FOSTERING COMMUNICATION AND COLLABORATION

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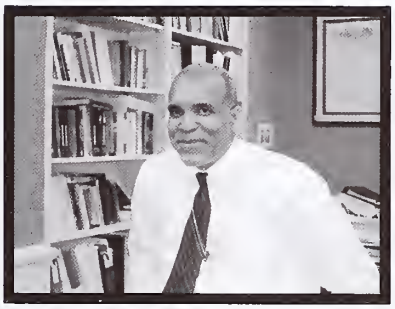
New Deputy Director

Introducing Raynard Kington To NIH—Again

by Fran Pollner

For the third time in two and a half years, Raynard Kington has taken on a new NIH role. Appointed in October 2000 by then–acting director Ruth Kirschstein to assume the directorship of the Office of Behavioral and Social Sciences Research (OBSSR) and again in February 2002 to serve as acting director of NIAAA, Kington succeeded Kirschstein as NIH deputy director in February of this year. He spoke with The NIH Catalyst *April 21.*



Fran Pollner

Raynard Kington

Q: Why were you selected to become the NIH deputy director? Was there a conceptual change in the nature of the role that pointed to the appointment of a person with your experience and skills?

KINGTON: The search for a new deputy director evolved from discussions between Dr. Zerhouni and Dr. Kirschstein, who has become senior advisor to the director and continues to play an imprtant role at NIH. An advisory committee was formed; I was invited to apply, along with others. Some applicants were interviewed by the committee, and then a short list was passed on to the director, who had a series of interviews with all the candidates.

As for a change in the role of

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The Agony and the Ecstasy: Clinical Research at NIH

by Fran Pollner

The public's substantial investment in the new Clinical Research Center (CRC) must be matched by outstanding contributions to the country's clinical research needs, NIH Director Elias Zerhouni challenged a critical mass of NIH investigators and clinical directors (and others) at the start of a daylong retreat March 21.

"NIH cannot be everything to everybody," but must select "top priorities," Zerhouni said, noting that 75 percent of health-care costs today is attributable to chronic disease.

He charged the assembly with crafting a new vision for the new CRC and with defining a "compelling" role for the NIH intramural research program in the translation of basic science discoveries that can continue to make a difference in human health.

"This is a leadership retreat to determine the right things to do," Zerhouni said, adding that the right things would necessarily be "trail blazing" and not "me, too" research.

The retreat was structured to review some of the exceptionally innovative and successful elements of the intramural clinical research program and to turn a critical eye on some of the burdensome realities that keep it from reaching optimal performance.

In his opening remarks, Deputy Director for Intramural Research Michael Gottesman reminded participants that the retreat was meant to be neither a "gripe session" nor a "pep rally" but a concept-oriented meeting that would lay the groundwork for the formation of working groups and an ensuing series of workshops aimed at:

- Defining and removing obstacles to clinical research at NIH
- Identifying mechanisms for collaborative, innovative clinical research unique to the CRC milieu that will result in the development of novel therapies for daunting diseases and for conditions that exact a huge public health toll
- Defining the goals of the CRC and how best to measure success

Ernie Branson

NIH provides medical services while conducting clinical research at a NIAMS-run community clinic

Central to achieving optimal use of the CRC, everyone seemed to agree, is attracting requisite numbers of clinical investigators and patients to NIH.

Welcome to the Clinical Center

"There's no other hospital like it," said CC Director John Gallin, quoting what is actually the little-known motto of the Clinical Center. Patients, he said, have

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Clinical research at NIH: Where Do We Go from Here?

Michael Gottesman

For the past 50 years, since the opening of the Clinical Center in 1953, the NIH intramural program has been a leader in applying basic biology to the understanding and treatment of human disease.

Landmark contributions—including the design and implantation of the first artificial heart valve, successful multidrug chemotherapy of cancer, use of lithium to treat manic-depressive mental illness and fluoride to prevent cavities, virtual eradication of hepatitis from the nation's blood supply, and the first effective treatment of AIDS—have lengthened and improved the quality of millions of lives and saved billions of dollars in health-care costs.

The nation continues to invest in the promise of NIH research, strongly supporting our research budget and the construction of the new Mark O. Hatfield Clinical Research Center at a time when it is becoming increasingly difficult to conduct clinical research in our academic medical centers.

What must we do to ensure that NIH continues to provide the greatest return on this investment through innovative clinical research?

Clinical research at NIH has been the subject of several reviews over the last decade. Ten years ago, the Marks-Cassell report addressed the importance of revitalizing the physical infrastructure for clinical research and recommended the phased renovation of the Clinical Center. The first step in that process—new construction of a Clinical Research Center, including a new hospital and some associated laboratories—is on schedule for completion in 2004. The timeline for future renovations in Building 10 is still under consideration.

In 1996, the Smits report recommended development of a new system for governance of the Clinical Center hospital—and the Clinical Center Board of Governors was born, followed by a novel funding system based on a school tax on all contributing Institutes and Centers.

Because of continuing concerns about declining utilization of the Clinical Center, attributed in part to reduced recruitment and retention of clinical investigators, the Straus committee report in 1997 (see *The NIH Catalyst*, May-June 1997 and September-October 1997; <**http://www.nih.gov/catalyst**>) initiated changes in salary support and career development of clinical investigators. These actions resulted in increased recruitment and improved retention of clinical investigators and more active clinical protocols.

The NIH Director's Clinical Research Panel, although focused more on the plight of extramural clinical research, did support an important role for the intramural program in training clinical investigators. It suggested the development of what has become the highly successful Clinical Research Training Program for medical students.

A retreat in March, co-chaired by Allen Spiegel and myself and including the NIH leadership and many clinical investigators, explored recent successes and continuing problems in the intramural clinical research program (see "The Agony and the Ecstasy: Clinical Research at NIH," page 1).

Dr. Zerhouni challenged the participants to develop plans to optimize use of the Clinical Research Center and other NIH clinical research resources—and to build on our proud history of research contributions that have improved the health of the nation.

At the end of the meeting, I made several general observations, which can be summarized as follows:

The level of energy, enthusiasm, and passion of NIH clinical investigators remains high. Our clinical investigators and leadership care deeply about the important role that intramural clinical research can play in the overall NIH-supported clinical research program.

NIH should continue to study diseases of public health importance for which good treatments are not available (obesity and SARS are two examples).

We need to study disorders that disproportionately affect populations that are currently underserved, including minority populations and patients with rare diseases.

It is essential to follow up on the retreat with a series of panels and working groups to develop specific plans.

As a result of continuing discussions with the Clinical Center Research Steering Committee, the NIH director, and the IC directors, the following actions will be taken over the next few months.

- First, a Blue Ribbon Panel, including renowned non-NIH clinical and translational researchers and senior NIH clinical research leadership, will be established to answer these questions: "What kinds of clinical research should be done at NIH?" and "How can we best evaluate the success of our clinical research program?"
- Next, a new working group on recruitment and career development of clinical trainees and investigators will be established. Its goal will be to continue to improve the working environment and the status of clinical investigators at NIH. Once research priorities have been established, the director of the Clinical Center and I will chair a working group to advise on assignment of resources needed to initiate and maintain the most effective and innovative clinical research programs.
- Finally, we will continue to work with the appropriate agencies and organizations, both at and outside of NIH, to reduce unnecessary bureaucratic burdens on the clinical research process, always mindful of the primary requirement to protect human research subjects.

This ongoing process cannot succeed without the ideas and cooperation of NIH staff at all levels. Please continue to send me your thoughts and comments.

—Michael Gottesman
Deputy Director for Intramural Research

Catalytic Reactions

On the Back-Page Space

How about an NIH Kids' Page?

- NIH Kids' Mentoring: Health Science Starts at an Early Age
- NIH Kids' Learning

...or maybe ...

- Kids' Health How-Tos
- Kids' Question Corner
- Kids' Health Comics Strip

or

- NIH Gee-Whiz: How'd They Do That? (lay-level science)

Hope this helps!

—Jon Rutherford, CIT

—Anybody out there interested in doing this? Contact us.—Ed.

Women's Health SIG

The Women's Health Special Interest Group has scheduled the following talks:

- "Sex Hormone Effects on Specific Brain Mechanisms and on Generalized Brain Arousal," **Wednesday May 21, 2003**, 10:30 a.m.–12:00 noon (Donald Pfaff, Rockefeller University)
- "Autoimmune Disease—Why Female?" **Wednesday, June 11, 2003**, 11:30 a.m.–1:00 p.m. (Nancy Olsen, Vanderbilt University)

The lectures will take place in Wilson Hall, Building 1. ■

Imaging in Living Cells

The National Institute of General Medical Sciences will sponsor a symposium, "Tools for Discovery: Imaging Molecular Events in Living Cells," on **Thursday, July 10, 2003**, 8:30 a.m. to noon, in Building 10, Lipsett Amphitheater.

Biological imaging of dynamic molecular events in living cells promises to provide new insights into fundamental cellular processes. Recent advances in the tools used for intracellular imaging have opened the door to new information on the spatial and temporal relationships between molecules within the cell. The complex behavior of individual molecules and molecular assemblies, and their movement within the cell, can now be captured by increasingly sophisticated optical microscopic techniques. This symposium will feature examples of leading technologies that extend the limits of biological imaging to give high resolution detail on dynamic cellular events in vivo.

