FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 17, ISSUE 2 ■ MARCH–APRIL 2009

ENDANGERED SPECIES?

NIH Examines the Role and Future of the Physician-Researcher

by Vanessa C. McMains

Some recovery efforts for endangered species are well known. Consider the rebound of the bald eagle and gray wolf, both recently removed from the endangered species list.

But who is looking out for the endangered physician-scientist? There are no "adopt a physician-scientist" programs; no organizations raising money through the sale of cuddly stuffed replicas of scientists or action figures with crisp, white lab coats and posable arms.

Fortunately, the NIH and other national organizations, aware of the diminishing numbers of physician-scientists since the 1980s, are developing a concerted plan to replenish the stock. The first step is to better understand the role of the physician-scientist through the years—that is, to understand its habitat and place within the larger research environment—and then use history to illuminate past and present policy.

On March 26–27, leading physician-researchers, organizational leaders, historians and social scientists gathered for a conference at NIH to explore the physician-scientist tradition and the challenges it faces.

Courtesy NIH Office of History

The golden era of physician-researchers briefly overlapped the golden era of bow ties. Concerted efforts are under way to reestablish the former at the NIH while maintaining excellence in basic bench science.

continued on page 10

NEI-NASA TEAM UP FOR EARLY CATARACT DETECTION TOOL

by Allyson T. Collins, NEI

It was a seemingly unlikely match: an ophthalmologist from the National Eye Institute and a physicist from the NASA Glenn Research Center. They were hundreds of miles apart, one in Bethesda and the other in Cleveland, and their research sites were thousands of miles apart—one in eye-care clinics *on* Earth and the other in satellites *orbiting* Earth.

But in 1994, a blinding eye condition, a fiber-optic probe, and an interagency agreement promoting collaborative research brought NEI researcher Manuel Datiles and NASA scientist Rafat Ansari together. The result, featured in the December 2008 issue of the *Archives of Ophthalmology*, has been the creation of a new cataract-detection tool that boldly goes where no probe has gone before.

In the 1980s, NASA's Ansari became intrigued by a physics technique known as dynamic light scattering (DLS). The process involves passing light through a material, such as a protein crystal, to determine the size of particles in solution. His DLS experiments were designed for the microgravity environment of space, which provided a setting for maximum crystal growth.

"We wanted to monitor these growth phenomena from the initial state of nucleation and then bring the crystals back to Earth to study their structure," Ansari said.

Then, years into his research, Ansari learned that his father was one of the more than 20 million Americans who have been diagnosed with a cataract. Cataracts account for nearly 50 percent of cases of blindness worldwide.

The news sent Ansari to medical libraries, where his literature search revealed that cataracts are caused by protein aggregation, a process similar to what he was studying in space. With this knowledge, he turned to a rather unconventional laboratory for

continued on page 8

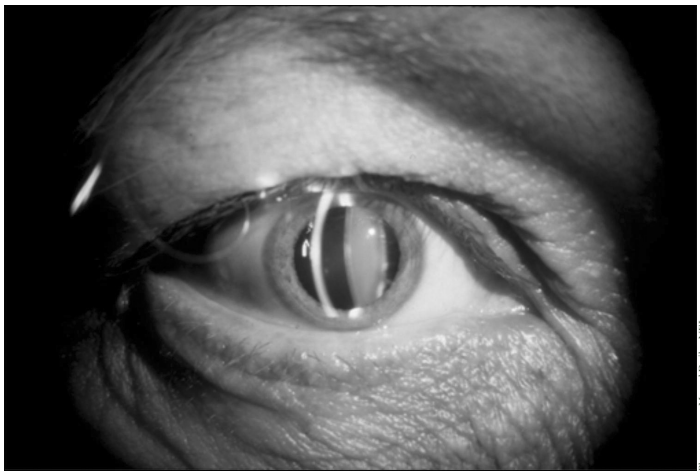


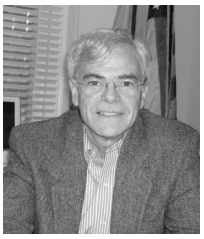
Photo courtesy Manuel Datiles, NEI

Looking in and looking out, a new tool developed by NASA and NEI can detect the onset of cataracts based on analysis of α-crystallin, a lens protein.

CONTENTS

From the Deputy Director for Intramural Research

Economic Stimulus and the NIH Intramural Research Program



Michael Gottesman

Many of you have been closely following the economic stimulus program—the American Recovery and Reinvestment Act (ARRA) of 2009, which was signed into law on February 17—and undoubtedly have heard that NIH is the recipient of $10.4 billion. This is an unprecedented opportunity to help stimulate the economy while furthering the NIH mission of seeking scientific knowledge to improve the health of all citizens. We are grateful to President Barack Obama and Congress for putting faith in our ability to spend this money wisely.

To quote the superhero Spider-Man, "With great power comes great responsibility." Having control over the $10.4 billion gives us great power. But we must exercise our responsibility by being diligent in disbursing that money. We must be willing to undergo the most intense scrutiny, and our efforts need to be transparent to anyone interested in determining whether all the funds are spent in support of ARRA goals (which include preserving and creating jobs to promote economic recovery, and providing investments needed to increase economic efficiency by spurring technological advancements in science and health).

In keeping with the intent of the Act to stimulate the entire U.S. economy, most of the NIH funds will be disbursed to the extramural program through a variety of existing merit-based mechanisms supported through the peer-review process:

- $8.2 billion to support scientific research priorities of the Institutes and Centers (ICs) and of the Office of the Director (OD), with $7.4 billion to the ICs and the NIH Common Fund and $800 million assigned to the OD
- $1 billion allocated to the National Center for Research Resources (NCRR) to support extramural construction, repairs and alterations of biomedical and behavioral research facilities
- $300 million to NCRR for shared instrumentation and other large capital research equipment
- $400 million for comparative effectiveness research (comparing two existing treatments to determine which is most effective)
- $500 million for high-priority repair, maintenance, and construction projects on the NIH campus that are "shovel-ready" but for which funds have not been provided through the regular appropriations process

The precise allocation of the NIH campus repair and construction funds has not been announced as of this writing, but—considering the need to distribute funds quickly and the backlog of incomplete construction projects and urgent maintenance needs—it is expected that the use of the funds will be determined soon. This quick use is a great boon for NIH-supported research as well as for the construction industry, because the funds will support local contractors as well as tradespeople from all over the United States.

Three additional intramural benefits will come out of the $7.4 billion in ARRA funds assigned to the ICs and Common Fund. The first is the expenditure of up to 0.5% of the amount designated for each IC for intramural equipment purchases (a total of approximately $36 million). Scientific Directors have provided us with lists of major equipment items that are essential to the mission of NIH, but that have not yet been purchased due to budget constraints. Larry Chloupek, the administrative liaison in the Office of Intramural Research, has created purchasing pools to achieve maximum savings when negotiating with the manufacturers. Each pool will be the responsibility of an IC that has expertise in that type of equipment. Purchases should begin soon.

The second benefit is funding for the Clinical Center, which has a large backlog of unordered equipment that will support the IC's clinical activities, to purchase critically needed large equipment.

And third, $1 million per year will be used to hire up to 200 highly qualified students (high school and college) to work at NIH this summer and next. These are students who had applied for summer positions but were not going to be hired because of a lack of funding. Qualified students had to have applied through the online system; have a grade point average of at least 3.0 and two outstanding letters of reference; and have described how their work in an NIH laboratory or clinic is likely to benefit them scientifically and in making career decisions. In addition, the research support and mentoring environment must be outstanding. A group consisting of NIH training directors from the ICs will review the applicants and make recommendations. Then, to ensure both the merit of the students and the quality of the mentoring, I will personally review all applicants before final decisions are made.

I trust you will all work with me to ensure that the highest standards are applied to the disbursement of all NIH ARRA funds that are assigned to the NIH Intramural Research Program.

—Michael Gottesman, DDIR

Catalytic Changes:
New Managing Editor and Writer for The NIH Catalyst

Science writer Laura Stephenson Carter is tackling her job as the new managing editor of *The NIH Catalyst* with enthusiasm. For years she has relied on NIH as the trusted source of health information in her work as a medical writer and editor and is pleased to get the chance now to work directly with NIHers.

Carter arrived in February 2009, filling a seven-month void left after the previous editor, Fran Pollner, retired.

Before coming here, Carter had spent nearly 10 years writing about biomedical research and clinical activities at Dartmouth Medical School (Hanover, N.H.), where she was the assistant director of publications and associate editor of *Dartmouth Medicine* magazine. From 1995 to 1999, she was a public affairs coordinator and legislative specialist for Dartmouth-Hitchcock Medical Center in Lebanon, N.H. And before that she wrote articles for *Natural History* and other magazines; wrote chapters in biology textbooks and articles for an engineering magazine; edited a science newsletter for a biological research station in New York State; and authored a children's book on plastics recycling, *How On Earth Do We Recycle Plastic?*

Carter holds a B.A. in psychology and biology from Upsala College in East Orange, N.J., and an M.A. in science journalism from New York University. She has won national awards for her work, including for her cover feature in *Dartmouth Medicine*, "Puzzling Over Medical Mysteries," which provided an inside look at a little-known aspect of medical practice, the Morbidity and Mortality Conference.

Carter has enjoyed getting to know people at NIH and looks forward to meeting more of you. She hopes to build on her work at Dartmouth by improving the look of *The Catalyst*, broadening the coverage of intramural research news, and creating a more appealing website with web extras, such as audio and video interviews, to complement *Catalyst* articles. She will also improve circulation and distribution. She welcomes your comments on *The Catalyst* and suggestions for future story ideas. She can be reached at carterls@mail.nih.gov or at 301-402-1449.

