

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

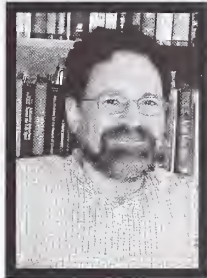
NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 14, ISSUE 4 ■ JULY–AUGUST 2006

Interview with David Abrams BEHAVIORAL SCIENCE: THE EVIDENCE IS IN

by Fran Pollner

David Abrams founded the Transdisciplinary Center for Behavioral and Preventive Medicine at Brown University in Providence, R.I., and was its director for the last 17 of his 25 years at Brown, as well as professor of psychiatry and human behavior and of community health.

He was a continuously funded NIH grantee from 1982 until he left Brown in 2005 to become the third director of the NIH Office of Behavioral and Social Science Research.



Fran Pollner

David Abrams

Abrams' research has focused on the interactions of risk factors of chronic diseases, addictions, and stress and has covered the bases from bench to bedside to public health and policy. *The NIH Catalyst* interviewed Abrams the week after the OBSSR's 10th-anniversary symposium, June 21–22.

Q: How do you define basic research in the behavioral and social sciences?

ABRAMS: The same as you would in any other science: the study of basic mechanisms without necessarily a defined endpoint or disease in mind. Examples would be cognitive mechanisms in motivation related to behavior change and fundamental mechanisms that explain the formation of social attitudes and beliefs that are the basis of stigma, stereotyping, and discrimination.

I think there's a misperception that the study of behavior and society must by definition be applied research.

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OBSSR 10th Anniversary

BEHAVIORAL RESEARCH SEEN AS KEY PIECE IN THE GENE-ENVIRONMENT PUZZLE

by Fran Pollner

During his two years as OBSSR director at the beginning of the 21st century, Raynard Kington made the rounds of institute and center program directors to gauge their behavioral research interests.

The idea that there could be any interest was dismissed entirely by one director, Kington recalled in his introductory remarks at the two-day OBSSR 10th-anniversary symposium. "This individual responded by telling me, 'but you must understand, the students in my program are the very brightest students.' I proceeded to explain that *even* the brightest students choose careers in behavioral and social science research!"

Nowadays, Kington observed, most people are more cognizant of the fact that it is behavioral science that will provide the missing links between gene-environmental interactions.

No less than 50 percent of the growing burden of chronic disease is related to behavioral and social factors, NIH Director Elias Zerhouni noted, advocating a shift from the "curative model of health," after the fact of illness, to one that recognizes that "chronic diseases do not occur on the day the patient visits the doctor but decades before."

A Place at Every Table

Today, noted OBSSR Director David Abrams, each of the 27 institutes and centers "has a niche" for behavioral and social science research.

Indeed, the ICs were out in force at the two-day meeting, filling the hallways with posters of their funded behavioral science research and brochures and other handouts on their BSSR programs and issues of particular relevance to their respective



Fran Pollner

OBSSR Directors Emeriti: Norm Anderson (right), who led the office from its inception in 1995 until 2000, chatting with his successor, Raynard Kington, now NIH deputy director, as the crowd assembled at Natcher to mark the 10th anniversary of OBSSR

missions.

They targeted the behavioral components of disease mechanisms, environmental contributors to disease, motivations for and against adhering to prescribed regimens, how best to impart health information, ferreting out the reasons for health disparities, and many other issues. For some, like NIDA and NHLBI,

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GUIDING PRINCIPLES AND ETHICAL PRACTICES



Michael Gottesman

On June 14, 2006, I testified before the House Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce regarding NIH rules and regulations governing conflict of interest, transfer of materials to private industry, and oversight of samples obtained from human subjects. This testimony was occasioned by a congressional investigation of the activities of one NIH scientist, but the issues raised and lessons learned have value for all NIH staff.

After pointing out the many complex regulations that our scientific staff must internalize to prevent future episodes of the kind under congressional scrutiny, I observed that NIH could facilitate this process in three ways:

- By communicating clearly just what the laws, rules, and regulations are and providing appropriate continuing education on the issues and requirements
- By providing expert administrative staff to help NIH employees navigate through regulatory language that may contain subtle distinctions related to exceptions, exemptions, waivers, and recusals that might be needed for us to carry out our work
- By reviewing the facts and imposing clear penalties in the event that rules are negligently or deliberately violated

Let's consider each of these points in turn.

Communication of Rules and Regulations

The rules covering conflict of interest, human subjects regulations, and technology and materials transfer are the subjects of courses required of all NIH scientists. If you have not taken these courses, or have not taken them for a while, please check out the websites below and take advantage of the concise, but complete, information in the accessible computer-based courses:

<<http://ethics.od.nih.gov/cbt.htm>>

<<http://ohsr.od.nih.gov/cbt/cbt.html>>

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

The principles underlying the messages contained in these subjects can be summarized as follows:

For conflict of interest: Do not use your government position for real or perceived financial gain for yourself, family members, friends, or significant others.

For human subjects research: All NIH researchers and research staff are responsible for knowing when their research activities involve human subjects. Such research may be conducted only after approval by an NIH IRB or the NIH Office of Human Subjects Research (OHSR).

For technology transfer: Inventions and discoveries made at NIH are the property of the U.S. government, whose intent is to encourage their dissemination to advance the development of research tools and biomedical products for the prevention, treatment, and cure of human diseases.

I recently sent out clarifications on the required IRB oversight of the continuing use of identifiable human tissue samples. See

<http://ohsr.od.nih.gov/info/DDIR_memo.html>

and <<http://ohsr.od.nih.gov/info/sheet14.html>>.

