

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 12, ISSUE 1 ■ JANUARY-FEBRUARY 2004

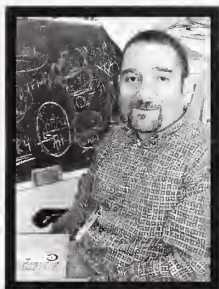
LETO'S OXIDASES: FROM IMMUNOLOGICAL SWORDS TO PLOWSHARES

by Peter Kozel

Thomas Leto has his finger on the button.

The head of NIAID's Molecular Defenses section, Leto studies genes that control the production of one of the body's most potent weapons for innate immunity—reactive oxygen species (ROS).

Produced by enzymes called oxidases, ROS are energetic compounds that react with just about anything. "We think that the production of reactive ox-



Peter Kozel

Tom Leto

idants is an aspect of innate immunity that's very ancient, going back before the split of plant and animal kingdoms," Leto says. The genes that produce, and systems that regulate, oxidant production also seem to be conserved across kingdoms.

The Double-Edged Sword

But ROS are a double-edged sword. "The good side to oxidases is that they can kill microbes; the downside is that you can damage your own tissues, and sometimes you can have uncontrolled inflammatory processes," Leto said in a recent interview with *The NIH Catalyst*.

Leto began his work on oxidases when he joined the NIAID Laboratory of Host Defenses in 1988. Harry Malech and John Gallin, now chief of that lab and CC director, respectively, had been working with patients with chronic granulomatous

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Scratching a Niche

BLUE RIBBON PANEL POINTS INTRAMURAL PROGRAM TOWARD CLINICAL RESEARCH UNIQUENESS

by Celia Hooper

Once upon a time, NIH was just about the only game in town, at least according to the NIH Director's Blue Ribbon Panel on the Future of Intramural Clinical Research. When the Clinical Center opened in 1953, it was one of the few—if not the only—place that had the staff, infrastructure, and resources to conduct cutting-edge clinical trials.

Introducing the report and the panel's chair, Edward Benz, at his Advisory Council (ACD) meeting on January 12, 2004, Elias Zerhouni said today's landscape is radically different. Outstanding scientists interested in training for or conducting clinical trials can now find such opportunities at dozens of academic health centers. Benz related the report's grounding in the fact that NIH's intramural clinical research program "is no longer unique or the only place for talented clinical investigators."

Benz described the report's recommendations as an effort to help the intramural program "find a niche that complements and is distinct from extramural clinical research centers." The panel tried not to be "too prescriptive," Benz said. (For example, he cited NIH's 14 Institutional Review Boards as being "too many" and likely contributing to duplication and unnecessary complexity—and thereby impeding research. One IRB probably wouldn't be enough, but the current number "sounds like too many," he said.)

The group also recognized that its report would be considered along with recent recommendations from the Institute of Medicine and ideas emerging from

NIH's Roadmap initiatives for reengineering clinical research. NIH Di-

rector Elias Zerhouni acknowledged that reconciling all the various inputs would be hard, and said he would begin sorting them out at a staff retreat later this winter and with the help of his intramural research working group.

Key recommendations from the report include establishing new pathways for clinical training and career development, emphasizing research on rare diseases, establishing partnerships with extramural investigators to advance translational research, and



Celia Hooper

Blue Ribbon co-chair Ed Benz directs the attention of NIH senior scientists and advisors to his panel's priorities for NIH clinical research

streamlining both the high-level oversight of clinical research and ground-level, administrative complexities that create unnecessary hurdles for clinical investigators.

Discussing clinical career issues, Benz decried what he perceived as a tendency to categorize people as "staff clinicians" who are actually conducting clinical re-

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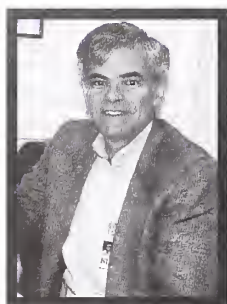
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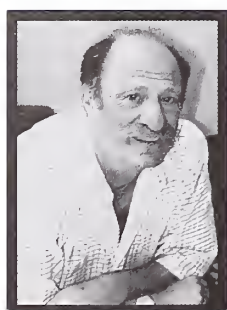
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WHERE TO FIND HELP AT NIH



Michael Gottesman



Howard Gadlin

At a recent town hall meeting, many of the questioners sought practical information about NIH services. The purpose of this column is to guide NIH staff to sources of information and solutions to a full range of work-related needs involving such issues as interpersonal interactions in the workplace, campus safety, transportation, and career development—or even the sense that something is just not right.

In general, if you do not know where to call or write, there are four central offices that can help you directly or refer you to the most appropriate resources: the Office of the Ombudsperson (for most work-related interpersonal issues) at

301-594-7231,

the Offices of Intramural or Extramural Research (for science or career issues) at

<<http://www1.od.nih.gov/oir/sourcebook/oir/oir-staff.htm#OIR>> and

<<http://grants.nih.gov/grants/ocr.htm>>, respectively,

and the Office of Research Services (for issues related to the campus, transportation, or security) at

<<http://www.ors.od.nih.gov/index.htm>>;

a comprehensive service directory can be found at

<<http://www.ors.od.nih.gov/scripts/directorylist.cfm>>.

The websites and offices of a variety of NIH service sources appear below.

WORK CONCERNS

Office of the Ombudsman/Center for Cooperative Resolution (OO/CCR)

<<http://www4.od.nih.gov/ccr>>

301-594-7231

Intramural Research Program Procedures

<<http://www1.od.nih.gov/oir/sourcebook>>

Contact lab chief or scientific director or deputy director for intramural research

Administrative Grievance Procedures

<<http://www4.od.nih.gov/ccr>>

Contact institute/center (IC) HR representative; Employees of pilot ICs (CC, NIA, NIAID, NHLBI, NINDS, OD), contact the OO/CCR

Negotiated Grievance Procedures

Contact union representative or **OHR Division of Employee Relations and Training**, 301-594-1460

Merit Systems Protection Board

<<http://mspb.gov>>

202-653-7200

U.S. Office of Special Counsel

<<http://www.osc.gov/index.htm>>

202-653-2253

Office of Technology Transfer

<<http://ott.od.nih.gov>>

301-496-7057

HUMAN RESOURCES INFORMATION

OHR office locations, awards, benefits, compensation, employee relations, and telework
<<http://hr.od.nih.gov>>

Electronic Human Resources initiatives, including Employee Express (now required for many benefits transactions)

<<http://ehr.od.nih.gov>>

NIH Training Center

<<http://learningsource.od.nih.gov>>.

If you can't find something on our websites, contact our webmaster at

<<mailto:ohrweb@od.nih.gov>>.

Applying for Jobs @ NIH

<<http://www.jobs.nih.gov>>

DHHS's new online recruitment tool—HHS Careers

<<http://www.hhs.gov/careers>>

Coming soon—one-stop shopping for NIH HR information through the NIH Portal at

<<https://my.nih.gov>>

RESEARCH TRAINING

Office of Education

<<http://www.training.nih.gov>>

301-496-2427

See also the **Virtual Career Center**

<<http://www.training.nih.gov/careers/careercenter/index.html>>

DISCRIMINATION

Equal Opportunity and Diversity Management

<<http://oco.od.nih.gov>>

301-496-6301; TTY: 301-480-3122

WASTE, FRAUD AND MISMANAGEMENT

Office of the Inspector General

<<http://oig.hhs.gov>>

202-619-1343; 1-800-HHS-TIPS (hotline)

Office of Management Assessment

<<http://oma.od.nih.gov>>

301-496-1873 or 301-496-5568

CAREER (AND FAMILY) ISSUES

Work/Life Center

<<http://wflc.od.nih.gov/careers/services.asp>>

301-435-1619; TTY: 301-480-0690

For access to all services provided by the Work/Life Center, see **<<http://wflc.od.nih.gov>>**

PERSONAL COUNSELING AND REFERRAL

Employee Assistance Program

<<http://www.nih.gov/od/ors/ds/eap/index.html>>

301-496-3164

TOWN HALL TAPESTRY

by Fran Pollner

WORKPLACE VIOLENCE CIVIL

<<http://civil.nih.gov/nih.html>>
911 (on campus); 9-911 (off campus)
for physical acts of violence; notify supervisors and/or call CIVIL at 301-402-4845 if you receive or hear verbal threats,
TTY: 301-402-9499

ETHICS

NIH Ethics Program

<<http://ethics.od.nih.gov>>
Contact your IC deputy ethics counselor, your IC ethics coordinator, or the NIH ethics coordinator

Office of Human Subjects Research

<<http://ohsr.od.nih.gov>> or
<<http://www.nihtraining.com/ohsrsite>>
301-402-3444

Animal Care and Use

Contact your IC animal care and use committee, your IC's animal program director, or the NIH Office of Animal Care and Use at
<<http://oacu.od.nih.gov>>
301-496-5424

Office of Research Integrity

<<http://ori.dhhs.gov>>
301-443-5330

SECURITY

Division of Public Safety

<<http://www.nih.gov/od/ors/dps/index.htm>>
301-496-6893
Emergency: 911; TTY: 911;
Non-emergency: 301-496-5685; TTY:
301-496-0063

TRANSPORTATION AND PARKING Shuttles

<http://des.od.nih.gov/eweb/NIHShuttle/scripts/shuttle_map_live.asp>
301-496-5037

Employee and Visitor Parking

<<http://parking.nih.gov>>
301-496-5037 or 301-594-PARK

Employee Transportation Services

<http://www.ors.od.nih.gov/service/chooseservice_I2.cfm?level2=7>
301-496-7433

NIH Transhare Program

<<http://www.nih.gov/od/ors/dtts/transhare.htm>>

Nary a sensitive issue went unnoticed in Elias Zerhouni's opening remarks at the December 16 NIH director's town hall meeting.