Edward Salmon
University of North Carolina at Chapel Hill

A mammalian tissue culture cell (PtK1) treated with an inhibitor of a mitotic kinesin, resulting in formation of a monopolar rather than a bipolar mitotic spindle. (The cell was fixed in prometaphase and stained green for microtubules and red for DNA, visible in the online Catalyst *at* **<http://www.nih.gov/catalyst/2003/05.03.01/page7.html#imaging>**.*)*

The program includes five speakers: Wolfhard Almers of the Vollum Institute, Oregon Health and Science University, Portland; Jennifer Lippincott-Schwartz of NICHD; Ted Salmon of the University of North Carolina, Chapel Hill; Roger Tsien of the University of California, San Diego; and Simon Weiss of the University of California, Los Angeles.

There is no fee, but advance registration is required. To register online, go to **<http://pub.nigms.nih.gov/imaging>**.

Sign language interpretation will be provided. For information or other accommodations, contact Terese Trent, **<trentt@nigms.nih.gov>** or 301-594-0828. ■

Learning from the Ancient Greeks

The first Annual Epidaurus Conference on Patient-Centered Care will be held **Friday, May 23, 2003**, from 8:00 a.m. to 5:15 p.m., with continental breakfast at 7:30 a.m. The conference is co-sponsored by the Uniformed Services University of the Health Sciences, Bethesda, Md., the Association of Academic Health Centers, Georgetown University, Washington, D.C., and NIAMS. Registration is free to the first 200 registrants and can be done online: **<http://hsa.usuhs.mil/epidaurus>**.

CoreBio Network Up and Running

NIH scientists can now discuss bioinformatics-related research problems with an on-site specialist via the NIH-wide Core Bioinformatics Facility (CoreBio).

All CoreBio representatives have completed a 9-week course at the National Center for Biotechnology Information (NCBI) focusing on the use of the NCBI suite of bioinformatics tools and databases. There are now 13 CoreBio representatives from 11 NIH institutes.

Individual or group training sessions can be arranged with the following representatives:

- NIAID: Mary Ann Robinson, 50 South Drive, MSC 8006, 301.402.6952 **<marobins@niaid.nih.gov>**
- NIAID: Glynn Dennis, PO Box B: 550-102, Frederick, MD- 21701, 301-846-1910 **<gdennis@niaid.nih.gov>**
- NHLBI: Eric Billings, Building 10, Room 4A15, 301-496-6520 **<ebillings@mail.nih.gov>**
- NHGRI: Tyra Wolfsberg, Building 50, Room 5228B, 301-435-5990 **<tyra@nhgri.nih.gov>**
- CBER: Tom Maudru, Building 29A, Room 1A21A, 301-827-1927 **<tm24k@nih.gov>**
- NCI: Howard Yang, ATC/HC/8424, Gaithersburg, 301-435-8956 **<yanghow@helix.nih.gov>**
- NCI: Peter Fitzgerald, Building 37, Room 1E04, 301.402.3044 **<pcf@helix.nih.gov>**
- NIMH: Ronald Finnegan, Building 10, Room 3N246, 301-594-3607 **<rwf@mail.nih.gov>**
- NIAAA: Julie Taubman, Park/413, 301-443-7632 **<jtaubman@niaaa.nih.gov>**
- NIDDK: Margaret Cam, Building 8, Room 1A11, 301-594-2493 **<maggiec@intra.niddik.nih.gov>**
- NIEHS: Bill Quattlebaum, Research Triangle Park, NC, 919-541-2146 **<quattleb@niehs.nih.gov>**
- CIT: Liming Yang, Building 12A, 301-402-4155 **<lyang@helix.nih.gov>**
- NINDS: Yang Fann, Building 10, Room 5S224, 301-451-5153 **<fann@ninds.nih.gov>**

Unrepresented NIH institutes can nominate a CoreBio representative for training at NCBI. ■

The Agony and the Ecstasy:
Clinical Research at NIH

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plenty of reasons to seek involvement in clinical research at NIH—free care, with travel expenses paid, if necessary; a superb nurse-to-patient ratio; highly educated nurses; and on-site "boutique" support services. The patients on protocol at the CC are also "invested in the clinical research process," Gallin said, noting that he meets quarterly with a patient advisory group.

Extramural clinical investigators also have plenty of reasons to seek involvement in clinical research at NIH, said Carl Barrett, director of the NCI Center for Clinical Research. "The CC accounts for more than half of NIH-funded general clinical research beds in the country. It's a technological center of excellence, offering proteomics, imaging, specialized therapeutic delivery systems, pharmacogenomics, and combination therapies," Barrett said. "And we have a national clinical research center with open access to clinical protocols and specialized early-phase studies."

Descriptions of NIH programs (see below) that are generating useful collaborations and exciting research capped off the morning.

Howard Fine

The Brain Tumor Program

Three years ago, NIH recruited Howard Fine as chief of the NCI Neuro-Oncology Branch. His mandate was to launch the Brain Tumor Program (BTP), a collaboration of NCI, NINDS, the extramural community, and the private sector.

The BTP mission is to develop novel therapeutic and diagnostic modalities for children and adults with central nervous system malignancies and to be a resource for patients and physicians.

The program is working "tremendously well," Fine said.

Before 2000, fewer than 30 patients a year with primary brain tumors were seen at NIH; last year, the BTP saw more than 300 such patients and anticipates about 400 this year; there are 13 clinical trials that are either active or going through the IRB-approval process; more than 20 new compounds are in preclinical or clinical trials; the program trains five neuro-oncology research fellows a year (for three years); and it has or is in the process of negotiating at least eight different CRADAs.

NIH can amass a critical number of patients for phase I/II trials at the Clinical Center, Fine said, and then return them to their communities to pursue conventional therapy. The BTP collaborates with area hospitals, including Johns Hopkins in Baltimore and George Washington and Children's Hospital Medical Center in Washington. It is also an active member of the three (two adult, one pediatric) NCI-sponsored phase I/II clinical trial consortia of national brain tumor centers. It has also set up a consultation service and a multidisciplinary NIH-wide Brain Tumor Clinic on the 12th floor of the CC, with monthly care conferences. Free diagnostic consults out in the community also result in many patient referrals.

Ira Pastan

The program "is particularly appropriate for NIH," Fine observed, "because this is a tumor type not frequently seen in the community and for which standard options are limited."

"Although we inform all patients about optimal standard treatment, we don't actually administer standard treatment here," Fine said. "Rather, we offer appropriate patients enrollment in clinical trials exploring novel anti-tumor agents such as EGFR [epidermal growth factor receptor] inhibitors and FTI [farnesyl transferase inhibitors]—and there are probably many scientists here at NIH working on research relevant to the BTP who just don't know about us," he added, in a call for collaborators.

Bench to Bedside—and Back

The notion that NIH is uniquely designed to be a testing ground for clinical applications of basic science discoveries is being realized in the five-year-old Bench-to-Bedside program.

This model for translational research has yielded new diagnostic and therapeutic approaches to a variety of both complex and common conditions (see *The NIH Catalyst*, "From Bench to Bedside Under the NIH Canopy," and accompanying stories, March-April 2002; **<http://www.nih.gov/catalyst/2002/02.03.01/>**).

Ira Pastan, chief of the Laboratory of Molecular Biology, NCI, discussed his own transition 10 years ago from a basic scientist with a 30-year track record at NIH to a translational scientist whose intention "to do something useful in cancer" generated research in recombinant immunotoxins that resulted in a Bench-to-Bedside project that yielded a therapy for drug-resistant hairy cell leukemia.

The site visit committee had deemed the research too risky and expensive, Pastan recalled, but the IRP did not, and the result was a great clinical success.

Alan Schechter, chief of the Laboratory of Chemical Biology, NIDDK, and Mark Gladwin, senior investigator in the CC Critical Care Medicine Department, were involved in several of the original Bench-to-Bedside awards that focused on sickle cell disease. These awards were important in the initiation of this collaboration, which subsequently involved others in NCI and NHLBI as well.

The goal of the work is to develop targeted delivery of nitric oxide by hemoglobin to improve regional blood flow in patients with sickle cell disease.

The CC, said Gladwin, "is a great place to develop protocols." Since the inception of the Sickle Cell/Nitric Oxide Therapeutics Program in 1998, the NIH's National Center for the Study of Minorities and Health Disparities and Howard University and the Cardozo Clinic in Washington, D.C. (see section below, "Community Clinic: Gateway to Trials") have been collaborators.

The program, said Schechter, has truly been "bedside to bench to bedside."

It has also generated 21 published papers and 12 review articles and editorials; it has launched six active IRB-approved protocols, with two more pending; it has enrolled 335 patients in clinical studies; and it has completed 564 outpatient and 384 inpatient visits.