It is not acceptable to use stored human samples obtained under a research protocol unless there is continuing IRB review and approval. This means that if you or a colleague have samples in a freezer from a protocol closed to further accrual and these samples have not been anonymized, the IRB must decide whether your proposed research use is appropriate. Exceptions for anonymized samples can be obtained from OHSR:

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

A committee of scientists and administrators has been assembled to clarify rules governing transfer of materials from the NIH. Currently, some kind of transfer document is required (for example, a simple letter agreement, a materials transfer agreement, a letter of collaboration, or a CRADA) for all such transfers, but it is clear that more precise advice is needed about which document is necessary for which transfer. For example, we will require that transfer of human samples be under the direct supervision of senior leadership in an institute. Every effort will be made to make the process as straightforward as possible. Further guidance will be forthcoming.

Where To Go for Administrative Help

NIH currently provides administrative support to NIH scientists to help them navigate the complex rules that govern many different activities.

■ If you have a question about a potential conflict of interest, see your deputy ethics counselor:

<<http://ethics.od.nih.gov/decs.htm>>.

■ If you have a question about human subjects regulations, check with OHSR:

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

■ For technology transfer questions, check with your technology development coordinator:

<http://ott.od.nih.gov/nih_staff/tdc.html>

or the Office of Technology Transfer:

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

■ For advice on reporting possible conflicts of interest, contact the Office of Management Assessment

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

Recently, I sent out a list of official duty activities that might require more administrative scrutiny. The NIH Ethics Office prepared the list with the help of various advisory committees to apprise our scientific principal investigators of activities that need review and approval. See

<<http://www1.od.nih.gov/oir/sourcebook/ethic-conduct/officialduty policy.htm>>.

For outside activities, supervisory, administrative, and/or DEC review and approval is required.

Consequences of Violating Rules

I am often asked whether the individuals whose names became known to NIH or who self-reported various violations of conflict-of-interest regulations were ever called to task. The answer is yes. There is a strong sense among NIH staff that individuals who willfully break NIH rules and regulations should suffer the consequences. To date, detailed investigations and analyses have been completed for all of the 44 persons in this category, with disciplinary action ranging from letters of reprimand to suspensions to termination of government employment, depending on the severity of the violation.

Although no simple set of principles or documents can fully capture the complexity of the laws, rules, and regulations that govern the work of federal scientists, it's up to each member of the NIH staff to be aware of their responsibilities, the basic principles that govern all of their official duty activities and outside activities, and where to seek help if they have any questions about a proposed course of action. I hope this column assists in achieving that objective.

That said, I believe that the vast majority of intramural scientists make every effort to comply with the myriad rules imposed upon them and that we must craft carefully any additional requirements to minimize additional time and effort.

—Michael Gottesman, DDIR

FRONTIER SCIENCE: SEPTEMBER 19 SYMPOSIUM SHOWCASES PIONEER AWARD PROGRESS

by Sarah Goforth

LETTER TO THE EDITOR

To the *Catalyst*,

I was pleased to read the article on the Bench-to-Bedside resiniferatoxin research project in the last issue ("Bench-to-Bedside Journey to Morocco: Novel Strategy to Vanquish Intractable Cancer Pain—Resiniferatoxin at Threshold of Clinical Trial," *The NIH Catalyst*, May-June 2006).

I was especially pleased to see that the pioneering work in this field by my colleague Peter Blumberg [senior investigator, Laboratory of Cellular Carcinogenesis and Tumor Promotion, NCI] was duly noted in a footnote to the article.

This gives me the opportunity to remark on how the critical discoveries of NIH scientists like Blumberg fuel not only their own continuing research but that of other NIH scientists who may or may not directly collaborate with them but who learn from them and readily express their indebtedness to them.

In the case of the very rewarding Bench-to-Bedside research of [Michael] Iadarola and [Andrew] Mannes and others, which has painstakingly tested and refined a promising approach to the relief of excruciating pain—culminating in a commercial-grade product on the brink of human trials—there is a foundation built by Blumberg. Blumberg discovered the resiniferatoxin-capsaicin connection, discovered the ability of resiniferatoxin to downregulate pain, and showed that it had a receptor (which resulted in the cloning of the receptor—TRPV1).

Blumberg continues to lead the field in TRP receptors and pain and is developing analogues of resiniferatoxin to use clinically.

Needless to say, the NIH infrastructure promotes not only the freedom to pursue at length tantalizing questions but also the cross-talk among basic and clinical researchers working in different institutes that electrifies the atmosphere around here.

Congratulations all around!

—*Stuart H. Yuspa, Chief,
Laboratory of Cellular Carcinogenesis
and Tumor Promotion, NCI*

—*Speaking of cross-talk, see the
Interinstitute Interest Group Directory,
pp. 10-14—Ed.*

A Stanford University (Stanford, Calif.) bioengineer is looking at the brain on millisecond-long time scales to understand how rapid changes in neural circuits relate to psychiatric symptoms such as anxiety and hopelessness.

Nearby at the University of California, Santa Barbara, an evolutionary psychologist is applying the tools of evolutionary biology, cognitive science, anthropology, neuroscience, and psychology to study human motivation.

Meanwhile at the University of Arizona Tucson, a biochemist is using her understanding of how gene expression is controlled in plants as a foundation for the study of similar pathways—some of which are associated with disease—in people.

On the East Coast, a neurobiologist at Duke University Medical Center in Durham, N.C., is blending molecular, behavioral, and computational approaches to study how songbirds learn to make music. His work could provide a foundation for new vocalization disorder treatments in humans.

At Rockefeller University in New York, a biochemist and expert in the study of telomeres is developing a new system for studying the biological response to DNA damage.

And across the Atlantic at the University of Cambridge in Cambridge, England, a computational biologist uses powerful mathematical models to understand how flu viruses and other pathogens evolve.

What do these varied and accomplished people have in common?

