FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 15, ISSUE 3 ■ MAY–JUNE 2007

How to Get the Real Story

NIH Holds Boot Camp For Health Reporters

by Stephanie Cooperstein

—Dog bites man; man bites back. Rabies is on the decline. Film at 11.

Huh?

In an effort to generate consistently accurate scientific news coverage in the mass media, NIH for the past six years has been hosting an annual boot camp for print and television health journalists.

Barry Kramer, OMAR director and course host

This three-day tutorial, held this year April 12–14, is aimed at arming reporters with the tools to understand and convey accurately the meaning of health-research findings; it's also designed to alert them to potential sources of distortion.

The workshop—"Medicine in the Media: The Challenge of Reporting on Medical Research"—is sponsored by the NIH Office of Medical Applications of Research (OMAR) and the NIH Office of Communications, in partnership with the VA Outcomes Group (White River Junction, Vermont, Department of Veterans Affairs) and the Center for the Evaluative Clinical Sciences of Dartmouth Medical School, Hanover, N.H.

"Oversimplification of scientific data has proved troubling in some press accounts," said Barry Kramer, OMAR director and host of the gathering. "But I have seen clear changes for the better among graduates of our program," for instance, he said, regarding the issue of cancer screening.

"Our graduates no longer confuse

continued on page 8

dbGaP, ClinicalTrials.gov, CellMiner, et al.

Software Heroes: NIH Homegrown Treasuries Enriching Scientists the World Over

by Christopher Wanjek

Every day more than two million users of the National Library of Medicine website download over 3.5 terabytes of data. That adds up to an entire Library of Congress' worth of information delivered every three days.

The website gets over 3,200 hits a second, and none of it for vapid gossip, unless one considers yeast cell division akin to the latest Hollywood scandal.

Draw up a list of top NIH intramural achievements—vaccine and chemotherapy development, PET imaging, early HIV work—and there's a good chance you might forget to add software and database development. Yet this is the backbone of much of the basic biomedical research that flows from NIH.

No one likely will win a Nobel Prize for developing such tools, but the next Nobel Prize in Physiology or Medicine will surely have relied on this homegrown innovation.

Some Heavy Hitters

PubMed is perhaps the most famous of NLM's databases, with more than 17 million citations from more than 19,000 life-science journals dating back to 1950.

The National Center for Biotechnology Information (NCBI) is the arm of the NLM tasked with managing the PubMed retrieval system and the increasing volume and complexity of raw scientific data. The gene repository GenBank and the BLAST gene-search tool are two other NCBI gems that have enabled the genomic revolution.

The NLM's Lister Hill National Center for Biomedical Communications maintains the largest trial registry—ClinicalTrials.gov—with 36,249 studies from nearly 140 countries. As highlighted in the May 16, 2007, issue of *JAMA*, ClinicalTrials.gov can serve as a standardization tool to ease the widespread problem of incomplete or delayed reporting of clinical trial results.

Over at NCI, a smaller enterprise, the Genomic and Bioinformatics Group, has developed its own set of software, the Miner Suite, with its focus on cancer research yet tied into NCBI's vast web of databases.

The NCI Cancer Genetic Markers of Susceptibility (CGEMS) project has developed the data architecture and analytical pipeline to conduct genome-wide association studies GWAS), which can typically include more than 1.5 billion data points. Currently, several GWAS have incorporated components of the data analysis pipeline. CGEMS studies in breast and prostate cancer have appeared in two recent publications in *Nature Genetics*.

In the coming months, NCBI and NCI plan not only to make these resources richer and more integrated but also to

continued on page 6

CONTENTS

Budget Blues

Michael Gottesman

The recent article in *Science* (**316**: 968, 2007) focusing on budget difficulties in the intramural program at NICHD underscores what intramural staff have known now for several years: that significant belt-tightening is necessary for intramural NIH to get through this period of flat budgets accompanied by inflation—and the resulting decrease in our buying power.

The intramural budget for 2007 has increased by 4.2 percent since 2004, from $2.66 billion to $2.77 billion, which includes a significant investment in biodefense. But when corrected for the biomedical inflator, this increase actually translates to a 7.5 percent decrease in buying power (the extramural NIH budget has felt the same pinch at a time of increasing grant applications, bringing pay lines for extramural grantees to historic lows).

In general, the budget taps that support NIH infrastructure have not increased at a rate greater than the average increase in the NIH intramural budget over the past three years. In other words, these taps have stayed at about the same percent of the NIH budget as they were three years ago—with three exceptions.

- The Clinical Center budget has actually declined as a percent of the total (this number may somewhat underestimate the effect on the intramural budget since some of the charges previously incorporated into the Clinical Center budget, such as laundry and housekeeping services, are now being paid directly by the Institutes and Centers).
- Increases in the budget of the Office of Research Facilities have been driven primarily by record utility-rate increases and the overall increase in IRP square footage; examples are the Porter Neuroscience Research Center, the Clinical Research Center, and the C.W. Bill Young Center for Biodefense and Emerging Infectious Diseases (Building 33).
- The budget of the Office of Research Services also has a slightly higher share related to increased security costs at NIH in the past three years. Overall, however, the ORS has had to identify $21 million in cost savings to cover inflationary increases during that time period.

Although most intramural investigators have felt the sting of this budget pinch, several steps have been taken by the scientific directors (SDs) to soften the blow for our most outstanding investigators.

A major step has been a reduction in scientific programs with 58 fewer principal investigators (PIs) at NIH than three years ago (a 5 percent decrease). During this period 108 PIs were hired (both tenured and tenure-track), indicating that a total of 166 PIs lost this status during this three-year period, but recruits continued to arrive to bring us to the current figure of 1194 PIs.

One trans-NIH approach to deal with our budget woes is to make the existing dollars go further, our dollar-stretching activities.

Committees dealing with procurement, travel, animal use, personnel, telecommunications, and space have made recommendations on ways to save money that are currently being implemented. More information about these dollar-stretching activities will be forthcoming.

Budget reductions are difficult for existing programs with large fixed personnel costs that have risen as a percentage of lab budgets over the past three years, and many intramural programs have seen significant reductions in their discretionary budgets (those parts of the budget for equipment, supplies and services).

The SDs have tried to avoid across-the-board budget cuts wherever possible, preserving funds for tenure-track investigators, new recruits, and especially exciting new science. This policy becomes more and more difficult to follow, however, as flat budgets and declining purchasing power persist. The result in some cases may be general budget cuts.

Ultimately, additional program cuts will be necessary, and the SDs will depend on the wise advice of our Boards of Scientific Counselors to make the right ones.

Intramural NIH has been through this kind of budget constriction in the past and has remained a vital, creative research facility.

—Michael Gottesman
Deputy Director for Intramural Research

Minding NIH Business

On June 4, NIH entered "wave 2" of the switch from the ADB to the NIH Business System (NBS). The first wave, involving buying from the NIH warehouse, was admittedly a little choppy, but most problems have been resolved.

The Office of Acquisition Management and Policy is hoping for a smoother transition for wave 2, which involves property, small purchases, contracts and p-cards. The ICs and NBS advocates have made extraordinary efforts to prepare for the switch, but a temporary productivity dip is to be expected. Tasks that once took a few minutes with the ADB, which has been in place for more than 20 years, might take an hour in the NBS until people become familiar with the new functionality. Patience is key, and every IC has an NBS advocate as well as NBS users to help out.

If you are an NBS user, you should log into the NBS "sandbox" and practice. The NBS is a point-and-click system with pull-down menus and, unlike the ADB, information must be entered correctly upfront. More information about the switch will be posted on the DDIR web board at **<http://www.nih.gov/ddir/>http://www.nih.gov/ddir/>**.

ORWH Welcomes First Two Awardees of the Women's Health Fellowship

The first two recipients of the NIH Women's Health Fellowship—a cornerstone of the Intramural Program on Research on Women's Health (IPRWH)—have taken up residence in their respective locations at NHGRI and NIEHS.

Developed through an OIR-ORWH collaboration, the three-year fellowships were funded through the Foundation for the NIH (FNIH) with donations from the Battelle Memorial Institute and AstraZeneca, the former in support of the Shared Postdoctoral Fellowship and the latter in support of the Clinical/Translational Fellowship.

Catalyst file photo

Vivian Pinn

Suzanne O'Neill, recipient of the postdoctoral fellowship, obtained her doctorate in clinical psychology from the University of Delaware in Newark, did a clinical internship in behavioral medicine at the Medical University of South Carolina in Charleston, and did postdoctoral work at the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill before joining NHGRI's Social and Behavioral Research Branch. Shannon Laughlin, awarded the clinical/translational fellowship, completed her final year of residency in obstetrics and gynecology at Loyola University in Chicago before joining the NIEHS Epidemiology Branch.

"Recruiting women into research positions and advancing their careers are important aspects of the ORWH mission, and promoting basic and clinical studies relevant to women's health, as well as studies involving sex and gender factors, are priorities for us," observed Vivian Pinn, ORWH director and associate director for research on women's health.

"We're excited to be able to offer the first formal opportunities for scientists to pursue fellowships in women's health research within the NIH intramural program," she said.

The goal of the IPRWH is to serve as the focal point for all NIH intramural women's health research, including sex and gender comparisons.

Pinn noted that more than 50 NIH labs offered to host and mentor the researchers. "There was no shortage of applicants, and I was very pleased with the number of NIH scientists who were interested and ready to accept and mentor a fellow," she said. There is also no dearth of innovative projects in the realm of women's health research. The one current limiting factor is the availability of fellowship opportunities, but Pinn is optimistic that continuing commitment from the FNIH and its private partners will enable the continuation and, she hopes, expansion of the program.