In a kind of good news-bad news delivery, Zerhouni counted off some of the more salient happenings since the last town hall session in June. On the positive side:

■ The home teams won both the major A-76 competitions for NIH jobs.

■ The public launching of the road map for medical research at NIH—at a National Press Club press conference attended by 54 reporters—received very positive coverage that affirmed NIH's preeminence in medical research management, funding, and creative thinking.

■ And NIH received a highly gratifying leadership award for best practices in achieving diversity in the workplace, the only federal agency among the ten national honorees.

On the downside, Zerhouni continued, there were some disparaging allegations about NIH priorities, peer review, and scientist integrity:

■ In letters and at a congressional hearing, some members of Congress expressed distaste for NIH funding of behavioral research related to HIV and other sexually transmitted diseases, drug abuse, sexual dysfunction, and sexuality in general.

■ A package of articles in the *L.A. Times* targeting outside consulting by NIH scientists as a conflict of interest that threatens research integrity has generated congressional inquiries and a review by NIH of related policies and practices.

In the matter of sex-related research, Zerhouni recounted his response to those who questioned the appropriateness of NIH priority-setting mechanisms: "I stated that the peer review process at NIH is the envy of the world, that NIH addresses the full spectrum of public-health problems, and that the burden of sexually transmitted disease is a *major* public-health issue that NIH will not shy away from."

He emphasized, however, that when questions regarding NIH stewardship of public money are raised, they must not be brushed aside. The burden of proof, he said, is on NIH

to lay out exactly why a questioned research project is important to the public health and not a frivolous expense. It should also be noted, he added, that NIH does not make decisions in a vacuum, but has thousands of individuals "advising us."

That same degree of openness and self-scrutiny must be brought to bear in responding to the newspaper allegations of unethical conflict of interest in the consulting activities of some NIH scientists—the story's "exaggerations and innuendo" notwithstanding, Zerhouni said.

In the matter of consulting in general, Zerhouni observed that it is desirable that the work and ideas of NIH scientists are of a caliber that their help would be sought beyond NIH, in accordance with one of NIH's essential obligations—to ensure that its science is translated into tangible public benefit.

But such exchanges, he said, must be transparent, with no conflict of interest, real or perceived. "We cannot afford to have our public trust diminished, or [to risk losing our ability] to attract the best and the brightest" . . . If there is a question, my job is to bring maximum light to it—and to ask, 'how can we do this better?'" he said.

An initial review of the documents related to the various consulting arrangements highlighted in the newspaper coverage leaves "no doubt that government ethics rules were followed," Zerhouni said. But he suggested that adhering to the rules might not be enough. Just because the "Ts are crossed and the Is dotted," he observed, does not necessarily mean that the public trust will be preserved.

"We will be proactive," Zerhouni said, "to avoid even the perception" of conflict. He said that NIH will conduct more internal reviews and is convening an inside Central Ethics Advisory Committee—and an outside blue ribbon panel to explore the issue thoroughly.

Other speakers addressed issues related more to the logistics of navigating NIH (see "DDIR," page 2).

A future town hall may focus exclusively on science at NIH, Zerhouni said. ■

LETO'S OXIDASES

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disease (CGD) for more than a decade. These patients, Leto noted, "present with certain problems with low-grade pathogens that don't affect the uncompromised host."

The team identified two of the mutated genes associated with different CGD types that figured in about one-third of cases. These mutations block the synthesis of ROS by neutrophils and other circulating phagocytes, impairing the ability of CGD patients to clear bacterial and fungal infections.

"These diseases are rare, affecting only five people out of a million," Leto said. "It's only because we have such a large cohort of these rare patients congregated here that we've made such headway. One of the phagocyte oxidase lesions is a component that affects only five percent of these patients. We have one patient with that lesion. He was the missing link. Using biochemical reconstitution, we put the system together and recognized that it is a multicomponent system."

After working out much of the molecular biochemistry of CGD, Leto's lab wanted to apply the knowledge to other tissues. "The new direction we're taking now is a byproduct of the Human Genome Project," he observed. Using the phagocyte oxidases as a starting point, Leto's lab mined databases to identify related new genes that produce oxidants in specific tissues throughout the body. The team found new genes and identified additional tissues where ROS are produced—and the new genes pointed to new molecular targets in other diseases, he said.

For example, excessive activity of another oxidase gene, *Nox1*, could lead to inflammatory conditions in the colon, such as inflammatory bowel disease. "It would be very interesting to identify whether *Nox* genes are affected in [IBD] patients," Leto noted.

Perhaps the most exciting finding is

the *Duox* gene family and its connection to lactoperoxidase (LPO), Leto says. LPO is a potent antimicrobial enzyme found in milk, saliva, and the mucosal layer of the airways. Scientists have long wondered what the purpose of LPO was in those locations since the source of hydrogen peroxide needed for LPO activity remained unknown. Recently, Leto's lab demonstrated that *Duox* genes are expressed in secretory and salivary glands, trachea, and bronchium—precisely the locations to synergize with LPO.

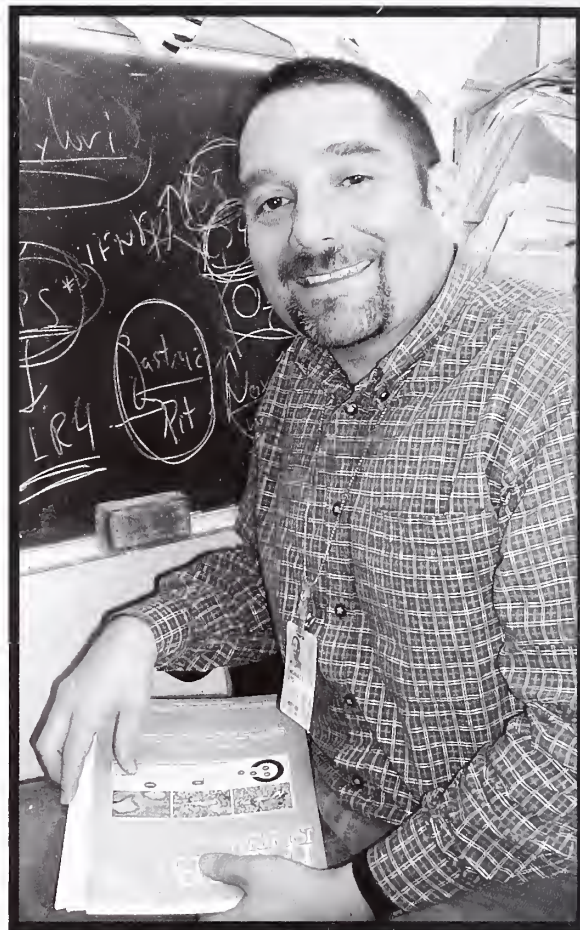
Clinical studies of severe hypothyroid patients demonstrated that *Duox* also plays a "critical role" in thyroxine synthesis. Low levels of oxidative output could lead to susceptibility to lung infections, whereas abnormally high oxidative output could contribute to inflammatory diseases of the airway, including asthma, chronic obstructive pulmonary disease, or even acute allergies.

"Who knows, it may represent an important antiviral system in airways," Leto speculates. "It could relate to control of respiratory viruses such as SARS—it might not be a stretch!"

It's unlikely every oxidase serves identically. Kidney tubule epithelium cells, for example, produce a renal-specific oxidase, *Nox4*. This protein may not play a role in host defense at all.

Noting that the kidney is "a key organ for sensing anemia" and is the source of red blood cell-promoting erythropoietin, Leto and his colleagues suggested early on that *Nox4* is an oxygen sensor. Because of difficulty getting human kidney tissue, the lab is study-

tion of reactive oxygen species is tightly regulated and their downstream targets exquisitely specific. This past year, several notable advances have been made in defining the specific redox-dependent targets of intracellular oxidants, as well as the myriad pathways that appear to employ oxidants as effector molecules. These new studies have significantly altered our understanding of how reactive oxygen species participate in diverse processes from tumorigenesis to ageing." ■



Tom Leto

Peter Kozel

ing a mouse model deficient in *Nox4*.

Although they may be serving different tissue-specific roles, all of the oxidases share an important feature: tight regulation. "Phagocytic cells work very hard in containing the sites at which these toxic, indiscriminate molecules are generated," Leto said. "It's compartmentalized within a phagosome where microbes are being engulfed."

Plowshares

Leto says location is one of the most important aspects of oxidase-based defense mechanisms "because it's right at the interface where you would want it." He has shown that all of these new genes are expressed predominantly on epithelial surfaces, "aimed away from the host."

Peroxidases in the mucosa, such as LPO, "seem to be tailored to make milder, less destructive oxidants"—an additional layer of control. "Oxidative capacity comes about very late in differentiation, only when cells get out there on the surface," Leto said, noting that this prevents damaging compounds from being created deep within tissues.

ROS in Print in 2003

A review article, "Oxidant Signals and Oxidative Stress," by Toren Finkel, senior investigator, NHLBI Cardiovascular Branch, appears in *Current Opinion in Cell Biology* (15:247–254, 2003) and cites 54 recent articles by NIH and other investigators.

