Fostering Communication and Collaboration

The NIH Catalyst

A Publication for NIH Intramural Scientists

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New Age Mutant NIEHS Researchers

Mutagenesis experts at NIH

By Brian Chorley

Some mutations defy explanation—for example, how a horrific toxin can ooze down a storm grate and smother discarded pet turtles with radioactive goo, transforming them into shelled humanoid creatures with super ninja powers.

Yet other mutations are now well understood, thanks in large part to nearly three decades of research by scientists in the Laboratory of Molecular Genetics (LMG) at the National Institute of Environmental Health Sciences (NIEHS).

From its base in Research Triangle Park, N.C., this tight-knit group of eight principal investigators and 70-some supporting researchers have come to dominate the field of mutagenesis research, authoring more than 250 publications within the past five years alone and commanding $6 million of NIEHS's $850 million annual budget.

These researchers track the replication, repair, and recombination activities of mutating DNA, the result of the mammalian genome modifying itself tens

Courtesy Frank Boelhmann

Scientists in NIEHS's Laboratory of Molecular Genetics have dominated mutagenesis research for decades.

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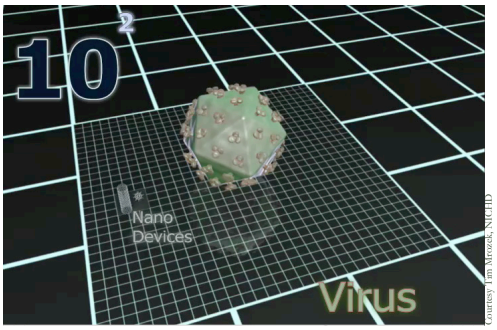
Everything's Coming Up Nanos

By Sarah Freeman

The first iPod Nano may have impressed consumers when it hit store shelves in 2005. But the mammoth 1.5-ounce, 3.5- × 1.6-inch digital music player towers over anything truly nano . . . and, at the risk of dissing Apple followers, is a far less impressive scale to tinker in compared to real nano. A real nano, or nanometer (nm), measures one billionth of a meter, or about half the diameter of a DNA double helix; 25.4 million nanos equal an inch, and upwards of five nanoseconds constitutes the average length of the career of a singer with a popular song on iTunes.



Courtesy Tim Mezzell, NICHD

Nano devices are about one-tenth the size of a virus. Nanotechnology involves imaging, measuring, modeling, and manipulating matter only a few nanometers in size.

Scientists at NIH and around the world are exploring ways to use nanoengineered particles for medical purposes such as advanced drug-delivery systems, tiny robots that can repair diseased or damaged tissue, and contrast agents to facilitate in vivo imaging. Nanotechnology's full potential, still years away, experts say, is nothing short of enormous.

Yet what is nanotechnology? Apple Inc. certainly took liberties in broadly defining the concept. Considering how NIH biologists and chemists study the nanoscale world of viruses (about 20 nm), membrane lipids and hemoglobin (as small as 5 nm), and sugar molecules (about 1 nm), isn't most everything we do at NIH nanotechnology? Isn't every lab a nano lab?

Some people question whether nanotechnology research is all that different from other bioscience disciplines. Although there's no clear-cut answer, the NIH and other leading research organizations are narrowing in on a definition and with it a better understanding of nano science's promise. More than mere wordplay, better defining nano could unlock research dollars.

"I have to admit that prior to learning something about nanotechnology I was one of the people who wasn't sure that nanotechnology was sufficiently different from molecular biology, structural biology, or the biochemistry of molecules at the nanoscale," said Deputy Director for Intramural Research Michael Gottesman during his opening remarks at NIH's first annual Nano Week, held in April 2009. "I now realize that nanotechnology encompasses not only traditional nanoscale science, but a whole new set of approach-

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From the Deputy Director for Intramural Research

Cultivating our Scientific Staff

Michael Gottesman

At times of transition, it is useful for successful institutions, such as the NIH intramural research program, to consider what ideals underlie success and how best to foster them. I think there would be little argument that much of the success of the intramural program has depended on the recruiting and cultivating of talented, diverse, and interactive scientists. So it seems reasonable to think about the demographics of our scientific workforce and to encourage the institutes and centers to make adjustments and formulate new ideas to ensure continued success.

Although scientists are discouraged from drawing conclusions based on analogy, it is tempting to compare the community of scientists at the NIH to a horticultural ecosystem.

The outlines of this analogy are obvious: We need to plant seeds and carefully water and fertilize our seedlings; we will grow more seedlings than we can bring to maturity and so we need to do judicious pruning and transplant some to other sites; we hope to create new and hardy hybrid varieties through cross-breeding and grafting; and we need to ensure that as seedlings mature they receive the necessary care to allow them to grow into durable and highly productive plants. If we do all that, we are sure to have a stable ecosystem that will thrive even in uncertain weather.

I would contend that we do a good job of applying sound "horticultural" principles to managing our "garden" of scientists, but we do need to attend to a few variations from best practice.

Recruit more independent PIs

We need to plant more seedlings. Although we recruit about 30 tenure-track investigators to NIH each year for a total principal investigator (PI) population of 1,150, we should try to double the number of recruits to increase diversity and bring new ideas and new technologies to the NIH. The new assistant clinical investigator positions at the NIH will encourage earlier career clinical investigators to enter the system as future fully independent PIs. And, of course, we can always improve our mentoring and funding of this precious resource.

Transition some successful PIs to academia

We should try to find ways to allow our early-career investigators to be transplanted easily to extramural sites so they can continue as independent scientists in their successful careers that they began at the NIH.

The scientific directors have been working on the idea of transition awards to facilitate this important process. Likewise we need to bring successful midcareer investigators from the extramural scientific community to the NIH to collaborate with and possibly join our research community.

Increase number of interdisciplinary researchers

Scientific success has frequently resulted from grafting two disciplines together; biochemistry and molecular biology are historical examples. Current efforts, such as one to apply computational approaches to biology (systems biology), will require additional investment of resources by the NIH.

Recently the NIH Director's Challenge Innovation awards have supported trans-NIH projects with the goal of transforming approaches to biomedical research. More investments of this type would be valuable, and additional interdisciplinary approaches should be encouraged.

Increase opportunities for career development

To allow space in our garden for early-career investigators, we need to continue to do selective pruning to weed out the less productive science.

In some ways this is the most difficult task, but with advice from our boards of scientific counselors, the wisdom of our scientific directors, and the cooperation of our scientific staff, we can make progress here as well.

—Michael Gottesman, DDIR

Catalytic Research:

Dem Cells Gonna Rise Again

Tiny specialized vibration detectors called hair cells send signals from the inner ear to the brain that are interpreted as sound and spatial orientation. If too many of these microscopic structures are destroyed by disease or injury, permanent hearing loss can occur. That may be a problem for humans and other mammals, but not for fish, amphibians, reptiles, and birds. They can regenerate their hair cells and avoid going deaf. NIH scientists may have figured out why.

The investigators, led by National Human Genome Research Institute senior investigator Shawn Burgess, found a gene responsible for regenerating hair cells in zebrafish. Named *phoenix*—after the mythical bird that perishes in a fire only to regenerate and rise from the ashes—this gene encodes a protein central to hair cell regeneration. The study was published in the April 2009 issue of *PLoS Genetics* and was a collaboration among members of the Burgess lab, the National Cancer Institute, the National Institute of Child Health and Human Development, and the Universidad de Chile (Santiago).

The researchers worked with a strain of zebrafish that had a mutation in the *phoenix* gene. When the *phoenix* mutants are exposed to chemicals that destroy the hair cells in their lateral line, they cannot regenerate those cells. The lateral line, related to the inner ear, runs along the sides of fish and amphibians and provides them with sensory signals that help them detect prey, avoid predators, find mates, and swim in schools. The mutated zebrafish are normal in most respects and can regenerate many other types of cells. So far there is no evidence that the *phoenix* gene plays a role in initial hair cell development; it seems specific to regeneration.

Fish with the mutated *phoenix* gene did not exhibit any other odd characteristics, such as bumping into aquarium walls or not schooling. However, other studies have shown that defective lateral lines lead to fish that fail to orient themselves against water currents. This is not surprising because loss of hair cells in humans can lead to spatial imbalance.

