-organize and undergo branching morphogenesis to form tissues with structural features characteristic of the intact gland. Branching morphogenesis, whereby a single epithelial bud branches repeatedly to become a complex network of tubules and cysts, plays a critical role in the development of many organs including the lungs, kidneys, mammary glands, and salivary glands.

Watching organs evolve may even help scientists such as developmental biologist **Matthew Kelley** (NIDCD) find a way to reverse deafness. Kelley is teasing apart the genetic pathways by which cells develop in the cochlea, a structure in the inner ear. NICHD colleague **Brant Weinstein** is equally determined to harness the power of angiogenesis. He uses the transparent zebrafish to study the development of the embryonic circulatory system and the signaling pathways that regulate the creation of new blood vessels. And **So Yoon Kim** (NIDDK) is investigating morphogenic factors involved in the development of the pancreas.

—Laura Stephenson Carter

Antibody-based Therapies for Human Disease: Hope of the Future

Antibodies can be used to neutralize or detect proteins and are being engineered to treat and diagnose disease, explained **David FitzGerald** (NCI), one of several NIH researchers developing antibody-based therapies.

Ira Pastan (NCI) described how he and colleagues David FitzGerald and Robert Kreitman generated recombinant immunotoxin BL22 by fusing a portion of a CD22 antibody to a portion of a toxin secreted by the *Pseudomonas aeruginosa* bacteria. The antibody portion of BL22 binds to the CD22 receptor, which is found in abundance on the surface of leukemia cells including the rare hairy cell leukemia (HCL). Several years ago Pastan and colleagues reported that BL22 produced complete remission in most drug-resistant HCL patients they treated.

Since then, researchers have made improvements in BL22 including increasing its activity so it will be more effective in harder-to-treat leukemias such as chronic and acute lymphocytic leukemias. They are also testing in patients ways to increase the efficacy of an immunotoxin that targets the mesothelin antigen expressed in mesothelioma (an aggressive cancer associated with exposure to asbestos fibers) and many other solid tumors.

Weiting Zhang (NCI) discussed using magnetic resonance imaging and positron-emission tomography to image the effects of therapeutic antibodies on the vascularity of glioblastoma, a fast-growing, usually fatal brain tumor. **Mitchell Ho** (NCI) shared his progress with antibodies to mesothelin. Antibodies have also been engineered against human immunodeficiency virus type 1 using the human variable and constant region 2 heavy chain domains (units of protein structure). According to **Dimiter Dimitrov** (NCI), these domain antibodies and "nanoantibodies" are the smallest functional fragments possible and show great promise in clinical trials.

Gastroenterological diseases can also be caused by immunologic abnormalities. **Warren Strober** (NIAID) is making cytokine-neutralizing antibodies for use against autoimmune inflammatory bowel diseases. Clinical trials are under way testing agents that neutralize interleukin-12 in Crohn's disease and interleukin-13 in colitis.

NIH researchers' continuing enhancements of early-generation antibodies are giving hope to patients with cancer as well as those with infectious and inflammatory diseases.

—Erika Ginsburg, NCI

The Plastic Nervous System

"The Jan Brady of the hippocampus" is what **Serena Dudek** (NIEHS) calls the underappreciated CA2 region. Like the TV character's more exciting sisters, who attracted attention for their cheerleading abilities and pigtails, hippocampal regions CA1 and CA3 are more noticed—for demonstrating long-term potentiation (LTP), a form of synaptic plasticity that is critical to memory. But like Jan Brady, the CA2 region is poorly understood other than for its insensitivity to toxins and trauma. Dudek's group, in helping to draw CA2 out of her sisters' shadows, has shown that CA2 neurons can demonstrate LTP when exposed to high levels of calcium. The findings suggest that CA2 plays a more nuanced and vital role than once suspected—like Jan Brady, who eventually realized she was just as groovy as her sisters.

Other research findings presented at the symposium were equally impressive. Graduate student T**ina (Tze-Tsang) Tang** (NINDS) described her efforts to shed light on the elusive mechanisms of dysbindin, a protein associated with schizophrenia. Tang's project has shown that dysbindin modulates hippocampal *N*-methyl-d-aspartate receptors that are associated with synaptic plasticity and disrupted in schizophrenic brains.

John Isaac (NINDS) reported on the role of synaptic plasticity in the development of the mouse barrel cortex, a brain region that processes signals from whiskers. **Michael Schmid** (NIMH) is trying to understand how the brain's visual circuits repair themselves after injury. Schmid's findings suggest that a recovery mechanism involves information bypassing the primary visual cortex, where visual processing in the cortex normally begins, and flowing directly to the visual association areas, where higher-level processing takes place.

Finally, **Leonardo Cohen** (NINDS) explained how transcranial direct-current electrical stimulation and magnetic stimulation can facilitate motor learning in stroke victims. He hopes that one day these techniques—in combination with other neurorehabilitative treatments—will be widely used to help stroke victims and people with artificial limbs regain motor function.