Community Clinic: Gateway to Trials

A NIAMS-run off-site clinic in the Cardoza community of Washington is examining health disparities and serving as a portal to state-of-the-art care for patients with unmet needs related to

chronic rheumatic diseases. It's also a portal to new patients and new protocols for NIH clinical investigators, while providing access to clinical trials for patients not typically in the loop. (See "NIAMS Turns Policy into Practice," *The NIH Catalyst*, January-February 2001; **<http://www.nih.gov/catalyst/2001/01.01.01/page1a2.html#niams>**.)

Barbara Mittleman

A "symbiotic relationship hard to achieve elsewhere" has been created among NIH researchers, community physicians, and predominantly African-American and Hispanic-Latino patients, said Barbara Mittleman, PI for the NIAMS protocol to study the "Natural History of Rheumatic Disease in Minority Communities."

The program has accrued 465 patients since both the clinic and this first protocol were launched in 2001. "Every patient enrolled in the clinic is enrolled in the protocol," Mittleman said. "At the beginning, until we had established a reputation, gained community trust, and gotten greater community awareness of what we do, we had few patients. As the word got out that we are okay people and take good care of patients, the calls began to pick up to the current rate. In fact, the number of patients seen continues to rise on a monthly basis."

Patients were glad to sign on to a research protocol that provides the standard of care and access to resources like imaging that might not otherwise be affordable.

There are no experimental modalities in the natural history protocol, but patients can be offered entry into other NIH studies for which they may also be candidates. This "spillover into other IC protocols has already begun," Mittleman noted, and other NIAMS protocols are in development, some in collaboration with other institutes. The community, she said, sees the NIH clinic as a "tremendous complement" to existing facilities and an excellent venue for clinical research training.

In an ensuing discussion focused on the benefits of such natural history of disease protocols, NIAID Clinical Director Cliff Lane noted that a protocol to study the natural history of HIV disease not only has scientific merit but also meets a critical requirement of the NIAID infectious disease fellowship program to retain its ACGME (graduate medical education) accreditation.

Carefully crafted natural history studies of common diseases for which therapy exists but is not effective enough is a fine means to accrue sufficient numbers of patients to yield meaningful findings, observed Dave Harlan, chief of the NIDDK Transplantation & Autoimmunity Branch. He sees such studies as a clinical research niche for NIH, in addition to studies of rare diseases with poor or no therapies and diseases that disproportionately affect the underserved.

Novel Cardiac Surgery: Another NIH Niche

In 1990, NHLBI's cardiac surgery program was closed for lack of patient volume. By the time Toren Finkel arrived at NIH in 1992, the NHLBI interventional cardiology program had "dissipated" for lack of cardiac surgery.

But interventional cardiology is now making a comeback at NIH, thanks to the reinstitution of cardiac surgery through the creation of a three-way partnership between Johns Hopkins University in Baltimore, Suburban Hospital in Bethesda, and the IRP, said Finkel, now chief of the Cardiovascular Branch and its cellular and molecular biology section.

This partnership encompasses an ongoing cardiology fellowship at Hopkins and an imaging program at Suburban run by Bob Balaban, chief of the Laboratory of Cardiac Energetics, NHLBI. "The research-driven component will be under the NIH umbrella," Finkel said.

While the partners are "still working out" the details of how decisions will be made regarding which patients will receive standard of care and which patients will be offered a protocol, discussions regarding where surgery will be done are pointing to Suburban—where volume and quality are high—as the site for "bread and butter" surgery.

"It's been proposed that the more novel research surgery might be routed to the CC," Finkel said. "If agreed upon, this could be an NIH niche."


Toren Finkel

In the ensuing discussion, Henry Masur, chief of the CC's Critical Care Medicine Department, cautioned against "just taking care of the problem specified in the protocol and not the whole patient," a practice, he said, that is not limited to any one institute and that frustrates the wishes of patients and referring physicians. Others expressed similar concerns.

Masur also advised that younger investigators with clinical programs be accorded more space in the new facility—and that efforts be made to correct hospital underutilization in general.

Mittleman suggested that NIH researchers generate hypotheses and think of new clinical trial paradigms that would address functional assessment and quality-of-life issues over the long term.


Harvey Klein with new cell processor, 1997

Partnering

CC Transfusion Medicine Department Chief Harvey Klein recounted a history of interactions with the private sector that have produced an array of groundbreaking instruments in the transfusion field. Over the past 10 years, he said, the department has negotiated 14 CRADAs and numerous material transfer agreements.

He described two win-win agreements with Baxter Healthcare of Deerfield, Ill., that resulted in a core-processing facility and pioneered novel cell separation and processing techniques, including mononuclear cell apheresis. "Baxter got the products, and we got extremely useful technology," Klein observed (see "Cell Processing Facility Debuts," *The NIH Catalyst*, November-December 1997; **<http://catalyst.cit.nih.gov/catalyst/back/97.11/addition.html#debut>**).

Another "marvelous example of partnering," NCI's Barrett said, is the collaboration of NCI's Lance Liotta and FDA's Emanuel Petricoin and their col-

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leagues in studies of molecular profiling and individualized therapies for patients with ovarian and prostate cancer. (For background info, see "Beyond Genomics to Clinical Proteomics," *The NIH Catalyst*, March-April 2001 and May-June 2001; **<http://www.nih.gov/catalyst/2001/01.03.01/page1.html>** and **<http://www.nih.gov/catalyst/2001/01.05.01/page4.html>**.)

At the NCI Center for Clinical Research, Barrett added, the Medical Oncology Clinical Research Unit provides interdisciplinary clinical research and training and serves as an "alpha site" for protocol development and standardization. Extramural basic scientists often join up with intramural clinical investigators; collaborators come from both academia and industry, he said.

The Afternoon and Beyond

The bag-lunch and afternoon sessions of the retreat addressed choosing relevant measures of success and overcoming clinical research barriers related to recruitment, career development, infrastructure, and bureaucracy and regulation (see "Obstacles on the Path" below)—all to be further pursued in ongoing workshops. ■

Obstacles on the Path to Clinical Research

The Visible Shield

"The brick wall is the regulatory process."

For Steve Rosenberg, NCI's chief of surgery for 26 years and PI on dozens of protocols, there's no greater impediment to translational research today than the multilayered review-committee bureaucracy that now stands between a pressing scientific question and a clinical protocol aiming to answer it.

Steve Rosenberg

Many attendees at the Clinical Research Retreat March 21 nodded in recognition as Rosenberg presented what he described as a typical example of the roadblocks placed in the way of launching what was a high-priority protocol examining autologous cell transfer as a new approach to advanced metastatic cancer.

From July 2001 to the day of the retreat nearly 20 months later, the protocol had been bounced back and forth between an alphabet soup of review committees—PRMC, OBA, IBC, IRB, and CTEP (Protocol Review and Monitoring Committee, Office of Biotechnology Activities, Institutional Biosafety Committee, Institutional Review Board, and Cancer Therapy Evaluation Program)—and the investigators.

During this time, the protocol accrued more than 200 stipulations as each rewrite and resubmission inspired additional stipulations from another, previously satisfied, committee. New members coming on to committees in the middle of this protracted review would further complicate the process.

"The enemy is us," Rosenberg said, noting that he hadn't even brought the FDA into the picture he was presenting.

Moreover, he said, the investigators submitted an amendment to a previously approved protocol so they might recruit additional patients to that one while waiting to begin the new one. Submitted last October, the amendment had yet to be okayed. "We're getting 100 referrals a day and can accept no one," Rosenberg commented.

"In the last two and a half years, we've had 30 audits of our tumor immunology protocols; we have 13 full-time people in the surgical unit just to to keep us in compliance; we have four PIs. I spend one day a week exclusively to keep us in regulatory compliance."

He asserted that each of the review groups does essentially the same thing, that the same risk-benefit considerations are applied to patients with terminal conditions as to healthy volunteers, and that the review process has evolved into an albatross that often dilutes the science, delays the pursuit of answers critical to patients, and discourages the pursuit of clinical trials in general and the involvement of young investigators in particular. He pointed to one of his especially dedicated and gifted postdocs whose career has been put "on hold" during this 20-month hiatus in his main research pursuit. "We are losing a generation of translational investigators," Rosenberg warned.

Tom Waldmann, chief of the NCI Metabolism Branch, noted that investigators such as himself and Rosenberg, who typically bring to trial novel therapeutics developed in their own labs, have the rockiest trip through the protocol-approval process. Things are a bit smoother, he said, when the agent being tested is supplied by a drug company.

There is a general perception across NIH, however, that the protocol review and approval process has become increasingly burdensome, Deputy Director for Intramural Research Michael Gottesman said, citing responses to an IRP survey sent to 568 PIs, institute directors, and scientific and clinical directors. Most people indicated that NIH is an excellent venue for clinical research, with a high level of support from the leadership, but many from the smaller institutes especially cited a need for more resources related to protocol coordination and data management.

Hierarchy

A dominant concern among retreat participants was the status accorded individuals whose primary focus is clinical research. There is a perception—not borne out by data supplied by the Central Tenure Committee—that clinical investigators do not fare as well as basic scientists on the tenure track and that they are less likely to even be put on that track.

Several speakers commented that designations like "fellow" and "staff clinician" are not acceptable to many MD/PhD applicants for clinical research slots and have actually been the reason for loss of potential recruits.

Gottesman noted that one of the major post-retreat working groups will focus on clinical investigator training and recruiting.