The scientists have located versions of the *phoenix* gene in other fish species, but finding a counterpart in other vertebrates has proved elusive so far. —*Tony Gill*

Research Briefs

NIAID

The ability to regrow wounded tissues is thought to occur only in salamanders, very young animals, and one strain of unusual albino mice. But NIAID researchers found that two common mouse strains regrew ear wounds with original tissues including cartilage, fat, skin, blood vessels, and, in black mice, melanin-producing cells. The data suggest that partial limb regeneration may be possible in adult mammals. [*Rejuvenation Res* 12:45–51, 2009]

NIMH (and NICHD)

NIH researchers may have identified a gene that is crucial for the pathophysiology of schizophrenia. The gene, which maintains the flow of potassium in cells and plays a role in cortical physiology, cognition, and psychosis, may be a potential molecular target for new treatments. [*Nature Med* 15:590–518, 2009]

NHGRI (and NCI)

A consortium of 12 research institutions and universities, including NIH scientists, has identified a gene associated with increased susceptibility to lung cancer in people with a strong family history of the disease. [*Clin Cancer Res* 15:2666–2674, 2009]

NIDCD

Hair cells in the inner ear used to get most of the credit for detecting sound, but NIDCD researchers determined that the tectorial membrane deserves credit, too. The scientists used nanotechnology techniques to show that the tectorial membrane, which lies immediately above the hair cells, plays a larger role in hearing than once thought. [*PLoS ONE* 4:1–9, 2009]

NCI

NCI researchers, in collaboration with other scientists, have identified in mice two proteins essential for ovulation to take place. The finding has implications for understanding and treating infertility as well as for developing new means to prevent pregnancy by preventing the release of the egg. [*Science* 324:938–941, 2009]

NICHD (and CIT and NIMH)

The pineal gland—integral to setting the body's sleep and wake cycles—may be involved in a broad range of bodily functions, according to a study by researchers at the NICHD. They found that the activity of more than 600 genes in the pineal gland are synchronized in some way with the 24-hour sleep and wake cycle. The genes influence inflammation and immunity. [*J Biol Chem* 284:7606–7622, 2009]

NIAMS

NIAMS scientists have discovered that tissue removed from traumatic wounds, traditionally considered medical waste, can be a source of progenitor cells. Progenitor cells can develop into several different types of tissue and could potentially be used to improve healing at the site of an injury, and traumatized tissue may provide an alternative source of cells for these therapies. [*J Bone Joint Surg Am* 90:2390–2398, 2008; *J Tissue Eng Regen Med* 3:129–138, 2009]

NIAMS (and NCI, NIAID, CC, and NHGRI and other institutions)

Researchers from several NIH institutes have discovered a new autoinflammatory syndrome, a rare genetic condition that affects children around the time of birth. The scientists have termed the new syndrome DIRA (deficiency of the interleukin-1 receptor antagonist). (*N Engl J Med* 360:2426–2437, 2009)

KEY

CC:	Clinical Center
CIT:	Center for Information Technology
NCI:	National Cancer Institute
NHGRI:	National Human Genome Research Institute
NIAID:	National Institute of Allergy and Infectious Diseases
NIAMS:	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD:	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDCD:	National Institute on Deafness and Other Communication Disorders
NIMH:	National Institute of Mental Health

The Training Page

From the Office of Intramural Training & Education: Finding and Landing Jobs

by Lori Conlan, Director, Office of Postdoctoral Services

Even in these tough economic times, the NIH is seeing its fellows and other trainees successfully land jobs once their training is complete. In the past few weeks, the Office of Intramural Training and Education (OITE) staff has learned of postdocs who have attained positions in academia, regulatory affairs, grants and program management, policy-making, industry (bench and non-bench), consulting, and even medical writing.

Because of the volatile job market, fellows have had to work harder than ever to find jobs. Luckily, they have been able to count on a supportive NIH network for assistance in the search. Mentors, training officers, and OITE and other NIH staff, as well as fellow trainees, make up the team that helps each fellow prepare for his or her next career step.

As job seekers strive to tailor their applications to the particular positions they are applying for, they are asking for NIH's help in ensuring that their documents are on target. In addition, many NIH offices have hosted trainees to provide them with non-bench work experiences. As trainees pick up new skills—such as program management, team participation, and science and medical writing for the public—they become more marketable job candidates.

Networking is also a critical component in any job search. NIH is helping fellows in that arena, too. For example, administrative officers can often assist current job seekers in connecting with previous postdocs. Online networking sites, such as LinkedIn, are also effective as search tools. There are at least 10 NIH-affiliated LinkedIn groups, including OITE's NIH Intramural Science group (which anyone at NIH is welcome to join). A trainee can easily find a person online through such sites and begin conversations that may lead to job offers. To join, go to http://www.LinkedIn.com.

Rest assured, the efforts of the NIH's collective team are noticed. Take it from a recent job hunter who sought OITE's help: "Thanks so much for helping me in my job hunting process! From the CV/resume to the cover letter, to interviewing, to negotiations, you helped me tremendously!"

We thank everyone for being part of our trainees' career searches. NIH will continue to be a leader in ensuring the success of the next generation of biomedical researchers as we encourage our fellows to choose careers based on their skills, interests, values, and passions. For more information, visit: http://www.training.nih.gov/. ■

From the Fellows Committee: Distinguished Clinical Teachers Award

by Jennifer Heimall, National Institute of Allergy and Infectious Diseases

Mentors have always played a key role in the professional development of physicians. Outstanding clinical mentors have been an important part of the Clinical Center's success. Each year NIH clinical fellows get the chance to bestow their highest honor on a mentor of their choosing.

The Distinguished Clinical Teachers Award (DCTA) is given to a deserving NIH senior clinician, staff clinician, or tenure-track clinical investigator in recognition of his or her excellence in mentoring of health-care professionals and teaching about issues related to direct patient care and for making outstanding contributions to the advancement of clinical research.

The award, established in 1985, is sponsored by the NIH Fellows Committee (FelCom) and the Office of Intramural Training and Education.

Clinical fellows who have direct patient-care responsibilities are eligible to nominate award candidates. Nomination letters must include specific comments describing the candidate's skills in mentoring, patient care, and clinical research. The FelCom clinical members and FelCom's DCTA committee review and vote on the nominations.

In the past five years, the award winners have been David Goldstein (Chief, Clinical Neurocardiology in the National Institute of Neurological Disorders and Stroke), Lynnette Nieman (Senior Investigator, Eunice Kennedy Shriver National Institute of Child Health and Human Development), Elaine Jaffe (Senior Investigator, Laboratory Of Pathology in the National Cancer Institute), John Gallin (Director of the Clinical Center), and Richard Childs (Chief, Section of Transplantation Immunotherapy, Hematology Branch, at the National Heart, Lung, and Blood Institute).

Award recipients are presented with a commemorative plaque, and they are invited to speak as part of the Great Teachers lecture series the following year.

Childs, the 2008 DCTA recipient, gave his Great Teacher's lecture on June 10, 2009, in a talk entitled "Transplanted Allogeneic T-cells Identify a Viral Corpse Resurrected in Renal Cell Carcinoma."

Nominations for the 2009 Distinguished Clinical Teachers Award are being accepted from June through August 2009 and will be presented in early fall.

A brief supporting statement should accompany nominations. Please send nomination letters to Grace Chen (chengra@niaid.nih.gov) by August 31, 2009. ■

Catalytic Tips: News You Can Use

Lab Safety at NIH

Here are a few tips for safety in the lab.

Laboratory supervisors should ensure that all personnel under their direction possess the requisite knowledge, training, and education to safely handle hazardous chemicals in the laboratory. All laboratory personnel are responsible for following the appropriate work practices when using hazardous chemicals:

• Minimize all chemical exposures and avoid underestimating the risk. Avoid unnecessary exposure by any route.

• Keep food, beverages, cosmetics, and medication outside the lab.

• Protect your clothes and exposed skin by wearing laboratory coats and gowns. Open-toed shoes, sandals, shorts, and other apparel that leave skin exposed are not appropriate in the lab, especially when handling potentially hazardous chemicals. Laboratory coats must not be worn outside the laboratory.

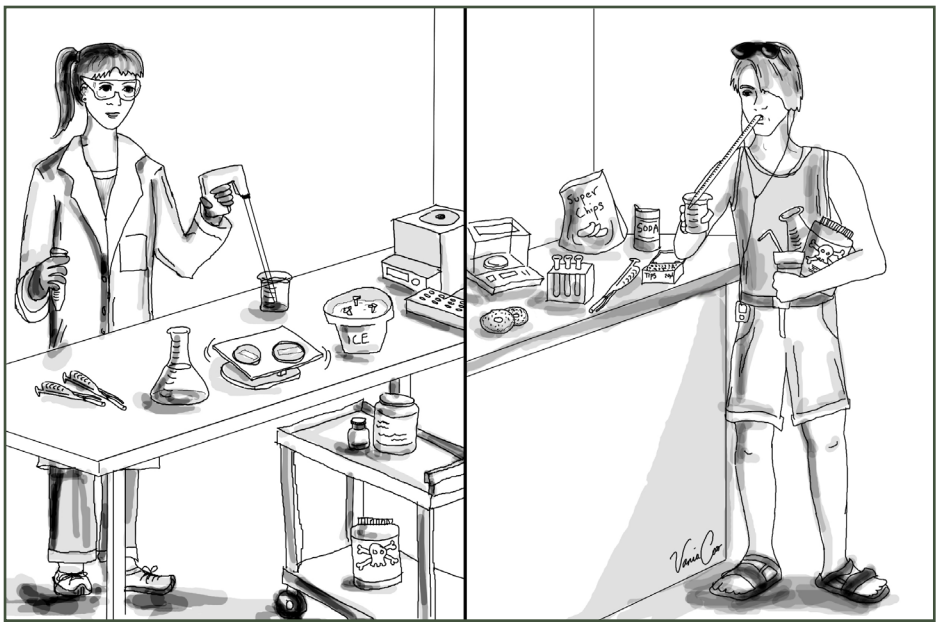
• Wear the appropriate gloves and eye and face protection whenever handling hazardous chemicals. These items should not be worn outside the laboratory.

• Ensure unimpeded access to safety showers and eyewash stations. Test flush eyewash stations weekly.

• Remove gloves carefully; thoroughly wash hands and forearms upon completion of work and before leaving the laboratory.