They are among last year's recipients of the NIH Director's Pioneer Awards, which recognize exceptionally creative scientists who bring their talents and expertise to bear on some of the biggest challenges in biomedical research.

Traditional NIH grants support research projects, but Pioneer Awards support individual researchers and allow an unusual degree of freedom to innovate and take risks. NIH made nine awards in 2004, the first year of the program, and 13 more in 2005.

The 2005 awardees will present their



progress at the second annual NIH Director's Pioneer Award Symposium on **Tuesday, September 19**, in Masur Auditorium, Building 10. The symposium will also feature the announcement of the third class of Pioneer Award recipients.

The day will kick off at 8:15 a.m. with opening remarks by NIH Director Elias Zerhouni and Jeremy Berg, director of the National Institute of General Medical Sciences, who shares responsibility for overseeing the Pioneer Award program. Next come talks by the

class of 2005:

Vicki L. Chandler, University of Arizona

Hollis T. Cline, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.

Leda Cosmides, University of California, Santa Barbara

Titia de Lange, The Rockefeller University

Karl Deisseroth, Stanford University

Pehr A.B. Harbury, Stanford University School of Medicine

Erich D. Jarvis, Duke University Medical Center

Thomas A. Rando, Stanford University School of Medicine

Derek J. Smith, University of Cambridge and Erasmus Medical Center, Rotterdam, The Netherlands

Giulio Tononi, University of Wisconsin-Madison Medical School

Clare M. Waterman-Storer, The Scripps Research Institute, La Jolla, Calif.

Nathan D. Wolfe, Johns Hopkins University Bloomberg School of Public Health, Baltimore

Junying Yuan, Harvard Medical School, Boston

Their research is described at

<<http://nihroadmap.nih.gov/pioneer/Recipients05.aspx>>.

Capping the event, from 3:40 to 5:30 p.m., will be a poster session by 2004 and 2005 Pioneers and members of their labs, along with a concurrent reception. Attendance is free, and no registration is required. For the agenda, see

<<http://nihroadmap.nih.gov/pioneer/symposium2006/>>.

For an overview of the Pioneer Award and its history as part of the NIH Roadmap for Medical Research, see

<<http://nihroadmap.nih.gov/pioneer/>>.

ABRAMS ON BEHAVIORAL SCIENCE

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That's not true. How we interact with others and how that relates to the society we construct is basic research.

We can work forward from basic biologic and sociobehavioral mechanisms through neuroscience, cognition, and emotion to understand the basic behavior patterns of groups, families, and nations. At that point, there may be implications for intervention and policy—the applied science of behavior change goes to prevention, treatment, and more global policy-making.

The starting point could also be a complicated problem with multiple causal pathways—research involving tobacco and health disparities are probably two of the best examples—from which you work backwards through different disciplines, different basic sciences, to the basic mechanisms, which lead to a fuller understanding and better interventions.

Q: Are your reasons for coming here materializing?

ABRAMS: Yes. Right now, we are at the crossroads of unprecedented discoveries and urgent demands for solutions. I am talking about the fact that the costs of maintaining quality health care will be unsustainable as aging baby boomers create a huge bolus of chronic diseases that threaten to overwhelm our acute-care medical services.

Behavioral and social sciences have a lot to contribute to potential solutions. We have very good principles and measures and evidence-based findings—and we will have more opportunity to share that knowledge. This is an exciting time for me to be here, to spur on the most pressing research questions and, perhaps even more important, the fuller use of what we know already. We need more integrative approaches and systems thinking.

For instance, there are 40 million people who still smoke. That's still the single leading cause of preventable death and costs more than \$160 billion a year in unnecessary health care and lost productivity. So while in the past 40 years we've had resounding success in cutting smoking in half and dramatically reducing associated death and disability, there are still 40 million smokers who need to be motivated to quit. Behavior therapy doubles the rate of quitting; add nicotine replacement therapy, and the rate is quadrupled. If we could get only 5 percent more smokers to quit each year, we could halve the number of smokers in the next 10 years. That might not sound as dramatic as the impact of a heart transplant on an individual, but it would make a huge societal difference in the burden of some of the biggest preventable killers

in our country—cancer, heart disease, and pulmonary diseases.

The behavioral and social sciences can also be brought to bear on the obesity epidemic and the emergence of type 2 diabetes.

Q: In his talk [at the 10th- anniversary symposium], Dr. Kington referred to pockets of resistance to behavioral science in the biomedical community. Is that at NIH or the biomedical community at large?

ABRAMS: I think both. It's also a two-way street. There is resistance among both the biomedical and the behavioral sciences. Each tends to protect its own guild-like interests.

There are still disciplinary silos, many people who are comfortable doing only what they were trained to do in graduate school, a persisting belief that the big discoveries are made by an individual who has become an absolute expert on a very narrow mechanism and wins a Nobel prize. There's a misplaced fear that transdisciplinary science will not solve the biggest problems.

Although there is an emerging openness to team science with the realization that no one discipline or causal model is adequate to address complicated problems—we are seeing this particularly in the area of systems biology—that openness is more within the broad disciplines of the biomedical sciences or within the broad disciplines of the behavioral, social, and population sciences. Each of these tends to resist learning from the other, resists crossing from one to the other to understand all the causal roles—sociocultural, psychosocial, biologic, genetic. Systems thinking can be expanded from biology to behavior to society, from genomics to “populomics.”

For instance, some in the population-public health science community have a causes-of-the-causes model: The real cause of preventable diseases and health disparities ultimately resides in the macrosocio-economic environment—poverty, lack of opportunity, pockets of prevalence of multiple risk factors, lack of access to health care and to fresh fruits and vegetables, reliance on fast foods, unsafe environments that prevent outdoor activity.