You may have already met or heard from Sarah Freeman, who came from George Washington University Medical Center (Washington, D.C.) in February 2009 to become the new coordinator for the NIH Director's Wednesday Afternoon Lecture Series (WALS) and a writer in the Office of Communications, Office of Intramural Research. WALS, held on Wednesday afternoons from 3:00 to 4:00 p.m. in the Masur Auditorium in Building 10, features scientific talks by leading biomedical and behavioral scientists from around the world and one "cultural" lecture each year by a prominent individual.

Sarah Freeman (left) is the new WALS coordinator and writer for the Office of Intramural Research; Laura Carter (right) is the new managing editor of The NIH Catalyst. *Both are new to the NIH.*

Freeman is well suited to coordinate this prestigious lecture series, having served as an organizer extraordinaire in George Washington University's Office of Communications and Marketing, where she was responsible for planning events that featured luminaries from the federal Executive Branch including Secretaries from the U.S. departments of Agriculture, Health and Human Services, and Homeland Security as well as members of Congress.

She was also the assistant editor for *GW Medicine & Health* magazine, and, working with the Mid Atlantic Regional Centers of Excellence, she helped develop media training curriculum for science and medical faculty. She also collaborated with senior leadership, department chairs, and faculty as well as with various university and outside organizations to help target communication strategies to promote GW programs via web and print, news media and community partnerships.

And, while working full time, she also managed to receive a master's degree in political management from GW. A native Ohioan, Freeman earned her undergraduate degree in both English and Communications from Mount Union College in Alliance, Ohio.

Freeman's plans for WALS include improving the CME process for WALS; advertising the lectures better via poster displays, targeted e-mails, outreach to the local non-NIH scientific community, and personal interviews with some of the speakers; improving the WALS videocast; creating a more dynamic web presence with easy access to video archives; and improving the process of nominating, choosing, and hosting speakers. Freeman is also writing articles for *The NIH Catalyst*.

She welcomes your suggestions or comments about WALS. She can be reached at sarah.freeman@nih.gov or at 301-594-6747. ■

The Training Page

From the Office of Intramural Training & Education: Discover Graduate Student Research at the NIH

by Betsey Wagener, Deputy Director, Graduate Partnerships Program

For the past five years, predoctoral students at NIH have been getting together in informal settings to present their research to each other. Now they have begun showcasing their talent for the whole NIH community, too.

The Graduate Partnerships Program and the Graduate Student Council are hosting the Graduate Student Seminar Series (GS^3) and NIH Thesis Talks to give graduate students doing research in NIH labs a chance to talk about their work with a wider audience. The seminars also provide training opportunities to help prepare students to make professional presentations at conferences and national meetings or at their thesis defense. At GS^3 seminars, students polish their talks in front of an audience and receive feedback from their peers. Thesis Talks are a culmination of the students' research activities at NIH.

Each GS^3 session includes two 20-minute talks on research within a given subject area. The theme of the March 2009 session was "Topics in Cancer Research" and featured graduate students Nicole McNeil from NCI and Howard University (Washington, D.C.) and Sandra Chapman from NIAID and Pennsylvania State University. In April, the talks focused on "Topics in Immunology" with presentations by two graduate students from NIAMS: Lydia Durant from University of Oxford (England) and Sophia Cleland from George Washington University (Washington, D.C.). In May, the theme will be "Topics in Genetics."

GS^3 seminars take place the third Thursday each month at 1:00 p.m. Through June, they will be held in Building 10, Room 6S235A. Beginning in August, they will be held in Building 50, Room 1227.

Thesis Talks are given by predoctoral students who are getting ready to graduate. Most graduate students who do research at NIH present their final defense at their degree-granting institution and few in the NIH scientific community get to witness these milestone events. Now students can sign up to give an NIH Thesis Talk and present their doctoral research project right at NIH. These talks are scheduled and advertised via e-mail.

Both the GS^3 seminars and Thesis Talks are posted on the NIH Events Calendar and Yellow Sheet. For more information, visit the GPP website (http://gpp.nih.gov) and click on "Activities." ■

From the Fellows Committee: Opportunity and Services for Visiting Fellows

by Catherine Jozwik, USUHS

Did you know that approximately 60 percent of NIH fellows are visiting scientists? Because the transition from an NIH fellowship to a successful career in their home country can be difficult, an NIH Visiting Fellows Committee (NIHVFC) was set up to help. This is an excellent resource for visiting fellows as well as for U.S. citizens who are interested in working abroad.

Established in 2003, the committee helps fellows maintain continuity in their research when they return to their home countries. The Committee hosts a website, sponsors several activities including the Science Voices from Home series and the annual International Opportunities Expo, and produces a quarterly newsletter. The NIHVFC is interested in establishing NIH Alumni Associations in other countries; one has already been established in Brazil.

The Science Voices from Home project is a series of informal meetings in which foreign scientists visiting NIH interact with visiting fellows from the same country or region. Through these meetings, NIH fellows can obtain information on career and funding opportunities in their own countries. Since the project's inception a year ago, meetings have been held with fellows and scientists from Greece, Spain, Australia, Israel, South Africa, Norway, Brazil, the Czech Republic, Sweden, the West Indies, China, Switzerland, and Canada. The meetings are announced in the weekly postdoc newsletter from the Office of Intramural Training and Education; fellows interested in meeting scientists from a specific country should e-mail vfc@od.nih.gov.

The annual International Opportunities Expo provides fellows with information on research, grants, and job opportunities available in other countries. The event features a keynote speaker as well as exhibits and presentations from participating organizations, and it helps fellows establish contacts with a wide range of science and technology representatives. Dr. Jeffrey Boutwell, Executive Director of Pugwash Conferences on Science and World Affairs, was the keynote speaker at this year's Expo, held on April 6. The Pugwash Conferences bring together influential scholars from the international community to discuss science and technology issues such as agricultural biotech, HIV and AIDS, and the security of nuclear weapons. Representatives from nearly 30 organizations and 15 countries provided information on overseas research, grants, and job opportunities.

The NIHVFC Newsletter is published quarterly and provides up-to-date information on the NIHVFC activities. The most recent issue includes a profile of Rita Isaac, a new investigator from India who recently received her first GRIP (Global Health Research Initiative Program for New Foreign Investigators) award.

For more information visit the NIHVFC website at http://felcom.od.nih.gov/subCommittee/vfc/index.aspx. To subscribe to the newsletter or to find out how to get involved with the NIHVFC, contact the NIHVFC Chairperson, Suman Das (dassr@niaid.nih.gov). ■

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

Four New NIH Scientific Interest Groups

NIH Nurse Practitioner Interest Group

The NIH Nurse Practitioner Interest Group provides a venue for NIH nurse practitioners (NPs) to gather monthly to discuss relevant practice, clinical, and research issues. It represents more than 100 nurse practitioners practicing within the Clinical Center and the various institutes. The group sponsors an NP Poster Day and has established a quarterly lecture series that features presentations by members on topics related to their clinical and research expertise.

In 2009, the Nurse Practitioner Interest Group hopes to offer CME/CEU credits for professional development presentations and will invite other members of the NIH community to attend. For more information, contact Stacey Solin at solins@mail.nih.gov or visit http://sigs.nih.gov/np.

Advanced Pharmaceutical Screening Interest Group

The NIH Advanced Pharmaceutical Screening Interest Group (APSIG) serves as a platform for scientific discussions of current trends and issues in pharmaceutical screenings and provides a forum for intramural and extramural scientists to interact. Discussion topics include emerging research, novel methodologies and technologies, biomarkers, personalized medicine, limitations to translation, clinical trials design, resources and training, and more. The APSIG Steering Committee coordinates the activities of this group.

The APSIG was an NIH scientific interst group for many years and has now reformed after a brief hiatus. For more information, contact June Lee at 301-435-6987 or jl109j@nih.gov, or visit http://sigs.nih.gov/apsig.

Biological Visualization Interest Group

The Biological Visualization Interest Group's main objective is to share information on and resources for creating animations and building interactive applications. The group also shares techniques for improving quality, including Section 508 requirements, and disseminates information about visualization technologies and services developed with NIH resources or of potential interest to the NIH community.

Creators (3-D animators, software developers and scientists creating animations) and content consumers (NIH staff who use technologies or view animations) will benefit from this group's activities. Meetings are held first Mondays monthly, 5:30–6:30 p.m., location to be determined. For information, contact Jeremy Swan at 443-538-8689 or swanjere@mail.nih.gov, or visit http://science.nichd.nih.gov/confluence/display/bvig/Home.

Metabolomics Scientific Interest Group

In the postgenomic era, metabolomics is gaining importance as another promising "omic" technology for understanding the biology of various diseases. Metabolomics is the study of the metabolome, the repertoire of metabolites, or small molecules present in cells, tissue, and body fluids. These molecules are the final products of interactions between gene expression, protein expression, and the cellular environment.

The metabolome is thus a close representation of a physiological state and biochemical pathways. It forms the integral part of systems biology in which the data from various omic technologies complement each other to provide a holistic picture of how various biological systems respond to external stimuli and in various pathophysiological conditions. It offers great promise for understanding the underlying principles of biological processes including various pathophysiological conditions such as cancer and other diseases.