• Use only an approved chemical fume hood when opening, pouring, or handling hazardous chemicals.

• Conduct all work within the chemical fume hood at a distance of at least six inches behind the face opening and position the vertical sliding sash at the height specified on the certification sticker. Avoid blocking the airfoil, baffles, and rear ventilation slot. Support large items with legs to minimize airflow disruption across the work surface. Minimize foot traffic around the hood during use because passing in front of the hood during its operation disrupts the airflow and may pull contaminants out of the hood. Do not use the fume hood for storage. By following these steps, the hood provides adequate containment for most chemical operations.



Remember the cartoon feature "Goofus and Gallant" in the magazine Highlights for Children*? Can you guess which character here represents the irresponsible Goofus and which one the responsible Gallant? How many dos and don'ts for lab safety do you see here? (Answers below)*
— Illustration by Vania Cao

• Keep all doors to the laboratory closed. Open laboratory doors can adversely affect hood performance and appropriate air flow through the building.

• Do not use or store chemicals or compressed gas in cold rooms and warm rooms because they have contained, recirculated atmospheres.

• Never pipette by mouth.

• Transport laboratory chemicals using bottle carriers and suitable carts.

• Follow the established procedures for the decontamination and safe movement of scientific and medical equipment.

• Maintain proper oversight of inexperienced personnel (high school students, etc.) working with potentially hazardous chemicals.

• Contact DOHS (301-496-2346) for clearance of the workspace when personnel have to enter laboratories to perform required services (such as maintenance). Remove hazardous materials from equipment and facilities to be serviced, and forewarn personnel of the need for protective equipment or work practices, etc. Decontaminate the equipment when possible. Provide the appropriate personal protective equipment.

• Follow the hazardous material spill procedure immediately in the event of a hazardous chemical spill.

Text courtesy of: Division of Occupational Health and Safety, ORS August 2008

ANSWERS TO CAPTION QUESTIONS:
DOs (left): goggles to protect eyes; hair tied back; lab coat; gloves; long pants; proper shoes; proper pipetting technique; chemicals transported on cart; no food in lab.
DONTs (right): pipetting by mouth; improper attire: shorts, sleeveless shirt, no lab coat, open-toed shoes; no socks; long hair not tied back; wires dangling around neck; carrying chemicals instead of transporting them on cart; food in lab; no gloves or eye protection.

NIH and the 2009 Flu: A Flu of Pandemic Proportions

By Laura Stephenson Carter

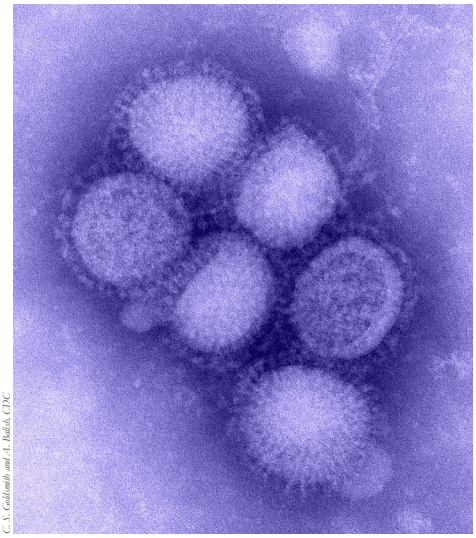
Over the past several years, the National Institute of Allergy and Infectious Diseases (NIAID) . . . has conducted a major research effort that builds on long-standing programs related to seasonal influenza in order to improve our preparedness for pandemic influenza. Although we have focused a good deal of attention recently on H5N1 avian influenza, it always has been clear that the next pandemic could come from another influenza virus altogether. . . . A virus with clear pandemic potential, the 2009 H1N1 influenza virus, has now emerged. NIH is fully engaged in an accelerated effort to understand this virus and rapidly developing countermeasures. (NIAID Director Anthony Fauci in his testimony to the Committee on Foreign Affairs Subcommittee on Africa and Global Health, U.S. House of Representatives, May 6, 2009.)

As the H1N1 flu has swept across the globe, international and national agencies have launched into high gear, mobilizing preparedness plans, distributing diagnostic kits, releasing stockpiles of anti-flu medications, and attempting to develop vaccines that would be effective against this strain of flu. On June 11, 2009, the World Health Organization (WHO) declared the outbreak a Level 6 on a six-point scale.

At press time, the H1N1 flu pandemic had spread to more than 100 countries with about 52,000 cases, including 231 deaths, worldwide. In the United States, nearly 22,000 people had been stricken and 87 had died. The last pandemic flu was the Hong Kong flu in 1968–1969, which killed more than one million worldwide and 33,800 people in the United States.

In addition to dealing with the public-health emergency aspects of the pandemic, government agencies are also conducting research on the H1N1 flu virus. NIH has ramped up its own flu investigation efforts, both in funding for other institutions and in research taking place at NIH itself.

At the National Institute for Allergy and Infectious Diseases (NIAID), scientists study the basic biology of influenza, including its pathogenesis, immunogenicity, transmissibility, and genetic variability; investigate host immune responses to the virus in animal models and in humans; develop vaccines to prevent influenza, especially strains with pandemic potential; and study influenza epidemiology. The Centers for Disease Control and Prevention has shared with NIAID samples of the new H1N1 strain for research purposes.



C.S. Goldsmith and A. Balish, CDC

This transmission electron micrograph of the newly identified H1N1 influenza virus was taken in the Influenza Laboratory at the Centers for Disease Control and Prevention.

Highlights of influenza research in NIAID labs:

Laboratory of Viral Diseases

Jack Bennink and **Jonathan Yewdell** lead investigations of the immunobiology of influenza A virus in mouse model systems. Their work focuses on antigen processing and presentation of viral proteins to T-cells, antigenic drift in influenza glycoproteins, the function of the PB1-F2 gene product in influenza pathogenicity, and the regulation of antiviral immunity by the nervous system.

Division of Clinical Research

Investigators conduct clinical studies and collaborate with clinical trial networks worldwide to develop vaccines, therapeutics, and diagnostics. NIAID is amending an established influenza research protocol at the NIH Clinical Center to allow enrollment of patients found to have the newly emerging H1N1 strain. Patients will receive the best available care while scientists conduct a careful study of their clinical history, measure the amount of virus in respiratory secretions, and evaluate various elements of the body's immune response to infection.

Vaccine Research Center

The Center has an ongoing program to develop novel vaccine approaches to seasonal and pandemic influenza and is testing gene-based and protein-based vaccines.

Laboratory of Infectious Diseases

Kanta Subbarao leads a group working with MedImmune, the manufacturer of the FluMist nasal spray influenza vaccine, to prepare to develop a vaccine against the newly emerging H1N1 virus. This collaboration is an expansion of ongoing work to develop live, attenuated vaccines against other influenza strains, such as H5N1, H7N3, and H2N2. Live, attenuated vaccines contain a version of the living microbe that has been weakened in the lab so it can't cause disease. Weeks before the H1N1 flu began making headlines, Subbarao gave a presentation about her work as part of the "Anita B. Roberts Lecture Series," named in memory of a pioneering NIH scientist who died of cancer in 2006.

Jeffery Taubenberger's lab studies the pathogenesis of influenza in diverse host species; influenza virus evolution and adaptation, especially the factors that lead to the emergence of pandemic strains; and the molecular basis for virulence of highly pathogenic influenza viruses, including the 1918 pandemic strain and H5N1 viruses.

His lab is currently studying the 2009 H1N1 flu virus to understand how this strain emerged and to identify factors that allow it to spread and cause disease in humans. He is also investigating how exposure to prior strains of flu may contribute to the immune response to the 2009 H1N1 flu virus.

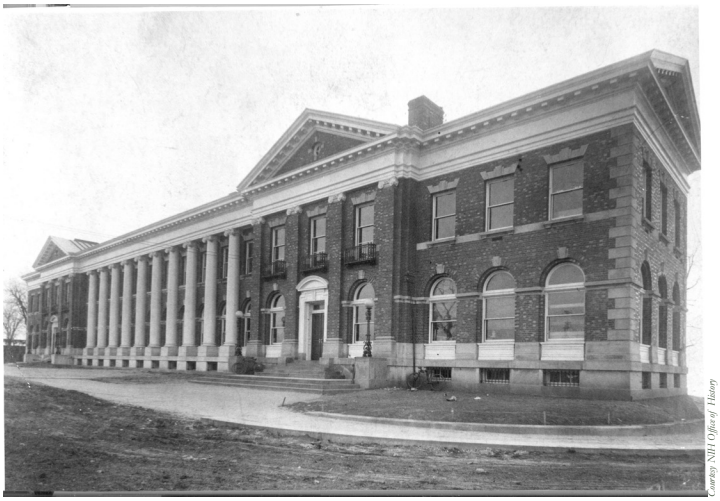
Before joining NIAID in 2006, Taubenberger worked at the Armed Forces Institute of Pathology in Rockville, Md., where he led the effort to reconstruct the 1918 flu virus. ■

NIH and the 1918 Flu

By Dan Lednicer

The pandemic influenza of 1918 lurks in the background of many discussions of the 2009 H1N1 flu. The 1918 flu was far more catastrophic than today's pandemic and killed 50-100 million people worldwide, including more than 500,000 in the United States.