—Stephanie Cooperstein

The Women's Health Special Interest Group sponsors a lecture series. For more information, go to the NIH Interest Group website at **<http://www.nih.gov/sigs/sigs.html>** *and scroll down to the Women's Health SIG.*

ORWH now airs a monthly podcast—called "Pinn Points on Women's Health"— with ORWH Director Vivian Pinn and NIH staffers involved in women's health research. These timely discussions can be found at **<orwh.od.nih.gov/podcast/>**.

O'Neill Joins NHGRI Study on Public Receptivity to and Use of Genetic Info

Fran Pollner

Suzanne O'Neill

Suzanne O'Neill, awarded the Shared Postdoctoral Fellowship, has examined the emotional and behavioral responses of women seeking genetic testing for BRCA1/BRCA2 breast- and ovarian-cancer susceptibility genes.

Her Women's Health Fellowship work in NHGRI's Social and Behavioral Research Branch is a "natural fit," she observes, with her research interest in "individualized preventive medicine based on genetic risk and differences in the processing of health risk information related to genetic disease."

O'Neill is working directly with Colleen McBride, the NHGRI branch chief and lead investigator in the newly launched Multiplex Initiative, a joint project of NHGRI and NCI and two extramural groups. The study will offer individuals genetic testing for genes that play roles in eight common conditions: diabetes, coronary heart disease, high cholesterol, hypertension, osteoporosis, lung cancer, colorectal cancer, and malignant melanoma.

O'Neill will analyze data from the Multiplex Initiative, which will examine family history and behavioral risk factors as predictors of disease attributions. This information will add to existing knowledge that will facilitate the development of interventions that address how people process and act on personal health information.

—Stephanie Cooperstein

Laughlin Seeks Clues to Vulnerability to And Prevention of Uterine Fibroids

Shannon Laughlin

Shannon Laughlin's Clinical/Translational Fellowship is advancing research on uterine fibroids, a condition that captured her interest during her residency in obstetrics and gynecology at Loyola University in Chicago.

She is particularly motivated by by the difference between African American and white patients in the prevalence and severity of fibroids.

This common disorder, though rarely malignant, can still lead to anemia and the need for blood transfusions and is also the leading reason for hysterectomies.

Laughlin's research plan is to identify factors that place women at high risk of developing fibroids and to determine whether early identification and treatment of high-risk women—or perhaps preventive measures—will reduce the need for surgery.

Her research aim is to elucidate how fibroids grow, why parity is protective, and what role race may play in disease development. She anticipates that her training in the Epidemiology Branch will also enhance her statistical and epidemiological skills for future research.

The fellowship, Laughlin says, confers another benefit: "the opportunity to have strong mentorship"—she is working with PI Donna Baird, a reproductive epidemiologist with a distinguished track record in public-health research.

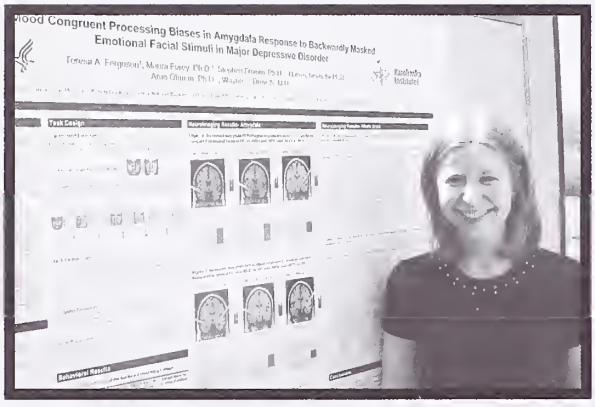
—Stephanie Cooperstein

May 4th GPP Student Research Symposium

Graduate Students at NIH Display the Research Doctorates are Made of

by Evan Galloway

Since its inception in 2000, the formal university-NIH Graduate Partnerships Program (GPP) has grown to more than 400 graduate students currently working in NIH labs in pursuit of their advanced degrees. Their degree-granting institutions are located across the United States and in 21 other countries. The fourth annual GPP Student Research Symposium, held May 4th, featured poster presentations and talks by more than 100 of these students—a third more than last year. Featured here are two of these posters.



Evan Galloway

Teresa Ferguson
(Mentors: Wayne Drevets, NIMH, and Arne Öhman, Karolinska Institutet, Stockholm)

"Mood Congruent Processing Biases in Amygdala Response to Backwardly Masked Emotional Facial Stimuli in Major Depressive Disorder"
Authors: Teresa Ferguson, Maura Furey, Stephen Fromm, Harvey Iwamoto, Arne Öhman, and Wayne Drevets

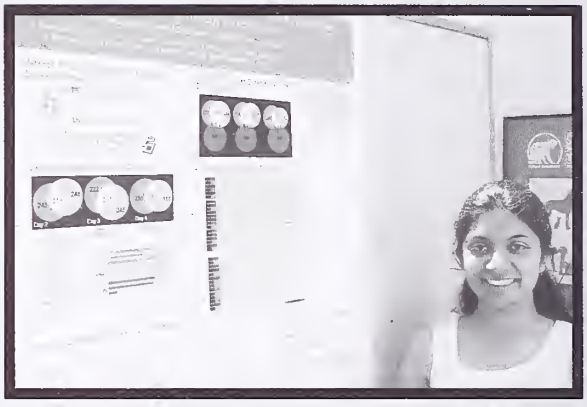
Dysfunctional activation of the amygdala, a major mediator of emotion, has been associated with various mood disorders, including depression. Specifically, the amygdala of a depressed individual tends to exhibit abnormal patterns of activation in response to negative or positive stimuli.

In this study, **Teresa Ferguson** and her colleagues used blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI) to further investigate this effect among patients with depression, patients in remission from depression, and healthy control subjects. Images of happy, sad, or neutral faces were presented to the cohorts for a brief-enough period of time to fall below the level of conscious detection, permitting the measurement of automatic or implicit responses.

Ferguson found that the amygdala of a depressed patient, compared with that of a healthy control subject, exhibited increased activation in response to sad faces. When presented with happy faces, on the other hand, the control subjects showed greater activation than both remitted and currently depressed patients.

These results support the idea that abnormal amygdala responses are a key attribute of depression, and they demonstrate the existence and influence of automatic or implicit responses.

Ferguson suggested that these findings might help explain why depressed individuals tend to ruminate on the negative aspects of their environment and their lives. She is currently investigating the effects of antidepressants in this response. ■



Evan Galloway

Amrita Ghosh
(Mentors: Fabio Candotti, NHGRI, and Hua Zhu, University of Medicine and Dentistry of New Jersey, Newark)

"Effects of In Vitro Culture Conditions on Gene Expression of CD34+ Human Hematopoietic Progenitor Cells Mimicking Gene Therapy Clinical Trials"
Authors: Amrita Ghosh, Chenwei Wang, Abdel Elkahoun, Hua Zhu, and Fabio Candotti

Amrita Ghosh presented both a talk and a poster on her research to replicate the in vitro conditions in two similar clinical gene-therapy trials. One, in France, had resulted in four cases of leukemia, and the other, in the United Kingdom, had not. Her interest, she said, is to optimize trial safety.

Ghosh used a stem-cell culture model to examine the differences in culture conditions in the French and British gene-therapy clinical trials. Both were equally successful at inducing the intended therapeutic response—amelioration of X-linked severe combined immunodeficiency—and both had used retroviral vectors, which are believed to preferentially integrate into actively transcribed genes.

Ghosh and her colleagues hypothesized that different outcomes may be explained by differential integration of the vector, which in turn is determined by differences in gene-expression profiles. Replicating the dissimilar conditions of these trials in vitro and assaying for RNA expression allowed Amrita to probe these differences.

She found that annotated cancer genes were indeed overrepresented among the activated genes in all the French culture samples, whereas this effect was observed in only one U.K. sample. If confirmed, these results may indicate preferential integration into cells cultured by French conditions, perhaps resulting in dysregulation of more cancer genes than in the U.K. cultured cells. Further work will be directed toward examining differences caused by the type of retrovirus used and ensuring that "upregulation equals integration."

Ultimately, Ghosh says, "the goal of this work is to help make gene therapy a part of conventional medicine." ■

See next page for GPP poster and mentor awards.

May 9th Postbac Poster Day

Postbacs Test the Waters of Biomedical Research

by Christopher Wanjek

The 2007 Postbaccalaureate Research Festival featured the display of 219 posters, representing 20 ICs. Begun in 2000 as a postbac poster day, the event became a two-day "festival" last year.

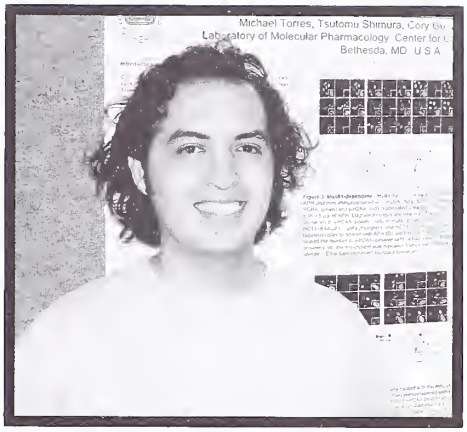
A member of the DNA Replication Group in the NCI Laboratory of Molecular Pharmacology, **Michael Torres** is studying how cells cope with perturbed replication. Environmental insults can cause DNA lesions, breaks, or mutations, compromising the genomic function.

Torres' focus is on DNA double-strand breaks (DSBs) that are under the threshold of S-phase checkpoint activation regulated by the ATR and ATM protein kinases, which attempt to correct or prevent further damage. DSBs are likely formed by the interaction of DNA polymerase with the collapsed replication fork.