NIH promoted the development of metabolomics technology through its Roadmap for Medical Research initiative, launched in 2004 to address roadblocks to research and transform the way biomedical research is conducted. In 2005, NCI, in collaboration with other ICs, conducted a successful and well-attended workshop to address the use of metabolomics in cancer research. In response to some of the workshop's recommendations, NCI and other institutes have since awarded grants to extramural researchers who use metabolomic tools. At least one NIH intramural lab is actively pursuing metabolomics technologies. Still, interest in metabolomics research is not as robust as it could be.

The new Metabolomics Scientific Interest Group was created to help stimulate more interest in the field and aims to bring interested NIH program officials and intramural investigators together. The group will meet periodically to discuss recent advances and hear from invited experts. The organizers hope that in the future there will be more programmatic initiatives that promote the application of metabolomics technologies to research in human health.

For more information, contact Padma Maruvada at maruvadp@mail.nih.gov or visit http://sigs.nih.gov/metabolomics.

Career Symposium Announcement

Build Your Career, Shape Your Future: The NIH Office of Intramural Training and Education (OITE) invites all NIH graduate students and postdoctoral trainees (basic scientists and clinicians) to the NIH Career Symposium on Tuesday, May 19, at the Natcher Conference Center (Building 45), from 7:30 a.m. to 5:00 p.m. Learn about scientific career options and explore factors that lead to career success. Panel sessions will focus on scientific writing, teaching in a variety of settings, grants administration, public policy, and research-intensive careers and careers away from the bench in all sectors. Experts will provide insights into their diverse career paths. Workshops will address professional skills including negotiation, interviewing, work-life balance, managing, and the uses of optimism. Toni Hoover, vice president of Pfizer Global Research, and Research and Development, will be the keynote speaker.

For more information and to register, visit http://www.training.nih.gov. This event is supported by OITE, the Fellows Committee, and the Graduate Student Council.

Cut It Out: The Laser Capture Microdissection Core

by Christopher Wanjek

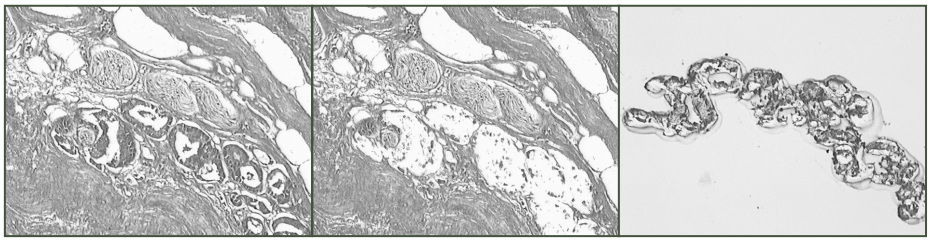
Deep in the underbelly of the Clinical Center lies the Laser Capture Microdissection (LCM) Core, a windowless two-room laboratory where histology, pathology, and molecular biology intersect with what appears to be hocus-pocus.

Here researchers employ five specialized machines that use lasers to carve out sections of tissue as small as a few cells across from a complex, heterogeneous specimen and then lift them away undamaged for further analysis, all guided by direct microscopic visualization via a computer monitor or traditional microscope.

Gone are the imprecise methods of negative selection or having a hodgepodge of unwanted cells and other impurities in a sample. The technique, called laser-capture microdissection, was invented by NIH investigators in 1996 and has become a commercial success via a Cooperative Research and Development Agreement (CRADA) with Arcturus Engineering (now MDS, Inc).

The field has advanced greatly, however, and all NIH researchers can take advantage of this homegrown innovation for free. The Core—led by one of the inventors of the LCM technique, Michael Emmert-Buck, who is head of the Pathogenetics Unit in the NCI Center for Cancer Research Laboratory of Pathology—offers assistance in project setup, tissue handling, laser microdissection techniques, molecular analysis of microdissected samples, and pathology evaluation for microdissection and research.

With new features available, such as an ultraviolet laser to cut through bone or to isolate samples as thick as 20 µm and an upgraded imaging system with diverse types of illumination, the Core hopes to expand the range of its collaborations. The Core offers weekly classes on demand.



An infrared laser carves out a tissue sample in the center of the first frame above. The same machine lifts the sample from the larger biospecimen, as seen (or not seen) in the second frame, and places it on a new slide.

"The technology has enabled a lot of projects that would have been impossible a few years ago," namely live-cell applications and high-throughput microarrays and protein analyses that were too time-intensive in the past, said Jeffrey Hanson, a biomedical engineer with the Core.

Jaime Rodriguez-Canales, a pathologist with the Core, explained how a clean cut makes a major difference in analysis. Tissues are complex and heterogeneous, containing several types of intermixed cells, with each type generating its own molecular signature. For instance, according to a 2008 (non-NIH) study comparing the gene expression of primary breast carcinoma and lymph node metastasis, the gene expression profile was completely different when RNA was extracted from the whole tissue by traditional methods vs. from samples using the laser microdissection method.

"As a pathologist I can say it is really cool how you can look at tissue under the microscope, extract the cells, and extract the RNA," said Rodriguez-Canales. When he first saw a demonstration, "it was like magic," he said.

Although more than 200 users have come to the Core in the past few years, Hanson said that the NIH community, particularly outside the NCI, either doesn't know of the free services or doesn't realize the potential of laser microdissection for individual projects.

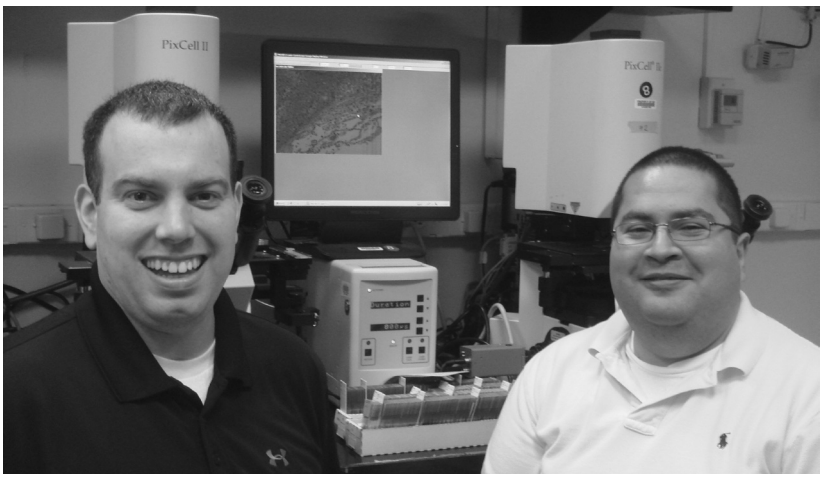
So in October 2008, Hanson and Rodriguez-Canales created the Tissue Microdissection Interest Group to share ideas and to spark collaborations. Other laboratories have laser microdissection scopes, and many researchers are interested in the diverse applications of this technology. But many users don't know how to use their instruments to their fullest capability.

The various machines housed in the Core have their strengths and weaknesses, and Hanson and Rodriguez-Canales move from one to another based on the nature of the task at hand. The newest machines are more automated, but Rodriguez-Canales is able to teach users how to finesse machines in their own laboratories. Like the tango, the art of dissection is a graceful learned skill.

Meanwhile, Emmert-Buck continues his work in dissection and imaging. As relayed on his NCI CCR Web page, his group and collaborators are developing expression microdissection (xMD), which converts microdissection from an operator-dependent to an operator-independent mode, eliminating the need to laboriously procure cells. Among many advantages, xMD will improve dissection rates by several orders of magnitude. Important collaborators and co-inventors include Bob Bonner (NICHD), Tom Pohida (CIT), and Mike Tangrea (NCI).

Emmert-Buck anticipates that xMD and LCM will become complementary tools that will assist investigators in phenotype- and expression-based profiling studies of cell populations in tissue sections.

To join the Tissue Microdissection Interest Group or to schedule a meeting with the Laser Capture Microdissection Core, e-mail ncilcmcore@mail.nih.gov. The facility is located on the Bethesda campus in Building 10, room B1B37. ■



Biomedical engineer Jeffrey Hanson and pathologist Jaime Rodriguez-Canales with some of their handiwork behind them in the Laser Capture Microdissection (LCM) Core, located in Building 10.

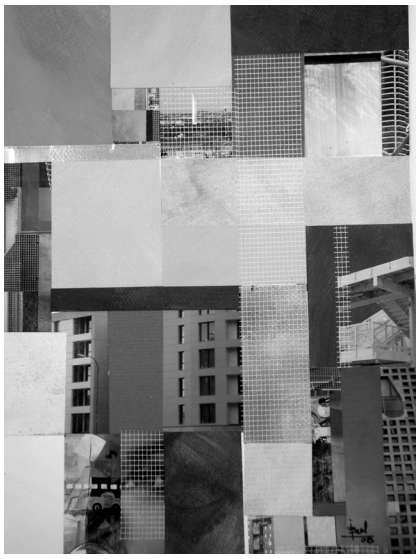
NIH Juried Art Show Returns in May

Don't miss the May 4 opening of the NIH Staff Art Show featuring paintings, drawings, photographs, and ceramic and stained glass pieces as well as fabric and mixed media arts by talented artists.

More than 100 employees from 21 institutes and seven campuses (including Executive Boulevard, Frederick, and Baltimore) vied for the chance to have their works exhibited in this juried art show.

The judges—show organizer Tyrone Spady (NHGRI), Lillian Fitzgerald (curator of the Clinical Center Art Program), Crystal Parmele (director of the CC Art Program) and Sandy Young (NCI)—had a difficult time choosing which creations to include out of the 580 submitted for consideration. Only 42 pieces made it into the show.