The U.S. Public Health Service (PHS), which included the Hygienic Laboratory (HL, the forerunner of NIH), played an important role in protecting the public's health as influenza spread almost explosively throughout the United States. Crowded locations such as military training camps and public gathering places were good breeding grounds for infection. In September 1918, U.S. Surgeon General Rupert Blue issued recommendations for coping with what was then often referred to as Spanish Influenza. The flu did not originate in Spain, however. It was so named because Spain was neutral during World War I and did not censor reports of flu cases the way the countries engaged in combat did.



Courtesy NIH Office of History

The Hygienic Laboratory (which became the National Institute of Health in 1930) was located at 25th and E streets, Washington, D.C., on the grounds of the Naval Observatory from 1904 until 1938, when it was moved to its current location in Bethesda, Md.

One of the early responses of the HL to the flu epidemic was intended to quell public concern that the disease had been introduced through infected Bayer aspirin tablets imported from Germany. The HL tested 200 tablets and determined that they did not contain any suspicious organisms. Incidentally, the then-primitive state of virology would have missed detecting the flu virus even if it had been present. The understanding of viruses that we have today did not begin until the 1930s.

At Blue's initiative, state and local health departments were urged to report flu cases weekly; the PHS distributed thousands of posters and millions of educational pamphlets throughout the country with the help of local health departments; states appointed influenza directors to coordinate distribution of funds and chief medical officers to oversee the assignment of doctors and nurses to areas where they were needed most.

Blue also appointed 64 commissioned officers for influenza duty and established the Volunteer Medical Service Corps, comprising more than 1,000 physicians and 700 nurses, to help. The PHS set up emergency hospitals and soup kitchens, too.

Even HL scientists, most of whom were M.D.'s, left their laboratories to help with patient care in Washington, D.C., as doctors and nurses in the region fell ill.

In October 1918, Congress passed an appropriation of one million dollars to pay for the PHS flu initiatives. Meanwhile, thousands of people were dying—4,500 in Philadelphia and 3,200 in Chicago in one week alone. Blue ordered the closure of all public places including churches and schools in hopes of keeping the disease in check.

The PHS failed in its attempts to find a causative agent for and develop a vaccine against the 1918 flu. Still, the agency succeeded in getting local, state, and federal health organizations to work together, and in so doing saved many lives.

Today, NIH and other scientists are unlocking the secrets of the 1918 flu as well as other influenza viruses in preparation for future pandemics. ■

Staff of Hygienic Laboratory, 1912.

Left to Right:

Row 1: 1. Dr. J. W. Kerr, 2. Dr. W. P. McIntosh, 3. Dr. W. J. Pettus, 4. Dr. L. E. Cofer
Row 2: 5. Dr. M. J. White, 6. Dr. L. L. Lumsden, 7. Dr. C. H. Lavinder, 8. Dr. R. H. von Endorf
Row 3: 9. Dr. M. H. Foster, 10. Dr. John McMullen, 11. Dr. L. D. Fricks, 12, Dr. J. F. Anderson

Courtesy NIH Office of History

Many of the Hygienic Laboratory researchers were physicians and left their laboratories during the 1918 flu pandemic to help with patient care in Washington, D.C., as doctors and nurses there fell ill. This photo was taken in 1912.

Courtesy NIH Office of History

One of the scientists who joined the Hygienic Lab in 1918 was bacteriologist Alice Evans, who confirmed that the source of most human brucellosis cases was milk from cows infected with Bacillus abortus. *She retired from the Laboratory in 1945, which had by then become the NIH, and died in 1975.*

Nanotechnology
continued from page 1

es to measuring nanoscale phenomena and to developing nanoscale machines such as nanotubes and devices to interrogate and treat cells at a subcellular level."

Defining Nano

Nanotechnology sets itself apart from other disciplines through the potential for using nano devices for highly sensitive and specific in vitro diagnostic assays and as carriers for localized drug delivery and therapy, said Piotr Grodzinski, co-chair of the Trans-NIH Nano Task Force and program director of NCI's Alliance for Nanotechnology in Cancer. "In the case of structural biology you depend on [the] building blocks of molecules and cells," he said. "Nanotechnology has access to [a] wide range of nanomaterials originating from both organic and inorganic sources."

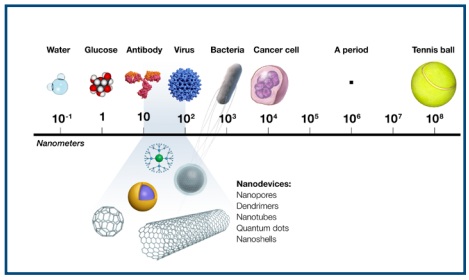
Invisible to the naked human eye, nano-size particles and entities can be as small as atoms. Particles—including nano devices designed to deliver drugs into the body—need to be smaller than 50 nanometers to enter cells easily and smaller than 20 nanometers to move through and out of blood vessels."

By these criteria, there are indeed several nano labs at the NIH. Researchers at the National Cancer Institute (NCI), for example, are exploring ways to use nanotechnology to deliver drugs directly to cancer cells. Nanoparticles are particularly useful for permeating tumors through the "leaky vasculature," said NCI researcher Robert Blumenthal during his lecture at Nano Week. Blumenthal, who studies lipid-based nanoparticles, is a member of the Trans-NIH Nano Task Force and director of NCI's Center for Cancer Research Nanobiology Program.

Putting targeting molecules on nanoparticle drug platforms allows them to bind to cell surface receptors that are overexpressed in tumor cells. Such targeted drug-delivery systems can treat cancer more effectively and with fewer side effects than traditional methods that kill healthy cells as well as tumor cells.

Blumenthal is also examining the possibility of using external forces such as heat or light to change the shape and structure of nanoparticles, once they have localized to the tumor, to help them release cancer-fighting drugs. "From a physics point of view and a chemistry point of view, it is very fascinating that the size and shape of a particle can change its physical properties," Blumenthal said.

Nano-size materials may exhibit unusual physical, chemical, and biological properties that differ from those of bulk materials and single atoms or molecules. For example, a gold particle can appear gold, silver, or blue depending on its size. This color difference and the ability to manipulate such a particle may help lead to improved disease-detection methods.



Nanoscale devices are 100 to 10,000 times smaller than human cells. Devices smaller than 50 nanometers can easily enter most cells, while those smaller than 20 nanometers can circulate through the body and move out of blood vessels.

Birth of Nano

Nanotechnology was born on December 29, 1959, when physicist Richard P. Feynman delivered a lecture entitled "There's Plenty of Room at the Bottom" at an American Physical Society meeting. He talked about the possibility of developing tools to manipulate atoms and molecules and suggested a new way of approaching the tiniest parts of our world.

"When we get to the very, very small world—say, circuits of seven atoms—we have a lot of new things that would happen that represent completely new opportunities for design," Feynman said in his lecture. "Atoms on a small scale behave like nothing on a large scale." Feynman went on to win the Nobel Prize in Physics in 1965 for his contributions to the development of quantum electrodynamics, but nanotechnology didn't catch on until later and didn't even get a name until the 1970s.

In 2001 the U.S. federal government established the National Nanotechnology Initiative (NNI), comprising 25 federal agencies today, to coordinate nanotechnology research and development. About $464 million was spent that year on federal nanotech research. Today, more than triple that amount is being spent annually, with an estimated $1.6 billion budgeted for federal nanotechnology in 2009.

NIH is ranked fourth in nanotechnology spending, behind the Department of Defense (DOD), the National Science Foundation (NSF), and the Department of Energy (DOE). DOD focuses on defense issues; NSF looks at research across all disciplines of science and engineering; and DOE searches for new energy technologies. NIH is studying the use of nanotechnology in medicine, representing the intersection of biology and physical science.

"It has been very valuable and useful to be part of NNI," says Jeff Schloss, member of the Trans-NIH Nano Task Force (established in 2006), program director of Technology Development for the National Human Genome Research Institute, and an NIH representative to NNI. "Much more rapidly we became aware of what other agencies are doing, and NNI spurred the development of nano at NIH."

Nano Budget

The NIH's nano budget, including both extramural and intramural research, increased from $40 million in 2001 to $304 million in 2008. About $31 million went to 29 investigators to do intramural research in eight NIH institutes; about $273 million is for extramural research. NCI led intramural nano spending with nearly $24 million.

But NIH is relatively new to nanotech research. In April 2006, NIH established the Trans-NIH Nanotechnology Task Force, which disseminates nano knowledge, addresses biomedical nano challenges and health and safety implications, and interacts with other federal agencies. As delineated in the Task Force's Statement of Purpose, "Nanotechnology offers promising solutions that are relevant to the mission of all NIH institutes because the knowledge and tools are applicable to any disease, organ, or cell type."

Which brings us back to NIH's first Nano Week. Sponsored by the Task Force and the NIH Roadmap Nanomedicine Initiative (composed of eight extramural Nanomedicine Development Centers), the week's activities emphasized both extramural and intramural nano programs. Many of the talks, available by videocast at http://videocast.nih.gov/launch.asp?15020, highlighted the intramural nanotechnology research on drug delivery and imaging. The organizers aimed to improve communications related to nanotech, provide answers to persistent questions, and promote the use of nanotech in intramural programs.