Torres is examining the role of the BLM protein implicated in Bloom syndrome, a disease characterized by a high frequency of breaks and rearrangements in a person's DNA, causing premature aging, cancer predisposition, and numerous other health problems. His group has found that low doses of DNA polymerase inhibitors induce transient DSBs, with the BLM helicase and the Mus81 endonuclease causing the breaks after inhibition of DNA replication. DNA-dependent protein kinase and the XRCC4 ligase can repair these transient DNA breaks.

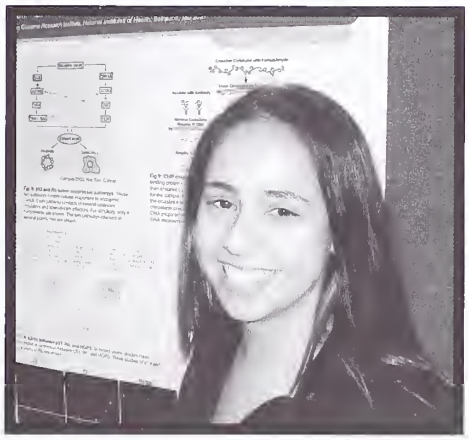
Torres was a recipient of the NIH Undergraduate Scholarship, a novel program that provides up to $20,000 per academic year to students from disadvantaged backgrounds. The program also provides paid research training at NIH during the summer and paid employment and training at NIH after graduation.

For each full scholarship year, the recipient must commit to one year of service at NIH, which brings an added benefit of more extensive NIH research experience early in one's career. Torres will study at the University of Texas Southwestern Medical Center, Dallas, in the fall. His mentor is Mirit Aladjem of NCI. ■



Christopher Wanjek

Michael Torres
"Orchestrated Response to Perturbed Replication"
Authors: Michael Torres, Tsutomu Shimura, Cory Gu, and Mirit Aladjem, Laboratory of Molecular Pharmacology, CCR, NCI



Christopher Wanjek

Dina Faddah
"Analysis of p53 and Rb in Hutchinson-Gilford Progeria Syndrome"
Authors: Dina Faddah, Kan Cao, and Francis Collins, Genome Technology Branch, NHGRI

In most cases of Hutchinson-Gilford progeria syndrome (HGPS), the rare genetic disorder that causes dramatically accelerated aging beginning in childhood, a single base change of C to T in exon 11 of the lamin A gene (*LMNA*) triggers the production of progerin, a mutant protein. Francis Collins' lab made this discovery in 2003, sparking renewed interest in the relationship between this rare disease and the common diseases associated with aging.

Dina Faddah, a postbac in the NHGRI Genome Technology Branch, is building upon this work, investigating the possible connection between HGPS and the infamous tumor-suppressor genes, *p53* and *Rb*. Previous research showed that p53 signaling is linked to premature aging and that disruption of the normal distribution of lamins A/C lead to similar disruption of Rb distribution.

Progerin, present in healthy bodies to some degree, is a derivative of the protein lamin A, with a 50-amino-acid internal deletion. This deletion gives rise to pathology by maintaining a farnesyl lipid side chain that is cleaved off in normal lamin A.

Faddah and her colleagues first identified reliable p53 and Rb antibodies. Then, using immunofluorescence techniques, Faddah compared their effect on HGPS and non-HGPS cells. She could find no visible difference of Rb in normal and HGPS cells. She cannot rule out interplay, but the connection isn't obvious from this experiment, she said. Progerin and p53, however, displayed an inverse correlation in HGPS cells.

Faddah is conducting follow-up studies using ENCODE DNA microarrays and ChIP sequencing. She believes this research is a solid step forward in the unfinished task of understanding the complicated process of HGPS and aging. She will spend another year at NIH before starting graduate school. ■

GPP Standouts: Eight Student Posters, Two Mentors

The following GPP students received poster commendations and a $500 travel award:

Molly Bright, University of Oxford, U.K. **"Characterization of Regional Variability and Correlated Processes in BOLD fMRI During Mild Hypercapnia"** (Jeff Duyn, NINDS)

Kee Chan, Yale University, New Haven, Conn. **"T-Cell Receptor Excision Circles: Application to Newborn Screening for Severe Combined Immunodeficiency and Understanding the Development of T-Cell Diversity"** (Jennifer Puck, NHGRI)

Gabriel Eichler, Boston University. **"Embracing the Complexity of Gene Expression in the Interpretation of Gene Microarrays"** (John Weinstein, NCI)

Athena Klutz, The Johns Hopkins University, Baltimore, Md. **"PAMAM Dendrimers Serve as Nanoscaffolds for G-Protein–Coupled Receptor Ligands"** (Kenneth Jacobson, NIDDK)

Paul Kriebel, George Washington University, Washington, D.C. **"Vesicle Trafficking is Essential for the Proper Cellular Distribution of the Adenylyl Cyclase ACA and cAMP Release During Chemo-taxis and Streaming"** (Carole Parent, NCI)

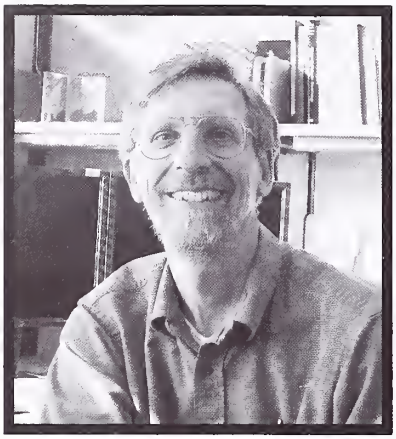
Justin Lathia, University of Cambridge, U.K. **"Neural Stem Cell Behavior Regulated by Integrin/Laminin Interaction in the Developing Embryo"** (Mark Mattson, NIA)

Thomas Lozito, University of Cambridge. **"Endothelial Cell Matrix Influences Mesenchymal Stem Cell Differentiation into Vascular Cell Types"** (Rocky Tuan, NIAMS)

Jennifer Schymick, University of Cambridge. **"A Genome-wide Association Study of Sporadic Amyotrophic Lateral Sclerosis"** (John Hardy and Bryan Traynor, NIA)

And **Francis Collins**, NHGRI, and **Kurt Fischbeck**, NINDS, were honored as this year's "outstanding mentors," chosen from among the nominations submitted by the graduate students. ■

Software Heroes
continued from page 1



Catalyst file photo

Jim Ostell, chief of the NCBI Information Engineering Branch

better educate the scientific community on how to use them.

Organizing The Organizing

As popular as NCBI's tools are, by and large its users are failing to see the dazzling interconnectivity, says Jim Ostell, chief of the NCBI Information Engineering Branch. Ostell's team often performs demonstrations for researchers on how to narrow literature searches on a human disease and to link, for example, to GenBank for annotated text about a newly discovered gene mentioned in an article, and to further link for nucleotide or taxonomy information, until ultimately one might stumble upon the same gene and its function in a microorganism.

"The almost uniform response from the audience is, 'Oh, I didn't know you could do that,'" said Ostell, who like a maestro can produce a symphony of data within seconds with his frenzied keystrokes and mouse movements. "You can get to these things by clicking down the links, but you have to kind of know that they're there."

From such audience feedback, as well as by tracing search-request patterns, the NCBI came to realize that most users don't go beyond retrieving top-level results from their query. In other words, scientists are using the database retrieval system more like Google, typing and retyping queries. To counter this, NCBI has launched the Discovery Initiative with the goal of making the user more aware of related data.

"The data in molecular biology are growing exponentially," Ostell said. "How do we build an information resource that not only can handle exponential growth but can also use it in some kind of positive way, as opposed to being basically destroyed by it?"

One of the first elements of the Discovery Initiative to be implemented is the prominent display of Abstract Plus by default, which through an advanced matching program finds articles similar to the one the user highlights and then displays their titles neatly to the right of the search. Abstract Plus is built on keywords and biological relationships, running circles around simple popularity matches on sites such as Amazon.com that merely provide Dylan fans a link to Grateful Dead merchandise.

Abstract Plus has existed for years, but its new prominence has resulted in about 30 percent of the users clicking on a related link, compared with only 3 percent before. Similarly, NCBI will soon highlight another cloaked feature—sophisticated searches based on related biological function, not text.

NCBI Director David Lipman, the originator and co-developer of BLAST, describes the Discovery Initiative as key to "making the kinds of connections that underlie the discovery process," bridging the collective knowledge of the genome over billions of years of evolution and bringing together scientists who otherwise do not read the same journals, go to the same meetings, or specialize in the same organism or disease.

The Next Big Thing: dbGaP

NCBI's latest creation, dbGaP, short for the database of genotype and phenotype, will enable comparisons of the genome-wide association studies expected to dominate genetic research. This database is designed to serve as a central depository for archiving and distributing genotype and phenotype data and can provide analyses of the level of statistical association between genes and selected phenotypes.

John Weinstein, NCI lab chief and head of the Genomics & Bioinformatics Group

"I think dbGaP is the single most exciting project we have, because it is connecting the promise of all the investment in the human genome to trying to come up with clinical information from it," Ostell said.

Currently dbGaP contains only two studies: the NEI Age-Related Eye Disease Study and the NINDS Parkinsonism Study. Starting in June, dbGaP takes a massive step forward with the gradual addition of several major projects: Genetic Association Information Network (GAIN); Genetics and Environment Initiative (GEI); the Framingham Heart Study; the Women's Health Study; ongoing NINDS studies on stroke, epilepsy, and ALS; medical resequencing studies from NHGRI that pinpoint rare mutations causing rare diseases; and kidney data from NIDDK.

By year's end, NCBI hopes to have thousands of human genomes archived for comparison, perhaps finding commonality in seemingly unrelated diseases and giving old data a new life.

"Framingham started in the '40s," said Ostell. "By this step, Framingham moves into the molecular age . . . . That's the molecular biology revolution. All the phenotype ideas you had—suddenly you have a paradigm shift when you go through sequence data."