—Fran Pollner

NIHers among Attendees at Talk Urging Research on Bioterror Countermeasures

Former Soviet Scientist Strikes a Responsive Chord

by Masashi Rotte

Ken Alibek, a world-renowned expert on defense against bioterrorism and former Soviet scientist, spoke at the Center for Advanced Research in Biotechnology in Rockville, Md., May 1. His talk was announced over the fellows' listserv at NIH two weeks earlier and attracted a contingent of individuals from NIH—and from some other governmental agencies, including FDA, DoD, and EPA. Academic institutions and commercial enterprises were also represented among the attendees. Alibek discussed domestic and international bioterrorism, weapons of mass destruction, and homeland defense.

Masashi Rotte

Ken Alibek

Some History

In 1969, President Richard Nixon, in a speech at Fort Detrick, ended this country's biological weapons program and pledged that the United States would never use biological weapons for any reason. (Laboratories housing bioweapons research at Fort Detrick were eventually converted to NCI labs; see "Build It and They Will Come: NCI-Frederick's Field of Dreams," *The NIH Catalyst*, July-August 1997, page 1; see **<http://www.nih.gov/catalyst/1997/97.07.01/page1.html>**.) The USSR, doubting the biological weapons pledge of the United States, continued research into offensive bioweapons, Alibek said.

After graduating from medical school in Kazakhstan in 1975, Alibek, then known as Kanatjan Alibekov, joined Biopreparat, the USSR's secret bioweapons development program. By 1983, he had become chief scientist and first deputy director of Biopreparat, where he supervised the production of an advanced smallpox weapon.

Alibek visited the United States in 1991 and began to have doubts about the legitimacy of his country's offensive bioweapons efforts. After the USSR broke up in 1991–1992, he defected to the United States and provided the CIA with information about the USSR's bioweapons programs. He is currently a distinguished professor of medical microbiology at George Mason University in Fairfax, Va., and executive director of the George Mason University Center for Biodefense.

Asked his opinion about future bioterrorist attacks, Alibek predicted that if they do occur, the most likely agent would again be anthrax—but on a much larger scale than several laced letters and with correspondingly greater psychological, economic, and health effects.

He observed that the anthrax episode—and more recently the SARS outbreaks—touched off fear and panic in the general population that, combined with necessary precautions, nearly shut down parts of society. In Washington, some government buildings were evacuated and remain closed even now; economic consequences linger. A larger-scale attack could have devastating effects, he said.

Alibek stressed that research to develop countermeasures to biological warfare is just as important as training first responders. He advised that the United States devise and test a national biodefense plan and improve its pharmaceutical stockpiles.

Reflections

Like most of the NIH attendees, Steve Tseng, of NCBI and a graduate student in bioinformatics at the Johns Hopkins University in Baltimore, said he was drawn to the talk by general scientific interest and the speaker's name.

Some others had a more direct connection to the subject matter of the talk.

Cindy Fuchs, a lawyer and technology development manager with NIAID, said she was interested in hearing Alibek's perspective on the bioterror threat, especially in light of NIAID's increasing portfolio in biodefense-related research.

Fred Dyda, an investigator in the Laboratory of Molecular Biology, NIDDK, has received a NIAID grant for biodefense research. Dyda's lab uses tools such as X-ray crystallography to study the molecular mechanisms of protein activity. The additional NIAID funding will be used to apply his research tools to *Yersinia pestis*, he said.

Kenneth Jacobson, chief of the Molecular Recognition Section of the Laboratory of Bioorganic Chemistry, NIDDK, noted that Alibek's talk was another in a series of talks sponsored by the Life Sciences Division of the Jewish Federation of Greater Washington that he regularly attends. But he was so struck by the gravity of Alibek's lecture, he said, that he might consider directing some of his work—which focuses on G-protein–coupled receptors—towards bioterrorism defense efforts. ■

Project BioShield

In his 2003 State of the Union address, President George W. Bush introduced the public to a White House initiative called Project BioShield aimed at expediting the development and stockpiling of drugs and vaccines to counter potential bioterror agents.

In a talk at NIH several weeks later, Bush specifically mentioned smallpox, anthrax, botulinum toxin, Ebola, and plague—all priority pathogens in NIAID's Strategic Plan for Biodefense Research—and cited NIH scientists as prime examples of Project BioShield foot soldiers.

His call for authorizing legislation was answered in the Senate's Project BioShield Act of 2003, which names NIAID the lead institute for carrying out the research and development of the necessary biological countermeasures. The bill was reported out of committee and awaits action by the full Senate.

In testimony April 4 before the House Government Reform Committee, NIAID Director Anthony Fauci supported Project BioShield for embracing a "new research paradigm" that provides expedited peer review of grants and contracts and streamlined procurement of needed material and human resources to "hasten the pathway from basic research concept to effective countermeasure."

He also applauded the provision of funds needed to assure industry of a market for antibioterror products in whose development they invest.

—*F.P.*

Introducing Raynard Kington

continued from page 1

deputy director, I think this type of job always changes depending on the skills, experience, and interests of whoever is filling it—that, and whoever is the NIH director, because he or she also shapes the role of the deputy director. My guess is that it's always been a somewhat fluid job. There are certain traditional aspects: The deputy director is like a 'director' for the OD—the day-to-day OD operations manager, the overseer of appointments to committees, that sort of thing, in some ways like like the chief operating officer of a corporation.

It's hard for me to say why I was selected. It probably helped that I had some managerial experience, but there's no school to teach you how to run an organization of this size. Nothing prepares you to help run NIH—and everything prepares you to help run NIH.

In a way, it's like being an intern again. I have a reasonable knowledge base to start from, but it's like going from medical school, where you're somewhat removed and buffered from decisions, into a place where suddenly you're making decisions, often by yourself, for a sick patient at 1:00 a.m. just a few weeks after you were a student. Suffice it to say, this is an intense period of learning—but exciting, too.

Q: What attracted you to the job?

KINGTON: The most influential factors were Dr. Zerhouni and the role of this institution in the scientific community and the nation. I was impressed by Dr. Zerhouni's vision for NIH scientifically and managerially, and I thought I would learn a lot from him.

I've always been interested in how science is managed. Most of the glory goes to the scientist—as it should—but the scientist does not work in a vacuum. I recently read a great article in the *Chronicle of Higher Education* by Stanley Fish, a creative thinker and a dean at the University of Illinois at Chicago. He writes about how faculty at universities often dislike administrators and then went on to make a compelling case for how complex and essential the administrator's job is. Echoing James I of England, who said "no bishops, no king," Fish wrote, "no administrators, no life of the mind," and I would say, "no administrators and no support, no science."

NIH is full of scientists who made the conscious decision to put the process first; they decided they could best contribute to science by helping to run the agencies that fund and guide science. I've always been interested in what goes on behind the closed doors that makes the glory of science possible, which is why during my training I also earned my MBA. I wanted to see how things work, how you get things done.

In terms of the challenge of getting things done and dealing with change, it's hard to pass up a job like this.

Q: What *is* your job? And what are your priorities?

KINGTON: I'm here to help Dr. Zerhouni implement his vision for NIH. My position is inherently collaborative; I work with the deputy and associate directors, with the IC directors, with Dr. Zerhouni, and with the various constituencies. In many ways, mine is a "glue" position.

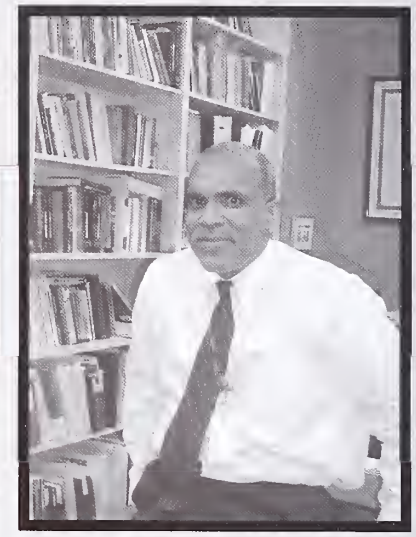
There are days I have scheduled back-to-back meetings from 7:00 a.m. to 6:00 p.m., with no time for lunch, no breathing space, which is new for me. And when there is some breathing space, there are usually countless ad hoc meetings throughout the day—hallway meetings—those informal quick exchanges of information that are so typical of scientific managers at most places this size.

Typically, my work combines forward-looking strategic development, responding to flares—or mini-crises of various sorts—and helping to guide those operational activities that keep NIH moving.

We often need to respond quickly and coherently to queries or concerns from the press, Congress, outside constituencies, or other parts of the Department. When that response requires the integration of information from our legislative, policy, and communications offices, as well as the scientists, and entails NIH responding as an institution, that's the kind of flare I'm likely to be involved in. We have a team-oriented approach. Response teams could involve all the associate and deputy directors—there are about 10 involved in this type of activity—and a subgroup of IC directors. Depending on the specific issue, the primary response could come from within a specific institute, with just OD oversight.

Q: What of some of the more intense issues of the day—the changing security alert levels, the need to address SARS (severe acute respiratory syndrome)?