NIH Nano Labs

NCI's Joseph Barchi began investigating nanotechnology platforms in 2003 to develop better drug-delivery methods. Barchi's team in the Laboratory of Medicinal Chemistry, based in Frederick, Md., is exploring tumor cell binding processes that are regulated by carbohydrate-protein interaction. Finding ways to inhibit cell-to-tumor adhesion could slow or prevent metastatic spread of cancer.

To facilitate his research Barchi relies on the Image Analysis Lab (IAL) and the Nanotechnology Characterization Lab (NCL), also on the Frederick campus. The IAL provides electron and confocal microscopy. The NCL makes available a tissue-culture room, an isotope laboratory, research bays, a cold room, a chromatography and electrophoresis area, microscopy rooms, a spectroscopy area, a synthetic lab with chemical fume hoods, and open floor space for free-standing instrumentation and equipment.

Barchi studies the special properties of materials in the nano-size range. Because materials assume different properties at the nanoscale level, building a nanoscale platform that better mimics cell properties is much easier, Barchi explained. "There is an overwhelming potential to help diagnose and treat cancer," said Barchi. "Nanotech can probably apply to many different labs at NIH."

Scientists at NCL are characterizing and standardizing nanomaterials intended for cancer therapeutics. "It's very hard to make predictions about how a nanomaterial or nanoparticle is going to behave in a tissue or environment if you haven't standardized the size, the chemical composition, or any of its characteristics," said Catherine Lewis (in the National Institute of General Medical Sciences), co-chair of the Trans-NIH Nanotechnology Task Force. "You can't make any kind of comparisons with previous experiments."

NCL is collaborating with the National Institute of Standards and Technology and the U.S. Food and Drug Administration to accelerate the use of nanoscale devices into clinical applications. "If you are going to do nano, then you need tools that are precise," said Schloss. "Developing those tools is part of the government's investment. You can't do the research if you don't use the tools."

The diameter of a therapeutic nanoparticle will determine whether it can cross into a certain type of cell. This standardization will serve as a baseline for the FDA once nano drug-delivery devices are further refined.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is using powerful tools to image proteins and contractile machinery at the nanoscale. Kuan Wang, member of the Trans-NIH Nanotechnology Task Force and chief of NIAMS's Laboratory of Muscle Biology, uses atomic force microscopy (a type of very high resolution scanning probe microscopy that applies a probe to scan and measure mechanical properties of specimens) to better understand how muscle proteins and muscle cells generate force and respond to stress.

Nanotechnology provides scientists with a unique perspective of living cells and how single molecules work.

By looking at single-molecule muscle proteins, such as titin and nebulin, Wang is learning how protein elasticity contributes to muscle motility, passive tension, disease, and more. Nanotechnology provides scientists with a unique perspective of living cells and how single molecules work, how robust they are, and how they manipulate and alter intracellular signaling pathways.

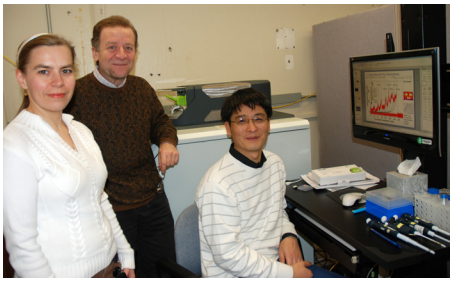
"Studying single molecules is like practicing psychiatry," said Wang. A psychiatrist tries to understand individuals whereas a sociologist observes groups. "Single-cell behavior can be very different from social behavior of, say, a bunch of molecules in a test tube or in a cell," he added. "Single-molecule research is important yet challenging, and not for the faint of heart."

Other institutes doing nano research include the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute of Environmental Health Sciences (NIEHS).

At NIBIB, Albert Jin and colleagues have used nanotech tools to characterize malaria vaccine components and DNA/HIV-integrase complexes. Richard Leapman, scientific director of the NIBIB intramural program, uses electron microscopy to characterize particles in hopes of developing nanoparticle drug-delivery platforms. NHLBI researchers Clare Waterman and James Sellers are using nanotechnology to observe how live cell organelles, such as single protein molecules, work and interact at the nano level. And scientists at NIEHS are examining potential environmental risk factors associated with nanoparticles and nanotechnology.

If past budgets are any indication, nanotechnology will continue to grow both at NIH and within other federal agencies. Like any other scientific discipline still young and facing uncertainties, the success of nanotechnology hinges on scientists continuing to push this discipline further, into a new realm.

"Nanospace may be the final frontier for a new class of diagnostic and therapeutic reagents that revolutionize medicine," noted Gottesman. "But before we boldly go there we need to develop the appropriate tools and understand the unique toxicology of nanomaterials."■



Carla Garnett

NIBIB researcher Albert Jin (right) has led the development of a comprehensive biological atomic force microscopy facility with colleagues Emilios Dimitriadis (center) and Svetlana Kotova (left). The facility's equipment includes a ForceRobot single molecule force spectroscope (shown in the background).

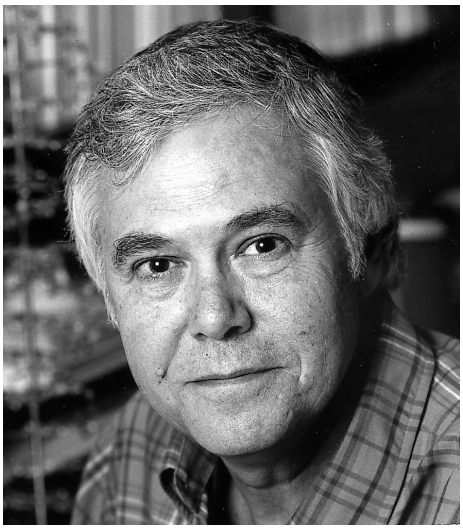
Carla Garnett

NHLBI biologist Clare Waterman can view the protein building process live using nanotech tools like this homemade total internal reflection fluorescence (TIRF) apparatus.

Mutagenesis Researchers

continued from page 1

Courtesy: Steve McCaw



Courtesy: Steve McCaw

Above: Fred de Serres, shown in 1979, helped spearhead mutation research at NIEHS and led international efforts in the field of mutagenesis and carcinogenesis. Below: Jan Drake redirected NIEHS's research from mutation classification to mutation mechanisms.

to hundreds of thousands of times each day to deal with environmental threats. What they have uncovered has been critical to elucidating the biological pathways of toxicity and developing new methods for preventing and treating disease.

In a paper published in the March 2009 issue of *Molecular and Cell Biology*, for example, LMG principal investigator Mike Resnick and staff scientist Dmitry Gordenin demonstrated how intracellular processes maintain genomic integrity and how defects in DNA replication, repair, and recombination can lead to age-associated diseases, especially neurodegenerative disorders, and cancer.

The LMG has been dubbed "Mutagenesis Central" by admiring colleagues because it is chock-full of mutagenesis researchers who are driven to achieve a noble mission: unlocking the mysteries of genome integrity.

Jan Drake's Vision

When mutation research began at NIEHS in 1972, the institute was only beginning to evolve as NIH's lead organization devoted to research on environmental health problems. The NIEHS was first established as a division of NIH in 1966 and elevated to institute level in 1969.

Former Oak Ridge National Laboratory geneticist Fred de Serres led NIEHS's Mutagenesis Branch, later renamed the Environmental Mutagenesis Branch (EMB). EMB scientists identified risks posed by environmental toxins, explored the causative agents of genetic damage, and developed assays to measure the effects of highly toxic pollutants such as polychlorinated biphenyls (PCBs) and dioxins that resulted from manufacturing processes. The EMB made significant contributions to the field of genetic toxicology in the 1970s and helped cement NIEHS's reputation as a leader in environmental mutagenesis research.

In 1977, NIEHS director David Rall hired University of Illinois (Urbana) geneticist Jan Drake as the new chief of EMB. Drake was already an established mutagenesis researcher and was fascinated by mutation rates in a wide range of organisms from viruses to humans. In his 1970 book, *The Molecular Basis of Mutation* (which became a classic in the field), he had made the case that the classification of mutations had been well studied but that the mechanisms by which they were generated had not. So it was no surprise when he decided to redirect NIEHS's research from mutation classification to mutation mechanisms. Before long, EMB was renamed the Laboratory of Molecular Genetics.

Drake wasted no time in recruiting other scientists who were interested in molecular mechanisms of mutation, and encouraged collaborations, particularly between geneticists and enzymologists.

Mechanisms

The first recruits in the late 1970s were Mike Resnick and Jim Mason. Their work contributed to the understanding of chromosomal stability and structure.

Before coming to the NIEHS, Resnick had held faculty positions at the University of Rochester (N.Y.) and the National Institute for Medical Research (London) and had proposed the first model for the repair of DNA double-strand breaks. These lesions are particularly dangerous because they can cause genomic rearrangements. Mason, fresh from a postdoctoral fellowship at the University of California–Davis, had been using Drosophila to delineate mutator mutants (DNA mutations that use a variety of mechanisms to enhance mutation rates).