I do believe that we have developed an industrial society that unintentionally has created an environment toxic to our genes, which are not capable of changing as fast. For instance, we have developed processed



Fran Pollner

David Abrams: “As we learn more about our genes and the biological vulnerabilities we all have to certain kinds of lifestyles and exposures to pathogens, we see how critically important it is to ensure that we create less toxic lifestyles, neighborhoods, communities, and societies.”

foods that tend to taste good and reward certain brain pathways but are unhealthy. We used to live in a world where pleasure was hard to come by—where we had to run many miles to catch a deer, which might have happened only every three weeks; but now if your brain craves fat and sugar, you can get it most any day and cheaply. So there is a lot to say for changing the environment and our behavior.

But you can't have disease unless those environmental exposures get under the skin and interact with genes that are vulnerable. There's still the questions of why do some of us get fat and others not, why some have heart attacks and others not, why some kids get addicted to tobacco and others not. Genes and biology are as important as environment. It's not one or the other but both. The action is in the interaction—it's really two sides of the same coin.

I see my job as helping to form partnerships, accelerate the sense of excitement among biomedical, psychosocial, and population scientists who are starting to embrace a paradigm shift based on the growing recognition that the 20th-century model of genetic determinism is incomplete. I see my job as challenging the resistant members of all the disciplines to roll up their sleeves and learn from and talk to one another.

Q: In that capacity, are you dealing mostly extramurally or intramurally—and how?

ABRAMS: At the moment, our office has been largely positioned and focused on enhancing extramural research, working with our 27 IC partners, some of whom were early enthusiastic supporters of our

OBSSR TENTH ANNIVERSARY

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program—such as NCI, NIMH, NIA, NHLBI, NIDA, NIAAA, NCCAM, NIDDK, NIDCR, NINR, ORWH, and NCMHD, to name a few.

We build consensus for new initiatives to bridge behavioral and biologic areas; we identify high priorities, see where things may be falling through the cracks, and use traditional program mechanisms, such as RFAs, to address issues that given ICs might not necessarily see as their domain—say, the issue of depression and cardiac disease.

I think this whole process will be facilitated by OPASI (Office of Portfolio Analysis and Strategic Initiatives), which is designed to look at trans-IC opportunities. My hope is that because OBSSR exists, there will be quicker, better, stronger trans-IC research initiatives.

Now for the intramural side—I also think we should play more of a role in looking at behavioral and social science in the intramural program. At this point, I would start simply by doing an inventory of what is going on intramurally and what needs strengthening. We need to go through that process.

Q: Do you fear the tightening budget will negatively affect your office?

ABRAMS: No. I think there is even more awareness of how valuable behavioral and social science research is. As Dr. Zerhouni said [at the anniversary meeting], this is a critical time in which so much of preventable disease clearly has changeable behavioral causes. If anything, that situation should enhance appreciation of the need for partnerships—working together to solve problems more efficiently.

Q: Did you find the OBSSR meeting exciting?

ABRAMS: It exceeded my wildest expectations. We don't often put together in one place all the amazing research—the discoveries, the applied research contributions—across the 27 ICs over 10 or more years. It's also great for behavioral and social scientists to see how far we've come, how much our science has matured, to see the evidence-based interventions that have been proven to work in randomized trials and other rigorous research designs—and that do work in the real world. We are a hard science that is actually improving the public health and the quality of care and reducing costs.

As the chairman of the British Medical Research Council recently said, the challenge now is to move from genomics to populomics to look at the patterns of disease in whole populations, which should facilitate understanding the gene-environment interaction for the major chronic diseases and most common diseases. ■

the behavioral “niche” was nearly everywhere; for others, more defined. Following is random sample of some of the NIH literature on display during the symposium, ranging from discrete studies to broader initiatives and programs. (This list does not reflect the sum total of the behavioral research of any of the institutes.)

NCCAM-funded research from the Institute for Behavioral Medicine Research, Ohio State University, Columbus, on “How Stress Kills and How Complementary/Alternative Medicine Interventions May Help: New Evidence from Psychoneuroimmunology” suggests that the effect of yoga on soluble IL-6 receptor levels may help buffer inflammatory responses in such conditions as arthritis, asthma, and inflammatory bowel disease.

NIDCR-funded research from the University of Michigan School of Dentistry, Ann Arbor, and the Detroit Center for Research on Oral Health Disparities: “Solving Community Oral Health Problems through Action-Oriented Research” is focusing on two major community-wide issues: dental caries in children and their caregivers and oral cancer in African American men in Detroit.

NIMH-funded research from the University of Maryland Psychiatric Research Center in Baltimore and the University of Iowa in Iowa City addresses the nature and impact of impaired attention control on cognition and overall functioning in schizophrenia, with implications for treatment. Issues addressed at recent NIMH-sponsored meetings include reward neurocircuitry in adolescents, treating children with depression, indigenous suicide-prevention programs, and HIV treatment adherence. Among potential new initiatives are translational research on the relationship between anxiety and depression, interventions and service-delivery models for youth transitioning to adulthood, and mental health issues in basic translational social neuroscience.

Dozens of published **NICHD**-funded studies on learning, obesity, and behavioral and social science research through the lifespan included such titles as “Dyslexia-Specific Brain Activation Profile Becomes Normal Following Successful Remedial Training,” “Developmental Changes in the Functional Brain Responses of Adolescents to Images of High- and Low-Calorie Foods,” and “Early Experience Alters Brain Function and Structure.”