"Works were entered from every corner of the NIH community," said Spady. "Artists range from postbacs to PIs, science writers to IT specialists."



"A View of Madrid from DC," a mixed-media piece by Jorge Bernal (NCI), is one of the artworks featured in the NIH Staff Art Show. The image is better viewed in color in the online version of The NIH Catalyst at http://www.nih.gov/catalyst—and, of course, best viewed at the exhibit.

The competition was strong "in both quality and quantity," added Young. "The jury feels that we have an exceptional exhibition for NIH staff and visitors to enjoy."

The Clinical Center is well known for its contemporary art, an eclectic mix of media composed of about 3,000 original pieces mostly from local artists, displayed in eight galleries and along Building 10's vast network of corridors, so that getting lost in the building is a little less frustrating. The pieces on display in the NIH Staff Art Show do not necessarily have overt scientific themes.

The opening reception is Monday, May 4, from 4:00 to 6:00 p.m. in the Clinical Center (Building 10) in Library Hall, which is near the NIH Library and the Clinical Center south entrance. The exhibition will continue through July 3, 2009. For more information, contact Tyrone Spady at spadyty@mail.nih.gov. ■

The Science of Campus Beautification

NIH Non-Juried Art Show Outdoor Also Returns

During the dreary winter months, the folks in the Office of Research Facilities Development and Operations (ORF) are responsible for clearing snow and ice from more than 12.5 lane-miles of road, nearly 40 acres of parking lots, the tops of six parking garages, 192 exposed handicap parking spaces, 621 building entrances, and over 21 miles of sidewalks as well as miscellaneous bus stops and shelters, nitrogen and oxygen tank areas, pedestrian and vehicle entrances, and patios and playgrounds. Whew!

But wait! The work doesn't let up when the last of the snow is gone. Now ORF has to concentrate on making the 320-acre campus look pretty. They oversee the mowing of 135 acres of lawn; maintain more than 12 acres of shrub and flowerbeds and seven acres of reforested and meadow "no mow" zones; and care for more than 8,000 native and ornamental trees.

But ORF landscape architect Lynn Mueller will take the dirty job of landscaping any day over snow removal. She tries to treat us to a little new variety each year.

"This year we installed several thousand small perennial coreopsis 'Moonbeam' and daylily 'Stella d'Oro' within most of the street tree wells," Mueller said. "They will eventually grow larger and fill up the wells with summer-long yellow and golden blooms. Over the past 20 years we have planted tens of thousands of 'King Alfred' daffodils across the campus. We tried tulips long ago but this area is too hot through the summer and the bulbs rot. The rhododendron 'PJM' variety blooms at the same time as the daffodils, and our Yoshino cherry trees are peaking now. Our 'Autumnalis' cherries will have a nice bloom in October and early November. Soon the azalea and later the rhododendrons will be blooming.

"We try to focus on native varieties of flowering trees—such as dogwoods, red buds, and serviceberries and flowering and fruiting shrubs—to encourage native wildlife and to minimize maintenance. Native material is better suited to survive the metropolitan area swings in weather, especially the almost yearly summer droughts." ■

NEI-NASA Cataract Tool

continued from page 1

Credit: NASA

Not just any crystals, but space *crystals, or more specifically, HIV reverse transcriptase protein crystals grown in the microgravity environment of the International Space Station. NASA's Rafat Ansari's early work in analyzing crystals grown in space led to a machine to examine proteins in the lens of the human eye.*

his next experiments—his kitchen.

"My daughter was in high school at the time, and she was dissecting excised cow eyes," Ansari explained. He brought a few home and asked her to remove the lenses. Then at his kitchen table, he conducted career-changing tests to see whether the made-for-space DLS probe could detect lens protein changes.

Seeing the Invisible

Datiles had been studying cataracts since his arrival at NEI in 1979. He first worked at the Laboratory of Vision Research, in the old Building 6. His team was searching for anti-cataract medical treatments and new clinical methods for grading and imaging lens opacities.

The preferred techniques at the time were the slit lamp, which provided a magnified view of the eye using high-intensity light, and the Scheimpflug camera, which captured high-resolution images of the eye's anterior portion. Though useful, these tools had three crucial limitations: a relative insensitivity, a high error rate, and an inability to detect pre-cataract molecular changes.

"We were also looking for a way to assess oxidative stress by analyzing molecular structure, rather than just the reflection of light," Datiles said.

Joram Piatigorsky, chief of the NEI Laboratory of Molecular and Developmental Biology, and his colleagues had laid the foundation for this work with their discovery that the major lens proteins, the crystallins, were often enzymes or had other metabolic functions. And other NEI-supported research in the early 1990s had revealed the significance of protein molecules in cataract formation. One of the three main lens proteins, α-crystallin, was identified as a "molecular chaperone" that serves as a built-in anti-cataract mechanism.

When other crystallins are exposed to sources of oxidative stress, such as sunlight, smoking, radiation, and some drug therapies, they denature and aggregate to form a cataract. However, α-crystallins can bind to and stabilize these altered proteins, thus preventing cataract formation. Humans are born with a fixed amount of α-crystallin in the central portion of the lens, which is most susceptible to cataracts. If all of the α-crystallins become denatured or saturated, a cataract forms.

"It is too late to reverse or medically treat this process at that point," Datiles said. "The time to start treating is actually before you run out of α-crystallin, so a cataract will never appear in the first place."

But NEI researchers needed a way to measure protein changes before a cataract became visible. Datiles had previously tested a DLS device from Japan, but found that it had poor reproducibility. So he was skeptical when Ansari contacted NEI about a possible collaboration. Nevertheless, NEI invited the NASA scientist to present a seminar about his preliminary work with the new probe.

"My attitude in the beginning was that he needed to prove that this could work, especially with regard to sensitivity and reproducibility," Datiles said.

But Ansari's talk piqued Datiles' interest. The two men entered into a head-to-head contest—Ansari's DLS probe vs. a Scheimpflug camera—to see which would detect a cataract first. In a 48-hour marathon of testing, they induced cataracts in 18 excised calf lenses by exposing them to varying temperatures of cold water to produce "cold" cataracts.

"The DLS detected a shift in lens proteins at 17° Celsius, while the Scheimpflug did not detect it until 9°," Datiles remembered. "That was quite a big difference, so I said, 'Okay, I'm convinced. Let's build a clinical device.'"

Uniting Ophthalmology and Physics

From the outset, Datiles knew little about biofluid sensor systems, and Ansari understood just the basics of ophthalmology. Their combined knowledge, however, was enough to earn the backing of a five-year, $2.5 million NASA-NEI Interagency Agreement, with NEI putting forth resources and facilities for animal and clinical studies and NASA contributing the probe and financial backing.

They then began animal experiments, testing the new DLS probe on more than a half dozen animal cataract models in collaboration with eye researchers across the United States. These tests showed that the DLS process could detect molecular changes much earlier than conventional methods.

A team of scientists constructed various clinical prototypes. Ansari's miniaturized probe, the size of a dime, needed to be incorporated into an eye instrument for proper focusing. They started by mounting the probe on a conventional slit lamp, but this instrument could not return to the same site in the eye for subsequent measurements. Next, they mount-

Photo courtesy of Manuel Datiles, NEI

NASA's Rafat Ansari (seated) and NEI's Manuel Datiles (immediate right) working out the details of their tool that uses dynamic light scattering (DLS) to examine α-crystallins, one of three lens proteins that, when denatured, allows cataracts to form. NASA technician James King looks on.

ed it on a keratoscope used for mapping the cornea. While the probe now stayed in a fixed position, it did not accommodate varying eye sizes. Finally, an additional computer-controlled carriage set the proper distance to the lens.

"That really worked perfectly," Datiles said. The error in returning to the same location in the lens was less than one percent. Thus the reproducibility problem was solved.

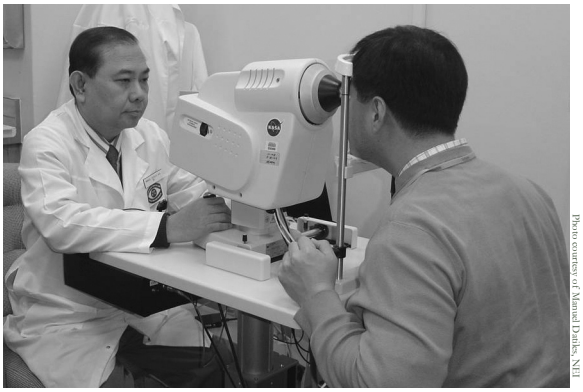


Photo courtesy of Manuel Datiles, NEI

Datiles tests the new cataract-dectection machine on a volunteer.

Before they could use the device on patients, however, they needed more information about α-crystallin's fingerprint, or its ability to scatter laser light. Though the light-scattering profile differs slightly among individuals, statisticians boiled down the fluctuations to a new clinical parameter, known as the α-crystallin index, which indicates the amount of unbound protein.

"Other researchers had been looking at these particle distributions for years," explained NEI clinical director Frederick Ferris. "But everyone was focusing on the larger proteins" because larger protein particles aggregate to form cataracts. "The new twist we put on this was to focus on the loss of smaller molecules, the α-crystallins, which are associated with early stages of cataract formation," he continued.

NEI researchers hoped that by detecting subtle protein changes before a cataract developed, they could advise patients to make simple lifestyle changes such as decreasing sun exposure, quitting smoking, stopping certain medications, and controlling diabetes in order to reduce the risk of developing cataracts.