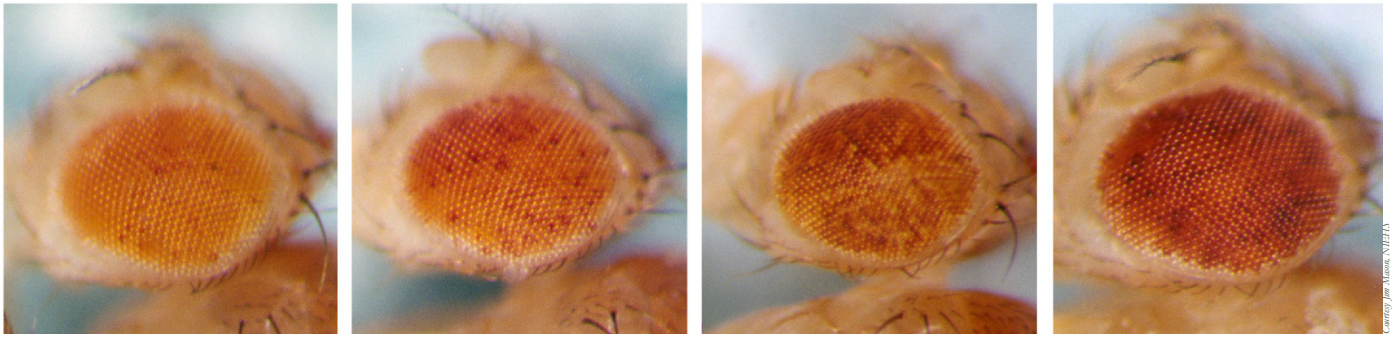
In the 1980s, two significant hires were University of Washington (St. Louis) researchers Tom Kunkel and Roel Schaaper, who both realized that the *Escherichia coli* bacterium was an affordable, useful, and easily manipulated tool for basic genetic and mutation studies. As a postdoctoral fellow, Kunkel had made several discoveries about DNA polymerase fidelity and was the first to establish the DNA-copying accuracy of a polymerase in *E. coli* (*J. Bio. Chem.* 255:9961-9966, 1980). Schaaper had expertise in using *E. coli* as a model to quantify specific types of mutations.

The LMG was quickly developing a worldwide reputation for experimentally delineating the mechanisms of mutation, and its researchers were publishing scores of highly regarded papers.

A notable paper, singly authored by Schaaper, appeared in the *Journal of Biological Chemistry* on November 15, 1993 (*J. Bio. Chem.* 268:23762-23765, 1993). The study was "an elegant genetic approach [that made] a seminal contribution to three related fields—DNA replication, DNA repair, and mutagenesis," said Kunkel. "I consider this study to be among the best ever published by an LMG scientist."

Kunkel was making important contributions, too. He developed a powerful assay for characterizing the kinds of mutations made by polymerases in vitro and probed the roles of two eukaryotic DNA polymerases in genome replication. His group also characterized the inherent inaccuracy of HIV reverse transcriptase, helping to explain the mechanism by which HIV rapidly evolves within each new host and can become resistant to drug therapy.

LMG scientists have been formally recognized for their accomplishments on many occasions. Kunkel and Resnick were named NIEHS Scientist of the Year in 2005 and 2008, respectively. In addition, LMG scientists were presented with Paper of the Year awards in 2003, 2004, 2007, and 2008. NIEHS's Board of Scientific Counselors chooses the best paper out of the more than 300 NIEHS peer-reviewed journal articles that are published annually. In 2008 the award went to Resnick for a *Nature* article, entitled "RNA-templated DNA Repair," that for the first time provided evidence of RNA's role in DNA repair (*Nature* 447:338-341, 2007).



Courtesy Jim Mason, NIEHS

Many mutagenesis scientists investigate genome stability in the fruit fly Drosophila. In Jim Mason's lab, researchers investigating chromosomal abnormalities rely on easily measured reporter genes, such as ones for eye pigmentation, that are linked to mutated genes. Shown here are fly eyes with increasing amounts of pigmentation.

Mutation Impact

By the mid-1990s the LMG was expanding its focus yet again as Drake added new investigators whose research focused on the consequences of mutations.

In 1993, Bill Copeland joined LMG after completing a fellowship at Stanford University (Calif.), where he had studied the enzymology of human replicative DNA polymerase.

His later work on the replication fidelity of the sole mitochondrial DNA polymerase quickly established that spontaneous errors in this normally accurate polymerase caused 85 percent of mitochondrial DNA mutations.

These mutations account for most mitochondrial-mediated diseases, such as late-onset ophthalmoplegia, which causes adult eye-muscle weakness, and atypical Pearson syndrome, a fatal pancreas dysfunction disease in children.

The more recent appointments of Marilyn Diaz and Doug Bell reinforced the LMG's emphasis on the consequences of mutations. Both sought to understand how mutation affects innate and adaptive biological processes.

Diaz had been a postdoctoral fellow in immunogenetics at the Scripps Research Institute (La Jolla, Calif.). At NIEHS, she investigated somatic hypermutation, a process of immunoglobulin formatting whereby immune cells use proteins involved in DNA repair to cause mutations that greatly increase the range of antibodies that ward off pathogens. Errors in this process can have debilitating consequences, including autoimmune disorders.

In 2002, she won the Presidential Early Career Award for Scientists and Engineers, the highest honor the U.S. government bestows on early-career scientists and engineers.

Bell had been a tenured NIEHS investigator in the former Laboratory of Computational Biology and Risk Analysis. He was interested in discovering mutations in human DNA that increase susceptibility to environmental mutagens. His work on mutation-mediated alteration of the tumor-suppression gene *p53* and the antioxidant-mediator gene *NRF2* has contributed to the knowledge of how genetic variability influences susceptibility to disease.

Drake's influence in mutation genetics has extended beyond his cadre of talented mutagenesis scientists. From 1982 to 1996 he was the editor of the prestigious journal *Genetics* and initiated a column called "Perspectives," which featured invited authors' retrospective views and prospective views on genetics issues. The April 1998 issue was a special collection of papers in honor of his 15 years as editor and commemorated the central role he played in the field of mutation.

In addition, Drake has continued his own research. His observations of spontaneous mutation and DNA repair have led to discoveries of constant genomic mutation rates in most microbes.

In 2000, he received the inaugural Biosphere and Humanity (Timoféeff-Ressovsky) Medal, a prestigious honor awarded by the Russian Academy of Sciences to scientists who excel in their field and whose work contributes to the betterment of mankind. Only two Americans, including Drake, have won this coveted prize so far.

Part of LMG's success can be attributed to collaborations with scientists in other NIEHS labs as well as with those at universities, private nonprofit laboratories, as well as in government agencies in the U.S. and in Europe.

Collaboration

The LMG has made its mark in the world of mutagenesis, DNA repair, and genome stability. Part of its success can be attributed to collaborations with scientists in other NIEHS labs as well as with those at universities, private nonprofit laboratories, and other government agencies in the United States and in Europe.

A strong connection has been established with NIEHS's Laboratory of Structural Biology (LSB), where LMG principal investigator Kunkel holds a dual appointment and works alongside LSB researchers. Many collaborative projects focus on protein structures involved in DNA replication and repair, providing evidence of how DNA mutation occurs.

NIEHS's location in Research Triangle Park, N.C., makes it easy for LMG investigators to share ideas, equipment, samples, and data with scientists at surrounding institutions including the University of North Carolina at Chapel Hill, Duke University (Durham, N.C.), and North Carolina State University (Raleigh). For example, the University of North Carolina Genome Analysis Facility provides genome-wide sequencing services to LMG investigators.

The Future

"Our future will surely see discoveries in the 'nomics' of DNA replication and repair, such as how multiprotein complexes form, operate, and dissolve, and in how cells evolve special fidelity mechanisms," Drake predicted. "There is a lot of work to do, and a lot of excitement to savor" as NIEHS's mutagenesis researchers continue their quest to unlock the mysteries of genome integrity. ■

Colleagues

Recently Tenured

Mary Lilly *is a senior investigator and the head of the Section on Gamete Development in the Cell Biology and Metabolism Program in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). After receiving a B.A. in biology from Pomona College (Claremont, Calif.), she earned a Ph.D. from Yale University (New Haven, Conn.) in 1992. She performed postdoctoral work in embryology at the Carnegie Institution for Science (Baltimore, Md.) and was a postdoctoral fellow of the American Cancer Society. She came to NICHD as a tenure-track investigator in 1998.*

My group studies cell-cycle regulation during oogenesis. Our long-term goal is to understand how the cell cycle program of the Drosophila ovarian cyst is coordinated with the developmental events of oogenesis. Chromosome missegregation during female meiosis is the leading cause of miscarriages and birth defects in humans. Recent evidence suggests that many meiotic errors are downstream of defects in oocyte growth and/or the signaling pathways that drive the differentiation of the oocyte. Understanding how meiotic progression and gamete differentiation are coordinated during oogenesis is essential to studies in both reproductive biology and medicine.

As is observed in mammals and Xenopus (a genus of sub-Saharan African frogs), the Drosophila oocyte initiates meiosis within a germline cyst. To understand the regulatory inputs that control early meiotic progression, we are investigating how the Drosophila oocyte initiates and then maintains the meiotic cycle within the challenging environment of the ovarian cyst.

Animal oocytes must inhibit the activity of the mitotic kinase Cdk1 at the onset of meiosis. But they must also be able to reactivate the kinase later in oogenesis as they undergo meiotic maturation and enter the first meiotic division. How cells within early ovarian cysts initiate the long-term inhibition of Cdk1 activity is poorly understood.