KINGTON: Regarding security, yes, absolutely, I'm involved in the planning that's largely led by Chick Leasure [deputy director for management] and the people from the security office. Regarding SARS, I'm kept informed of developments but



Fran Pollner

Raynard Kington came to NIH from the Centers for Disease Control and Prevention in Atlanta, where he was director of the Division of Health Examination Statistics and led the landmark and ongoing NHANES study (National Health and Nutrition Examination Survey). Before that, he was a senior natural scientist at the Rand Corporation, co-director of the Drew/Rand Center for Health and Aging, and assistant professor of geriatric medicine at UCLA.

A former NIA grantee, Kington's research has focused on the relationship of socioeconomic status and health status, racial and ethnic differences in health status, factors affecting health-care utilization by the elderly, the economic impact of health-care expenditures on the elderly, and health behaviors of Hispanic and black immigrant populations.

Kington was recruited to NIH in October 2000 to succeed Norman Anderson, the first director of the Office of Behavioral and Social Sciences Research, begun in 1995. In February 2002, he was named acting director of NIAAA (in which position, he told the Catalyst, *he "got to see from the inside how the institutes work and all the countless decisions that go into being an institute director").*

Kington got his M.D. degree from the University of Michigan School of Medicine, Ann Arbor, and his M.B.A. and Ph.D .in health policy and economics at the Wharton School, University of Pennsylvania in Philadelphia. He is board certified in internal medicine and public health and preventive medicine.

have not been directly involved in activities. Dr. Zerhouni is, and Dr. Fauci [Anthony Fauci, NIAID director] has clearly played a leading role. This is a very content-specific issue that does not cut across NIH. Should it achieve a dimension that requires legislation or a broad communications strategy or have policy implications requiring coordination of multiple institutions and domains, then I might be more involved, along with the appropriate lead associate or deputy director.

Q: And the priorities?
KINGTON: Dr. Zerhouni has clearly identified priorities in a number of areas where NIH is changing, and I'm hoping I can have a positive impact.

For example, we're rethinking broadly how governance decisions are made here. Now we have lots of committees and informal structures, and we—the OD and the IC directors—are asking ourselves how we can do things better.

The roadmap process is also very much a priority [see "Roadblocks, Road Maps, and 'The Perfect Storm,'" *The NIH Catalyst*, January-February 2003, page 5; **http://www.nih.gov/catalyst/2003/03.01.01/page1.html#storm**]—and the managerial challenge of A-76 [competitive sourcing; see <**http://a-76.nih.gov/**>].

Q: Do you anticipate any changes in the way intramural science is managed—regarding selecting research projects or striving for particular goals? Do you anticipate less autonomy for the scientists here?
KINGTON: The intramural program is a unique national biomedical research resource, and it has a continuous, orderly process of review. There are specific ongoing efforts related to planning for specific parts of the intramural program—for instance, the recent daylong meeting on clinical research here [see "The Agony and the Ecstasy: Clinical Research at NIH," page 1] and how it's connected to the clinical research roadmap. Another area of the roadmap is multidisciplinary research, which is related to the intramural program but goes beyond it.

The important question is: Given the scientific opportunities we are now facing, are our scientific activities organized in a way that makes sense? Does the way we think about how research is done need to change, to become more diverse, to respond to interdisciplinary research opportunities? What are the right team structures for responding to the scientific challenges ahead of us? Those issues cut across both intramural and extramural activities.

Q: Is there a possibility that the NIH organizational IC structure might change?
KINGTON: I don't see large structural change here in the near future. And I would be surprised if the report being prepared by NAS [National Academy of Sciences] recommended the wholesale restructuring of the ICs.

I understand the concerns that generated the request by Congress for an NAS report, but this is not just about external views or pressures on NIH—the basic issue should also generate an internal NIH discussion. Any good organization knows that in order to stay good, you have to ask yourself constantly, are we doing things the right way for where we are now and for where we want to go? If you don't do that, you're dead in the water. That's the normal process at any good institution.

Whenever a new director comes in, there's always a rethinking. NIH is a huge, future-oriented institution, and change is inevitable—and still unsettling. But circumstances are constantly changing, especially in a scientific institution. I don't know of any scientific institutions that are static because what we know and what we know we don't know are constantly changing. Science is all about challenging the status quo.

Q: How does the economy play into these deliberations?
KINGTON: Our economy is in a very different place from where it was in recent years. We have a recession. Budgets are restricted—not just ours, but [those of] foundations and state and local governments as well.

Doing the work of government is more complicated and harder during a time of more limited resources. That's a big external driver—but in any case, irrespective of the state of the economy, we need to make sure we're the most efficient, productive agency we can be in terms of meeting our mission to advance science to promote the health of the American people.

My training is also in health economics, and a core tenet of economics is that there will always be unlimited wants and limited resources. That's just the nature of the human condition. Humans always have the ability to imagine a better existence. We could be in a booming economy, and we'd still have to make tradeoffs. We have to prioritize, to decide how we'll spend the resources we have to achieve our mission. It's harder when the resources to make those decisions are growing at a slower rate, but those decisions are always hard, in good and bad economic times—and you have to admit that thanks to the doubling [of the NIH budget over the last five years], we have a lot of resources. The worst thing would be to make those decisions by default.

Q: Do you have your own preferences regarding where research resources should be placed? In discussions, are you an advocate or more of a moderator?
KINGTON: As OBSSR director, I was an advocate for behaviorial and social sciences research, working to advance the incorporation of those disciplines into the ICs here—a "hearts and minds" kind of job. The research I've done, the disciplines I've been interested in, clearly influence how I think about science. But I cannot be that kind of advocate in this position. I have to be responsive to all 27 institutes and the thousands of diseases and disciplines they represent. But make no mistake about it, the scientific mission I see for NIH is broad.

Deciding where to place resources should be driven by an assessment of where the science is and where the needs are in terms of public health. We integrate our assessment of the scientific opportunities and the needs into our decisions—but always in the background is our knowledge of how science works, that humbling experience of seeing how advances in one area or in basic science not obviously tied to any specific disease end up providing an answer to an entirely different or unanticipated health problem. So we recognize our limited ability to predict the future. But we also know we have brains and can use them to make thoughtful decisions—knowing that there's got to be wiggle room, that this is an inexact process.

Q: Do you have any particular message for the NIH community?
KINGTON: I have great respect for the entire workforce here, and I want to get to know what specific challenges different employees face. I'm exploring doing a once-a-week brown-bag lunch to which five or six people from different parts of NIH would be invited each time. I think that might be a good way for me to become more informed and for individuals across NIH to discuss issues with me. ■

The Rites of Spring: Postbac Poster Day

by Nicole Kresge and Fran Pollner

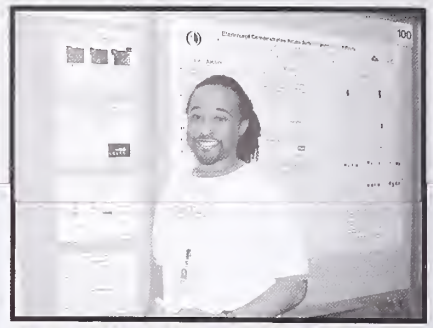
More than 150 postbaccalaureate trainees displayed and discoursed upon the nature and meaning of their NIH research at the fourth annual Postbac Poster Day, May 7.

Postbacs are recent college graduates with an aptitude for and inclination toward biomedical research who were selected to spend a year or two in training at NIH to find out if the life of a research scientist actually suits them. The great majority apply to (and are accepted into) a Ph.D. program and/or medical school during their stay at NIH.

Emilyn Alejandro, University of Washington, Seattle: *Granulin-Epithelial Precursor (GEP): A New Molecular Target in Ovarian Cancer.* Preceptor: Elise Kohn, NCI Laboratory of Pathology

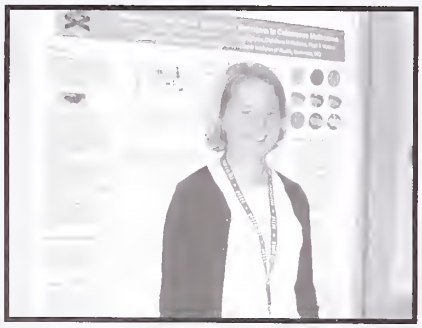
It was recently discovered that granulin-epithelin precursor (GEP) is upregulated in invasive ovarian cancer, a finding revealed via cDNA library comparison of microdissected ovarian tumors with low malignant potential and invasive ovarian tumors. Alejandro's research focused on learning about the regulation of GEP expression by characterizing its signaling pathways.