Moving to the Clinic

The miniaturized fiber-optic probe built to look at proteins in space was now fit for use on humans as the first compact, noninvasive, early-detection device for cataracts. The test was simple: A patient rested his chin on the device; a technician aimed the probe at the lens nucleus; a photodetector collected information on the laser light scattered over a five-second period; and a statistician deconstructed the resulting diffusion coefficient to determine the α-crystallin index.

This process provided molecular information about cataract formation that had never before been obtained from patients in the clinic, prompting NASA to contribute another $2.5 million over five years, enough for a major clinical trial on 380 eyes in 235 patients.

The results, published in the December 2008 issue of *Archives of Ophthalmology*, showed that as lens opacities increased, the α-crystallin index decreased. Unbound protein levels also decreased with increasing age, even when the lenses were still transparent, suggesting that the device could be useful in detecting early signs of oxidative stress related to aging.

"From my perspective, the biggest benefit is that we have an opportunity to learn more with regard to the natural history of cataract progression, and we also have an instrument that can help us assess whether there is toxicity [affecting] the lens," Ferris said. "This may turn out to be one of the most important advances in the field of lens[es] in the last two decades."

Finding New Applications

Before the creation of this device, clinicians had no way to confirm external influences on cataract formation, though they believed that the environment, medications, and certain surgeries could contribute. "It is like going on vacation and getting sick when you return home," Datiles said. "There is no way to prove that you caught something on the trip, even though you believe it to be the case."

Now, researchers have an early alarm system for lens damage. It will allow them to look at long-term cataract progression in patients who undergo vitrectomy, the surgical removal of the eye's vitreous gel, as well as in those who have not undergone eye treatments, to confirm that the α-crystallin index is a valid measure of cataract risk.

Ferris hopes that ophthalmologists will be able to one day use α-crystallin measurements to track cataract progression in a way similar to the way nephrologists use creatinine clearance measurements to track kidney function.

Datiles believes that the technology could also prove valuable in other medical specialties that are concerned with oxidative stresses' damaging effects, including the acceleration of aging.

"Unlike most other organs, the eye is readily accessible to testing," Datiles said. "If researchers could use this test to measure oxidative stress in the eye, then it could help reflect the status of other, inaccessible organs. That's the exciting part."

Although NEI is focusing on helping patients, Ansari said that additional research will come full circle to where it began: the space program. He is modifying the device to fit in an astronaut's helmet and monitor the effects of cosmic radiation on the lens. The device will then deliver real-time lens protein measurements to specialists on the ground.

"This technology could help us understand the mechanism for cataract formation," Ansari said. "We can work to develop effective countermeasures to mitigate the risk and prevent [cataracts] in astronauts."

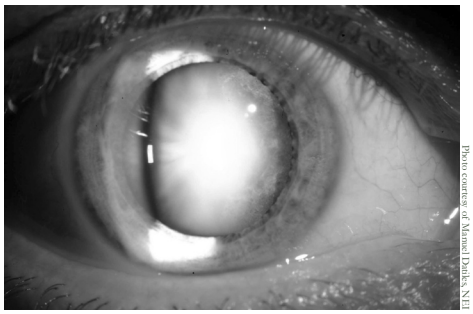


Photo courtesy of Manuel Datiles, NEI

This dense white cataract photographed through a dilated pupil using a wide beam of a slit lamp camera illustrates how an advanced cataract can block one's vision.

Adopt a NASA Colleague

Datiles, who has spent three decades at NEI researching cataracts, acknowledged that without the interagency agreement, neither NASA nor NEI scientists would have progressed so quickly.

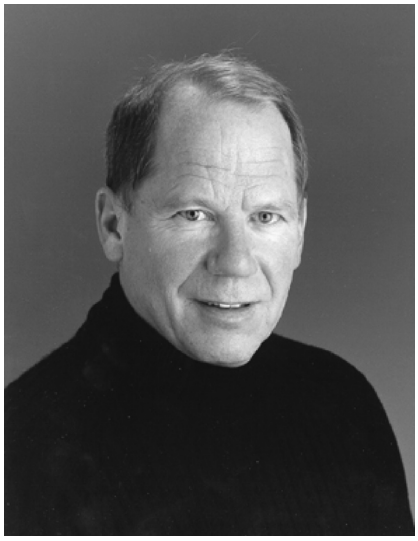
"NASA provided the machine, and NEI made it possible to test the probe on animal models and patients," he said. "These kinds of risky, long-term projects are only possible at government institutions."

Ferris agreed. "We need to keep our eyes open for opportunities to work with people that we in the medical field would not normally collaborate with, such as NASA."

"Our aim has always been to find a cure for cataracts to serve mankind," Datiles said. "So whether mankind is in space or here, this technology is extremely valuable." ■

Physician-Researcher

continued from page 1



Robert Martensen, NIH Office of History director

"We want[ed] to look at changes that are less apparent to administrators, changes in the nature of scientific disciplines over the last 50 years, changes in how science operates, and changes in models of what it means to be a physician in medical research," said Robert Martensen, director of the NIH Office of History, which sponsored the conference, called "The Role of the Research Physician: From Golden Past to Threatened Future."

"One of the problematic areas is knowing where physicians stand in relation to the old disciplines [i.e., biochemistry and molecular and cellular biology]," Martensen said. "Analyses of grant awards suggest that it matters little if researchers know how to take care of sick people or have any clinical training at all. That was not the case in the 1960s and early 1970s."

Physician-scientists are M.D.s or M.D.-Ph.D.s who are primarily engaged in biomedical research. They bring a unique perspective to their work because they have cared for patients and have a "knowledge of disease [that] permits them to identify what the basic problems are," explained physician-scientist Irwin Arias (Eunice Kennedy Shriver National Institute of Child Health and Human Development) who has written extensively on the subject of physician-scientists and leads a program at NIH called DeMystifying Medicine.

"Knowing the important questions to be asked is a unique capability of the physician-scientist . . . often lacking in the basic scientist," he said.

Over the past 30 years, the number of physicians involved in patient care has been growing while the number involved in research has been declining. "The number of physicians engaged in research as their major professional activity declined from [a] peak [of] 18,535 in 1983 and 23,268 in 1985 to 14,340 in 1995, where it has since remained virtually constant (14,521 in 2003)," according to an article by Timothy J. Ley and Leon E. Rosenberg published in the *Journal of the American Medical Association* in 2005. "Moreover, the percentage of physicians engaged in research has declined steadily from a peak of 4.6% in 1985 to a level of 1.8% in 2003."

Disrupted Ecosystem

There have been major advances in biomedical research and many exciting discoveries in genetics and in cellular and molecular mechanisms of disease. But the shortage of physician-scientists threatens to limit the opportunities to develop better diagnostics, new treatments, and preventatives of disease—essentially, the way NIH does business.

Just as the loss of a plant or animal species upsets an ecosystem, loss of physician-scientists has disrupted the ecological balance in medical research. There is a disconnect between the practice of medicine, which involves treating patients, and the process of biomedical research, which explores the biological function underlying health and disease. That disconnect limits the potential to improve overall health and decrease human suffering and disease.

Just as the loss of a plant or animal species upsets an ecosystem, loss of physician-scientists has disrupted the ecological balance in medical research.

Physician-scientists have held a special place in research. "We want physicians in medical research since physicians have bedside knowledge," Martensen said. "They make diagnoses, they provide treatments, and they deal with real people and real problems."

Basic researchers, on the other hand, are trained to work with animal models and with cells in culture dishes. Although their work contributes to the greater understanding of biological systems, it often does not translate directly into clinical therapeutics.

At one time medical schools did not offer Ph.D. programs, and biomedical scientists were trained as M.D.s. They were taught to understand pathobiology and encouraged to pursue their interests in basic science research, too.

A Golden Era?

After World War II, federally funded research was considered to be in the public's best interest, according to Arias in "Bridge Building Between Medicine and Basic Science," a chapter in a report published by the National Research Council in 2004. Postwar growth of basic science at the NIH and of basic science departments at medical schools was based on the concept that "diseases will be cured only when science produces fundamental understanding of physiology and pathophysiology," he wrote. "Federal funding converted U.S. universities and medical centers into research-intensive institutions. Physician-scientists and basic scientists flourished as did scientific interactions between them."

Soon medical schools started offering Ph.D. programs. The underlying premise was that physicians with a better understanding of basic science could be more effective in understanding, diagnosing, and treating disease as well as in helping to develop treatments.

The next 20 years or so (1950 to the mid-1970s) were known as the so-called "Golden Era" of physician-scientists. Ph.D. and M.D. researchers worked closely together, collaborating on basic and clinical research projects. Translational research was at an all-time high, bringing findings from the laboratory bench to the bedside for treatment of patients.

Depleted Stocks

But by the mid-1970s, the number of M.D.s interested in research began to decline and the downward trend continues today. There are several contributing factors. Biomedical science has become more complex, and it takes longer to train researchers than in the past. Typically, training for clinicians includes four years of medical school plus five to seven years of residency. For M.D.-Ph.D.s, medical school training alone is eight years or more. Career opportunities are more limited for researchers and obtaining research funding is very difficult.

In addition, students reported an average debt load of over $140,000 (and nearly 18 percent of them had educational loans of $200,000 or more), according to a recent survey conducted by the Association of American Medical Colleges. Anxious to repay that debt, many students prefer to enter clinical practice, which offers higher salaries than research positions do.