We have demonstrated that the RNA binding protein Bruno maintains mitotic quiescence during prophase of meiosis I by inhibiting the translation of cyclin A, an activating subunit of the mitotic kinase Cdk1. In the absence of Bruno, ovarian cysts enter meiosis but rapidly accumulate high levels of cyclin A protein and return to the mitotic cycle.

Bruno had previously been implicated in the translational inhibition of two genes involved in the differentiation of the egg and embryo, *gurken* and *oskar*. Our findings suggest that Bruno may coordinate cell-cycle regulation with gamete differentiation during oogenesis. We continue to use Bruno as an entry point to better define the pathways required to establish and maintain the long-term inhibition of Cdk1 activity within ovarian cysts.

To protect genome integrity, the oocyte must guard against inappropriate DNA replication. We have explained how Drosophila oocytes prevent inappropriate DNA replication during meiosis I. We determined that high levels of the Cdk inhibitor Dacapo inhibit DNA replication in the oocyte by preventing the activation of the S-phase kinase Cdk2. Recent evidence suggests that the Dacapo homolog p27Kip1 may play an important role in regulating growth and cell-cycle progression in prophase-I-arrested mouse oocytes. We are extending our studies on how Cdk2 activity influences both meiotic progression and the differentiation of the oocyte.

Finally, we are using genetic strategies to identify new genes that influence meiotic progression and oocyte development. From these studies we identified the gene *missing oocyte* (*mio*). The *mio* gene encodes a highly conserved protein that accumulates in the oocyte nucleus during early prophase of meiosis I. In *mio* mutants the oocyte fails to maintain the meiotic cycle and develops as an accessory cell. Thus, *mio* is required for meiotic progression and the maintenance of the oocyte identity. Currently, we are exploring the relationship between *mio* and the regulation of the nuclear pore complex.

Mary Ward is a senior investigator in *the Occupational and Environmental Epidemiology Branch in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute (NCI). She received her B.S. in Biochemistry from the University of Dallas and a Master of Science in Ecology from the University of Tennessee (Knoxville). Before her decision to pursue a Ph.D. in environmental epidemiology, Ward spent time as a research assistant in the microbiology departments at the Australian National University in Canberra and the University of the Witwatersrand in Johannesburg, South Africa.*

In 1994 Ward received a Ph.D. in epidemiology from the Johns Hopkins School of Hygiene and Public Health (Baltimore, Md.) while completing her dissertation research in NCI's Occupational Studies Section. Ward started as a tenure-track investigator at NIH in 1999 and received tenure in 2008.

Ward is also an affiliate faculty member at Colorado State University (Fort Collins) and an adjunct faculty member at the Uniformed Services University of the Health Sciences (Bethesda, Md.). She serves as an associate editor for Environmental Health Perspectives*, one of the leading environmental health journals. She has served on various scientific and regulatory review committees, most recently as a member of the President's Cancer Panel on "Environmental Factors in Cancer: Agricultural Exposures," and chaired the epidemiology subcommittee of the World Health Organization's International Agency for Research on Cancer Working Group to evaluate the carcinogenicity of ingested nitrate and nitrite.*

My research focuses on 1) the evaluation of cancer risks associated with environmental exposure to pesticides and 2) the role that *N*-nitroso compounds and their precursors may play in cancer develop-

ment, particularly exposure to nitrate from drinking water and diet. Cancers of specific interest include non-Hodgkin lymphoma, childhood leukemia, colorectal cancer, and stomach cancer. To help identify elevations in cancer risk that are likely to be caused by environmental exposures, I developed an interdisciplinary research program that draws on the expertise of environmental scientists, environmental engineers, hydrogeologists, geographers, and biostatisticians. We estimate exposure to environmental contaminants using environmental monitoring data, land use maps, and geographic-based fate and transport models.

N-Nitroso compounds, formed endogenously from drinking water and dietary sources of nitrate and nitrite, are potent animal carcinogens that cause tumors at numerous anatomical sites. In epidemiologic studies of gastrointestinal and urinary tract cancers, I evaluated the risk of people who were most likely to have high rates of endogenous nitrosation, that is, those who had a higher intake of nitrate from drinking water and either low vitamin C or high red meat intake. Our studies revealed, for the first time, that there are significant positive interactions between water nitrate ingestion and high red meat and low vitamin C intake, and these interactions are associated with the risk of developing kidney and colon cancers.

These findings have important public health and regulatory implications because the drinking water nitrate concentrations in these studies are commonplace around the world and are below the U.S. and World Health Organization regulatory guidelines.

The general population has widespread exposure to pesticides and other chemicals used in industry, and cancer risk may be elevated in susceptible groups such as children. I am particularly interested in agricultural pesticide exposure among the general population living in agricultural areas. I worked with experts in remote sensing, environmental engineering, and environmental science to develop a new approach based on land-use maps, meteorology, and other data to estimate pesticide levels in homes.

We demonstrated that crop acreage within 750 meters of homes was a significant predictor of agricultural pesticide concentrations in house dust samples and that pesticide concentrations approached the levels found in homes of farmers and other agricultural workers.

With a validated new exposure method, studies of environmental exposure to agricultural pesticides and cancer are now possible; we are applying this exposure-assessment method in studies of cancer among adults and children.

On Tenure Track

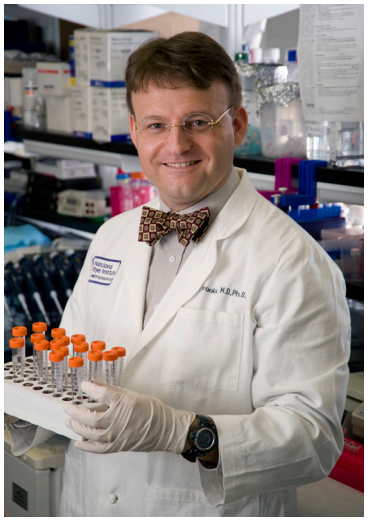
Brian Brooks

Uveal coloboma, a potentially blinding developmental abnormality of the eye, is one of those rare nonlethal genetic diseases that might be neglected if it weren't for the curiosity of physician-scientists such as Brian Brooks.

As chief of the Pediatric, Developmental, and Genetic Ophthalmology Unit at the National Eye Institute (NEI), Brooks appreciates the "opportunity to walk seamlessly between patient care and the laboratory as well as the opportunity to work on uncommon diseases," he said.

He hopes to better understand the genetic and developmental mechanisms of optic fissure closure, failure of which causes uveal coloboma (sometimes described as a keyhole-shaped pupil), and also to provide better diagnostics and genetic counseling for patients and develop prevention strategies or treatments.

Raised in Bel Air, Md., Brooks studied biochemistry at the University of Maryland (College Park) and later graduated from the M.D./Ph.D. program at the University of Pennsylvania (Philadelphia). He did a residency in internal medicine at Allegheny Health Science Center (Philadelphia)



and a residency in ophthalmology as well as a fellowship in pediatric ophthalmology at the University of Michigan (Ann Arbor).

In 2002 he came to NIH to do a fellowship in medical genetics at the National Human Genome Research Institute and in 2004 became a staff clinician in NEI. Last year he received the NIH Director's Award as the founding director of eyeGENE, the National Ophthalmic Disease Genotyping and Phenotyping Network.

Brooks' greatest joy in his work "is to be able to make novel insights into a patient's disease, be it in the clinic or in the laboratory," he said. He takes pleasure in making his young patients happy, too. "As a pediatric ophthalmologist, I use all manner of silliness, imitating animal noises and an entire repertoire of children's songs in the process of obtaining an examination," he said.

He finds joy outside the workplace, too, and loves spending time with his wife and children, usually doing outdoor activities such as camping. He also enjoys hiking, swimming, and reading non-science books and publications.

To others interested in pursuing a research career, he recommends taking advantage of every opportunity to learn, working hard, staying organized, and maintaining balance. "Always be willing to reassess your situation and change direction if necessary," he advised. —*Tony Gill*

Colleagues
On Tenure Track (continued)

Giovanni Cizza

When Giovanni Cizza left his home in the beautiful southern Italian town of Catanzaro to pursue his education, he planned to become a lawyer. But soon after he started law school in Rome, he changed his mind and transferred to medical school at the University of Pisa. Today as a principal investigator in the Clinical Endocrinology Branch at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), he explores how the endocrine system interacts with the immune and nervous systems to fight obesity, depression, osteoporosis, and other diseases.

After Cizza completed his M.D. degree he stayed at the University of Pisa to do a residency in constitutional medicine and postgraduate training in endocrinology. Later he trained at the Mario Negri Institute for Pharmacological Research (Milano, Italy), where he participated in a now-much-cited study showing how acetyl-L-carnitine slows the decline of cognitive functions in Alzheimer's patients. He also collaborated with colleagues to study the effects of hypothyroidism on the brain in an animal model.

Cizza first came to NIH in 1989. He was a Fogarty International Fellow from 1989 to 1994 in the Clinical Endocrinology Branch of the National Institute of Mental Health (NIMH) and a clinical fellow from 1994 to 1996 in the Eunice Kennedy Shriver National Institute of Child Health and Human Development. He earned a Ph.D. in experimental pathology from the University of Pisa in 1995 and a master of health sciences in clinical research from Duke University (Durham, N.C.) in 2005. From 1996 to 2000 he worked in the Endocrine Division at Merck Research Laboratories, in Rahway N.J. He returned to NIH in 2000 to work at NIMH and joined NIDDK in 2004.