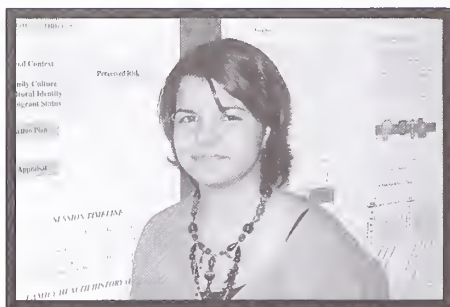
NIAAA provided an overview of institute-supported behavioral research on alcohol dependence; alcohol across the lifespan; the varying influences of genes and environment on different alcohol-related behaviors; behavioral phenotypes and alcohol-related problems; human genes affecting clinical and other phenotypes; the relationship of alcohol sensitivity and problematic use in adolescents; learning about drinking behavior from animal models; decisionmaking about alcohol; the affects of alcohol on brain and behavior; and behavioral approaches to intervention. ■

The Health and Retirement Study, a cooperative agreement between **NIA** and the University of Michigan Institute for Social Research in Ann Arbor amasses biomedical, psychological, genetic, and economic data that is a public resource for thousands of researchers. The institute's Behavioral and Social Research Program embraces individual behavioral processes and population and social processes.

The Models of Infectious Disease Agent Study (MIDAS), supported by **NIGMS**, involves transdisciplinary collaborations to develop computational models of the interactions between infectious agents and their hosts, disease spread, and response strategies. “Basic behavioral science research informs MIDAS modeling of human behavior under normal conditions and in response to an infectious disease outbreak.” Other **NIGMS** initiatives with basic behavioral research components are a new program for Collaborative Research for Molecular and Genetic Studies of Basic Behavior in Animal Models and awards for Training at the Interface of the Behavioral Sciences and Biology.

NHGRI's Ethical, Legal, and Social Implications (ELSI) Research Program, with **NICHD** and the Department of Energy, funds four multidisciplinary Centers of Excellence in ELSI Research that address such issues as genomic health care and the medically underserved and the integration of research on genetics and ethics. Under consideration are centers for the study of health disparities in tobacco dependence, asthma, and diabetes; social and cultural identities of individuals and communities of African descent and how they influence attitudes about genomics, health care, and health behaviors; and how information from genetics studies is used in biomedical research related to newborn screening, adolescent health, and centralized DNA banking.

NCI partners with **NIDA** and **NIAAA** (and the Robert Wood Johnson Foundation) to fund eight Transdisciplinary Tobacco Use Research Centers and with **OBSSR**, **NIEHS**, **NCMHD**, and **NIA** to fund eight Centers for Population Health and Health Disparities. One of these centers, based at the University of Chicago, is exploring “Breast Cancer and Social Interactions: Identifying Multiple Environments that Regulate Gene Expression,” which aims to explore the “influence of social environment and psychological factors on the epigenetic regulation of breast cancer gene expression.” This research is designed to address the question of why “African American women develop a premenopausal form of breast cancer that is more lethal and aggressive than that experienced by white women.” ■

A Poster Day Sampler of 9 from among 200+**POSTBACS EXPLORE PATHWAYS TO DISEASE, APPROACHES TO TREATMENT**by *Dustin Hays*
and *Karen Ross***All in the Family**

Karen Ross

*Aixa Alemán-Díaz***Aixa Alemán-Díaz, University of Michigan, Ann Arbor*****The Role of Family and Culture in Health Decision Making: A Conceptual Model Preceptor: Laura Koehly, Social and Behavioral Research Branch, NHGRI***

During the past year, Alemán-Díaz and Koehly have developed a protocol to study how family interactions affect the sharing of accurate health information and health-promoting behaviors.

The study will focus on multigenerational Latino families living in the United States. Several members of each family—typically the parents and grandparents of young children—will be asked about their family social structure and their perceptions of common health problems such as diabetes and heart disease. The same family members will then complete a Family Health History (FHH) tool, such as the CDC's Family Healthware™, which will assess risk for various diseases based on genetic, environmental, and behavioral factors.

Upon completing the FHH, participants will be told of their disease risk based on family health history and given tips for disease prevention based on behavioral assessments.

The researchers are interested in what happens next, when the participants go back to their families armed with this new information. They will do two follow-ups, at several weeks and six months after the administration of the FHH, to look for changes in perceptions of what causes common diseases and their own risks of disease, as well as changes in health-related attitudes and behaviors.

Importantly, says Alemán-Díaz, they want to focus not just on individual family members but on how the information affects the entire family system.

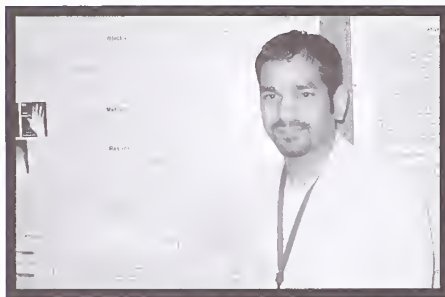
For example: Has the family changed the way it shares information about health

issues or makes health-care decisions? Have family members developed a more accurate picture of their risk of disease based on what the study participants learned about their risk? Have family members made lifestyle changes to reduce their disease risk?

This study is part of a larger effort to understand how family relationships influence health perceptions and decision making. Studies on other demographic groups are in the works, says Alemán-Díaz, who graduated from the University of Michigan in Ann Arbor in 2005 and plans to study cultural anthropology and public health in graduate school.

She will stay at NHGRI through this fall and help put her protocol into action working with families in the Houston, Texas, area in partnership with the University of Texas M.D. Anderson Cancer Center.

—Karen Ross

Cortisol-RA Connection

Karen Ross

*Shaan Alli***Shaan Alli, Baruch College, City University of New York*****Circadian Rhythm of Pro-inflammatory Cytokines in Rheumatoid Arthritis Preceptor: Raphaela Goldbach-Mansky, Office of the Clinical Director, NIAMS***

Patients with rheumatoid arthritis (RA), an autoimmune disease that causes pain, swelling, and stiffness in the joints, often observe that their symptoms are worst in the early morning.