The difference in the type of training that scientists and physicians receive is also a problem. Today most medical

The shortage of physician-scientists threatens to limit the opportunities to develop better diagnostics, new treatments, and preventatives of disease—essentially, the way NIH does business.

school graduates are not well versed in the principles and methodologies of translational and clinical research. Such knowledge would prepare them to evaluate the significance of published discoveries and new therapies as well as to communicate with researchers. Ph.D. candidates (even those in biomedical programs) are not taught to have an understanding of pathobiology and have little or no interaction with patients. The stereotype persists; M.D.s treat patients and Ph.D.s do basic research.

Many Players, Many Solutions

Federal agencies, private foundations, industry, and national medical organizations have launched programs to stem the loss of physician-scientists. Efforts to "sustain physicians in research careers need to develop in three dimensions at once," Martensen explained. They include "'fixing the physicians' through sustained development programs beginning [in the] first-year [of] medical school, 'fixing the system' through sustained support of research time and facilities [in] translational research programs, and 'fixing the knowledge,' which requires a reassessment of the value of old concepts of 'fundamental' and 'clinical' research."

Credit: NIH, William Branson

Irwin Arias established and runs the Demystifying Medicine course, which brings together researchers, trainees and clinicians to help bridge the gap between advances in biology and their application to major human diseases.

Fixes in the first two areas are already being addressed. The Association of American Medical Colleges has recommended that future physicians receive a thorough education in the basic principles of translational and clinical research in medical school and during residency. Medical education accrediting organizations are instituting new requirements for medical students and residents to be provided with that education. And private foundations have created new awards for young and established physician-scientists.

NIH has long recognized the problem and has launched several initiatives that are helping to rebuild the connection between medicine and basic research. In 1964, the National Institute of General Medical Sciences established the Medical Science Training program, a combined M.D.-Ph.D. program, which is still going strong today. Other long-standing research training programs for medical students at NIH include the HHMI-NIH Research Scholars Program, established in 1985 and funded by the Howard Hughes Medical Institute; and the Clinical Research Training Program, established in 1997 and funded by Pfizer and the Foundation for NIH. In 1999, NIH started the Bench-to-Bedside program to integrate the work of basic and clinical NIH scientists; in 2006 the program was expanded to encourage partnerships between intramural and extramural researchers.

There are no "adopt a physician-scientist" programs; no organizations raising money through the sale of cuddly stuffed replicas of scientists…. Rather, the NIH and other national organizations, aware of the diminishing numbers of physician-scientists since the 1980s, are developing a concerted plan to replenish the stock.

Within the past four years there has been a major emphasis on translational research with funding, new programs, and recruitment. NIH's Clinical and Translational Science Awards program, which provides funding to research centers, also aims to train a new generation of clinical and translational researchers.

At NIH the Demystifying Medicine course—established in 2001 by Arias, who ran a similar one at Tufts University (Boston) for 16 years—brings together researchers, trainees and clinicians to help bridge the gap between advances in biology and their application to major human diseases. The series includes the presentation of patients, pathology, diagnosis and therapy in the context of major disease problems and current research.

With all these recovery efforts to replenish the stock of these researchers, perhaps one day soon the physician-scientist will be taken off the endangered species list.

Discussions from the March Meeting

"The Role of the Research Physician: From Golden Past to Threatened Future" sought to elucidate the many different meanings of the term "research-physician," whether there ever was a "golden past," and whether the future is really so bleak as the title of this meeting suggests. Martensen gave a historical perspective of the issue. DDIR Michael Gottesman talked about the future and how NIH programs have made a significant contribution to the training of a whole new generation of physician-scientists. Other speakers discussed the roles of universities, government, industry, foundations and women in addressing the shortage of physician-scientists; and commentators gave historical perspectives.

David Korn, Vice Provost for Research at Harvard University, Professor of Pathology at Harvard Medical School, and formerly on the staff of the Association of American Medical Colleges, spoke about the important role of academic medical centers, AAMC's recommendations and new requirements being instituted by medical accrediting organizations. NIH Acting Director Raynard Kington spoke about the role of government and gave an overview of NIH initiatives to address the shortage of physician-scientists.

P. Roy Vagelos, former President, Chief Executive Officer, and Chairman of Merck, stressed how crucial it is to have physicians with clinical experience involved in all aspects of drug research and development and in interpreting the results of clinical studies for regulatory agencies. Elaine Gallin, Program Director for Medical Research at the Doris Duke Charitable Foundation, described the role of private foundations in funding programs to train physician-scientists. And Barbara Alving, director of the National Center for Research Resources, discussed the importance of promoting the advancement and minimizing the attrition of women in physician-scientist careers.

Conference proceedings will be posted on the NIH History Office website at http://history.nih.gov. The organizers hope to develop a list of suggestions or guidelines as a reference for research organizations in dealing with physician researchers. ■

Colleagues

Recently Tenured

Bradford Wood *is the chief of the Clinical Center Interventional Radiology Laboratory in the Radiology and Imaging Sciences Department. He is also the director of the new Center for Interventional Oncology, which was formed by the CC, National Cancer Institute, and National Heart, Lung, and Blood Institute, and an adjunct investigator at NCI. After earning his undergraduate and M.D. degrees from the University of Virginia (Charlottesville), he completed a residency in radiology—and served as chief resident in diagnostic radiology—at Georgetown University (Washington, D.C.). He went on to complete a double fellowship in abdominal imaging and intervention, and vascular and interventional radiology at Harvard's Massachusetts General Hospital (Boston) before coming to NIH in 1998. Wood is an active member of the Society of Interventional Radiology, the Radiological Society of North America, and the European Society of Radiology. His publications include a book on radiology as well as more than 350 manuscripts, chapters, and scientific abstracts. He has 17 patents or patent applications and was awarded the NIH Director's Award for Interim Leadership of Radiology and the NCI Top CCR Advances for 2008 for the development of an MR-guided ultrasound biopsy and therapy platform for prostate cancer.*

We have a focused mission in the Interventional Radiology (IR) Lab that we hope resonates in every bench-to-bedside effort we explore. We are developing multidisciplinary approaches to integrate imaging into procedural navigation, and we aim to develop drug-plus-device combinations that translate to new paradigms of image-guided "molecular interventions." I take the credit but I am held up high on the shoulders of many coworker friends.

Brad Wood

We explore novel ways to translate clinically relevant interventional tools—from basic science to initial validation studies in patients—while supporting translational and clinical research and training programs of the Clinical Center and Institutes. Three examples of our first-in-human work include "medical GPS," or electromagnetic tracking or fusion for minimally invasive interventions; "drug dose painting," in which engineered nanoparticles (heat-deployed liposomes) are locally activated with imaging guidance by minimally invasive devices (radiofrequency ablation or microwave needles) or noninvasive energy (high-intensity focused ultrasound); and the "operating room of the future" in which novel technologies, devices, robotics, and imaging methods are combined to optimize minimally invasive, image-guided therapies.

Image guidance and minimally invasive approaches have revolutionized the management of many common diseases. However, further interdisciplinary coordination could leverage this "drug-plus-device-plus-imaging" paradigm for other invasive procedures such as endoscopy, laparoscopy, and surgery. All research efforts in the IR Lab are developed with a clear translational route to the clinic and address areas of well-defined clinical need.

Other areas of research include temperature-sensitive liposomal drug-delivery vectors with cancer-targeting motifs carrying chemotherapy and MRI contrast; anti-vascular agents (to decrease convective heat loss) combined with thermal ablation; sequential fusion biopsy for drug discovery; and imageable drug-eluting beads that deliver doxorubicin or irinotecan for dose painting (distributing higher drug doses to desired areas without harming normal tissue).

We are trying to narrow the gap between diagnosis and therapy by using information during the procedure that would otherwise not be available, such as metabolic or functional spatial data from PET scans for ablations or prostate MRI information during prostate biopsy. "Medical GPS" needles navigate to a tumor target for biopsy or ablation with real-time feedback from PET, CT, MRI, and ultrasound using a platform developed here at NIH.

Working with multiple public and private partners, we have developed a multimodality interventional radiology suite that uses a CT coordinate frame to co-register different devices and pre- or intraprocedural images (ultrasound, CT, PET, rotational fluoroscopy, robotics, electromagnetic tracking, and ablative devices such as therapeutic ultrasound, microwave, and radiofrequency). This suite allows the best combinations of techniques and guidance methods to be tailored to an individual patient. Combining imaging modalities can take advantage of each modality's strength.

Real-time feedback and temporal resolution of ultrasound can be combined with functional and metabolic data from PET and the spatial resolution of MR or CT, all on one seamless Star Trek–like platform for treatment planning, targeting, procedural navigation, monitoring, and verification of treatment.

The diversity of these projects requires an interdisciplinary team of researchers as well as the interdisciplinary resources found within the Clinical Center and NIH's Intramural Research Program. We believe that by combining imaging tools with engineered drug vectors and GPS-enabled medical devices, we can suggest novel paradigms for treatment of both localized and systemic diseases, such as cancer. I have been fortunate to be surrounded by quality people who have been the motivation and drivers of our modest success: the Interventional Radiology staff, Matt Dreher, Ankur Kapoor, Julia Locklin, and Aradhana Venkatesan, to name but a few.