Cancer Tools

Among the bioinformatic enterprises that make extensive use of NCBI's tools is the Genomics & Bioinformatics Group, headed by John Weinstein, of the NCI-CCR Laboratory of Molecular Pharmacology. The group has developed the Miner Suite of web-based software, which, as the name implies, focuses on data mining. The Miner Suite tools are inherently generic but rigorously and widely used by cancer researchers.

SpliceMiner, for example, is a web interface for working with data from NCBI's Entrez Gene and Evidence Viewer tools to analyze splice variants, which may pop up in a microarray experiment. Cancer has been referred to as a disease of splicing. That is probably an overstatement, Weinstein says, but SpliceMiner does provide a solid, user-friendly platform for figuring out what roles splicing really does play in the disease.

MedMiner expedites PubMed searches for gene-gene and gene-drug relationships; GoMiner leverages the Gene Ontology project to provide functional interpretation for microarray experiments; and CIMminer creates the clustered heat

maps that have become the ever-present visual icon of "postgenomic" research.

Weinstein is now working with Steven Chanock, a senior investigator in the NCI-CCR Pediatric Oncology Branch, and with others to apply the Miner software and databases to the genome-wide association studies and dbGaP.

For example, if a particular chromosome region shows up as important in the association between mutations and a particular type of cancer, the question becomes, "Which gene in that region is driving the association and which genes are just passengers," Weinstein said.

When that question arises, CellMiner databases can find out which genes are overexpressed, duplicated, rearranged, or otherwise abnormal, suggesting "impaired-driver status," Weinstein said. CellMiner includes molecular profiles at the DNA, RNA, protein, chromosomal, and small-molecule levels, reflecting the richest, most varied molecular profiling of any set of cells in existence.

Catalyst file photo

Clement McDonald, director, NLM Lister Hill National Center for Biomedical Communications

The compilation reflects what Weinstein has termed "integromics." The integromic hypothesis poses that looking at the cancer cell from many different molecular angles can yield additional insight into the biology and pharmacology. Much of CellMiner's data are on 60 diverse cancer cell types—the NCI-60—used by the NCI's Developmental Therapeutics Program to screen more than 100,000 chemical compounds and natural products.

Data Quality

With advances in bioinformatics, Weinstein hopes to strike a balance between the observation-driven biology of Linnaeus and Darwin and the hypothesis-driven research that dominated the latter half of the 20th century. Access to information on tens of thousands of genes, hundreds of thousands of splice variants, and millions of protein states has placed researchers once more in the role of taxonomists. Yet real value will be realized, Weinstein said, when scientists can integrate all this information smoothly and meaningfully into hypothesis generation and testing.

We are now at a crossroads, Weinstein said, where the data are given short shrift. Genomic data are collected, but perhaps a half a year passes as the researchers attempt to find a hypothesis-driven story worthy of journal publication, and another half a year passes as that hypothesis is validated. In the end, the data release is delayed and "the tail ends up wagging the dog," Weinstein said, with an article focusing on downstream hypothesis testing related to one or a few of the genes.

"There are many kinds of contributions that intramural scientists can make in addition to curing a disease," Weinstein said. "Less attention is given to the kinds of research based on databases and bioinformatics. Very often, those contributions set the table for other researchers focused on particular genes or disease states."

Weinstein has faced such prejudice from editors in publishing data from the NCI-60 cancer cell lines, with submissions rejected because they lacked a hypothesis. The audience certainly exists, Weinstein said. Six out of seven of his group's most influential papers in the last 10 years were initially rejected at least once, yet they have collectively garnered thousands of literature citations.

Can We Talk?

Acute attention must be paid to interoperability to avoid the Babel effect—locally invented and idiosyncratic codes—the main barrier to deploying fluent database-management tools, according to Clement McDonald, director of NLM's Lister Hill National Center for Biomedical Communications.

NLM Director Donald Lindberg led the development of the Unified Medical Language System (UMLS) at NIH in the early 1980s, foreseeing the necessity to retrieve information from disparate sources, syntaxes, and vocabularies. The UMLS now maintains a list of more than five million names for more than a million concepts, as well as more than 12 million relations among these concepts.

Two offspring of the UMLS concept are are the homegrown RxNorm, helping researchers and consumers make sense of myriad pharmaceutical trade names and chemical names, and LOINC, short for Logical Observation Identifiers, Names, and Codes, to standardize the language of laboratory observations.

In this spirit, Lister Hill maintains ClinicalTrials.gov, originally created to inform the public of NIH-funded clinical trials but now serving as an even more important tool for researchers. Although not all the pieces are fully in place, ClinicalTrials.gov is positioned to meet policy initiatives calling for the development of a database of trial results that is informative and current and meets ethical concerns about consent and privacy, according to Deborah Zarin, a senior scientist at Lister Hill and lead author of the May 16 *JAMA* report.

The investment in database management tools will be wasted if users cannot access all that is available, a situation analogous to providing workers BlackBerrys just to tell time. The designers must continuously receive input from the end users to assess usability, an obvious but remarkably overlooked principle in systems design, McDonald said.

The NLM is constantly reinventing itself, meeting the demands of data influx but also of the user. McDonald calls the book *Wicked Problems, Righteous Solutions: A Catalogue of Modern Software Engineering Paradigms* by Peter DeGrace and Leslie Hulet Stahl required reading for anyone who designs such systems. Too often, he said, the user is blamed for a poorly engineered system.

The Web

As NCBI takes researchers from abstract to zygote, Ostell strives to provide content that informs rather than distracts, for much of the Internet has lost its web-ness and become a series of treacherous and tedious one-way streets.

There are "underlying principles behind the projects that we take on and the way that we put them together," Ostell said. "We try to hit that gray zone where things are in transition from research to resource. We have to be there as they move out of the research phase." ■

NCBI's web is captured by an animated diagram at
<**http://www.ncbi.nlm.nih.gov/Database/datamodel/**>.
NCI's Miner Suite is detailed at
<**http://discover.nci.nih.gov/**>.

continued from page 1

longer survival postdiagnosis with decreased mortality," Kramer said.

"They've also captured the concept of overdiagnosis of non–life-threatening conditions that can result in serious side effects from unneeded interventions.

"Our graduates have incorporated ways to judge study design and to emphasize in their reporting when results of a trial are considered preliminary. And they have learned the importance of reporting absolute rates to judge the impact of an intervention" on disease incidence.

Dartmouth photos

***Going by the Numbers**: (left to righ) Gil Welch, Steven Woloshin, and Lisa Schwartz, physician-researchers, Dartmouth Medical School and VA Outcomes Group*

The Class of 2007

The 50 attendees at this year's workshop, chosen from 275 applicants, varied in the size of their audience and in their medical-science training. Among them were a Lincoln, Neb., newspaper reporter, a newly hired *Wall Street Journal* reporter, an established ABC News World News producer, and a medically trained writer for a German health magazine.

Some had been assigned the health beat armed only with their journalism training and perhaps a few long-forgotten biology classes.

Just the fact, noted by several of the physician-researchers who served as faculty, that only 50 percent of media-hyped health items eventually appear in scientific journals within five years surprised most attendees.

Kramer listed some of the general impediments to a reporter's success in telling an accurate story: "lack of formal scientific training, editorial pressures, text space availability, staffing cutbacks, and an overall interpretation bias that is inevitable in this field."

He noted that hot-button political issues, sensational anecdotes, and celebrity involvement often trump actual scientific data in the competition for media coverage of health and biomedical science.

Generally, NIH websites and public information offices can be relied upon for objective information. And researchers themselves can be contacted directly for results and data clarification, he said.

The VA Outcomes–Dartmouth cohort—Gil Welch, Steven Woloshin, and Lisa Schwartz—led most of the nuts-and-bolts sessions that delved into the intricacies of study design and outcomes, selection bias, *P* values, the meaning of numbers, and how to assess the quality of data and their relevance to their reading and viewing audiences.

JUST THE FACT . . . THAT ONLY 50 PERCENT OF MEDIA-HYPED HEALTH ITEMS EVENTUALLY APPEAR IN SCIENTIFIC JOURNALS WITHIN FIVE YEARS SURPRISED MOST ATTENDEES

Basics: Know the Numbers, Look Before You Leap

In each module, research findings were tackled with analytic tools to clarify the nuances of relative risk, absolute risk, or just plain inevitable events in human existence.

Topics for lively interactive discussions included hope vs. hype in reporting on "breakthroughs" and "cures," distinguishing between randomized controlled trials and observational studies and anecdotes, and the need for reporters to identify and avoid expert sources of health information who may have either intellectual or financial conflicts of interest.

Reporters were told to exercise caution and skepticism in gathering information for stories on screening for disease or on the widespread incidence of a previously unrecognized condition (to thwart potential "disease mongering").

They were advised to question whether findings are verifiable, corroborated by previous findings, biologically plausible, or, where appropriate, exhibit a dose-response effect..

"Report the numbers; use charts" were frequent suggestions. Absolute rates, especially, were cited as the most helpful in painting an accurate picture of a drug's effect on a condition. And no story would be complete without asking about and reporting on potential harmful side effects from any given intervention.

Presenting data on preliminary scientific findings (from uncontrolled trials, trials involving just a few people, or from animal studies), especially, requires painstaking accuracy and cautionary qualifiers, Woloshin and Welch emphasized in closing remarks.

All the attendees questioned (in an unscientific poll) agreed that the seminar would influence their future reporting efforts.

One television news producer sighed while exiting the final lecture, acknowledging to a colleague that she'd definitely have to keep her huge seminar binder around for future reference. ■

Not for Reporters Only

Physicians, too, sometimes overinterpret evidence from nonrandomized, observational studies, OMAR Director Barry Kramer observed a few weeks after the media tutorial. He pointed, as an example, to the long-held assumption proved false by the results of the Women's Health Initiative that postmenopausal hormone-replacement therapy is cardioprotective.