Finkel's abstract reads: "Although oxidants clearly possess the capacity to behave in a random and destructive fashion, growing evidence suggests that in many instances the produc-

NINE LABS CAPTURE FIRST-ROUND AWARDS FOR NEUROSCIENCE-IMMUNOLOGY RESEARCH

by Esther M. Sternberg, M.D.
INIP Program Director

The Integrative Neural Immune Program (INIP) has launched its research awards program with funds for four interdisciplinary projects that span nine laboratories from five institutes (NINDS, NIMH, NEI, NIA, NCI).

These collaborative research projects in neuroscience and immunology encompass basic and translational research and explore the following:

- Identification of diagnostic and prognostic biomarker proteins in virus-associated neurologic and hematologic diseases
- Exploration of migration of hematopoietic and neural/glial progenitor cells and validation of their use in repair therapies in experimental allergic encephalomyelitis
- Localization of chemokines in the eye
- Distribution of HTLV-1 binding receptors at the immune synapse.

The involved institutes will support jointly supervised postdoctoral fellows.

The INIP Program and its awards exemplify the interdisciplinary research teams of the future called for in the NIH

director's road map for medical research at NIH.

The experience gained from developing the INIP awards program could help in developing similar mechanisms for multi-institute support of interdisciplinary projects in other intramural research areas.

Eight participating institutes (NIMH, NINDS, NIA, NIAID, NCI, NEI, NIDCR, and NIDA) agreed to provide shared postdoctoral research fellow positions and appropriate research funds to successful applicants.

Applicants from participating institutes submitted proposals in response to a call in February 2003. An ad hoc panel reviewed the proposals and sent their evaluations to the scientific directors of participating institutes through the INIP Steering Committee. In February 2004, INIP will issue a second call for proposals to support a next round of interdisciplinary research projects. This will be posted on the web at

www.neural-immune.nih.gov.

For more information, contact Craig Smith, INIP program manager, at craigsmith@mail.nih.gov.

INIP AT A GLANCE

The Integrative Neural Immune Program is an intramural, NIH-wide multi-institute research program in neuroscience and immunology designed to foster interdisciplinary research in the field of neural-immune interactions, the biological basis of the so-called "mind-body" connection.

The program is structured to facilitate interinstitute, interagency, university, and private-sector partnering and to address cutting-edge multidisciplinary research questions, while consolidating investments in permanent staff, highly specialized methodologies, physical space, and equipment.

Key components of the program are:

- Steering committee, including representatives from each of the eight participating institutes—NIMH, NINDS, NIA, NIAID, NCI, NEI, NIDCR, and NIDA
- Scientific exchanges through a lecture series, conferences, and workshops designed to highlight cutting-edge topics in this field

- An active Listserv and developing website to disseminate information on program activities.

- An Intramural Research Awards program to support collaborative research in neuroscience and immunology through jointly sponsored postdoctoral IRTA positions and associated research funds.

Awards are shared between collaborating laboratories of partnering institutes to provide formal training in integrative neuroscience and immunology research.

Research areas include molecular, cellular, and neuroanatomical mechanisms of neural immune interactions and systems-level analysis of communications between the central nervous, endocrine, and immune systems.

These explorations shed light on the role of the immune system in neuronal cell death and repair, neuronal development, and plasticity and the role of the nervous and neuroendocrine systems in susceptibility and resistance to autoimmune/inflammatory, infectious,

and allergic diseases.

Basic research in this area has important clinical implications for understanding the pathogenesis and treatment of diseases such as multiple sclerosis, Alzheimer's disease, neuro-AIDS, stroke, and nerve trauma.

This research will enhance our understanding of the relationship between depression and immune diseases, and the effects of stress and belief on immune-mediated diseases, such as arthritis and allergic and infectious diseases.

Knowledge of these interactions also has relevance to neural and neuroendocrine factors in shock and tissue damage, and has therapeutic implications for biodefense.

Through partnership with the Intramural Program on Research in Women's Health, the scope of related research extends as well to sex and gender factors in health and disease.

—Esther M. Sternberg, INIP director
Craig Smith, INIP program manager

Tight control over the quality and location of oxidase activity gives ROS their utility beyond defense. "The diversity of the tissue-specific isozymes is nicely matched with the diversity of functions of reactive oxidants that have already been recognized," Leto observed.

ROS in cells with high oxidative out-

put typically act as potent weapons, while "cells with lower oxidative capabilities can use the oxidants as signals such as in growth-factor signaling, regulation of proliferation, cellular senescence, apoptosis, and vasoconstriction," he said.

Perched high on the top floor of the

Clinical Center, Leto's lab looks out over the new Mark O. Hatfield Center, where the clinical sections of the Laboratory of Host Defenses will move. The future may also reveal new functions of oxidases and new diseases to study, as well as more peaceful but no less exciting cellular processes. ■

BLUE RIBBON PANEL

continued from page 1

search and thus more appropriately deemed "clinical investigators."

When Zerhouni asked about this perceived reluctance to count clinical research as "real" research, Benz said that the nuances contributing to the phenomenon are quite similar to what he's witnessed at academic health centers: Bench research proceeds faster, generates more publications more quickly, and is somehow easier to judge on its merits soon after it is published. Clinical research often involves complex teams, with each individual's contribution somewhat fuzzy and with its quality embedded in the overall quality of the hospital's services.

"And it's hard to tell good from excellent from outstanding clinical investigation," until it is manifest in clinical practice long afterwards, Benz said, jokingly suggesting it was only possible posthumously. "How do we evaluate excellence in clinical research?" he asked rhetorically. "What we saw here was very familiar."

The panel did suggest a couple of ways that NIH could improve training and thereby help stem the national depletion in numbers of clinical investigators. It suggested establishing a postdoctoral fellowship in translational research for recent PhDs and an advanced visitors' training program, similar to the Fogarty Scholars program, which would bring in senior scientists

for 12 to 18 months to learn clinical research skills, including access to the latest therapeutic approaches and gadgets.

Discussing the report's recommendations for the type of clinical research the intramural program should pursue, Benz said "excellence and distinctiveness" were the key. One recommended route to this distinctiveness is emphasizing research on diseases that are so rare that patients must be collected from all over the country—or the world—to reach informative numbers. Benz suggested that NIH could serve as the hub of a network of health centers studying rare diseases. NIH could conduct lengthy initial work-ups, maintain tissue banks, train research nurses, develop biomarkers of the disease processes, and coordinate follow-up, treatment, and data collection by this network of partners.

This model also demonstrates another recommended path for intramural clinical research: collaboration with extramural partners. Benz said the committee had seen some nice examples of such partnerships already in place, but that there should be a systematic pursuit of such relationships, not a series of one-of-a-kinds.

Benz said that before NIH can reclaim and retain its legacy of attracting the world's most elite clinical investigators, "you first need to improve governance." To this end, the panel recommended es-



Celia Hooper
Ed Benz

tablishing a single clinical research oversight committee as well as an external advisory pane of scientists for whom

clinical research is "a front-burner issue." These committees and a proposed "deputy director for clinical research" in the Office of Intramural Research would set priorities and cut away unnecessary administrative hurdles and duplication of efforts across IC clinical programs. Where duplication and complexity exists, there should be a rational reason for it, Benz said.

Recalling a highly territorial environment in the intramural program before he left to become an executive vice-president at Lilly Research Laboratories in Indianapolis, ACD member Steve Paul applauded the report—and observed that the great challenge would be in its implementation.

NIH leaders who will implement the report are optimistic. "With the opening of the new Clinical Research Center next year," says Michael Gottesman, deputy director for intramural research, "we will take into our hands the most powerful tools and the best-designed environment ever created for clinical research. This report will assure that the human components—the management, training, career development, organization, and, most importantly, the definition of our clinical research niche—are as excellent as our state-of-the-art facilities." ■

BLUE RIBBON PANEL RECOMMENDATIONS

1. Revise the NIH intramural clinical research oversight structure.

■ Create a single high-level oversight committee to replace all existing governing bodies that have oversight responsibilities for intramural clinical research.

- The new committee should report to the NIH director.
- The committee should include representatives of institute and center (IC) directors, scientific directors, clinical directors, the Clinical Research Center (CRC) director, and outside representatives.
- The committee should be staffed by the Office of the Director.
- The committee should be responsible for governance, strategic planning, priority setting, and budget development. Importantly, this committee would make recommendations about transdisciplinary clinical initiatives and resource allocation.

■ Create an external advisory committee to the NIH director to periodically and systematically consider the overall quality and vitality of the NIH intramural clinical research program (ICRP).

- This committee would function in an analogous fashion to the IC Boards of Scientific Counselors (BSCs), but would evaluate clinical research across the entire NIH, reporting to the NIH director at least biennially.
- Although the committee would be advisory only, it should be composed of visible and influential leaders.

■ Strengthen the roles of the Office of the Director and IC leadership in clinical research.

- Revise the internal structure for coordinating and managing clinical research at NIH, including the creation of a new position of Deputy Director of Clinical Research in the Office of Intramural Research, who also would assume an influential role in the Office of Extramural Research.
- Maintain the role of the CRC Director as an influential senior leader. It is essential that the position of CRC Director remain an attractive and prominent position within NIH. By recommending the creation of a Deputy for Clinical Research, reporting to the NIH Deputy Director for Intramural Research, it is not the Panel's intent to demote the position of Director of the CRC. The NIH Director should determine what reporting relationships best meet the needs of the NIH.
- Strengthen the role of the IC clinical directors. The Panel respects the need of each IC to craft its own organizational structure. However, the position and role of the clinical director in each unit was regarded by the Panel as too variable and, in some cases, weak. The clinical directors should be highly placed, with a direct reporting relationship to the institute director.