Sophia S. Wang *is a senior investigator in the NCI Division of Cancer Epidemiology and Genetics and an adjunct faculty member at Johns Hopkins University Bloomberg School of Public Health (Baltimore). She received a B.S. in biology from the Massachusetts Institute of Technology (Cambridge) in 1992 and a Ph.D. in epidemiology from the Johns Hopkins Bloomberg School of Public Health in 1998. From 1998 to 2000, she served as an Epidemic Intelligence Service Officer at the Centers for Disease Control and Prevention and investigated avian influenza. Wang joined the NCI as a tenure-track investigator in 2000 and was tenured in July 2008. She has made numerous presentations; published more than 100 peer-reviewed articles, book chapters, and abstracts; and is the recipient of several awards, including the NCI Bench-to-Bedside Award and a mentoring award. In addition she is on the editorial board of* Cancer Epidemiology, Biomarkers and Prevention, *and* Leukemia and Lymphoma.

My research focuses on understanding the genetic susceptibility to and molecular pathogenesis of non-Hodgkin lymphoma (NHL) and cervical cancer. We are conducting molecular epidemiology studies to identify genetic markers of susceptibility, in the exposure-to-disease continuum, as

Sophia S. Wang

well as biomarkers of cancer development with particular emphasis on immune and immune-related genes.

In our NHL research—work largely from the NCI-sponsored NHL multicenter case-control study in the United States and InterLymph, an international lymphoma epidemiology consortium of case-control studies worldwide—we are evaluating the role of genetic polymorphisms in NHL susceptibility. Although the major risk factors for NHL are not yet known, studies have shown a strong relationship between the disease and factors that alter the immune system. We have demonstrated that a promoter polymorphism in the tumor necrosis factor (TNF) gene is associated with an increased risk for NHL, particularly the diffuse large B-cell subtype. We are further investigating the role of genes within the NF-κB pathway to evaluate the role of inflammation in NHL and genes within the chromosome 6p21.3 region, which encompasses both TNF and the major histocompatibility complex. With funding from the NIH Bench-to-Bedside Award, we are also evaluating the role of immunogenetics in relation to NHL survival according to subtype.

In our cervical cancer research, we are studying the mechanisms of cervical carcinogenesis and working toward developing a new set of biomarkers that can distinguish women at highest risk of cervical cancer from those with benign infections. I am the principal investigator on the Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) in which we are using microdissected frozen cervical tissues and other biospecimens combined with an epidemiologic study design to identify, validate, and quantify the risk relationships of candidate biomarkers in cervical carcinogenesis. By measuring gene expression profiles, we hope to gain a comprehensive in vivo picture of cervical carcinogenesis.

Finally, we are conducting several studies to determine the role host genetics plays in the progression of persistent human papillomavirus (HPV) infection to cervical precancer and cancer. Although HPV infection is considered the central risk factor for cervical cancer, it is unlikely to be sufficient for developing cancer. Only some HPV-infected individuals develop persistent infection and, of those, only a subset develops high-grade lesions and subsequent cancer. In the NCI-sponsored cohort of 10,000 women in Costa Rica, we are examining the association between cervical cancer and polymorphic genes important to immune function. Within the HPV vaccine trial in Costa Rica, we are also pursuing the evaluation of host genetics in vaccine reactogenicity, antibody response, and HPV persistence.

On Tenure Track

Matthias Machner

In 1976, at an American Legion convention in Philadelphia, a mystery pathogen sickened more than 200 people with pneumonia and killed 34 of them. At the same time, across the Atlantic Ocean in Osnabrück, Germany, a six-year-old boy's interest in science and nature was just beginning.

"I was fascinated by nature's secrets and beauty," said **Matthias P. Machner**, a recently named tenure-track investigator in the Eunice Kennedy Shriver National Institute of Child Health and Human Development. "I wanted to understand how reality works." Today he's analyzing how *Legionella pneumophila* infects human cells and ultimately causes Legionnaires' disease, so named for that convention.

This bacterium commandeers an infected cell by injecting a multitude of effector proteins. Machner's lab is determining the molecular function of these bacterial proteins and developing methods to interfere with their activity. This work will help to decipher the molecular processes used by *L. pneumophila* to exploit the human host and may help to develop strategies to fight Legionnaires' disease and related illnesses.

Machner's formal study of science began when he was an undergraduate at the University of Osnabrück, where he studied cellulose-binding proteins from *Streptomyces reticuli*. He completed his graduate work at the Helmholtz Center for Infection Research in Braunschweig, Germany, where he analyzed Listeria monocytogenes. In 2002 Machner travelled to the United States to begin his postdoctoral work in Ralph Isberg's laboratory at Tufts University School of Medicine (Boston). That's where he first began his work on *L. pneumophila*. In 2008, he began his career at the NIH.

Machner appreciates the unique opportunities offered by NIH. "The NIH provides the freedom and the resources to tackle big scientific problems," he said. "Try to combine your own research with the expertise and knowledge of your NIH colleagues, and good things will happen."

When Machner is not in the lab, he enjoys bird watching and photography. Had he not become a scientist, he confesses he might have pursued a career in wildlife cinematography. He also admits to being a huge fan of the American actor David Hasselhoff (star of the television shows "Knight Rider" and "Baywatch"), who was a popular singer in Germany. "Someone has to fit the German stereotype," Machner said.

—text by Sarah A. Freeman

Colleagues

And the Winners Are…

The intramural NIH Director's Challenge Innovation Award Program is pleased to announce the award recipients for 2009–2010. The program, which aims to encourage trans-NIH institute collaborations, provides seed money for innovative and high-impact research. The topics this year include biomarkers and personalized medicine; epigenetics and gene expression; and stem cells. A total of $3 million ($1.5 million per year) was awarded for two-year grants ranging from $75,000 to $250,000 per year. Recipients will present their work at a minisymposium in spring 2010. The next competition will be held in fiscal year 2011.

Chemical profiling of drug sensitivity in *P. falciparum* malarial strains

Christopher Austin (NHGRI) with researchers from NHGRI and NIAID

Although we have made great progress in fighting malaria, including the sequencing of several Plasmodium genomes and collection of genotypic data, we know very little about the role genomic differences play in variations in drug resistance among parasite strains. We will use an assay that measures parasite proliferation in red blood cells to profile more than 100 *P. falciparum* field strains for sensitivity to almost 3,000 approved drugs. This work will identify genes involved in malarial drug resistance, map the geographic distribution of drug responses, dissect the metabolic pathways of malaria parasites, and potentially discover new antimalarial drugs or drug combinations.

Source: NHGRI

Kalypsys robots at the NIH Chemical Genomics Center used for plate handling, which will help scientists profile more than 100 P. falciparum *malaria field strains. Credit: Maggie Bartlett, NHGRI.*

Function and mechanisms of gene movement in living cells

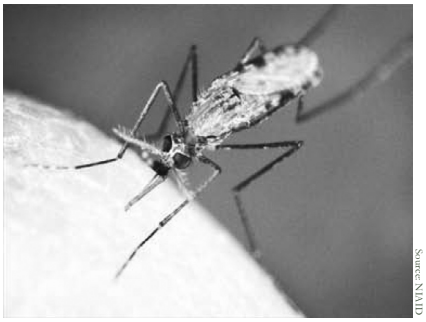
Ranjen Sen (NIA) with researchers from NIA and NCI

Gene regulation is mediated by multiple superimposed mechanisms. A gene's location within a cell nucleus is a critical component of gene expression. Parts of the nucleus, such as the periphery, are associated with gene silencing whereas other parts, such as "transcription factories," are associated with gene activation. Because our investigations have been in fixed cells, we have a limited understanding of how genes are targeted to nuclear subcompartments, what machinery moves them, or how location affects gene expression. In our study, we will combine advanced live-cell imaging methods with gene targeting to visualize gene movements in real time and study the function and mechanisms of gene movements in living cells.

Early biomarkers of nephropathy in type 2 diabetes

Frank Gonzalez (NCI) with researchers from NCI and NIDDK

Human disease biomarker investigations should begin with well-defined and well-characterized human populations that are predisposed to diseases for which early detection would be beneficial. One such population is the Pima Indians of the Gila River Indian Community (Arizona). They have very high rates of type 2 diabetes mellitus and diabetic nephropathy. These diseases have been well characterized in a longitudinal study over the past 43 years and there are banked blood and urine specimens for thousands of subjects. Using the latest in metabolomics technology to identify biomarkers (in urine samples) of diabetic kidney disease, we may find ways to identify those at greatest risk. We will develop protocols for metabolomic-based biomarker investigations in other chronic diseases, including cancer case-control studies.



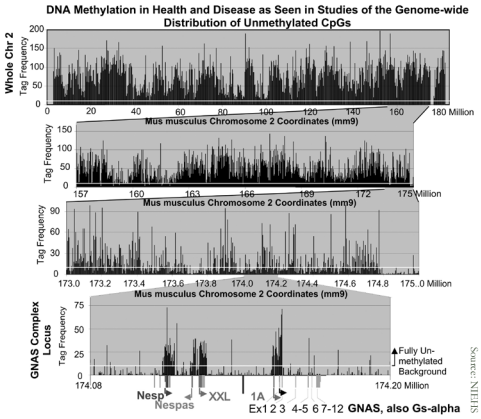
Source: NIAID

A female mosquito drawing human blood to nourish her eggs passes along the parasite that causes malaria.