Work by Alli and Goldbach-Mansky in collaboration with Marc Blackman's group at NCCAM suggests that this phenomenon may be associated with natural daily variations in cortisol, a steroid hormone produced by the adrenal gland that can suppress the immune system.

Secreted at high levels in stressful situations, cortisol increases blood pressure and blood sugar and suppresses the production of some inflammatory agents of the immune system. Aside from stress-related spikes, cortisol levels exhibit a cir-

cadian rhythm—predictably low in the middle of the night and peaking in the morning.

Alli and his colleagues hypothesized that the secretion of hormones might be influenced by the hyperactive immune system of RA patients and contribute to the development of their signs and symptoms. So they collected blood from RA patients and healthy control subjects at 20-minute intervals for 24 hours and measured the levels of several hormones and inflammatory molecules that might contribute to RA symptoms: TNF- α , GM-CSF, IL-8, and IL-6.

In both patients and control subjects, all four molecules showed a circadian variation, with the highest levels occurring in the early morning near the end of the low-cortisol period.

Although analysis of their data is ongoing, one interesting finding, says Alli, is that RA patients had significantly higher levels of IL-6 levels in the early morning than did control subjects, suggesting that cortisol might be important to keep IL-6 levels in check in RA patients. In general, RA patients had higher levels of immune mediators than control subjects at all times of day, but the differences were often not statistically significant.

The correlation between daily fluctuations in cortisol and RA symptoms fits in nicely with clinical data showing that steroid hormones similar to cortisol are often an effective treatment for RA, says Alli. Future studies on the behavior of the immune system in RA patients, he adds, might do well to take into account the time of day that samples are collected.

—Karen Ross

Prolactin–Breast Cancer

Karen Ross

*Kamun Chan***Kamun Chan, Bard College, Annandale-on-Hudson, N.Y.*****Effects of Prolactin Over-expression on the Progression of Breast Cancer Preceptor: Barbara Vonderhaar, Mammary Biology and Tumorigenesis Laboratory, NCI***

Chan has been studying breast tumor development in Vonderhaar's lab since August 2005. Her research concerns the complex and poorly understood relationship between the hormone prolactin and the development of breast cancer. Prolactin promotes breast milk production and is secreted in large amounts by the pituitary gland in pregnant and breastfeeding women. Prolactin is also made locally by breast tissue and breast cancer cells.

In addition, the Nurses' Health Study at Harvard University, Boston, showed that pre- and postmenopausal women with the highest serum prolactin levels have an increased risk of developing breast cancer.

To explore this dynamic on a cellular level, Chan designed a system to overexpress prolactin in four cell lines that represent different stages of breast cancer development—normal breast tissue, preneoplastic (some oncogenes have been activated but the tissue has not yet succumbed to the uncontrolled proliferation of full-blown cancer), invasive breast cancer, and metastatic breast cancer. Chan can control whether or not prolactin is overexpressed in her cells by adding the antibiotic doxycycline to the culture medium.

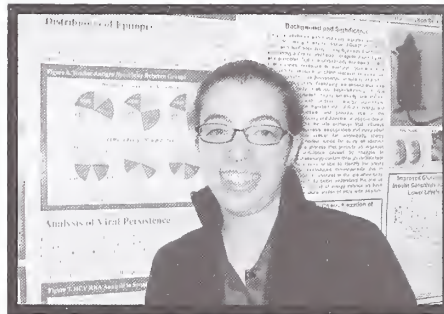
Chan plans to stay in the lab for another year to continue her project. Now that her system is ready to go, she will test how prolactin affects cell proliferation and cell motility, which is necessary for cancers to metastasize. Then she will inject her prolactin-overexpressing cells into mice and look at the aggressiveness of any resulting tumors. She hopes eventually to tease out the cellular signaling pathways that prolactin uses to influence tumor growth.

Chan is also a fellow in the NIH Academy, a program that aims to educate young researchers about health disparities in the United States. In addition to conducting her research, she has been participating in workshops and seminars on how and why disease and health care differ among population subgroups in this country.

—Karen Ross

Immunity to Hepatitis C

Hepatitis C, a liver disease caused by an RNA virus (HCV), spreads from person to person through contact with infected blood or blood products. Occasionally, people who contract hepatitis C recover spontaneously, especially if they are "young, lucky, and



Karen Ross

Brittany Holmes

Brittany Holmes, University of Colorado-Boulder

Immunological Memory in Hepatitis C: A Comparison of Treatment-induced Recovery and Spontaneous Recovery
Preceptor: Barbara Rehermann, Liver Diseases Branch, NIDDK

female," says Holmes, who has been studying the disease in Rehermann's lab since last October.

In most cases, however, HCV causes chronic hepatitis, and treatment with interferon and the antiviral drug ribavirin is necessary to stamp out the infection. If left untreated, HCV infection can cause liver failure or liver cancer.

Interestingly, people who fend off HCV on their own develop an immunological memory of the virus, so that if they encounter HCV again, T cells optimized to kill the virus are rapidly activated. People who require treatment to be cured appear not to develop this population of protective memory T cells. Holmes aimed to understand why.

She mixed immune cells from patients who had recovered spontaneously from hepatitis C with HCV proteins and saw a vigorous immune response. T cells proliferated and began to secrete interferon- γ , an important weapon in the immune system arsenal.

When she did the same experiment with immune cells from HCV patients who recovered after treatment, she got a much weaker response. There was no difference between patients who were treated within the first six months of contracting the virus and those who were treated later, she says.

She found that T cells from both untreated and treated patients were able to respond to many different pieces of HCV, but in each case the response in the untreated cohort was more intense. The immune response of the treated patients fell shorter in "strength, not breadth," she observes.