A tutorial for health professionals, organized by Kramer at the request of NIH Director Elias Zerhouni, was held at NIH a few years ago. It was called "Moving from Observational Evidence to Clinical Trials: Why Do We Sometimes Get It Wrong?" ■

Office of the NIH Ombudsman: Basic and Applied Problem Solving

by Christopher Wanjek

Like many of the denizens here at NIH, Howard Gadlin advocates for preventive medicine. His five-member staff handles about 600 cases a year, and often he laments that he could have resolved some of his visitors' problems better if only they would have come to him sooner.

Gadlin is not a medical doctor, though. He's the NIH Ombudsman.

Gadlin's office, the Center for Cooperative Resolution, is open to NIH staff at all levels for nearly any kind of work-related problem. And more than 200 researchers take advantage of this service each year. Issues range from simple clarification of policies, to unmanageable interpersonal conflicts, to scientific disputes involving authorship or differences interpreting data—all handled confidentially. His office offers facilitated conversation, shuttle diplomacy, or sometimes just sage advice.

"Some people are apologetic about coming in," Gadlin said. "If it seems important to you, then we're interested in helping you resolve it." And the sooner his team can get involved, the better, Gadlin said, because problems can "intensify exponentially."

Gadlin is the first full-time, center-wide ombudsman at NIH, arriving here nine years ago after directing the ombudsman's office at the University of California, Los Angeles. He holds a doctorate in experimental psychology and understands the laboratory environment, a former workplace for many years. So he's not surprised by his office's own statistics revealing that cases involving scientists, while comprising about 40 percent of the caseload, encompass about 60 percent of his time.

"Scientists tend to think that a problem will eventually clear up, like a head cold," he said. "The more [a problem] continues, the more self-fulfilling it is."

In a complex organization like NIH, Gadlin said, there are many issues that fall outside the purview of formal grievance and dispute-resolution systems. Common problems entail staff-management interaction, performance appraisals, interpersonal misunderstandings, and awkward office or lab situations, such as noise or messiness. Managers make the most serious errors when they are certain they are correct and forget about procedures, Gadlin said. This leaves them with little negotiating strength in the long run.

Christopher Wanjek

***Here to Help**: Ombudsman Howard Gadlin (center), flanked by (left to right) Guillermo Aviles-Mendoza, Kathleen Moore, Linda Brothers, and Kevin Jessar*

Much of Office of the Ombudsman's energy is spent coaching scientists on how to manage conflict—to "minimize its destructive element," Gadlin said, but not to simply suppress it, because sometimes a certain level of conflict is needed in the scientific process.

Gadlin's staff—Kevin Jessar, Kathleen Moore, Linda Brothers, and Guillermo Aviles-Mendoza—offer a range of expertise in counseling, employee relations, and law. They have assisted NIHers who are unclear about NIH policies, who need an independent facilitator, who feel they have been treated unfairly, who want coaching about constructive ways to handle a difficult situation, or who have concerns about mentoring, authorship, resources, or intellectual property rights.

Sometimes they can facilitate dialogue. Other times, when it is not wise to bring two people face to face, the staff may shuttle between the quarreling parties, as is done in a bitter divorce. Conflicts are sometimes resolved by parting and not by group hug.

In way of preventive medicine, the Office of the Ombudsman can identify potential problems, such as internal practices that can lead to conflict. The office provides training and presentations in this regard. Particularly for the scientific staff, the office has developed customized dispute-resolution mechanisms. These include a process called partnering, in which scientific collaborators develop an agreement about a project upfront to clarify roles and expectations.

Should individuals bring a problem to the office for which there is actually a more appropriate resource—for instance, the NIH Employee Assistance Program for family or other nonwork concerns—they will be channeled in the right direction.

The office does have its limitations: Its representatives cannot serve as an advocate, conduct investigations, make policy decisions, or determine rights. It is best to think of the ombudsman's office, Gadlin said, as a means to develop and understand ways to resolve problems.

And despite the pleasant working environment at NIH, problems are inevitable. "When you have highly creative people working within a government bureaucracy, issues arise," Gadlin said.

A two-foot inflatable replica of the well-known character from Edvard Munch's *Scream* graces Gadlin's desk, perhaps to reflect the kind of reaction the ombudsman's office was created to avoid. ■

For a full list of ombudsman office services and contact information, see **<http://www4.od.nih.gov/ccr/>**.

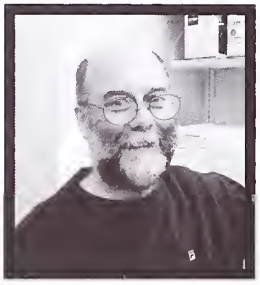
Speedy Ethics Course For Summer Interns

A valuable (and required) course for NIH summer interns is a web-based training module on ethics, called the Ethics and Scientific Research Study Guide. The course, humorous at times, walks the student through temptations of scientific dishonesty. Some examples are obvious; others, such as the right of authorship, lie in a gray area.

The course takes only 15 minutes and is available at **<http://web.ncifcrf.gov/campus/ethicscourse/>**.

Recently Tenured

Rémy Bosselut *trained at the Institut Curie in Orsay, France. He earned his M.D. degree in 1992 from the Xavier Bichat School of Medicine and his Ph.D. degree in 1993 from the University Denis Diderot, both in Paris. After postdoctoral training at the NCI Experimental Immunology Branch with Al Singer, he joined the Laboratory of Immune Cell Biology as a tenure-track investigator in 2000 and is currently a senior investigator in that lab.*



Christopher Wanjekr

Rémy Bosselut

Our laboratory investigates the transcriptional control of T-lymphocyte differentiation. A critical component of the immune system, T cells derive from bone marrow precursors that undergo extensive proliferation and differentiation in the thymus. The two main T-cell subsets have notably different functions: Those that express the CD4 surface molecule control the function of most other immunocompetent cells, and those that express the CD8 surface molecule hunt and destroy cells infected by intracellular pathogens. These subsets actually constitute two separate lineages that diverge in the thymus from a common precursor, the so-called double positive (DP) that expresses both CD4 and CD8.

Our work focuses on the differentiation in the thymus of mature T cells from immature precursors (thymocytes)—and, specifically, on how DP thymocytes choose either the CD4 or CD8 lineage.

Our current approach to this question began a few years ago with microarray gene expression analyses that led us to identify a zinc-finger transcription factor, known as cKrox or Thpok, as a major CD4-differentiating factor.

We showed, first, that this gene is expressed in CD4- but not CD8-lineage cells and, second, that enforcing cKrox expression in DP thymocytes prevents their differentiation into CD8 cells. The cells that would normally become CD8 adopt a CD4 fate; that is, cKrox both inhibits the CD8- and promotes the CD4-differentiation program.

Our current research focuses on these questions:

- How is cKrox expression controlled in thymocytes and, especially, how is it confined to the precursors that will eventually become CD4 T cells?
- How does cKrox promote CD4 differentiation in the thymus? What are its target genes? Does it interfere with other transcription factors involved in CD4–CD8 differentiation and, if so, how?
- Our third area of investigation derives from experiments in which we forced the expression of cKrox in mature CD8 T cells (in which it is normally not expressed). We found that cKrox downregulates expression of genes characteristic of CD8 differentiation, including those encoding CD8 molecules themselves or cytotoxic proteins such as perforin or granzyme B. These findings indicated that that these fully differentiated CD8 T cells remained sensitive to the repression by cKrox of the CD8 differentiation program. However, unlike in thymocytes in which cKrox both prevents CD8 and promotes CD4 differentiation, expression of cKrox in differentiated CD8 cells failed to revert them to the CD4 lineage.

We are currently investigating the bases for this difference and notably whether epigenetic marking of CD4-lineage genes in CD8 cells would prevent their reactivation despite cKrox expression.

We expect that these experiments will shed light on the mechanism of CD4-CD8 differentiation in the thymus, a process crucial to the proper functioning of the immune system. From a broader point of view, these analyses should contribute to deciphering the mechanisms by which lineage fate is determined and maintained during mammalian development.

Richard Childs

Richard Childs *received his medical degree from Georgetown University in Washington, D.C., in 1991. He completed his internship and residency in internal medicine at the University of Florida in Gainesville and served as the chief medical resident there from 1994 to 1995 before coming to NIH in 1995. He completed a fellowship in medical oncology at NCI and then trained as a hematology fellow at the Hematology Branch, NHLBI, where he conducted research on allogeneic bone-marrow transplantation in the laboratory of John Barrett. He became a tenure-track investigator in 1999 and is currently a senior clinical investigator in that branch and a commander in the United States Public Health Service.*

My research interests have focused on tumor immunology and allogeneic immunotherapy for solid tumors and hematologic malignancies. Research conducted during my hematology fellowship showed that metastatic solid tumors could be killed by allogeneic T cells.

My clinical research program has focused on expanding the application of nonmyeloablative allogeneic hematopoietic stem-cell transplantation to treat solid tumors and nonmalignant hematological disorders such as paroxysmal nocturnal hemoglobinuria (PNH).

We demonstrated that PNH, a debilitating disorder of hematopoietic stem cells associated with bone marrow failure, red blood cell hemolysis, and blood clot formation, could be cured immunologically by transplanted donor T-cells that eradicated PNH stem cells.

Since 1999, more than 225 patients have undergone allogeneic hematopoietic stem-cell transplantation on our protocols. These clinical research trials advanced the field of hematopoietic stem-cell transplantation, providing new insights into the full therapeutic potential of allogeneic immunotherapy to treat both nonmalignant hematological disorders and metastatic kidney cancer.