The methylome in health and disease: survey of unmethylated CpGs

Lutz Birnbaumer (NIEHS) with researchers from NIEHS and NIDDK

Among dinucleotides, CpGs are unique in that they are underrepresented in the genomes of higher eukaryotes and can operate as on-off switches depending on their methylation status. Methylation of CpGs constitutes an epigenetic mark that is at the core of cellular differentiation. Abnormal removal or deposition of methylation marks occurs in diseases such as cancer and complex syndromes such as allergic asthma and may include pre-obesity and the metabolic syndrome. But it is not known whether the methylation marks are cause or consequence. We will



Source: NIEHS

The first step for colleagues at NIEHS and NIDDK was to make this graph. Now they will attempt to determine whether methylation marks are the cause or consequence of diseases such as cancer and complex syndromes such as allergic asthma, pre-obesity and metabolic syndrome.

A total of $3 million was awarded for two-year grants ranging from $75,000 to $250,000 per year for research on biomarkers and personalized medicine, epigenetics and gene expression, and stem cells.

prepare libraries from a variety of cells, extract the corresponding genome-wide high confidence UMRs, and compare transcriptome hybridization patterns.

Subcellular microdissection for the identification of organelle proteins

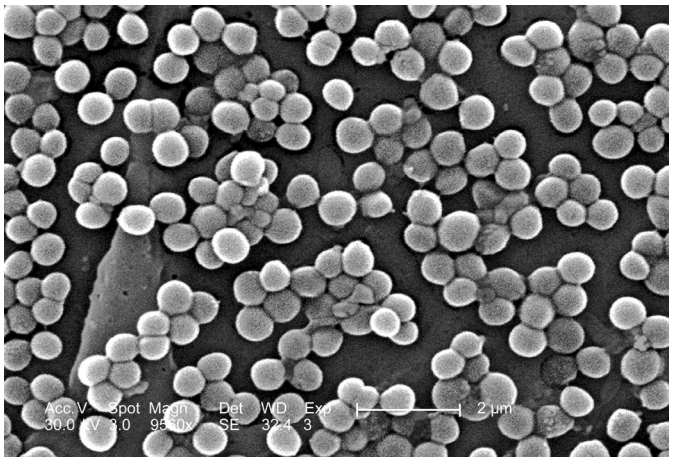
Sanford Markey (NIMH) with researchers from NIMH and NICHD

Currently there is a dearth of technologies for subcellular proteomic analysis. We will develop methods for direct tissue-based capture of spatially resolved, optically defined subcellular proteins and their neighboring interactors for mass spectrometric proteomic analyses. First, we will refine xMD using metal (osmium or lead) to allow direct thermal melting and ultrahigh resolution capture of the labeled proteins. Second, for GFP-labeled proteins, we will use prism-based total internal reflection to introduce excitation light from the reverse side of a tissue, preferentially exposing an emulsion with fluorescence emission to create a mask for unguided capture of the fluorescing regions. Using this method we will eliminate artifacts resulting from tissue homogenization, and identify species relevant to targeted membrane proteins.

Epigenomic regulation of mammalian development and differentiation

Vittorio Sartorelli (NIAMS) with researchers from NIAMS, NEI, NCI, AND NHLBI

NIH recently launched the Epigenome Roadmap, which supports the production of reference epigenome maps in a variety of primary human cell lines. The Roadmap does not, however, elucidate how individual histone modifications contribute to the establishment and maintenance of other epigenetic marks. Nor does it answer the question of how individual histone modifications regulate cell differentiation. We will address these questions by mapping the epigenomes in human hematopoietic stem cells and other cells such as B, T, NK, skeletal muscle and retinal pigment epithelial. We will also investigate the mechanisms that establish these epigenomes by deleting critical histone-modifying enzymes. By integrating this large amount of epigenomic data using statistics and bioinformatics models, we hope to determine how the epigenome contributes to cell differentiation.



A scanning electron micrograph depicting numerous clumps of methicillin-resistant Staphylococcus aureus *bacteria, MRSA, magnified 9560X. The bacteria commonly are carried on the skin or in the nose of healthy people. Credit: Janice Haney Carr and Jeff Hageman, CDC.*

Sequence-based investigation of MRSA infection

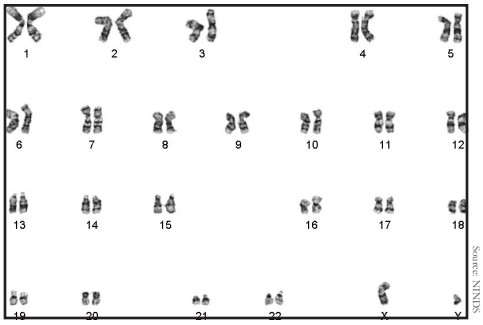
Julie Segre (NHGRI) and researchers from NHGRI, CC, NIAID, and NCI

There are approximately 18,000 deaths in the United States each year from methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Although MRSA was initially associated with hospitalization, community-acquired MRSA has now emerged as a public health crisis. We hypothesize that the transition between asymptomatic MRSA colonization and infection correlates with differences in the local microbial community structure or changes in the MRSA genome. We will collect microbiome samples from age-matched controls (MRSA and non-MRSA carriers) and patients with both the common skin disorder atopic dermatitis and the rare primary immunodeficiency Hyper-IgE. These patients have recurrent staphylococcal infections, including MRSA. We will use next-generation DNA sequencing technology to characterize the microbial communities.

Induced pluripotent stem (iPS) cells for the study of human disorders

Heiner Westphal (NICHD) and researchers from NICHD, NHGRI, NIDA and NIAMS

NIH intramural clinical protocols on patients with specific disorders offer a unique opportunity to compare iPS cells from individuals with well-characterized genetic disorders to iPS cells derived from healthy donors. We will derive iPS cells from patients with disorders for which there is no effective therapeutic intervention: Smith-Lemli-Opitz syndrome (an inborn error of cholesterol synthesis; phenotype includes mental retardation, aberrant behavior and autism) and Niemann-Pick disease type C (a neurodegenerative disorder characterized by impaired intracellular cholesterol and lipid transport). We will develop a panel of induced pluripotent stem cells with defined mutations representing the phenotypic for both diseases. These cell lines will be invaluable tools for understanding the neuronal pathophysiology of these diseases and for use in high-throughput drug screens to identify potential therapeutic agents.



G-banding image of NIH-registered WA01 hES cell line, formerly known as H1.

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...

- Intramural program as a Fortune 500 company
- New NIH Library
- Nano at NIH

Mandatory Non-Mandatory Training

We all hear about required courses and training at NIH. But there are many lesser-known educational electives that could play a key role in your own and in your employees' professional development.

Scientific and Technical Writing: Are you having trouble getting your scientific report published? Do you spend endless hours writing and rewriting scientific and technical papers and reports? In this two-day interactive workshop, you will receive an individual review of selected pages from your own reports and papers, along with a personalized list of areas needing improvement. Discussions and writing exercises will help you learn to dissect the writing style used in journals and other publications and then model your writing accordingly. You will learn how to streamline the writing process so that you can organize your content and write more clearly, concisely, and quickly, and you will learn to present data, schematic diagrams, technical graphics, and other information more clearly. We are currently accepting enrollment for July 13–14. For details and to register, visit http://trainingcenter.nih.gov/app/show_details.aspx?cd_crs=2154.

Concepts of Biotechnology for Non-Scientist: Ever wish that your nonscientist employees, colleagues and lab mates better understood the scientific concepts and terminology of the work you do? This two-day class provides administrative professionals with a solid understanding of the science, technology, and terminology that make up much of the work being done within NIH. Taught by a former NIH scientist, the course will allow nonscientist professionals to converse more easily with their scientist colleagues and customers through shared understanding of scientific jargon and concepts. Biology basics, genetics, genomics, cancer, immunology, drug development, and other concepts will be covered in the open enrollment course. Institute, division or lab leaders can contact the NIH Training Center to arrange for a class that is tailored to their staff and that will address particular concepts and terminology relevant to their research. We are currently accepting enrollment for the May 14–15 and July 21–22 classes. For details and to register, visit http://trainingcenter.nih.gov/app/show_details.aspx?cd_crs=5881.

These two courses, as well as tailored courses, are offered by the NIH Training Center (NIHTC). For more information, contact NIHTC at 301-496-6211 or training1@od.nih.gov.

— Elena Juris

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 160, NIH, Bethesda, MD 20892. Ph: 301-402-1449; fax: 301-402-4303; e-mail: catalyst@nih.gov

Catalyst online:
http://www.nih.gov/catalyst

Publisher
Michael Gottesman
Deputy Director
for Intramural Research, OD

Editors
John I. Gallin
Director, NIH Clinical Center

Henry Metzger
Scientist Emeritus

Managing Editor
Laura Stephenson Carter

Writer-Editor
Christopher Wanjek
Director of Communications, OIR

Copy Editor
Shauna Roberts

Contributing Writers
Allyson T. Collins, Sarah A. Freeman, Elena Juris, Catherine Jozwik, Vanessa C. McMains, Betsey Wagener

Editorial Advisory Board
Dan Appella, NIDDK
David Davies, NIDDK
Elise C Kohn, NCI
Susan Leitman, CC
Germaine Buck Louis, NICHD
David Miller, NIEHS
Bernard Moss, NIAID
Paul Plotz, NIAMS
Joan Schwartz, OIR
Julie Segre, NHGRI
Andy Singleton, NIA
Gisela Storz, NICHD
Ronald Summers, CC

U.S. Department of Health and Human Services
National Institutes of Health
Building 1, Room 160
MSC 0235
Bethesda, Maryland 20892

FIRST-CLASS MAIL
POSTAGE & FEES PAID
DHHS/NIH
Permit No. G-802
Publication No. 09-6250

Official Business
Penalty for Private Use $300

Printed on at least 20% recycled content paper and can be recycled as office white paper.