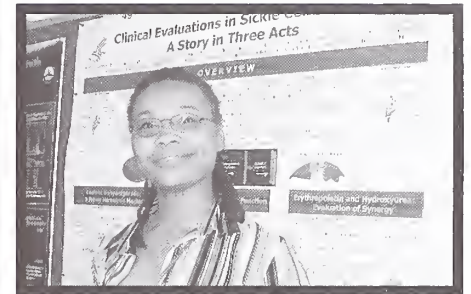
Before she heads to Nashville, Tenn., to Vanderbilt Medical School in the fall,

Holmes will continue her research from a couple of new angles.

She will explore whether genetic differences in HLAs, immune system molecules that help recognize foreign invaders, affect the ability to recover from HCV without treatment, as well as whether the frequency of spontaneous recovery varies with different HCV strains.

—Karen Ross

Sickle Cell Strategies



Dustin Hays

Vicki R. McGowan II

Vicki R. McGowan II, University of Maryland, Baltimore County

Clinical Evaluations in Sickle Cell Disease: A Story in Three Acts
Preceptors: Mark Gladwin and Jane Little, Cardiovascular Branch, NHLBI

Sickle cell disease is a genetic disorder that causes red blood cells, normally doughnut-shaped, to become rigid and misshapen. These abnormal cells obstruct blood vessels and are prone to rupture, causing an array of health complications, including anemia, chronic renal failure, stroke, and pulmonary hypertension. There is no cure for the disorder. Effective management of sickle cell complications relies on addressing symptoms early.

Pulmonary hypertension (increased blood pressure in the artery leading from the heart to the lungs) is a major complication of sickle cell disease. The most accurate test currently for measuring pulmonary hypertension—right heart catheterization—is invasive and therefore less than ideal for use in frequent monitoring. McGowan is exploring the value of two less-invasive alternatives for routine monitoring of pulmonary hypertension.

McGowan's team measured serum lactate dehydrogenase (LDH) levels taken from 213 sickle cell patients and ranked them into three groups: low, medium, and high. LDH is usually present in serum only when cells rupture, a characteristic of sickle cell disease. Seventy percent of pa-

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POSTBAC POSTERS

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tients with high levels of LDH also had pulmonary hypertension, suggesting that “LDH shows promise as a marker for hemolysis in sickle cell patients and may suggest a risk of pulmonary hypertension,” says McGowan.

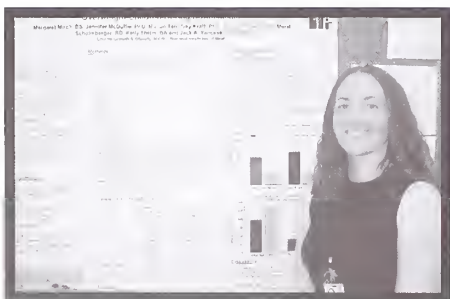
The team also demonstrated the value of echocardiography in assessing pulmonary hypertension. Tricuspid valve regurgitant jet velocity (the speed at which blood flows back into the atrium through the tricuspid valve), as measured by echocardiogram, correlated well with pulmonary pressures measured directly by right heart catheterization and with patients’ performance of a timed six-minute walk used to assess cardiopulmonary function. These results bolster previous findings that echocardiography is a reliable means of measuring pulmonary hypertension.

A third area of her work involves the design of a clinical trial to further study benefits of treating sickle cell disease with a combination of hydroxyurea and erythropoietin—two drugs that typically are administered independently but were reported by NIDDK’s Griff Rodgers in a 1993 article in the *New England Journal of Medicine* to have a synergistic effect.

The “essential goal is to extend [Rodgers’] findings,” says McGowan, who begins medical school this fall at the Virginia College of Osteopathic Medicine in Blacksburg.

—Dustin Hays

Binging and Weight Gain



Margaret Mirch

Margaret Mirch, Cornell University
Effects of Binge Eating on the Energy Intake, Satiety, and Satiety of Overweight Children during Buffet Meals
Preceptor: Jack Yanovski, Developmental Endocrinology Branch, NICHD

The percentage of overweight children in the United States has tripled since 1980. Overweight children who binge-eat gain more weight and fat mass than overweight children who do not exhibit this tendency. It is speculated

that external stimuli, such as the sight and smell of food, motivate binge-eaters to consume food beyond satiation. Margaret Mirch’s research explores the role binge-eating plays in the developmental progression of obesity.

Mirch’s lab conducted an experiment to assess energy intake and satiety duration of overweight children and to examine the contribution binge-eating behavior plays in food consumption. Study participants were overweight children, ages 6 to 12. Each participant completed two surveys: One addressed eating and weight patterns; the other was a 57-item food-preference questionnaire.

After an overnight fast, the children were presented with a 27-item food array and told, “Let yourself go and eat as much as you like. You may eat as much of anything that you would like to, but you do not have to eat anything you do not like.” The duration of the meal and the calories consumed were recorded. To establish the duration of satiety, participants were asked to refrain from eating or drinking until they reported the onset of hunger.

On the second day, after an overnight fast, participants consumed a standardized breakfast consisting of a 500-cc shake containing 787 kcal. Again, the satiety duration was recorded. After reporting hunger onset, the children were presented with a second buffet identical to the one of the previous day. Again, calories consumed were recorded. Immediately before and after food was presented, participants were asked to rate on a visual analog scale their hunger, their desire to eat, and their fullness.

Overweight children who exhibited binge-eating behavior had a significantly greater desire to eat and, when given access to large quantities of palatable food, consumed more calories than children who did not binge. The study also showed that binge-eating children feel hungry sooner than their non-bingeing counterparts.