Our publication in the *New England Journal of Medicine* in 2000 showed that renal cell cancer could be eradicated in patients with treatment-refractory metastatic disease after nonmyeloablative stem-cell transplantation, which spawned the development of allogeneic transplant trials nationally and internationally for a variety of solid tumors.

In addition to our clinical research program, my laboratory conducts basic and translational research in the field of tumor immunology. We are currently focusing on tumor antigen discovery and methods to enhance graft-vs.-tumor (GvT) responses against cancer using natural killer (NK) cells.

Using human T cells obtained from kidney-cancer patients whose tumors regressed after nonmyeloablative transplantation, my group recently identified a novel gene derived from a human endogenous retrovirus (HERV) whose expression appears restricted to clear-cell

renal-cell carcinoma.

Importantly, more than 50 percent of kidney cancers express this gene, and peptide antigens derived from this HERV are immunogenic, eliciting a tumor-specific T-cell response against kidney cancer. We are actively investigating the function of HERV in kidney cancer and the development of a tumor vaccine targeting HERV-derived antigens.

We have also focused on methods to enhance the antitumor effects of both allogeneic and autologous NK cells. Through in vitro experiments, we discovered that allogeneic NK cells with KIR (killer inhibitory receptor) incompatibility have enhanced antitumor activity against kidney cancer and melanoma compared with autologous NK cells.

When adoptively infused in tumor-bearing mice that have undergone an allogeneic transplant, these NK cells reduce graft-vs.-host disease (GvHD) and mediate potentially curative graft-vs.-solid tumor effects. Based on these findings, my group is designing a clinical trial to test the ability of in vitro expanded and adoptively infused allogeneic NK cells to prevent GvHD in patients with PNH and aplastic anemia and to enhance GvT effects in patients with malignancies who are undergoing hematopoietic stem-cell transplantation.

In our exploration of ways to potentiate the antitumor effects of autologous NK cells isolated from cancer patients, we discovered that tumors exposed to the proteosome inhibitor bortezomib and the histone-deacetylase inhibitor depsipeptide are more vulnerable to autologous NK effects. Both drugs were found to upregulate death receptors on the tumor surface for ligands expressed on NK cells. Furthermore, in a tumor-bearing mouse model, we found that pretreatment with bortezomib enhanced the antitumor activity of adoptive infusions of autologous NK cells.

Based on these findings, our group received a "bench-to-bedside" award in 2006 to evaluate the potential of bortezomib to enhance the antitumor effects of adoptively infused NK cells in humans with variety of metastatic cancers. A scale and validation testing of this approach is currently being performed in the CC Department of Transfusion Medicine. We anticipate enrollment of patients in this trial within the next three to six months.

Ira Daar *received his Ph.D. from the State University of New York at Buffalo in 1988 and came to NIH for postdoctoral training with George Vande Woude in the ABL/Basic Research Program. In 1992 he became a senior staff fellow and in 1997 a principal investigator in the Regulation of Cell Growth Laboratory and the Laboratory of Protein Dynamics and Signaling. He is currently head of the Developmental Signal Transduction Section and a senior investigator in the Laboratory of Cell and Developmental Signaling, NCI.*

Ira Daar

My long-standing interest is to understand the basic signaling pathways that regulate morphogenetic events during development. These pathways control cell movement and tissue reorganization during early embryogenesis and, when deregulated, may contribute to human disease.

The Xenopus model system has proven to be a tractable one for uncovering signaling pathways that regulate cell cycle progression and cell movement. My primary focus is on members of the Eph family of receptor tyrosine kinases and their membrane-bound ligands, the ephrins. The Eph/ephrin signaling pathway plays an important role in controlling the movement and positioning of cells during development.

Eph receptors and ephrins are also overexpressed in a wide variety of human tumors and cancer cell lines, with a particularly high frequency of deregulation observed in metastatic tumor cells. Moreover, these proteins have been implicated in tumor-cell invasion and tumor angiogenesis.

Therefore, further elucidating the precise mechanisms and proteins involved in Eph/ephrin signaling is likely to provide valuable insight into cancer dynamics as well as into normal morphogenetic processes.

My laboratory has explored a new concept for the signal-transduction cascade initiated by ligand-receptor interactions known as "bidirectional signaling," in which a transmembrane ephrin ligand not only activates a cognate Eph receptor on a neighboring cell, but also transduces a signal through its own intracellular domain. These studies have revealed that signaling from ephrinB1 affects cell adhesion and movement.

Further, my laboratory has shown that there is signaling cross-talk between the Eph and FGF receptor (FGFR) tyrosine kinase pathways. Through biochemical studies, we have found that activated FGFRs can interact with and regulate the signaling properties of ephrinB1 via tyrosine phosphorylation of the ephrinB1 intracellular domain.

In collaboration with Sally Moody, of George Washington University in Washington, D.C., and Kathy Moore, of the University of Utah, Salt Lake City, we have been using the Xenopus eye field as a model system. We have been able to demonstrate the functional consequence of FGFR/ephrinB1 signaling cross-talk in the regulation of stem-cell movement and cell fate. This work linked these two key signaling pathways (Eph and FGFR) as co-regulators of an important morphogenetic process and provided evidence that alterations of cell fate can result from changes in cell movement.

Based on these findings, my colleagues and I have proposed a model in which the appropriate in vivo positioning of cells occurs as a result of the expression patterns and interactions between ephrins and their cognate receptors and alternative growth factors.

My laboratory has continued to take advantage of the eye-field system, and our most recent studies have revealed that ephrinB1 controls retinal progenitor cell movement by interacting with the Dishevelled (Dsh) adaptor protein and co-opting downstream members of the noncanonical Wnt/planar cell polarity (PCP) pathway.

Importantly, these studies connect ephrin signaling with the PCP pathway and have set the stage for my future studies examining the mechanism by which ephrinB1 influences this pathway.

We now have evidence that ephrinB1 interacts with the Par polarity complex, which is a major determinant in establishing tight junctions. Through this interaction ephrinB1 can exert regulatory control over tight-junction assembly. Using in vivo approaches, we can now mechanistically test how ephrinB1 regulates cell-cell adhesion during development.

We will continue studies to broaden our concept and knowledge of signaling pathways that regulate cell move-

Recently Tenured

ment and cell polarity during embryogenesis, with the idea that this knowledge may also affect how we approach therapeutic applications for metastatic disease.

Daniel Douek *received his medical degree from the Universities of Oxford and London in 1990 and then his Ph.D. in immunology from the University of London in 1996. He did his postdoctoral training with Richard Koup at the Rockefeller University in New York and at the University of Texas Southwestern Medical Center at Dallas and became a tenure-track investigator at the Vaccine Research Center, NIAID, in 2000. He is currently a senior investigator, leading the Human Immunology Section in the Laboratory of Immunology, VRC.*

We in the Human Immunology Section study the processes that determine the course of human diseases in which the immune system, particularly its T-cell arm, plays a central role in pathogenesis and outcome. We aim to use the knowledge gained to initiate clinical studies of new therapeutic and vaccine approaches.

Our overriding strategy is to address questions of human disease directly in humans and nonhuman primates, with as little in vitro manipulation as possible and with an emphasis on elucidating the basic mechanisms that underlie disease processes.

We are studying the nature and dynamic interactions of HIV-specific T-cell clones in HIV disease and after vaccination against HIV; our goal is to establish correlates of effective and protective immunity.

Such findings will in turn open lines of further inquiry for researchers in developing strategies using T-cell immunity to fight HIV infection.

Specifically, our recent studies have shown that the use of HIV-specific CD8 T-cell clones with particular T-cell receptors (TCR) may affect biological outcome in infected individuals. We aim to understand these phenomena at the level of TCR affinity, precursor frequency, cross-reactivity, and structure.

By studying the mechanisms underlying HIV pathogenesis and immune reconstitution after therapy, we aim to understand the tempo and mechanism of HIV disease progression and how recovery from HIV disease can be enhanced.

The main thrust of our work at the moment is to investigate CD4 T-cell depletion at mucosal sites, the consequences of damage to the gut mucosa, and how such damage underlies disease progression to AIDS. We recently reported that microbial translocation from the gut lumen into the systemic circulation causes immune activation and may contribute to progressive disease.

Christopher Wanjekr

Daniel Douek

We hope that these approaches contribute to both prevention and treatment of HIV disease in humans.

Stewart Levine *received his M.D. from the State University of New York School of Medicine, Stony Brook, in 1983. He completed an internship and residency at St. Vincent's Hospital and Medical Center in New York City and a fellowship in pulmonary medicine at the Memorial Sloan-Kettering Cancer Center before coming to NIH in 1989 for clinical and postdoctoral training in the CC Critical Care Medicine Department. He subsequently became a staff clinician in that department. In 1998, he joined the Pulmonary-Critical Care Medicine Branch, NHLBI, as a tenure-track investigator and is now a senior investigator and head of the section on lung inflammation in that branch.*

Christopher Wanjekr

Stewart Levine

Our research has focused on identifying molecular mechanisms by which inflammation can be regulated. Because of the important role of tumor necrosis factor (TNF) in inflammatory lung diseases and critical illness, we have studied the type I, 55-kDa TNFR1 (TNFRSF1A) as a model system. One mechanism by which TNF bioactivity is regulated involves the shedding of cell surface receptors, which then function as soluble TNF-binding proteins. Prior work in the field established that soluble TNF receptors are generated by the proteolytic cleavage of receptor ectodomains by a sheddase, such as TNF-α converting enzyme (TACE), also known as ADAM17.

Our studies have identified new molecular mechanisms regulating the release of TNFR1 to the extracellular space. We discovered that a full-length TNFR1 is constitutively released from human vascular endothelial cells within the membranes of exosome-like vesicles.