2. Develop new training and career pathways in patient-oriented research.

C RTP REVISITED: AN ALUMNUS PERSPECTIVE

by Javier Lorenzo

Ask Uri Lopatin about his experience in the Clinical Research Training Program (C RTP), and you'll get a no-nonsense response: "Unabashedly one of the best academic experiences in my life. Period."

This comes as no surprise to anyone who knows Lopatin. One of the nine fellows in the C RTP inaugural class in 1997, he is now back at NIH for an infectious diseases fellowship that will center in the NIAID laboratory of Brian Kelsall, where he plans to study the role of the gastrointestinal dendritic cells in the mediation of immunologic tolerance.

Former NIH Director Harold Varmus, and OIR's Michael Gottesman and Richard Wyatt, designed the C RTP to expose interested medical and dental students to clinical research—and to inspire them to pursue clinical research in their careers, much as Lopatin is doing.

C RTP fellows gain insight into translational research by participating in it from bench to bedside on the NIH campus for at least a year, says Frederick Ognibene, director of the program since 2000. It's NIH's way of "enticing those creative minds to follow a career as clinician scientists," he observes.

Students who have completed their clinical rotations and have permission from their home institution can apply for the program. Fellows attend ambulatory

clinics, see patients on the wards, and work with an established NIH investigator in laboratories on selected clinical and translational research projects.

Fellows may stay a second year, depending on support from the sponsoring NIH institute and permission of the student's home institutions.

When Lopatin had that opportunity, he grabbed it. A third-year medical student at the University of Medicine and Dentistry, New Jersey Medical School, Newark, he worked with Stephen Straus (now NCCAM director) in the NIAID Laboratory of Clinical Investigation elucidating the basic biological mechanisms of autoimmune lymphoproliferative syndrome. He also conducted chart reviews to assess clinical relevance, interviewed patients, and attended related seminars.

"I had these amazing opportunities as a medical student," Lopatin says—an experience that did indeed prove so enticing that after graduating from medical school and completing an internal medicine residency at New York University, Lopatin returned to NIH for a more intensive immersion in infectious diseases research. Now in the first year of the ACGME-accredited three-year fellowship, directed by John Bennett,



Javier Lorenzo
Uri Lopatin

Lopatin anticipates a future in academic medicine and, ideally, translational research.

Lopatin is not alone among C RTP alumni who are returning to NIH after completing their residencies. Joshua Kouri (C RTP 1998-1999) is doing a brain tumor fellowship in the NINDS Surgical Neurology

Branch, and Will Savage (C RTP 1999-2000) will join the NIH-Johns Hopkins program in pediatric hematology-oncology in July 2004.

Begun with NIH funding, the C RTP attracted support during its second year from Pfizer Pharmaceuticals, which provided a grant to the Foundation for the NIH that enabled the program to grow from 9 to 15 scholars. Pfizer continues to provide financial support.

For the 2004-2005 academic year, the program has the potential to double its capacity, taking up to 30 fellows from medical and dental schools from all over the country. Support for the enlargement of the program has been provided by funds in the NIH Roadmap initiative addressing "re-engineering the clinical research enterprise."

For more C RTP information and access to an online application, see <http://www.training.nih.gov/crtp/overview.htm>.

■ Strengthen career pathways and mentoring in the ICRP for patient-oriented research that culminate in tenure.

— Individuals in these pathways should be provided with the necessary infrastructure to achieve success as defined by clearly defined benchmarks. Clear distinctions should be made between the clinical service role and that of investigators with independent research resources.

■ Establish a premier, highly visible postdoctoral fellowship program in translational research, administered by the CRC director, for individuals who have finished clinical residency training.

■ Create an advanced research training program for extramural faculty members in academic health centers who wish to take a sabbatical at the CRC as a means of obtaining "on-the-job" experience in clinical research.

■ Foster the recruitment and retention of innovative patient-oriented investigators in the ICRP by assuring salaries and benefits that are competitive with those at academic health centers.

■ Foster an interactive and creative clinical research environment that will attract outstanding postdoctoral fellows. Postdoctoral fellows will want to participate in those programs that are carrying out disease-oriented research or investigating timely clinical problems that cannot be easily studied in the extramural academic health centers.

3. Continue to emphasize the study of rare diseases at the CRC, and promote a strong emphasis on pathophysiology and novel therapeutics in the ICRP.

■ Initiate trans-NIH programs of patient-oriented research that combine the expertise of several ICs.

■ Make the best use of the unique features of NIH's intramural research program and its ability to undertake bold and innovative research.

4. Create translational, multidisciplinary intramural and extramural partnerships involving the General Clinical Research Centers (GCRCs), the Children's Clinical Research Centers (CCRCs), NIH-funded extramural networks, the CRC, and the ICRP.

5. Intramural clinical research, including new programs in patient-oriented investigation, should be excellent and distinctive, as well as distinguishable from research conducted at academic health centers.

■ This mandate for change should be the responsibility of the NIH director, IC leaders, the advisory committees, and the BSCs.

6. Regulatory barriers and impediments to clinical research should be reduced. This would include streamlining the regulatory process and providing adequate, effective infrastructure for supporting clinical research.

PATHOLOGY SERVICE UNCOVERS HIDDEN TALENTS OF GENETICALLY ENGINEERED MICE

by Celia Hooper

The rest of the world may be in perpetual need of a good 10-cent cigar, but NIH scientists have been calling for something else for the past decade: a good, inexpensive, nose-to-tail pathology scan of the mouse models they are churning out via genetic engineering.

NIH's Division of Veterinary Resources Pathology Service is now offering a service intended to do just that.

Led by veterinary pathologists Michael Eckhaus and Georgina Miller, the group has been piloting a package of phenotyping services that methodically work through a mouse model, generating data on blood cells, serum chemistries, and organ weights, followed by careful necropsy, microscopic evaluation of 40+ organs (see box), and statistical analysis of the data.

The cost for this comprehensive analysis is \$450 per mouse, approximately half what a small number of outside contractors charge for similar services. Mice between 10 and 14 weeks of age are preferred, but any age can be examined, including embryos (see "fetal urogenital tract," p. 9).

The phenotyping team anesthetizes the mice, draws a small blood sample for the hematological and serum analyses, and then sacrifices the mice while they are still under anesthesia. Hema-

tology and a panel of serum chemistries are run, using in-house equipment optimized for small sample size.

The team performs a detailed necropsy, collects the tissues, and weighs selected organs. Fixed tissues are sent to a contract histology lab, where they are embedded in paraffin, sectioned, stained, and then returned to the pathologist for microscopic examination.

Due to the small size of embryos, blood work and organ weights are not performed on them. Embryos are embedded in paraffin, and step sections are cut and stained. Depending on the embryo size, 50 to 100 sections are examined microscopically, allowing evaluation of all organs in situ.

It takes three to four weeks to complete a study. The pathologists deliver to the investigator an Excel spreadsheet with raw data from the blood chemistry, hematology, and organ weights; statistical analyses (if numbers permit); a list of gross and microscopic diagnoses; and a report on the significance of the findings.

Investigators are also provided the paraffin blocks and slides of the tissues analyzed and digital photographs of gross and microscopic lesions.

Miller recently told NIH's Scientific Directors that so far, in the 18 months



PHENOTYPING REPERTOIRE

HEMATOLOGY

Blood Smear CBC and Differential

WBC count
neutrophils
lymphocytes
monocytes
eosinophils
basophils
RBC count
Hematocrit
Mean Corpuscular Volume
Hemoglobin content
Platelets

SERUM CHEMISTRIES

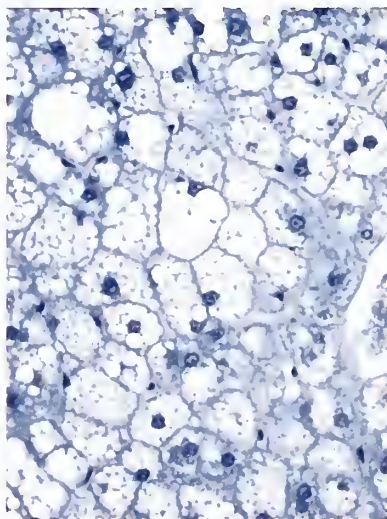
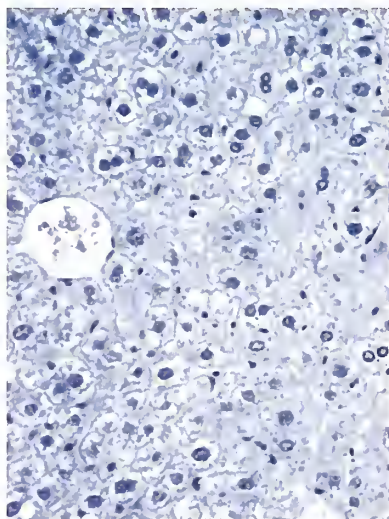
Glucose	Alanine Transferase
Cholesterol	Aspartate Transferase
Triglycerides	Bilirubin, total
Amylase	Blood Urea Nitrogen
Albumin	γ -Glutamyl Transferase
Calcium	Lactate Dehydrogenase
Phosphorous,	Protein, total
Inorganic	Uric Acid
Alkaline Phosphatase	

BODY/ORGAN WEIGHTS

Body	Thymus
Heart	Spleen
Liver	Kidneys
Brain	

NECROPSY/TISSUE COLLECTION

Skin	Lungs/trachea
Salivary glands	Reproductive tract
Lymph nodes	Kidneys/adrenals
Thymus	Esophagus
Heart	Muscle/nerves
Thyroids	Eyes
Spleen	Brain
Pancreas	Pituitary
Liver/gall	Femur/knee joint
bladder	Spinal cord
GI tract	Middle and inner ears



Cross-section of liver from mouse (left) with wild-type ADP ribosylation gene (left) and from mouse with knockout for ADP ribosylation gene (right), which results in hepatocyte defects and hypertrophy

of the pilot service, the program has completed 52 projects from 12 different ICs, turning up potential genotype-associated changes in about half of the models.