Alejandro found that GEP is expressed in the HEY-A8 ovarian tumor cell line. She also found that lysophosphatidic acid, an ovarian cancer growth factor, stimulates GEP production in HEY-A8 cells in a dose- and time-dependent manner. In the future, she hopes to determine the biological function of GEP and to transform GEP as a molecular target for the treatment of epithelial ovarian cancer. *—N.K.*



Brent Elliott, George Mason University, Fairfax, Va.: *Gamma Secretase: The Role of Nicastrin and Presenilin.* Preceptors: Alan Kimmel and Lisa Kreppel, NIDDK Laboratory of Cellular and Developmental Biology

Nicastrin (NCT) and presenilin (PS) are two components of the enzymatic complex γ-secretase, which processes β-amyloid precursor protein and others. Defects in γ-secretase are linked to Alzheimer's disease. To investigate the biological role of γ-secretase, Elliot and his coworkers knocked out NCT and PS in the slime mold Dictyostelium. The resulting mutants experienced delays in development, suggesting that γ-secretase plays a developmental role. In the future, the laboratory hopes to knock out the other known components of γ-secretase—PEN-2 and APH-1—make rescue vectors and GFP fusion proteins, and determine whether there are other unknown components of γ-secretase. *—N.K.*



Laura Yudt, Gustavus Adolphus College, St. Peter, Minn.: *Mutations in a Growth Factor Receptor Tyrosine Kinase in Cutaneous Melanoma.* Preceptor: Paul Meltzer, NHGRI Cancer Genetics Branch

The ligand to a growth factor receptor tyrosine kinase is highly overexpressed in melanoma cell lines compared with normal melanocytes, leading to the speculation that a mutation in the receptor increases its affinity for the ligand, with accompanying effects on such cell functions as cell division and angiogenesis, Yudt said.

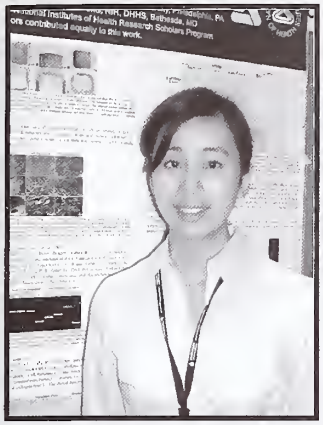
She and her colleagues found mutations in 5 of 47 melanoma cell lines—"not a phenomenal percentage, but the mutations occur in highly conserved residues," she said. The next step is to explore at the protein level the mutations' effect on function. Constitutive action through phosphorylation, Yudt noted, would be a key finding. *—F.P.*

Erica Westly, Marlboro College, Marlboro, Vt.: *Linkage-based Study of GABA Receptor Gene Clusters at Chromosome 4 and Alcoholism in Two Populations.* Preceptors: David Goldman and Ke Xu, NIAAA Laboratory of Neurogenetics

Whole genome linkage scans have implicated the chromosome 4 cluster of GABA receptor genes in vulnerability to alcoholism, so now these investigators are using the multilocus haplotype linkage approach to close in on the location of the effective locus.

The NIAAA team looked for linkage disequilibrium among 27 polymorphisms from chromosome 4, comparing findings in more than 1,200 probands, family members, and controls in two populations, one Finnish and the other Southwest American Indian. The team was blind to the phenotypic diagnosis. "We're still analyzing the data," Westly said.

Determination of whether particular linkages are functional or not will fall to another research team, "who will look at the molecular biology of the proteins for correlations with alcoholism," Westly said. *—F.P.*



Xiaoxue Huang, University of Maryland, Baltimore: *A Tissue Engineered Osteochondral Construct Based on Human Mesenchymal Stem Cells: Potential Application for Articular Cartilage Repair.* Preceptors: Rocky Tuan, David Hall, and Richard Tuli, NIAMS Cartilage Biology Branch

A tissue-engineered osteochondral plug constructed using autologous mesenchymal stem cells displayed tissue morphology similar to that of native cartilage and subchondral bone in a study that could eventually have dramatic implications for the treatment of diseases such as osteoarthritis, which affects more than 90 percent of the population over 40.

Mesenchymal stem cells derived from human trabecular bone and grown in culture can differentiate into cartilage, bone, and fat cells, Huang said. Using a patient's own mesenchymal stem cells minimizes the risk of immunologic rejection and infectious disease transmission. Such a cartilage-and-bone construct may eventually serve as a therapeutic substitute for total knee and hip replacement surgery. Once the laboratory model is optimized, the research will move toward the clinical arena. *—F.P.*

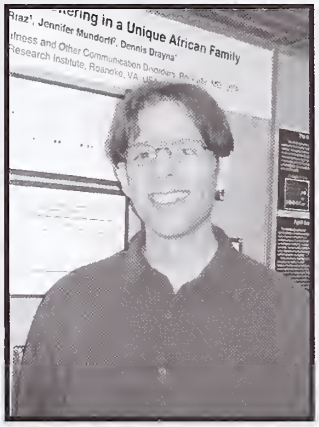
Bone marrow stem cells (BMSCs) can potentially offer a renewable, easily accessible, noncontroversial source of pluripotent stem cells.

It is hoped that transplanted BMSCs will integrate and function as normal differentiated cells in the treatment of neurodegenerative disorders.

Hsu's research centers on manipulating the in vitro environment to encourage neuronal differentiation and integration. He attempted to co-culture rat hippocampal neurons with rat BMSCs and found that astrocytes, but not neurons, grew among the BMSCs. He also cultured mouse BMSCs and treated them with basic fibroblast growth factor. Immunostaining demonstrated that neuron-specific proteins were present inside the cells.

Antony Hsu, New York University School of Medicine, New York City: *Bone Marrow Stem Cells.* Preceptors: Ronald McKay and Florian Then Bergh, NINDS Laboratory of Molecular Biology

Hsu plans to obtain functional data from the differentiated mouse cells to prove they are indeed neurons. *—N.K.*



Bailey Levis, St. Mary's College of California, Moraga, Calif.: *Genetic Studies of Stuttering in a Unique African Family.* Preceptor: Dennis Drayna, NIDCD Laboratory of Molecular Genetics

There are more than three million Americans who stutter, a speech disorder for which there are no cures today. Drugs, speech therapy, and medical devices aimed at reducing stuttering are not always successful.

Levis, a mild stutterer himself, is interested in finding the genetic causes of stuttering, which are known to exist. He and his colleagues analyzed both the speech and DNA samples collected from a 100-member African family, 45 of whom stutter. He is using PCR and gel electrophoresis to genotype the family members. Once the genotyping is completed, he will use computer programs to determine regions of the genome showing a linkage to stuttering.

Finally, homing in on the responsible gene(s) could shed light on the causes of and best approaches to curing this enigmatic disorder, Levis said. *—N.K.*

Anna K. Donovan, Grinnell College, Grinnell, Iowa: *Proteins Interacting with Lens MIP (Major Intrinsic Protein)/ Aquaporin 0.* Preceptor: Ana B. Chepelinsky, NEI Laboratory of Molecular and Developmental Biology

The aim of this research was to elucidate the function of MIP, a protein found in the lens fiber cell membranes that plays a role in ocular lens transparency and, when mutated, is associated with genetic cataracts. A yeast two-hybrid screening and confirmatory assays established that MIP interacts within the lens with the γE-crystallin protein and could therefore be involved in lens structure organization, Donovan said. She characterized the study as a basic research project that will provide insights into the mechanisms of genetic cataracts. *—F.P.*

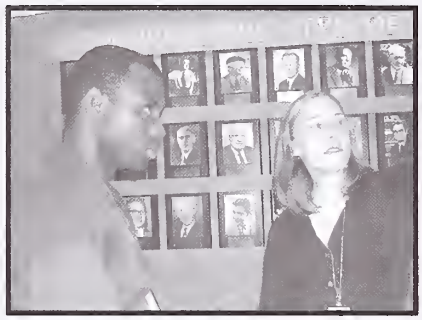
More Postbac Posters

Seitz and her colleagues are using saliva from sand flies to design and synthesize a DNA vaccine for Leishmania. Sand flies often carry the Leishmania parasite, and their saliva exacerbates infection. However, in humans, exposure to sand fly saliva has been found to correlate with increased resistance to the parasite.

Seitz determined the protein content of salivary gland homogenate from sand flies and expressed some of the proteins in the T7NT vector. She then confirmed that mice exposed to salivary homogenate contained antibodies to the proteins.

Next, Seitz hopes not only to use the DNA from these proteins to make a vaccine, but also to analyze salivary homogenates from other species of sand fly.

—*N.K.*



Amy Seitz, University of Maryland, Baltimore: *Sand Fly Saliva as a Leishmaniasis Vaccine?* Preceptor: Jesus Valenzuela, NIAID Laboratory of Malaria and Vector Research (Also shown is postbac Collins Karikari, Morgan State University, Baltimore, Md., a labmate who presented his own poster on *Developmental Regulation of Necrotic-like Serpin in Human Malaria Vector,* Anopheles gambiae. Karikari's preceptors are Mohammed Shahabuddin and Xinzhuan Su)

Joseph Nezgoda, Georgetown University, Washington, D.C.: *Experimental Analgesic Actions of Vanilloid Agonists.* Preceptor: Mike Iadarola, NIDCR Pain and Neurosensory Mechanisms Branch

Nezgoda and his colleagues are trying to make a neuron-killing pain reliever for people experiencing great discomfort, such as end-stage cancer patients. A species of Moroccan cactus contains a compound called RTX, which binds to the vanilloid pain receptor known as VRI. When administered in high enough amounts, RTX can selectively kill these pain-signaling neurons.