This release of TNFR1 exosome-like vesicles represents a novel alternative pathway for the generation of soluble cytokine receptors that is distinct from the proteolytic cleavage of receptor ectodomains or the translation of an alternatively spliced mRNA. We confirmed the in vivo significance of these observations in clinical studies, which demonstrated TNFR1 exosome-like vesicles in human plasma and bronchoalveolar lavage fluid.

To better understand the intracellular pathways that modulate soluble TNFR1 generation, our laboratory identified, cloned, and characterized ARTS-1 (aminopeptidase regulator of TNF receptor shedding) as a type II integral membrane zinc metalloprotease. ARTS-1 is a TNFR1-binding protein that regulates both the constitutive release of TNFR1 exosome-like vesicles and the IL-1β–mediated inducible proteolytic cleavage of TNFR1 ectodomains, but does not appear to function as a TNFR1 sheddase. We also showed that ARTS-1 regulates the release of the soluble cleaved forms of IL-6Rα and IL-1RII.

Therefore, ARTS-1 regulates the release of three distinct cytokine receptor superfamilies: those of the TNF receptor superfamily (TNFR1), the class I cytokine receptor superfamily (IL-6Rα), and the immunoglobulin/Toll-like receptor superfamily (IL-1RII).

Our laboratory subsequently identified nucleobindin 2 (NUCB2, NEFA) as a calcium-dependent, ARTS-1–binding protein that associates with intracytoplasmic TNFR1 vesicles. We showed that the calcium-dependent formation of ARTS-1/NUCB2 complexes are required both for the constitutive release of TNFR1 exosome-like vesicles and for the IL-1β–mediated, inducible proteolytic cleavage of TNFR1.

Therefore, NUCB2 and ARTS-1 regulate two zinc metalloprotease–dependent mechanisms of cytokine receptor shedding: the sheddase-independent constitutive release of exosome-like vesicles containing full-length TNFR1 receptors and the sheddase-dependent

inducible proteolytic cleavage of receptor ectodomains.

In collaboration with Martha Vaughan and Joel Moss in our branch, we recently identified a vesicular trafficking pathway that mediates the release of TNFR1 exosome-like vesicles. We showed that the brefeldin A–inhibited guanine nucleotide-exchange protein BIG2 associates with TNFR1 and selectively modulates the constitutive release of TNFR1 exosome-like vesicles via an ARF1- and ARF3-dependent mechanism. This functional interaction between TNFR1 and BIG2 is downstream from the ARTS-1/NUCB2 complexes.

Our research program will remain focused on investigating regulatory mechanisms that modulate inflammation. In particular, we are continuing our studies to identify and characterize the molecular pathways that regulate the release of soluble cytokine receptors that can modify inflammatory and immune events.

We are also planning clinical and translational studies to identify new therapeutic approaches for patients with asthma, especially those with severe disease that cannot be adequately controlled with current medications.

Ian Macdonald *received his M.D. degree from McGill University in Montreal in 1979. He did his postdoctoral training at the University of Ottawa and became professor and chairman of the Department of Ophthalmology at the University of Alberta in Edmonton before joining NIH in 2007 as chief of the Ophthalmic Genetics and Visual Function Branch, NEI.*

Medical genetics is about people and journeys in time. During my undergraduate days at McGill University, I was introduced to genetics by Clarke Fraser and Charles Scriver, who were keenly interested in the genetics of human dysmorphology and human metabolic conditions. That experience set the mold for a lifetime interest in genetics and led me to a career in medical genetics.

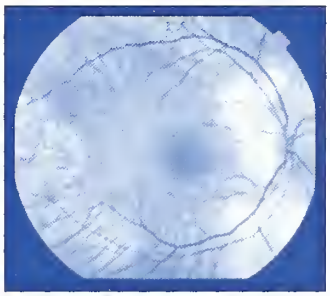
I was introduced to vision research early in my fellowship training in clinical genetics with Alasdair Hunter at the University of Ottawa: A patient asked if I would do research on her family, many members of which were affected by a degenerative retinopathy called choroideremia (CHM). I was just learning to use restriction-fragment-length polymorphisms as markers to map a genetic locus. CHM was X-linked, and there were few markers beyond Xg and color-blindness that one could use to determine linkage.

Molecular markers offered the potential to link the eye disorder to a specific arm of the X chromosome and, with luck, to get close enough to make some guesses as to where the gene was.

Christopher Wanjekr

Ian Macdonald

I was successful in linking the disorder to the long arm of X. At that time, single-nucleotide polymorphisms did not exist and there were few other markers available to refine the map location. Having exhausted genomic markers, I began with a then-graduate student, Paul Wong, to isolate expressed sequences from the X chromosome that might be part of candidate genes for CHM. In the early 1990s, I began to characterize mutations in the choroideremia gene (*CHM*) in families originally involved in mapping. That activity enabled what became a reference laboratory for this condition, funded by the Foundation Fighting Blindness.



Fundus of a male patient with choroideremia

The CHM gene product, Rab escort protein–1 (REP-1), has an important role to play in the trafficking of vesicles involved in intracellular transport in all cells—in particular, trafficking within the eye. In collaboration with NEI's Bob Fariss and Chi-Chao Chan, I have shown that the REP-1 protein is expressed abundantly in the eye. This work, as well as my continuing study of CHM gene expression in the eye, has promising implications for future therapeutic approaches.

For the past 15 years, I have studied genetic isolates from people living in the province of Alberta, where heritable ocular conditions are prevalent. Our early mapping studies in a family with autosomal dominant form of Stargardt-like macular dystrophy lead to the isolation, with collaborators, of *ELOVL4*, the gene that is mutated in this condition. This gene is thought to be involved in the pathway of de novo synthesis of very-long-chain polyunsaturated fatty acids, including docosahexaenoic acid (DHA). DHA is the major fatty acid of the retina and is essential for normal retinal development and physiology.

I have completed two pilot clinical studies on the effect of DHA as a nutritional supplement on macular function in patients with this form of Stargardt disorder. The resuts have been encouraging, and a clinical trial of DHA supplementation in patients with the dominant form of Stargardt-like macular dystrophy is planned to begin at NIH.

Meanwhile, because launching clinical trials in families with few affected members can be challenging, and animal studies can be helpful in suggesting clinical study design and potential outcomes, I am also continuing to work with animal models with colleagues at the University of Alberta—Yves Sauvé and Silvina Mema. We are carefully studying the effect of an *elovl4* mutation on the retina and on measurable functional changes in these mutant mice as they age, as well as whether a high-DHA diet will alter their retinal function.

Ruth Pfeiffer *trained in applied mathematics at the Technical University of Vienna and received a Fulbright Fellowship to study applied statistics. She earned a Ph.D. in mathematical statistics from the University of Maryland, College Park, in 1998, and joined NIH as a Cancer Research Training Award fellow in the Division of Cancer Epidemiology and Genetics (DCEG), NCI. She was promoted to research fellow in October 2000, and, since 2001, has been a principal investigator in the Biostatistics Branch.*

In recent years, I have initiated methodologic projects in several areas, including latent class models for viral epidemiologic and laboratory studies, design of genetic epidemiologic studies, models for family-based association studies, and statistical methods for risk projection and classification.

A focus of DCEG is to clarify the relationship of infectious agents, especially viruses, to human cancer. I have been involved in several studies focused on the biology, transmission routes, and

Recently Tenured

natural history of human herpesvirus 8 (HHV-8), also known as KSHV, the infectious cause of Kaposi's sarcoma.

Ruth Pfeiffer

I developed a Markov model to estimate the risk of transmission of HHV-8 from transfusion in Ugandan children with sickle cell anemia. The analysis was based on cross-sectional age-specific seroprevalence data and on the individuals' transfusion histories; it estimated that the risk of transmission of HHV-8 from blood transfusions was about 2 percent.

This model was crucial to the study because standard statistical approaches would not have estimated the critical quantity of interest, namely, the per-transfusion risk of infection with HHV-8. This analysis also allowed investigators to compare transfusion risk with background sources of risk.

Another challenge is estimation of HHV-8 prevalence. Although infection status with HHV-8 can be assessed by several serological assays, there is no gold-standard measure for a definitive diagnosis. To address this issue, I developed and applied mixture models to estimate the prevalence of infection of agents for which there is no definitive assay.

The mixture approach assumes that the observed assay distribution in a population is generated by different distributions for infected and uninfected subjects; this assumption allows one to determine the fraction of the population that is infected. I have used this approach to estimate the prevalence of HHV-8 in several African populations.

DCEG is leading many studies of genetic contributors to cancer etiology. Assessing whether disease aggregates in families is a first step in identifying a genetic component of that disease. I have adapted survival methods to test for familial aggregation of disease in cancer registry data that define familial relationships and identify all diseased cases in a population. I used these methods in collaborative studies of familial aggregation of lymphoproliferative disorders in Denmark and Sweden.

I also developed multilevel random-effects models that were used to analyze the effects of covariates in family-based case-control studies in which families are ascertained only if they have several affected members. This model accounts for random family effects as well as random genetic effects that induce specialized forms of correlation within families. Because these families are specially ascertained, methods for simple random samples of families do not apply, and special computational methods are needed.

The candidate-gene approach to studying genetic associations with disease is based on investigating several single-nucleotide polymorphisms (SNPs) in a gene that may be associated with disease. I have assessed sample-size requirements and power for population-based and family-based case-control studies to detect associations between disease and a genetic marker, instead of the true disease gene locus. Such calculations are crucial in designing association studies.

Christopher Wanjekr

Ying Zhang

I am also interested in risk prediction, discrimination, and related issues and have developed an absolute risk–prediction model for colorectal cancer, the second leading cause of cancer death in the United States. The absolute risk is the probability that an individual with given risk factors and a given age will develop colorectal cancer over a defined period of time.