Some of these differences have come as a big surprise to the investigators who'd engineered the mice. She cites as an example a mouse that was created by Richard Proia, chief of NIDDK's Genetics of Development and Disease Branch.

Proia says his group made the mice as they "were looking for functions of G-protein-coupled receptors for sphingolipids."

Initially, things weren't looking very good because the mutant mice bore no overt phenotype. "Anytime that happens you're a little disappointed," Proia says.

Under those circumstances, the phenotyping service—free at the time—was hard to resist. "The results came back indicating from the pathology that the mice had degeneration of the spiral ganglia of the inner ear, suggesting they should be deaf," Proia recalls.

"We tested our colony and the mice were, in fact, deaf." He says the result was "totally unexpected" and points to "a new function for these receptors. We are currently working on this with collaborators in NIDCD."

Pursuing this unexpected lead will mean looking at the protein expression patterns in the ear and sorting out the mechanism that causes the cells to degenerate. Proia notes that the ear problems could be secondary to some other functions of the gene.

The phenotyping service won't provide the details that come from careful molecular dissection of a pathology, but Proia credits it with opening a new door in his research. He also gives the service high marks for its timeliness and responsiveness.

So, for all interested NIH investigators, the mic is open and the spotlight's on in Bldg. 28A's theatre, awaiting the chance to expose the hidden talents of the next murine American Idol. ■

Contacts

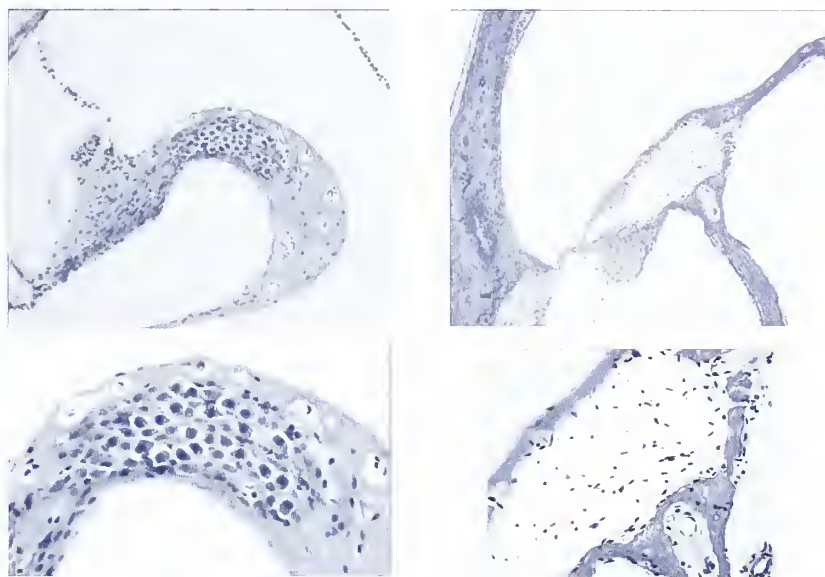
Investigators interested in the phenotyping service should contact either Michael Eckhaus (301-496-4465)

<me18m@nih.gov>

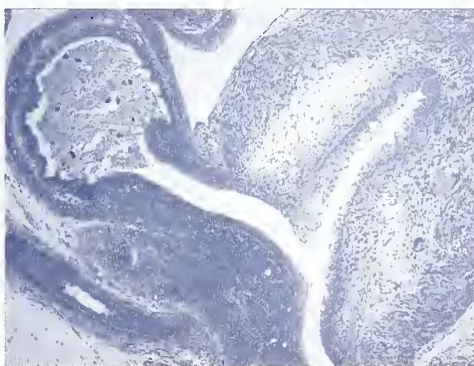
or Georgina Miller (301-496-4465)

<gm25f@nih.gov>

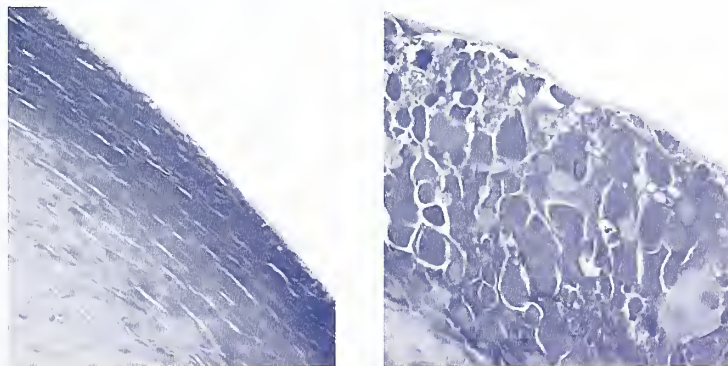
for more details. ■



Cross-section of inner ear (close-ups below) from mouse with wild-type G-protein receptors for sphingolipids (left) and from G-protein receptor mutant (right), which results in degeneration of the spiral ganglia of the inner ear and deafness



Cross-section of fetal urogenital tract from a mouse with deletion of Sc5d gene, which is involved in cholesterol synthesis. Shown here is fusion of the urogenital tract, one of multiple congenital defects (including cleft palate, dental hypoplasia, fusion of tongue, fusion of urethra and rectum, segmental aplasia of intestines, underdeveloped lungs) associated with this deletion, which results in death of homozygotes at birth



Cross-section of the lens of the eye from a mouse with wild-type iron regulatory proteins (right) and from a knockout (left) of iron regulatory proteins, which results in microcytic anemia and cataracts

TRANSATLANTIC DOCTORAL PROGRAMS

Two doctoral programs partner NIH with either Oxford or Cambridge University in the U.K. to offer students scholarships to earn a D.Phil. degree in biomedical and health research—the NIH-Oxford University Scholars in Biomedical Research Program and the NIH-Cambridge University Health Sciences Research Scholars Program.

Scholarship recipients participate in an interdisciplinary training program and a collaborative research project under the joint mentorship of intramural faculty of two institutions: the NIH and either Oxford or Cambridge University. Participants spend equal time in NIH and U.K. laboratories as they progress towards their degrees. These programs have succeeded in attracting excellent American science students.

Projects currently pursued span a broad range of disciplines, including neurobiology, genetics, structural biology, molecular biology, immunology, cancer biology, and clinical sciences.

To Be a Mentor

Intramural investigators in all institutes (including those who are not stationed at the Bethesda campus) are eligible to collaborate in the training of a scholar. To serve as a mentor, the principal investigator (that is, tenure track and above) must be supervising an independent research program.

The potential mentor's first step is to contact investigators at Oxford or Cambridge (also tenure track and above) and determine areas of interest for collaboration.

Second, the mentor sends a brief description of collaborative project area(s), with links to the web pages and/or e-mail addresses to Andre Nussenzweig at

<nussenza@exchange.nih.gov>.

Nussenzweig can also provide more details about the responsibilities of being a mentor in this program. The next class of Scholars will begin laboratory selection in April, 2004, so it would be best to submit your collaboration prior to that time.

These investigator-initiated projects will then be advertised to scholars, who



Cambridge

are encouraged to discuss them directly with the PIs. It is also possible for a scholar to create a course of study with a particular mentor in mind and initiate contact with that person.

To Be a Scholar

To be eligible for this program, a student must be a U.S. citizen or permanent resident with a bachelor's degree from an accredited U.S. college or university. There is also limited eligibility, determined on a case-by-case basis, for British students at Oxford or Cambridge universities. All applicants are expected to have had undergraduate preparation in biology, chemistry (inorganic and organic), physics, and mathematics.



Oxford

Candidates should demonstrate outstanding academic performance and promise for a career in biomedical research. Previous laboratory research experience is also a strong qualification for this program.

Students already enrolled in medical schools, as well as college graduates interested in pursuing a D.Phil., are encouraged to apply.

There is also an Advanced Scholar track for second- or third-year graduate students in the biomedical sciences at Oxford or Cambridge, which provides support for additional years of graduate work to carry out research in an intramural laboratory at NIH.

This past summer, program mentors and scholars gathered at Oxford for the programs' first scientific colloquium. Scholars' work was showcased, and Nobel laureate Baruch Blumberg gave an after-dinner talk on his life in research.

For more information on the Advanced Scholar track or for other questions relating to the Oxford and Cambridge programs, contact Michael Lenardo, who coordinates both, at <lenardo@nih.gov>.

For further information on these as well as other new doctoral programs for the intramural program, view the Graduate Partnerships Programs web page at <<http://gpp.nih.gov>>.