—Eric Schaffer

Immunity in Tropical Parasitic Diseases

NIH researchers are bent on defeating filariasis, malaria, leishmaniasis, and other tropical parasitic diseases that entrap their victims in a vicious cycle of poverty and disease.

Lymphatic filariasis, also known as elephantiasis, affects nearly 130 million people worldwide in more than 80 countries. The disease is caused by parasitic worms that reside in the human lymphatic system and produce microfilariae that circulate in the blood, where they can be picked up by mosquitoes for transmission.

Amy Klion (NIAID) described her work on post-treatment reactions in filariasis. And **Thomas Nutman** (NIAID) proposed several mechanisms to explain the observation that T cells are hyporesponsive in filariae-infected patients. The Nutman lab also probes whether chronic filarial infections modulate the immune responsiveness to and clinical expression of malaria.

Malaria is the focus of **Carole Long's** research at NIAID. She is analyzing the interface between the erythrocytic stage of parasite infection and the immune system of children and adults. *Plasmodium falciparum* is the protozoan parasite responsible for the most dangerous of malaria infections.

In humans, these mosquito-transmitted parasites multiply in the liver and then infect red blood cells. Immune resistance is slow to develop in children, and the investigators are trying to understand the acquisition of natural immunity.

Yang Huang (NLM), who is also working on malaria, reported on a novel computational approach to detect the link between genetic variation and gene regulation in *P. falciparum*.

David Sacks (NIAID) is investigating the immunology and cell biology of another tropical disease—leishmanial infections carried by Leishmania parasites, which are spread by sandflies. He is developing immune-based therapies to treat the visceral (most severe) form of the disease. What he learns may also have relevance to diseases, such as tuberculosis, caused by other intracellular pathogens or to other vector-borne diseases, such as malaria.

—Angel Davey, NIAID

High-risk Susceptibility Genes

Discovering rare high-risk disease susceptibility genes is a complicated business, but NIH researchers are up to the challenge. **Joan Bailey-Wilson** (NHGRI) cited the challenges and successes of genome-wide association studies (GWAS) and traditional linkage studies in identifying risk genes. GWAS allows scientists to study genetic variations across the entire human genome by comparing the DNA of individuals with and without a particular disease. Through GWAS, scientists have detected many common genes associated with a low risk for disease but have not yet been able to identify high-risk genes. Other types of studies, however, such as familial linkage studies—in which researchers look at the relationships of genes located near one another on a chromosome in parents and offspring with particular diseases—have identified several high-risk susceptibility genes.

By combining linkage studies with genome-wide analysis for copy-number variations in sequences of DNA, **Rose Yang** (NCI) identified a risk gene for familial chordoma, a rare bone tumor that occurs in the base of the skull, the vertebrae, or the sacrum. Linkage analysis implicated a gene that encodes brachyury, a regulator of the development of the notochord (the embryonic precursor to the spinal column), but detected no genetic mutations. The researchers then looked for copy-number variants in the entire genome in families afflicted with the disease and successfully identified a genetic duplication in four families affected with chordoma.

Computational geneticist **Jim Mullikin** (NHGRI) discussed his use of large-scale medical sequencing to identify significant risk genes for cardiovascular disease. In an ongoing NIH study of cardiovascular risk factors in which 735 participants have been enrolled and 320 candidate risk genes have been examined to date, researchers have identified significant mutations within a few genes.

Alexander Wilson (NHGRI), **Alisa Goldstein** (NCI), and **John Choy** (NCI) also described efforts to discover ways to identify high-risk susceptibility genes and opportunities to improve gene discovery.

—Lisa Nichols, NIMH

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In Future Issues...

- Undiagnosed diseases
- Prions
- Stem Cells

Laboratory Confessions:

My Love Affair with Drosophila

By Name Withheld

Perhaps not even my wife knows the full extent of my love affair with Drosophila. I'm not particularly discreet, though, when I see a good-looking fruit fly in the office or on the street. I'll gawk. I'll go out of my way to get closer and make my move. My heart will start to race as I try to get to know it a little better, you know, ascertain its sex and eye color—perhaps not unlike what some people do when they encounter members of their own species. I can make some fairly detailed observations without a microscope; impressive considering the fly is only a few millimeters long.

In contrast, half the time I can't remember the names of people I have just met, and I most certainly couldn't describe their eye or hair color or even clothing. I'd make a lousy witness. (No, your honor, I don't remember whether the suspect was flashing a gun. I was distracted by the brilliant vermilion eyes on a fruit fly dining on an overripe banana. No doubt a wild type. Sigh.)

A lot of research has been done on Drosophila mating. Unlike dogs and other lower animals, fruit flies don't do it with just anyone. There's an elaborate courtship of dancing, singing, and licking. I've collected a lot of images, which fortunately are not (yet) banned on the NIH computer system. Yet is my compulsion really so strange? We and the flies have much in common, roughly 75 percent of the same genes. You might grow to love them, too. I'm not jealous. There's enough to go around. I'll be watching them tonight, once I phone the wife to tell her I'll be late again.

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

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