Cizza has made important contributions in linking abnormalities in bone metabolism in premenopausal, depressed women taking part in the POWER (Premenopausal, Osteoporosis Women, Alendronate, Depression) study. In other work, he demonstrated that premenopausal women in remission from clinical depression exhibited abnormal patterns of proinflammatory cytokines and neuropeptides in skin sweat and in blood plasma.

Currently, Cizza is working on nonpharmacologic approaches to combating the obesity epidemic. He is conducting a large prospective, randomized, and controlled clinical study with obese patients to determine whether a healthy amount of sleep (7 to 7.5 hours) can help people lose weight.

The NIH is "a wonderful place with an informal style that promotes exchanging ideas among talented individuals from all over the world," he said.

In his free time, he listens to classical music, sees movies, and visits bookstores to hear authors present their latest books.

—Iddil Bekirov

Raja Jothi

Outperforming expectations is typical for Raja Jothi. "Performance is everything, potential is nothing," he said, quoting former National Football League coach Bill Parcells. "It doesn't matter where you get your education [or] training," continued Jothi. "All that matters is what you do with it." Jothi brings a history of performance to his new role as the head of the Computational Biology Group in the National Institute of Environmental Health Sciences' Biostatistics Branch.

Jothi, who grew up in Chennai, India, received an undergraduate degree in computer science and engineering from the University of Madras in India. After earning M.S. and Ph.D. degrees in computer science from the University of Texas at Dallas, he decided to pursue a career in computational biology and came to NIH, where he did two postdoctoral fellowships. First, he worked with Teresa Przytycka at the National Center for Biotechnology Information (a division of the National Library of Medicine), where he developed computational approaches for predicting protein-protein and domain-domain interactions.

Later, working with Keji Zhao at the National Heart, Lung, and Blood Institute, he demonstrated extensive co-localization of the binding sites for the major insulator-binding protein, CTFC, with chromatin boundaries. In a collaborative work with researchers at Stanford University, he implicated esBAF, an embryonic stem cell chromatin remodeling complex, as an essential component of the core pluripotency transcriptional network.

At NIEHS, research in Jothi's group involves generating genomic data sets with help from NIEHS core facilities and experimental collaborators, developing testable hypotheses using computational approaches, and designing follow-up experiments. Jothi is primarily interested in understanding how transcription regulators and epigenetic modifications control gene expression during cellular development and differentiation. He is also integrating heterogeneous genome-scale data sets to identify tissue-specific gene regulatory elements such as enhancers, silencers, and insulators. On a systems level, he is investigating inherent network structure in gene regulatory networks.

Jothi enjoys NIH's "highly collaborative environment [which is] ideal for carrying out interdisciplinary research spanning my areas of interest." He is already forging collaborations with researchers in other institutes.

—Jody White

Gregory Kato

The key to success in medical research is a "passion for science and discovery [and] detective work," said Gregory Kato, who heads the Sickle Cell Vascular Disease Section of the Pulmonary and Vascular Medicine Branch in the National Heart, Lung, and Blood Institute (NHLBI). He takes pleasure in "developing new knowledge that impacts the understanding and treatment of human blood diseases."

Kato's lab is investigating the mechanisms of blood vessel abnormalities

Gregory Kato

and designing drug therapies to improve blood vessel health in sickle cell disease. He and other NIH scientists have found that sickle cell vasculopathy is associated with pulmonary hypertension, cutaneous leg ulcerations, and other problems. Kato's group is investigating causes of the vasculopathy syndrome and conducting trials of new drugs to treat it.

A Los Angeles native, Kato earned a B.S. in biochemistry from the University of California at Los Angeles. He went on to earn an M.D. degree from the George Washington University School of Medicine (Washington, D.C.), completed a residency in pediatrics at Children's Hospital of Los Angeles, and held a fellowship in pediatric hematology-oncology at Johns Hopkins Hospital (Baltimore, Md.). He later joined the faculty at Johns Hopkins.

In 2003 he came to NIH as a senior staff physician in the Clinical Center's Critical Care Medicine Department; in 2004 he began his work at NHLBI. He is also an associate professor at Johns Hopkins and an adjunct investigator in pediatric oncology at the National Cancer Institute.

Kato was drawn to NIH because it provided "opportunities for rapid innovation in translational research" and the chance to work with talented scientists like former NHLBI pulmonary researcher Mark Gladwin.

When he isn't in the lab, Kato loves spending time with two sons and his wife (he confided that he met her at a pool and later wooed her with a serenade—not under a window but at a karaoke bar). He also loves gardening. In fact if he hadn't become a physician-scientist he admitted he might have pursued a career as a "master gardener or arborist."

—*Tony Gill*

ANNOUNCEMENTS

Research Festival
Poster Abstract Submissions
Deadline: July 20, 2009

Mark your calendars for the 2009 NIH Research Festival, the annual showcase of our world-class NIH Intramural Research Program, October 6–9, 2009, on the Bethesda campus. The festival begins with a plenary session on "Influenza," which will be held in Masur Auditorium (Building 10) on Tuesday, October 6, 9:00–11:30 a.m.

All NIH investigators and Bethesda FDA and CBER investigators are invited to submit poster abstracts online. Posters from any research area within the NIH Intramural Program will be considered; limit of one poster submission per first author. Notification of acceptance will be e-mailed to applicants in late August.

For a preliminary schedule of events and online poster registration, go to http://researchfestival.nih.gov. For more information, contact researchfest@mail.nih.gov.

BTRIS
Launch: July 30, 2009
Town Hall Meeting: Sept. 15, 2009

BTRIS, a new intramural NIH information system for managing research data, functions as a repository for clinical research data collected from NIH research protocols, intramural as well as extramural. By aggregating and organizing enormous amounts of information, the system will be able to provide researchers with easy access to clinical and nonclinical data from all different fields of study, facilitating cooperation between researchers in disparate institutes and centers. Principal investigators with active protocols will be contacted in late July or early August regarding access to BTRIS.

All staff are welcome to attend the BTRIS Town Hall Meeting on Tuesday, September 15, at 2:00 p.m. in the Lipsett Amphitheater (Building 10). Jim Cimino, Director, BTRIS Project and Chief of the Clinical Center's Laboratory for Informatics Development, will talk about how BTRIS will provide powerful new tools for enhancing the research process. For more information, go to http://btris.nih.gov.

Frontiers in Basic Immunology
October 1–2, 2009
NIH Main Campus

Hear about the latest findings in lymphocyte development, signaling pathways and molecular mechanisms, and immunity and disease. Registration is free, but seating is limited, so please register early.

Deadlines:
Poster abstracts: August 14, 2009
Registration: September 1, 2009

Online registration and instructions for abstract submission:
http://web.ncifcrf.gov/events/basicimmunology2009/default.asp
For questions, contact Karen Kochersberger at kochersbergerks@mail.nih.gov or 301-228-4027.

Cancer Prevention Fellows
Application Deadline: Sept. 1, 2009
Start Date: July 2010

The NCI-FDA Cancer Prevention Fellowship Program provides postdoctoral training opportunities in cancer prevention and control to individuals from many health sciences disciplines. For information go to http://cancer.gov/prevention/pob or http://iotftraining.nci.nih.gov/index.html.

Volunteers Needed for Recording for the Blind and Dyslexic

Recording for the Blind and Dyslexic (RFB&D) is a national nonprofit volunteer organization that provides recorded textbooks to people who cannot read the printed word because of visual, learning, or other disabilities. Readers with expertise in scientific and technical areas, especially anatomy, microbiology, and biochemistry, are needed. Interested NIH researchers and other staff with scientific knowledge can volunteer to read for an hour or more a week during the day or before or after work. The recordings take place in Building 31. This is an opportunity to provide a much-needed service to future scientists. To volunteer, contact Kathryn Sparks at 202-244-8990 or ksparks@rfbd.org.
For more information, visit http://www.rfbd.org.

Catalytic Reactions?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not send it to us via e-mail: catalyst@nih.gov; fax: 301-402-4303; or mail: Building 1, Room 160.

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

In Future Issues...

- Porter Neuroscience Research Center
- NIH Library
- Pirate viruses?

What I Learned at NIH

On Thursday, April 23, 2009, my mom took Wendy, Kenny, and me to NIH (National Institutes of Health) because it was "Take Your Child to Work Day!" We learned about a sickle cell disease and we voted if studies were necessary. In "Bones and Evolution" we learned about bones of different animals. We saw a genuine fox skeleton. We had a splendid experience!

The first activity was "I Want to Build a Rocket." We voted on whether we should start certain studies. My favorite study is that scientists are adding an iPod to toothbrushes. Some kids were afraid that the kids would outwit the toothbrush. Even though we had some stubborn competitors, we still had a thrilling time.

Another activity was called "Interview with a Mouse." A woman pretended she was Meredith, a lab mouse that has a sickle cell disease. Animals used for scientific study are protected by the government rules. A sickle cell disease is where the animals' red blood cells have varied shapes. Scientists put a gene in a virus and then sent it to the organ that makes functional red blood cells. Can you believe that a virus can deliver genes to an organ?

Bring your kids to work day was great fun. There are many interesting places in this immense institute. I hope next year the activities will be even better at NIH. — Kendy Li (Age 10)

Kendy's mom, Jingrong Tang, works in Building 10 in a clinical lab at the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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