Estrogen Receptor -/-

The Women's Health Special Interest Group is hosting a lecture on "Evaluating Differential Estrogen Receptor Activities Using Knock Out Mouse Models," Friday, **February 6, 2004**, 11:30 am–12:30 pm, Lipsett Amphitheater, Building 10, 1st floor.

The speaker is Kenneth Korach, director of the Environmental Disease Medicine Program and chief of the Laboratory of Reproductive & Developmental Toxicology, NIEHS. Discussion will follow. Sign language interpretation will be available.

The lecture is sponsored by the Office of Research on Women's Health and the Integrative Neural Immune Program. ■

FAES Late Registration

Late registration for the Spring 2004 semester at the Foundation for Advanced Education in the Sciences (FAES) Graduate School at NIH is being accepted in Building 60, Suite 230, **January 14 through February 13** with a \$5 late fee and from **February 16 through March 5** with a \$10 late fee.

The FAES Spring 2004 Course Catalog is available online at the FAES website:

<<http://www.faes.org>>.

The catalog is also available at the FAES Scientific Bookstore, Clinical Center, B1 level, and at the FAES Graduate School office at One Cloister Court, Building 60, Suite 230.

Required textbooks are available at the FAES bookstore. The bookstore will have extended hours the first week of classes, Monday through Thursday, **January 26 through 29**, 5 p.m. to 8 p.m.

For more information, call 301-496-7976. FAES has a continuing need for classroom space; suggestions are welcome. ■

NCI Director Series Debuts in 2004

On **February 2, 2004**, NCI Director Andrew von Eschenbach was to launch a new lecture series at NIH, the NCI Director's Seminar Series. The first of three speakers scheduled for 2004, was to be FDA Commissioner Mark McClellan.

The series focuses on collaborative efforts to meet a national goal of "eliminating the suffering and death due to cancer by 2015."

McClellan was to discuss electronic health information, FDA-NCI collaboration, and the FDA initiative to speed the development of new drugs and therapeutics. The talk was scheduled from 9:00 to 10:00 a.m. in Masur Auditorium.

Carl Feldbaum, president of the Biotechnology Industry Organization, will speak **March 19** at 2:00 p.m., and Julie Gerberding, director of the Centers for Disease Control and Prevention, will speak **September 16** at 1:00 p.m. Both will speak in Masur Auditorium.

The lectures will be webcast at <http://videocast.nih.gov>, and sign language interpretation will be provided. For more information, or for reasonable accommodations, contact Kate Haessler at 301-348-1662 or the Federal Relay at 1-800-877-8339.

More information about the series can be found at

<http://cancer.gov/directorscorner>.

Annual NCI Retreat Goes Colonial

All NCI postdocs and other trainees are invited to an NCI annual retreat **March 9-11** in Williamsburg, Va. Abstracts were due by **January 20**; registration is due by **February 6**.

Organized by the the Center for Cancer Research-Fellows and Young Investigators Association (CCR-FYI), the retreat is always held off-campus and is designed to pull researchers out of the laboratory into a milieu that encourages them to present their research and interact with other scientists. Retreat events include seminars by prominent scientists in the field, oral poster presentations by attendees, and workshops geared toward fellows' needs.

This year's planned workshops are:

- Negotiating skills for the job seeker
- Being a professor: what you thought you knew!
- Grant writing
- Team science
- A career panel

Keynote speakers are Stephen Lippard, MIT, Cambridge, Mass.; Robert Weinberg, Whitehead Institute for Biomedical Research, MIT; Shiv Grewal, NCI; J. Carl Barrett, director, NCI CCR; and Nobel laureate Stanley Prusiner, University of California, San Francisco.

To register, visit

<http://palladianpartners.com/postdoc4>.

For more information about the CCR-FYI, visit:

<http://ccr.nci.nih.gov/careers/fellows/default.asp>.

Just over 3 years old, the CCR-FYI represents more than 1,000 basic science and clinical fellows, graduate students, and other investigators-in-training at NCI and is the largest organization of its kind on the NIH campus. Its goal is to foster the professional advancement of its members by organizing and promoting career development activities, assisting in the orientation of new trainees, and identifying employment opportunities in traditional and nontraditional career paths. The largest undertaking of the CCR-FYI is planning the annual retreat, which is organized entirely by the CCR-FYI steering committee members and funded by the CCR Office of the Director.

A program called "GuideDocs" pairs seasoned postdocs with incoming postdocs to help them navigate and acclimate to the NIH community. A weekly fellows' seminar series gives researchers a chance to present their studies to a friendly audience of their peers and get valuable feedback on oral presentation skills.

The CCR-FYI Newsletter provides a forum for all researchers, postbaccalaureate to PI, to submit articles and read about topics pertinent to the CCR-FYI community. The CCR-FYI steering committee also welcomes ideas, questions, comments, criticisms, or concerns regarding the CCR training experience at nciccrfyi@mail.nih.gov.

Collaborative Clinical Research Training Programs: A Reminder

Two deadlines are coming up **March 1**: the NIH-Duke Training Program in Clinical Research and the University of Pittsburgh Training in Clinical Research Program.

The Duke program is designed primarily for physicians and dentists; it's offered via videoconference at the Clinical Center and includes formal courses in statistical analysis and clinical research design and management.

Academic credit may be applied toward a Master of Health Sciences in Clinical Research degree from Duke University School of Medicine,

Durham, N.C.

The Pittsburgh program is designed for Ph.D.s and allied health professionals (though physicians and dentists may also enroll) and spans three semesters, starting with an intensive eight-week summer session, the first five days of which are held at the university.

Participants can earn either a Certificate in Clinical Research (15 credits) or a Master of Science in Clinical Research (30 credits) from the University of Pittsburgh School of Medicine.

Applications for the 2004-2005 sessions of both these programs are avail-

able at the Clinical Center, Office of Clinical Research Training and Medical Education, Building 10, Room B1L403.

For more information on the Duke program and tuition, visit

<http://tprc.mc.duke.edu> or e-mail tprc@mc.duke.edu.

For more information on the Pittsburgh program, visit

http://www.cc.nih.gov/cc/cc_pitt/index.html

or e-mail

tcrp@pitt.edu.

PEOPLE

RECENTLY TENURED

Bruce Cumming earned his D.Phil. and M.D. degrees at Oxford University in the U.K. in 1985 and 1988. He did his postdoctoral training at Oxford and came to NEI in 2000. He is now a senior investigator in NEI's Laboratory of Sensorimotor Research.

Action potentials generated by neurons in the cerebral cortex eventually give rise to conscious sensations. To understand the relationship between neural firing and conscious judgments, I study both of them simultaneously in awake, behaving monkeys. I study a relatively simple perceptual system—stereopsis, the ability to perceive depth by combining images from the two eyes. Stereopsis is sufficiently well understood that the goal of explaining perceptions in terms of the activity of cortical neurons is feasible with this experimental system.

One focus of the lab has been on explaining the exact neuronal mechanisms that generate signals related to binocular disparity (differences between the images falling on the two retinæ) in single neurons. Over the last 10 years, detailed quantitative models have successfully described how neurons respond to a wide range of binocular stimuli. This is especially true of neurons at the earliest cortical stage, known as V1.

An ongoing experimental effort by my lab and by others to test this model has generated a growing body of evidence at odds with the original model. Recently, Jenny Read, working in my group, successfully reconciled all of this evidence with a modified version of the model of the mechanism of disparity selectivity, making it one of the best-understood functions of cortical neurons.

Although the psychophysical properties of stereopsis have been extensively studied in humans and monkeys, many of these properties are not straightforwardly reflected in the activity of single neurons, at least in V1. One of my important contributions was to use our knowledge of the underlying neuronal mechanisms to devise a variety of stimuli that reliably altered the activity of disparity-selective neurons without producing the corresponding depth sensation.

By dissociating the activity of early cor-

tical neurons from visual perception, we gain important insights into subsequent neural processing that is required from other parts of the brain. At the same time, we can identify what properties of perceptual experience are constrained by this early processing.

In parallel experiments, I demonstrated that neurons in subsequent brain areas—"extrastriate" cortex—are more closely linked to the perception of stereoscopic depth than V1 neurons. Small groups of cortical neurons can be artificially activated by passing current out of recording electrodes. I found that stimulating a brain area

known as MT in this way systematically biases animals' depth reports, in the direction expected from the tuning properties of neurons recorded at those sites.

I also demonstrated a close connection between the activity of single neurons and perception by exploiting ambiguous stimuli: An identical visual stimulus is seen as close on some trials but distant on other trials. By recording the activity of single MT neurons while animals report the perceived configuration, I showed that the neuronal activity was correlated with the animals' reported sensation. We measured this correlation between neuronal and behavioral responses to the same physical stimulus; thus, the activity of single neurons in this area carries information not only about the disparity of external stimuli, but also about the depth sensations experienced by the animal.

These experiments offer insights into how hierarchical processing by a series of cortical areas leads from machine-like processing of input images to conscious perception of the visual world. My lab will aim to advance this understanding through three approaches:

1. Challenging current mathematical models of the mechanism of disparity selectivity in V1 with new stimuli. Measuring neuronal responses to these

stimuli will improve our understanding of the underlying mechanisms.

2. Exploiting these models to construct explicit models of how neurons in extrastriate cortex generate new signals from the outputs of V1. Combining these two approaches will identify what aspects of perception are supported by processing in extrastriate cortex, and how.