Nezgoda injected a single dose of RTX into the spinal cords of rats and tested their pain responses over the next 18 weeks. He found that low doses of RTX affected only the hind paws, indicating a localized effect. Surprisingly, high doses of RTX numbed sensation in the hind paws, front paws, and corneas, indicating a general analgesic effect. At all dose levels, there was no apparent toxic effect on the rats.

To complete his analysis, Nezgoda plans on doing a histological analysis of the animals to confirm nerve cell death. He hopes that RTX will eventually be tested in clinical trials. —*N.K.*

Juliessa Pavon, Duke University, Durham, N.C.: *The Development of Functional Limitations in Elderly Short- and Long-Term Cancer Survivors.* Preceptors: Tamara Harris and Lisa Colbert, NIA Laboratory of Epidemiology, Demography, and Biometry

Given that you survive cancer and come through in good health, does having cancer influence risk for developing a functional limitation? One of the first longitudinal studies to examine this question and look at the risk of functional disability in elderly cancer survivors has amassed results that suggest that being a cancer survivor—at least in the short term of under five years—confers an advantage not evident in elderly people who have not had cancer.

Short-term cancer survivors, aged 70 to 79, were at less risk of developing functional limitation than similarly aged controls who had not had cancer. Functional limitation was defined as difficulty walking a quarter-mile or climbing ten steps. Among cancer survivors of greater than five years, however, men were at greater risk than their noncancer counterparts, and there were no differences among the women.

The study was part of the Health, Aging, and Body Composition Study, which was begun in 1997 and is ongoing. More research is needed, Pavon said, to understand the mediating effects within those first five years and to correlate stage of cancer at diagnosis as well as treatment with long-term developments. —*F.P.*

Recently Tenured

Andrew Blauvelt *received his medical degree from Michigan State University, East Lansing, in 1988 and completed his dermatology residency training at the University of Miami, Coral Gables, Fla., in 1992. He then began his research career as an NIH fellow, working first with Stephen Katz at NCI on Langerhans cell–HIV studies and later with Kuan-Teh Jeang at NIAID performing Kaposi's sarcoma–associated herpesvirus research. He is currently a senior investigator in the Dermatology Branch, NCI.*

Scientific work in my laboratory has focused on defining interactions between HIV, herpesviruses, and skin.

Fran Pollner

Andrew Blauvelt

Specifically, my laboratory has contributed to two major research areas: 1) examining the role of Langerhans cells and other types of dendritic cells in the pathogenesis of HIV and 2) studying the role of Kaposi's sarcoma–associated herpesvirus (KSHV) in the pathogenesis of Kaposi's sarcoma.

In the first area, my lab has been involved in the delineation of the cellular and molecular events that occur when Langerhans cells encounter HIV. Langerhans cells are specialized types of dendritic cells (professional antigen-presenting cells) that are located within the skin and genital mucosal epithelial surfaces, where they serve as sentinels for the immune system.

After encountering complex antigens, Langerhans cells emigrate from epithelial tissues to draining lymph nodes, where they present processed antigenic peptides to T cells.

Most of my HIV research has been driven by the hypothesis that Langerhans cells also serve as initial "targets" for HIV after sexual exposure to virus.

Specifically, we have described HIV co-receptor expression, function, and regulation on Langerhans cells; assessed, in detail, HIV infection versus virion "capture" pathways in Langerhans cells and other dendritic cells; and identified genotypes that predispose to (or protect from) Langerhans cell infection.

An interesting new direction is my recent involvement in translating this basic knowledge into the development of microbicides, which are topical agents designed to block sexual transmission of HIV.

The most promising drug we have studied in this regard is a chemical analog of the chemokine RANTES, a drug that binds to the HIV co-receptor CCR5 on the surface of Langerhans cells and blocks subsequent infection of HIV.

I hope that my research findings on the biology of sexual transmission of HIV will some day prove to be important in decreasing the number of HIV transmissions that occur daily throughout the world.

In a second area of research interest, my lab has contributed to the understanding of how KSHV leads to the development of Kaposi's sarcoma, the most common cancer found in AIDS patients. KSHV was discovered in 1994 as the long-sought etiologic agent of Kaposi's sarcoma.

Our early work in this area involved the identification of clinically relevant drugs and biologic conditions that either blocked or induced KSHV reactivation within latently infected cells.

For example, we showed that KSHV was sensitive to cidofovir and ganciclovir, yet relatively insensitive to acyclovir and its derivatives. Our prediction, although not yet realized, was that this information could ultimately be translated into clinically meaningful treatment advances for patients with Kaposi's sarcoma.

With this same goal in mind, we have recently turned our attention to analyzing specific KSHV viral proteins that we believe are critically involved in the maintenance of Kaposi's sarcoma tumors. We have successfully created novel transgenic mice that express two of these viral proteins—LANA and k-cyclin—in vivo.

My hope is that we can improve these mouse models of Kaposi's sarcoma even further and that they will allow us to preclinically test agents that interfere with LANA and/or k-cyclin expression and function.

Identifying LANA and k-cyclin as novel molecular targets for Kaposi's sarcoma may eventually help patients with this disease and may also serve as a paradigm for targeting key viral proteins that are involved in the formation of other virus-induced cancers.

Allen R. Braun *received his M.D. in 1980 from Rush Medical College in Chicago, where he also completed a residency in neurology. His postdoctoral training was at the NIH Clinical Center in the Experimental Therapeutics Branch of NINDS and in the Department of Nuclear Medicine, where he completed an additional residency with an emphasis on PET imaging. He joined NIDCD in 1991 and is currently acting chief of the Language Section, Voice, Speech and Language Branch.*

Our lab uses a variety of neuroimaging methods—functional and structural MRI, PET, electro- and magnetoencephalography—to study auditory processing, voice, speech, and language in the human brain. Each of these methods provides qualitatively different information. Our multimodal approach thus yields complementary and converging evidence that we use to pinpoint normal brain-language relationships and the ways in which these relationships are altered in neurological disorders that affect the ability to communicate.

We investigate the use of complex natural language, that is, language as it is used in everyday communication, rather than performance on highly structured artificial tasks commonly utilized in neuroimaging research. Thus, we study both comprehension and production—in the real world these are essentially inseparable. We look at language at multiple levels: We study receptive language from basic auditory and visual perception up to the level of discourse comprehension; we study production from the level of language formulation to overt articulation.

By studying language in this more natural context, we have been able to show that there are emergent features—activation of a host of regions outside what is traditionally considered "language" cortex—that are seen during the processing of narrative discourse. This activity is not apparent during simple processing of isolated sentences or words, typically investigated in neuroimaging studies of language. Our approach also permitted us to demonstrate dynamic fluctuations in brain activity during discourse processing and to locate brain systems that are responsible for making inferences when subjects read a complex narrative text.

Beyond this, we've gone on to com-

Recently Tenured

pare the *production* of narrative in English and American Sign Language in bilingual subjects and have found that there is a core, unitary network for the production of language that is independent of the modality in which the language is expressed. Studies of overt speech production in monolinguals have capitalized on the complementary features of fMRI and EEG: fMRI shows us where in the brain lexical access or semantic decisions occur, and EEG shows us how information flows between these regions over time.

Fran Pollner

Allen Braun

We are evaluating the use of gesture in conversational discourse and the ways in which the brain processes music—how we perceive and produce both melody and rhythm. We recently identified unique, lateralized differences in brain activity during singing (vs. speaking), an issue that may seem arcane but actually may be clinically important: Such mechanisms may enable fluent speech production in developmental stuttering and in certain types of aphasia.

Indeed, many of our approaches have been developed in control subjects with the idea of translating these into clinical studies of neurological illnesses affecting speech, voice, and language—in order to characterize the pathophysiology of these disorrders and to monitor the effects of treatment.

Examples of our translational work include investigation of ways in which dysfunction in the basal ganglia—likely mediated by dopaminergic mechanisms—affects speech and language. We have demonstrated abnormal patterns of activity in developmental stuttering that implicate the basal ganglia and their projections. We also characterized cerebral responses to dopamine agonists and deep brain stimulation during speech and language production in Parkinson's disease. We described functional abnormalities in basal ganglia circuitry in Tourette's syndrome and demonstrated clinically significant responses to botulinum toxin treatment in spasmodic dysphonia. We are currently using neurochemical PET methods to characterize pre- and postsynaptic dopamine mechanisms, which we hypothesize may play a central role in the pathophysiology of stuttering.

Functional neuroimaging can also be a powerful counterpart in the genetic investigation of communication disorders: In collaboration with NIDCD's Dennis Drayna, our lab is investigating a heritable disorder of musical pitch perception. For those studies we are using electrophysiological and MRI methods to provide phenotypic markers for linkage studies. We hope ultimately to clarify the role a defective gene product may play within the CNS.

Our lab is increasingly interested in neuroplasticity—the capacity of the brain to adapt and reorganize in response to experience, trauma, or stress. One way we are pursuing this is through longitudinal PET studies of central auditory processing by deaf people who have received cochlear implants. Initially, following activation of the implant, most recipients cannot understand the auditory input they receive. Over months to years, however, their auditory understanding improves to a remarkable degree, although signals from the implant do not change. These individuals may thus provide a unique chance to study neural reorganization in response to sensory input.