In collaboration with my branch chief, Mitchell Gail, I defined loss-function–based criteria tailored to specific applications to evaluate models of absolute disease risk. This approach showed that models with modest discriminatory power may not be useful for screening but may be useful in making clinical decisions that involve potential for both benefit and harm.

I have also developed classification algorithms for high-dimensional data—for example, microarrays, mass-spectrometry data, and denaturing high-performance liquid-chromatography curves. With my fellow Annette Molinaro, now at Yale, I compared cross-validation methods used to estimate prediction errors for various discrimination algorithms based on high-dimensional data.

All of my work has been directly or indirectly motivated by collaboration with my colleagues at the DCEG and elsewhere at NIH. My training in mathematics and the scientific environment of DCEG have yielded a rich and enjoyable statistical and collaborative research program for epidemiological and laboratory studies.

Ying Zhang *received her Ph.D. from the University of Wisconsin–Madison in 1995, carried out her postdoctoral training with Rik Derynck at the University of California, San Francisco, and joined the Laboratory of Cellular and Molecular Biology , NCI, in 2000 as a tenure-track investigator. She is currently a senior investigator in that lab.*

The research focus of my laboratory is on the roles and signaling mechanisms of the TGF-β superfamily of peptide growth factors that perform a diverse array of functions during development and cancer.

My interest in the TGF-β pathway began during my postdoc training at UCSF, where I was among the first few scientists to identify and clone the mammalian Smad proteins that later turned out to be the substrates of TGF-β receptor kinases and the major intracellular signaling mediators for all members of this family. My work there also helped to define the mechanism of Smad3 in cooperatively interacting with c-Jun/Fos to control TGF-β target gene expression, which is still today is the paradigm for how all Smads function in transcription.

After joining the Laboratory of Cellular and Molecular Biology at NCI, I directed the effort of my group to three unresolved issues in the TGF-β pathway—the nature and significance of a Smad-independent TGF-β receptor-signaling mechanism, the physiological functions of two newly isolated ubiquitin E3 ligases for Smad proteins, and the role of Smad3 in tumorigenesis.

Based on the crystal structural data and kinase-substrate interaction, we constructed a mutant type I TGF-β receptor that is incapable of recognizing Smad3 but still retains its kinase activity. With the aid of this key reagent, we were able to show that TGF-β can signal through a separate conduit via p38 MAPK to control apoptotic gene response. This finding provided a biochemical proof for the long-suspected Smad-independent TGF-β receptor signaling.

Currently we are pursuing the missing link between the TGF-β receptor and activation of p38 MAPK in this alternate signaling route. I believe these studies will result in our being able to paint a comprehensive picture of how TGF-β signals to control its target genes, a necessary step in our quest for manipulating this pathway for therapeutic goals.

The diverse biological functions exerted by TGF-β demand that its signaling pathway have built-in mechanisms for the integration of multiple cell-signaling inputs. The Smad-ubiquitin-factor, or Smurf, is one such regulatory node.

Based on interaction and biochemical characterization data, we and others have found that mammalian genomes carry two Smurf genes capable of directing Smads and the type I TGF-β receptor to proteasome-mediated degradation.

To assess the biological significance of this regulation, we created mouse null alleles for both Smurf1 and Smurf2 by homologous recombination. The Smurf1-null mice are viable but display an age-dependent increase in bone mass due to elevated osteoblast activity.

Although this phenotype is consistent with the activation of the bone morphogenic protein pathway, neither the level of Smad1 nor the level of its receptor was changed in the Smurf1-null mice. Instead, Smurf1 removal resulted in MEKK2 activation, which in turn caused the increase in osteoblast function.

It is possible that the MEKK2 loop is part of the Smad-independent signaling mechanism and that the deficiency of Smurf1 in Smad degradation was compensated by Smurf2. We are currently testing these hypotheses by characterizing mice deficient in Smurf2 alone or in combination with Smurf1.

In the third line of inquiries, we created several lines of mouse liver-tumor models expressing different Smad3 transgenes. We showed that forced expression of Smad3 protects the liver from chemically induced carcinogenesis, and we demonstrated that this protection was afforded by the ability of Smad3 to execute the TGF-β–induced apoptotic instruction by downregulating the expression of Bcl-2.

This finding sheds light on the molecular mechanism that controls the liver-tumor growth and offers new insight in our pursuit of novel approaches to treat liver cancer. ■

On Tenure Track

photos by Christopher Wanjekr

Roberto Weigert started working at NIH full-time six years ago, in NHLBI. He now leads his own lab in the Intracellular Membrane Trafficking Unit of NIDCR in building 30.

His focus is on understanding the molecular mechanisms regulating membrane traffic and protein secretion in salivary glands.

Hundreds of proteins are likely implicated, and few are known, he says, making this a field ripe for discovery.

Understanding these mechanisms may have an immediate relevance to the design of strategies to cure two of the major disorders affecting salivary glands: Sjögren's syndrome, an autoimmune disease affecting millions of Americans, predominantly women, in which the body's immune system attacks moisture-producing glands; and the damage induced by radiation treatment for head and neck cancer.

The field has progressed much since Pavlov's day, mainly through research with cell-culture models. Weigert is transitioning to three-dimensional systems and live organisms using two-photon microscopy.

By exposing the salivary glands of living rats, his group can penetrate several hundreds of micrometers into the tissue to obtain a subcellular view of the intracellular organelles.

"With a cell culture, at some point you ask, 'Is this physiologically relevant,'" Weigert said. "We are now looking at cellular events in their physiological context and we see clear differences from the tissue-culture models."

It is known that saliva is first produced in acinar cells and is then transported through ductal cells. Weigert's group is narrowing in on how secretory proteins are stored in granules and transported to the apical plasma membrane, as well as how proteins and nutrients are delivered and transported from the cell surface to inside the cell. One goal is to elucidate the molecular mechanisms regulating both exocytic and endocytic events in mammalian

Zheng Li is studying synaptic plasticity, or how the connections between neurons change in strength and how this change is related to cognition and neurological disorders. She joins the Genes, Cognition and Psychosis Program of NIMH after five years as a postdoc at the Massachusetts Institute of Technology in Cambridge.

During her postdoc, Li discovered that apoptotic molecules mediating programmed cell death can be activated in normal healthy neurons by electrical stimulations that cause long-term synaptic depression.

Li is investigating how the cell-death mechanism is involved in the decrease in synaptic transmission seen in develeopmental, cognitive, and neurological disorders, with an emphasis on schizophrenia.

Hundreds of proteins are involved in the action of a single synapse, and the details of this protein regulation are largely unknown.

Li's lab in Building 35 uses molecular and cellular biology, live imaging, and electrophysiological techniques to study the electrical and chemical signaling occurring in the hippocampus and other brain slices of rats.

The hippocampus is involved in memory, emotion, and spatial navigation and is one of the first regions of the brain damaged in Alzheimer's disease.

By taking a "bottom's up" approach of searching for the protein interaction in synapses, Li hopes to contribute to the understanding of how and why synapses wither. Her most recent work entails the nonapoptotic role for caspase-3 in long-term depression and AMPA receptor internalization in hippocampal neurons.

—Christopher Wanjek

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 2E26.**

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

In Future Issues...

- Infectious Disease/ Biodefense Research
- A New Bacterium
- Interest Group Directory

New Interest Groups Forming: In Search of Interested Members

Mucosal Immunology Interest Group (MIIG)

The goal of the MIIG is to provide a forum for scientific discussion and sharing of reagents and models in the field of mucosal immunology (nasopharyngeal, gastrointestinal, respiratory, genitourinary, oral, and ocular mucosal tissues, as well as basic, clinical, and translational topics. We anticipate a monthly journal club and a yearly symposium, but would first like to hear from people who might like to become members. Please send us a sentence or two describing your area of interest, a website to your laboratory or department, if available, and any suggestions for future activities. We will plan on listing members names, interests, and contact information on the MIIG website, once it is functional.

Yasmine Belkaid <ybelkaid@mail.nih.gov>
Brian Kelsall <bkelsall@mail.nih.gov>
Warren Strober <wstrober@mail.nih.gov>

AIDS Interest Group

To promote more contacts and collaboration across the Institutes and scientific fields, we are going to revive the NIH AIDS Interest Group. If you are interested in HIV/AIDS research please, add your name to the list of members. To do this, go to:

<https://list.nih.gov/cgi-bin/wa?SUBED1=aidsintg-l&A=1>

enter your e-mail address and full name and click the button to join.
In June-July, I will solicit suggestions from those who register, and we shall then discuss plans for an attractive and fruitful interest group.

Leonid Margolis, Chief, Section of Intercellular Interactions, NICHD

Pediatric Neuroimaging Group

The Pediatric Neuroimaging Group is a newly formed NIH Scientific Interest Group (SIG) that will bring together interested intramural and extramural participants for a series of speakers on such topics as methodological, analytic, and ethical issues relevant to pediatric neuroimaging basic and clinical research, as well as discussions on current databases and software resources. If you would like to attend our first meeting (June 22, 2007) or to learn more about the group, contact:

Lisa Freund, NICHD, 301-435-6879 or e-mail: <**freundl@mail.nih.gov**>.

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2E26, 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
John I. Gallin
Director, NIH Clinical Center

Henry Metzger
Scientist Emeritus

MANAGING EDITOR
Fran Pollner

WRITER-EDITOR
Christopher Wanjek
Director of Communications, OIR

COPY EDITOR
Shauna Roberts

CONTRIBUTING WRITERS
Stephanie Cooperstein
Evan Galloway
Jennifer White

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Building 2, Room 2E26
MSC 0235
Bethesda Maryland 20892

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

Official Business
Penalty for Private Use $300

Printed on 50% recycled content paper and can be recycled as office white paper.