3. New stimuli may then allow us to activate extrastriate neurons without producing corresponding depth sensations. Demonstrations of a tight link between neuronal activity and perceptual states mentioned above may be possible in the same neurons. The ultimate goal will be to control separately neuronal activity, perceptual state, and the correlation between these two. This process will identify features of activity in populations of neurons that are required to support perception.

Myriam Gorospe received her 'Licenciatura' in biology from the Universidad Complutense de Madrid in Spain in 1990. She earned her Ph.D. in cell and developmental biology from the State University of New York in Albany in 1993. In 1994, she joined the NIA intramural program as a postdoctoral fellow in the Laboratory of Biological Chemistry, later renamed the Laboratory of Cellular and Molecular Biology (LCMB), where she worked under the mentorship of Nikki Holbrook. She currently heads the RNA Regulation Section, LCMB.

I have had a long-standing interest in understanding basic mechanisms of gene regulation. My graduate studies in the laboratory of Corrado Baglioni focused on the investigation of post-transcriptional mechanisms regulating cytokine expression. Subsequent postdoctoral work centered on the transcriptional and post-transcriptional regulation of genes associated with cancer and cell cycle

control.

As a tenure-track scientist, I investigated basic mechanisms of post-transcriptional gene regulation in mammalian cells. These studies focused primarily on genes whose production is linked to stressful and proliferative stimulation—two important responses that are critically impaired with aging.



Fran Pollner

Bruce Cumming



Myriam Gorospe

While the bulk of my lab's work has centered on the analysis of mRNA turnover affecting specific genes, we have also investigated the regulation of protein degradation by the von Hippel-Lindau tumor-suppressor protein. More recently our research efforts have expanded to include mRNA transport and translation, events that are functionally coupled with mRNA stability.

Over the years, our work has provided insight into basic mechanisms of mRNA stabilization and mRNA decay by uncovering RNA elements and RNA-binding proteins involved in regulating mRNA stability and signaling events influencing these processes.

Specifically, we have demonstrated the critical role of RNA-binding protein HuR in the stabilization and enhanced translation of mRNAs encoding proteins that control cell growth and proliferation (such as p21, cyclin A, cyclin B1, and p53). Our studies have shown that through its influence on target mRNAs, HuR plays a pivotal role in important processes such as the cellular stress response, the cell division cycle, carcinogenesis, and the maintenance of a 'young' phenotype in models of cellular senescence.

Our research has also contributed significantly to the demonstration that, on a global level, changes in mRNA stability are critically involved in regulating gene expression patterns during complex cellular processes such as the cellular response to genotoxicity, heat-shock, and oxidative stress.

Through the development of a nuclear run-on protocol adapted to cDNA arrays, we have studied the relative contribution of transcriptional events to the implementation of changes in gene expression patterns.

Using the cellular stress response as study system, we discovered large sets of mRNAs whose altered steady-state levels did not result from transcriptional control, but were instead due to changes in mRNA stability. These studies demonstrated the central role of mRNA turnover in gene regulatory events.

Looking ahead, my lab is uniquely poised to address fundamental aspects of post-transcriptional gene regulation and cell biology. We are currently pursuing this goal by investigating, on a global scale, links between mRNA stability and translation in response to

genotoxic damage and endoplasmic reticulum stress.

Other studies are underway in our laboratory to identify sets of mRNAs that are jointly regulated by specific RNA-binding proteins, such as HuR, AUF1, TIAR, TIA-1, and TTP, as we seek a more complete understanding of post-transcriptional gene regulation.

Larry Kwak received his M.D. in 1982 through an accelerated 6-year B.S.-M.D. honors program and his Ph.D. in tumor cell biology in 1984 from Northwestern University Medical School in Chicago. He completed clinical training in internal medicine and medical oncology at Stanford University in Stanford, Calif.. Originally recruited to the Biological Response Modifiers Program at the NCI-Frederick campus in 1992, Kwak joined the Experimental Transplantation and Immunology Branch in 1996, where he is now a senior investigator.

My interest in tumor immunology, in general, and the idea that the host immune system might be harnessed to neutralize cancer cells, in particular, began as an M.D.-Ph.D. student. My laboratory is now focused on the hypothesis that B-cell tumor-derived Ig idiotype can serve as a tumor-specific antigen for therapeutic vaccine development.

My work studying this specific tumor antigen began as a fellow in the laboratory of Ronald Levy, where I led the first human study of idiotype vaccination. This work suggested that antibody responses were possible. Our central hypothesis now is that sustained, potent, T-cell-mediated responses, especially CD8+ T-cell responses, will be required for achieving clinical efficacy.

At the forefront of my lab's current efforts is a multicenter, randomized, controlled Phase III clinical trial, designed to provide a definitive answer to the question of whether a prototype Id-KLH protein plus GM-CSF vaccine, developed in my NCI laboratory, can achieve clinical benefit in patients with follicular lymphoma.

This trial is now the subject of a Cooperative Research and Development Agreement with an industry partner. To date, more than 150 of an eventual 450

patients have been enrolled.

Central elements of my lab research program are its translational orientation and the bidirectional flow of unique materials between the clinic and the lab to study biology. As an example of this, pre- and post-vaccine T cells, tumor cells, and purified idiotype protein from vaccinated patients have been prospectively stored and will serve as source reagents for characterizing and determining the precise specificity of human idiotype- and lymphoma-specific T-cell clones in the patients.

We are now actively investigating:

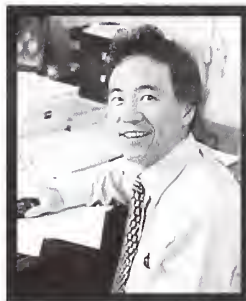
- The dominant and subdominant peptide epitopes derived from Ig V_H and V_L sequences

- Evidence for epitope spreading (in this case, cross-presentation of non-idiotype lymphoma antigens) in vivo

- The cellular and molecular mechanisms by which T cells kill autologous lymphoma targets

Further characterization of human T-cell responses from vaccinated patients has the potential not only to identify the precise peptide determinants recognized, but may also increase our understanding of the role of such T cells in anti-lymphoma immunity.

Another major focus of my research lab is elucidating the mechanism of action of sec-



Larry Kwak

ond-generation DNA vaccines, encoding chemokine-antigen fusions, which we pioneered as a novel strategy for targeting tumor and HIV vaccine delivery. Our current results are consistent with the proposition that plasmid DNA is first taken up by cells that are not necessarily professional antigen-processing cells (APC)—for example, epidermal cells.

In this pathway, the cell that takes up the DNA expresses the protein and secretes this chemokine-antigen fusion protein into the extracellular milieu, where it is then selectively taken up by professional APCs, which have the relevant chemokine receptor. Uptake of the fusion protein is therefore chemokine receptor-mediated.

Once the chemokine-antigen fusion protein has been internalized, antigenic determinants are then processed and subsequently presented on the surface of the APC, complexed to major histocompatibility complex molecules for

PEOPLE

RECENTLY TENURED

presentation to T cells. In addition to targeted antigen delivery, it is also highly possible that such chemokine-antigen fusion vaccines trigger chemokine receptor-mediated maturation of dendritic cells, as we reported recently in *Science*.

We hope to develop novel second-generation idotype vaccines and apply them clinically to other B-cell malignancies in the future. In addition to using this approach in follicular and mantle cell lymphomas, we are considering future collaborative trials in chronic lymphocytic leukemia. In collaboration with Mike Bishop, a colleague in my branch, we are already testing a novel strategy of stem cell transplant donor immunization for multiple myeloma.

Rui-Ping Xiao was trained as a cardiologist and physiologist at Tong-Ji Medical University in Wuhai, China, and the University of Maryland Medical School, Baltimore, where she earned her M.D. in 1987 and Ph.D. in 1995, respectively. She joined the Laboratory of Cardiovascular Science, NIA, in 1990 as a postdoctoral fellow. In 1996, she became the head of the Receptor Signaling Unit at LCS, where she is a senior investigator.

The scope of my research covers three intertwined programs:

- β -Adrenergic receptor subtype signaling in the cardiovascular system

- Modulation of cardiac excitation-contraction coupling by Ca/calmodulin-dependent protein kinase II (CaMKII) in normal and failing hearts

- Identification and characterization of cardiovascular disease-related genes

My main scientific focus has been G-protein-coupled receptor (GPCR) signaling in the cardiovascular system. Using interdisciplinary approaches, including physiological and pharmacological techniques in conjunction with genetic manipulations (such as gene-targeted animal models and adenoviral gene transfer systems), I revealed the dual coupling of β_2 -adrenergic receptor (β_2 AR) to two functionally opposite G-protein families, Gs and Gi proteins.

This counterintuitive finding was the first demonstration that a given GPCR can couple to more than one class of G-proteins in a physiological context—such as in intact cardiac myocytes.

My research has demonstrated that the additional Gi coupling creates a microscopic compartmentalization of the concurrent Gs-cAMP signaling and, more importantly, dictates the opposing outcomes of β AR subtype stimulation with respect to cardiac cell survival and apoptotic cell death.

I envisioned and promoted the perception that β_1 AR and β_2 AR subtypes play distinctly different—even opposing—roles in the context of heart failure. Specifically, while β_1 AR is widely recognized as a “foe,” β_2 AR might be a “friend in need” due to its concurrent anti-apoptotic effect and contractile support.

This new perception of β AR signal transduction has been increasingly appreciated in the cardiovascular research community and provides a novel rationale for new therapeutic strategies, particularly a combination of β_1 AR blockade with β_2 AR activation for improving the function of the failing heart.