Over the next several years, we also plan to use neuroimaging and neurobehavioral and pharmacological methods to study the natural history of language recovery in stroke patients with aphasia. In this work, we will follow patients with different degrees of language loss and recovery and monitor their progress over time. We will look for correspondences between linguistic performance and the neural processes that are visible with our imaging techniques—such as cortical map expansion or changes in neurochemical or electrophysiological function. Such correspondences could point to ways in which recovery of function may be facilitated by behavioral and pharmacological intervention.

The concept of use-dependent plasticity—recovery of function after training and repeated experience—is now well established. Recent studies have shown that some degree of motor recovery—likely mediated by synaptic plasticity or structural reorganization—can occur in stroke patients, even years after brain damage has occurred. We hypothesize that there will be similar, significant responses in aphasics who receive intensive training aimed at correcting specific psycholinguistic deficits.

If we can demonstrate this, we intend to conduct clinical trials of drugs that, by modulating signal transduction mechanisms, may facilitate use-dependent neuroplastic effects—by amplifying late-phase long-term-potential–like responses, stimulating neurotrophin transcription and synthesis, or enhancing the reorganization of axonal or dendritic architecture. In each case, we will use our armamentarium of imaging tools to evaluate outcome.

Carter Van Waes *received his Ph.D. in tumor immunology in 1985 and his M.D. degree in 1987 under the NIH Medical Scientist Training Program at the University of Chicago. He completed a cancer research fellowship and residency in otolaryngology–head and neck surgery at the University of Michigan, Ann Arbor, between 1988 and 1993. He developed the Tumor Biology Section in the Head and Neck Surgery Branch, NIDCD, where he is now a senior investigator and acting clinical director.*

In the process of trying to understand the molecular basis for immune recognition, inflammation, and angiogenesis in human and murine squamous cell carcinomas (SCC), my colleagues and I detected a diverse repertoire of cell recognition and cytokine molecules that are usually expressed in response to injury. I noted that the promoters of the genes encoding many of these molecules contain sites for activation by an injury-response transcription factor, nuclear factor–kappa B (NF-κB), originally identified in the laboratory of David Baltimore. I hypothesized that NF-κB may contribute to regulation of gene programs that contribute to the malignant phenotype, including proliferation, cell survival, tumorigenesis, angiogenesis, and inflammation.

My lab demonstrated that NF-κB is constitutively activated and that multiple genes related to the NF-κB pathway are expressed at increased levels with metastatic tumor progression (*Cancer Res.*, **59**:3495–3504, 1999; *Mol. Carcinog.*, **26**:119–129, 1999; *Cancer Res.*, **61**:4797–4808, 2001).

Inactivation by dominant negative mutants of inhibitor-κB or pharmacologic inhibitors of proteasome-mediated

activation blocked proliferation and cell survival in vitro, and angiogenesis and tumorigenesis in syngeneic murine and human xenograft models (*Cancer Res.*, **59**:3468–3474, 1999; *Clin. Cancer Res.*, **7**:1419–1428, 2001).

Recently, my lab has used microarray profiling to confirm an important role of NF-κB in the cumulative changes in gene expression with progression of SCC, and after switching off NF-κB by an inhibitor-κB mutant.

Fran Pollner

Carter Van Waes

Remarkably, inhibition of NF-κB restored the expression of more than 60 percent of the 308 genes differentially expressed in metastatic murine SCC cells compared with expression in normal keratinocytes.

Most of the NF-κB–upregulated genes contained NF-κB promoter sequences, and most of the downregulated genes contained homologous 7-nucleotide motifs involved in the NF-κB–dependent downregulation of mRNA. Inhibition of NF-κB corrected expression of representative mRNAs and proteins, and inhibited malignant phenotypic features, including cell survival, proliferation, migration, and angiogenesis. These results indicate that NF-κB is an important molecular switch for the gene expression program and malignant phenotype in SCC.

Inhibition of NF-κB also sensitized squamous carcinomas to radiation, one of the important therapies for patients with head and neck cancers.

In collaboration with colleagues in NCI medical and radiation oncology, I am engaged in a phase I clinical trial of concurrent therapy with a proteasome inhibitor and radiation in patients with inoperable SCC of the head and neck.

My lab is examining the ability of the drug to inhibit proteasome and NF-κB activation in tumor, and NF-κB–regulated cytokine levels in serum as a marker of response and recurrence.

There are several important questions raised by these observations:

- What molecular events affecting known or unknown oncogenes and tumor suppressor genes can result in activation of NF-κB as an important common pathway to the malignant phenotype?
- Are most of the genes apparently regulated by NF-κB regulated directly—or indirectly via activation of other transcriptional programs?
- Which target genes are responsible for the key changes in proliferation, survival, angiogenesis, and inflammation?
- Is NF-κB one of several pathways co-activated in SCC that cooperate in activation of different repertoires of genes that together determine the differences in malignant behavior and resistance to therapy?

I hope that studies directed at these questions will help us develop improved methods for molecular diagnosis, treatment selection, and molecularly targeted therapy of SCC and other cancers. ■

Salutaris Noons-in-June

This year the NIH Salutaris Employee Group will celebrate Gay Pride Month by sponsoring two lunchtime programs focusing on health disparities within the gay/lesbian/bisexual/transgender (GLBT) community:

■ **June 20, 2003**: C. Earl Fox, former administrator of HRSA, will discuss GLBT health disparity initiatives and the federal government, 11:30 a.m.–1:00 p.m., Building 40, Conference Room 1201.

■ **June 23, 2003**: Katherine O'Hanlan, a gynecologic oncologist from California, will address how civil rights affect GLBT health disparities, 11:30 a.m.–1:00 p.m., Building 40, Conference Room 1201.

Sign language interpretation will be provided. For reasonable accommodation, please contact Shannon Bell at 301-594-3767. ■

Director's Town Meeting

The Town Hall meeting with NIH Director Elias Zerhouni has been rescheduled for Wednesday **June 18** from 1:00–2:00 p.m. in the Natcher auditorium.

Questions or concerns you'd like discussed should be submitted online by noon, **June 11:**

<http://townhallmeeting.nih.gov/feedback.taf>.

Questions previously submitted need not be resubmitted.

The meeting will also be videocast: **<http://videocast.nih.gov>**.

For more info, contact Carol Jabir in the Special Projects Branch of the Office of Communications and Public Liaison, 496-1776. ■

Catalyst Items of Great Interest

Interest Group Directory: The July-August issue of *The NIH Catalyst* will, as is traditional, include a complete directory of NIH Special Interest Groups—complete, that is, if all interest-group contact persons verify their group's listing for correct meeting time and place and contact person(s). Within the next few weeks, the *Catalyst* will e-mail the contact people for all of last year's 89 listed groups asking for verification that the previous listing is still valid or for a corrected update. The deadline for responding is **June 25**. If you are a contact person for a **new** interest group, please let the *Catalyst* know the group exists. ■

Online Catalyst and Listserv: The *Catalyst* is available online at **<http://www.nih.gov/catalyst>**, and there is now a listserv address for those of you who would like to know the moment each issue has been launched in cyberspace. To subscribe, send an e-mail message to this address: **<Listserv@list.nih.gov>**. The body of your message should say: Subscribe catalyst-l Your Name. ■

Call for 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...

- Nora Volkow: New NIDA Director
- Biomedical Engineering Startup
- Interest Group Directory

A Scientist's Dozen

Howard Young

1. Choose a job you love, and you will never have to work a day in your life.
2. Never burn your bridges, especially if you pursue science as a career.
3. You can go anywhere you want if you look serious and carry a rack of microfuge tubes.
4. Take your work seriously, but not yourself.
5. The last person who left the lab will be the one held responsible for everything that goes wrong.
6. Your background and circumstances may have influenced what you are, but you are responsible for what you become.
7. Only work with people who like chocolate.
8. If you keep your standards high, people will always find a place for you.
9. When the lottery hits $100 million, get everyone in the lab to put in a dollar apiece (and only a dollar) and buy a pool of chances. You will have a million dreams.
10. A pat on the back is only a few centimeters from a kick in the pants.
11. Treat the administrators and administrative assistants whom you deal with well, for if you take care of them, they will take care of you.
12. Everything in moderation except love, understanding, and the number of experiments you do for your supervisor.

—Howard Young's parting points—culled and adapted, he says, from a variety of sources—delivered at a May reception to outgoing and incoming high school students at the NCI–Frederick Cancer Research Center student intern program (see The NIH Catalyst, *July 1997). Young, a senior investigator in the Laboratory of Experimental Immunology who has overseen the student program since its inception 14 years ago, says he's handing the program over to a "younger scientist"—Warren Johnson, in the Laboratory of Genomic Diversity—with whom the teenagers may feel more comfortable. Young just started a mini-sabbatical in France, where he will learn the latest mass-spec technology and study the effects of oral interferon on the innate immune system. He'll be back in the fall. Asked to provide the* Catalyst *with a photo to replace the small blurry one we had available, Young said the only thing better than a small blurry photo would be no photo at all.*

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>

Publisher
Michael Gottesman
Deputy Director
for Intramural Research, OD

Editors
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Director, Warren Grant Magnuson Clinical Center, and Associate Director for Clinical Research

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