The Human Genome Project has demonstrated that the GPCR family is the largest gene family in the human genome. This superfamily has also long been considered the most important target in the pharmaceutical industry. Remarkably, 70 percent of today's therapeutic agents used for the treatment of cardiovascular diseases are targeted at GPCR signaling pathways.

Thus, one of my major future goals is the identification and target validation of orphan GPCRs. These studies will not only provide novel insights into basic mechanisms of novel GPCR actions, but also reveal new rationales for ligand screens as well as clinical applications.

My research has not been limited to G-protein-coupled receptor signaling. I was also the first to characterize the role of CaMKII in regulating cardiac L-type Ca²⁺ currents and in the control of cardiac pacemaker activity.

Our recent in vivo and in vitro studies have shown that activation of p38 MAPK produces a potent inhibitory effect on cardiac contractility. I'm also aiming my research at understanding the mechanisms underlying cardiac aging and heart failure.

Identification and characterization of cardiovascular disease-related genes is another new initiative of my lab. Using RNA differential display analysis of vas-



Rui-Ping Xiao

cular smooth muscle cells from spontaneously hypertensive rats and Wistar Kyoto rats, we have identified seven novel genes:

- Murine and human hyperplasia suppressor gene, *HSG*, (GenBank U41803-rat, AF3841-mouse, and AF03653-human)

- Hyper-hemocysdine-induced gene *HCY2* (AF036537)

- Apoptosis-related genes: *TFAR19* (AF014955); *TFAR15* (AF022385); *bbLIM*, also known as Myogenic Factor LIM3 (AF12126).

Among our ongoing research aims is to characterize the function of the identified gene in vivo and in vitro. We also plan to develop gene-targeted mouse models to characterize the physiological and pathological functions of these genes. ■

More Demystifying

The third year of the popular "Demystifying Medicine" course began January 6 and will continue through May 26—every Tuesday from 4:00–5:30 p.m. in the ground-floor auditorium of Building 50.

The course is designed to help bridge the gap between basic science and clinical medicine and is open to all students, fellows, and staff, although it is designed primarily for Ph.D. scientists and students.

Individuals seeking academic credit may register with FAES. Those not seeking academic credit should register through the course e-mail list. For more information on registration and to see the class schedule, go to:

<<http://www1.od.nih.gov/oir/DemystifyingMed/index.html>>.

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ETHICAL AND REGULATORY ASPECTS OF CLINICAL RESEARCH: THE TEXTBOOK

The seven-week, 21-hour course in "Ethical and Regulatory Aspects of Clinical Research" that has taken NIH by storm since its inception in 1999—and has been taken on the road to developing countries since 2001—can now be absorbed at one's leisure in a favorite reclining chair, or even under the trees by a lake.

An offering of the CC Department of Clinical Bioethics and directed by department chair Zeke Emanuel, the course has attracted a steadily increasing enrollment each fall—from 162 the first year to an overflowing 550+ this past fall.

The documentary substance that structures the course has been collected into a comprehensive and diverse text of nearly 500 pages, including 86 entries and nine appendices.

The text is edited by Emanuel and Christine Grady, who heads the department's section on human subjects research, and three other prominent biomedical ethicists: Robert A. Crouch of McGill University, Montreal, and John Arras and Jonathan Moreno of the University of Virginia, Charlottesville. It's available at the FAES Bookstore, Building 10, B1 level, and at other bookstores. Cost is \$39.95.

Contents

Part I. Scandals and Tragedies of Research with Human Participants (including Nuremberg and Tuskegee)

Part II. Ethical and Regulatory Guidance for Research with Humans (including the Declaration of Helsinki and the Belmont Report)

Part III. The Ethics of Clinical Trial Design (including the distinction between research and treatment and the role of placebos in clinical research)

Part IV. The Ethics of Research Participant Recruitment (including payment of research participants and informed consent)

Part V. Informed Consent in Research

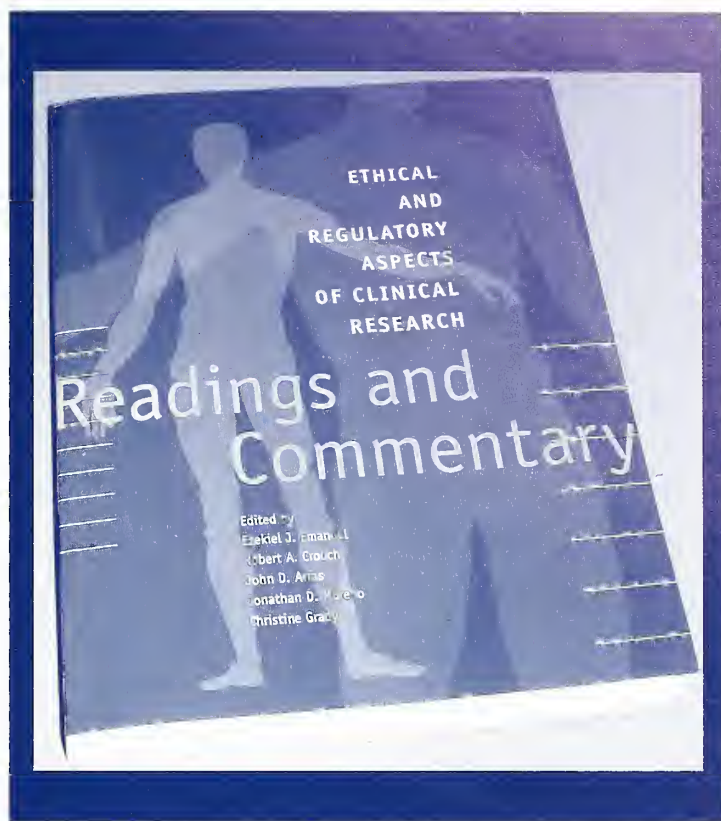
Part VI. Clinical Research with Special Populations (including children and cognitively impaired people)

Part VII. Special Topics in Research Ethics (including genetics, human embryos, stem cells, and international research)

Part VIII. The Behavior of Clinical Investigators: Conflicts of Interest (including finder's fees and the validity of clinical trials)

Part IX. Scientific Misconduct (including altering data and the rules of authorship)

Part X. Challenges to the Institutional Review Board System (including conflict of interest and commercial research review boards, and a central institutional review board for multi-institutional trials) ■



Published by the Johns Hopkins University Press, Baltimore and London, 2003

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New Year's Resolutions

1) I will not surf the internet while I am working on the computer



computer — except during lunch, and even then only news headlines and stock market quotes



market quotes — and the occasional op-ed column



column — but never any political blogs!



column — but never any political blogs!!!!



ONE HOUR LATER...



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: 402-4303; or mail: Building 2, Room 2W23.**

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

In Future Issues...

- On the Road(map): A Series
- Intramural Database
- Dipping Into Poolesville

Kids' Catalyst

SWEET SUSPENSION: AN EXPERIMENT WITH CHOCOLATE

Who said science couldn't taste good? In this experiment, you'll see how three ingredients produce very different results—all delicious! We're making chocolate icing.

For the shopping cart, you'll need: ■ Twelve ounces (oz) of semisweet chocolate broken into four 3-oz groups. Subdivide these groups into squares, about six each. Keep them separate and don't nibble! ■ A half-pound of butter (two sticks), divided into four 4-tablespoon (Tbsp) groups that have been cut into pea-size chunks (about 60). Put two of the 4-Tbsp groups in the freezer; keep the others at room temperature. ■ Three-quarters of a cup of coffee, with or without caffeine.

For hardware, you'll need: ■ A large coffee mug ■ A small whisk or large fork ■ A tablespoon measure. ■ A microwave set to half-power. ■ An oven mitt (the cup will be hot). ■ Taste buds!

Now we'll see how combinations make all the difference.

First Experiment: Take 3 Tbsps of coffee and put it in the coffee mug. Take one 3-oz chocolate group, and add one small square of chocolate to the coffee. Put this in the microwave on half-power for 15 seconds. Check the mixture. The chocolate should be soft enough to melt into the coffee when stirred. Now repeat with each square of chocolate. All melted? Now, take one 4-Tbsp group of cold butter and add that, one pea-sized chunk at a time. What do you get? Cool this mixture for 15 minutes, stir again, and taste! Yum!

Second Experiment: Take the second 3-oz group of chocolate and put it ALL in the coffee mug. Heat at 15-second increments (still on half-power) and stir each time until it's all melted. (This whole process should take about a minute.) Add 3 Tbsps of coffee all at once. It looks a lot different, right? Add the cold butter using the same method as the First Experiment. This looks different, too. Wonder why?

Third Experiment: Take 4 Tbsps of room-temperature butter, melt that in the microwave (about 15 seconds), then add one of the 3-oz groups of chocolate all at once. Stir until melted, then add 3 Tbsps of coffee. It tastes good, but it's not icing!

Fourth Experiment: Take 3 Tbsps of coffee, add the last 4-Tbsp room-temperature butter group, and heat these two ingredients until the butter melts. Then add the final 3-oz group of chocolate, one square at a time, to this mixture. Wow!

You have just produced chocolate icing, paste (ganache base—look that one up), unusable glop (unless you can figure out a way to use it), and a base for very rich hot chocolate. Which is which? You can also experiment with cooling and reheating these mixtures. What you're doing is creating—or breaking—a suspension of chocolate in relation to the liquid and the fat. . . . What would happen if you used chocolate with a higher fat content?

—Jennifer White



The *NIH Catalyst* is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: catalyst@nih.gov

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