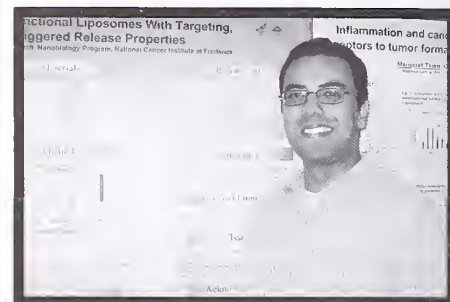
“Training children to attend to physical hunger signals” rather than sensory cues, Mirch says, might be a way to slow weight gain in children with binge-eating tendencies.

More studies are needed to elucidate the “behavioral, genetic, and neurohumoral mechanisms” that may account for deficits in appetite regulation among binge-eating children, she adds.

Mirch plans to continue her work in nutrition science this fall when she enters Boston University’s graduate program in nutrition.

—Dustin Hays

Anticancer Liposomes



Karen Ross

Shrikant Tele

Shrikant Tele, University of Maryland, College Park

The Development of Multifunctional Liposomes with Targeting, Imaging, and Triggered Release Properties

Preceptors: Robert Blumenthal, Anu Puri, Nanobiology Program, NCI

Most anticancer drugs are good at killing cancer cells, but they can also wreak havoc on healthy tissues. Encasing drugs inside a protective lipid particle and targeting the particle directly to the tumor would go a long way toward increasing the efficacy and decreasing the toxicity of chemotherapy, says Tele, who has been developing this technology with Blumenthal and Puri.

Tele is working on two aspects of drug delivery using lipid particles—how to target the particle to the tumor, and how to get the particle to release its contents once it gets there. The route of delivery of the lipid particle is determined by the targeting ligand(s) and the biophysical properties of the liposomes.

To get the particles to congregate at the site of the tumor, Tele plans to decorate the outside of the particles with specific antibodies that bind to molecules found only on the surface of tumor cells. Each type of tumor will probably require a different antibody, he says.

At first he will use the anti-HER2-neu antibody, which recognizes a growth factor receptor expressed by about one-third of breast cancers. He will also experiment with anti-HER2-neu AffibodiesTM, commercially available molecules that function like antibodies but are smaller and easier to handle.

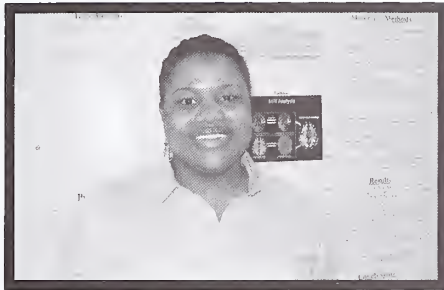
Liposomes “dump their payload” upon temperature regulation, says Tele. The particles they use hold together very well at body temperature (37 °C) but disintegrate at slightly higher temperatures (41–42 °C). He plans to use a focused ultrasound device for local heating of breast cancer tissue.

To help during the development and

testing stages, Tele has incorporated dyes into the particles so they can be tracked inside the body with imaging equipment. After several attempts, he found a dye that doesn't adversely affect the structure of the particles or their temperature-dependent breakdown. He plans to continue his stay and this research for another year, after which he hopes to go to graduate school.

—Karen Ross

Autistic Traits



Karen Ross

April Timberlake

April Timberlake, Harvard University
The Relationship between Temperament, Autistic Traits, and Cognitive Functioning in a Sample of Typically Developing Children and Adolescents
Preceptor: Jay Giedd, Child Psychiatry Branch, NIMH

People with autism spectrum disorders (ASD) have difficulty communicating, interacting socially with others, and adapting to change. ASD now affect about 0.3–0.6 percent of the population and are becoming more common, says Timberlake, a 2005 Harvard graduate who came to NIH last October to study social cognition with Giedd.

ASD cover a wide range—from the relatively mild behavioral and pragmatic speech abnormalities of people with Asperger's syndrome to the odd, repetitive behaviors and very limited speech and social interaction observed in people with severe classical autism.

Studies have shown that people with ASD have problems with specific skills, such as strategizing, planning, and shifting attention back and forth among tasks that are collectively called executive functioning. The brains of people with autism also look a little unusual in MRI studies—for example, they have less gray matter than normal in the temporal lobes.

Because ASD comprise a spectrum of conditions, conceptually this continuum could be extended down to the general population. Timberlake wanted to know whether autistic traits in typically devel-

oping people are associated with ASD-like findings in executive functioning and brain structure. Also, because ASD disproportionately affect males, she asked whether males were generally more likely than females to have many autistic traits.

Timberlake worked with a group of 88 typically developing children, half male and half female, from ages 8 through 18. Their parents filled out the Social Responsiveness Scale (SRS), a 65-item questionnaire that assesses social and communication skills and flexibility; the children underwent tests for executive functioning and an MRI to look at brain structure.

Timberlake emphasizes that the study “needs more power”—the number of subjects was too small and the analysis of brain structure too rough to glean very many statistically significant results. She is working to overcome these limitations.

But, she notes, there were a few significant findings and many interesting trends. Children with poorer communication skills on the SRS tended to do less well on the executive functioning tests. Children with high SRS scores (many autistic traits) had reduced gray matter in the right temporal lobe. Finally, boys on average had higher SRS scores than girls.

Such findings suggest that autistic traits in typically developing children are associated with executive dysfunction and some group-level brain differences, as observed in ASD, says Timberlake, who begins medical school in the fall.

—Karen Ross

Bone Density Blues



Dustin Hays

Caitlin Toomey

Caitlin Toomey, Cornell University
Is Major Depression Associated with Decreased Bone Mineral Density? A Comprehensive Meta-Analysis of All Published Studies

Preceptor: Giovanni Cizza, Clinical Endocrinology Branch, NIDDK

More than 1.5 million osteoporotic fractures occur annually in the United States, many requiring hospitalization. Low bone mineral den-

sity (BMD), usually determined by dual-energy X-ray absorptiometry, is viewed as a major risk factor for osteoporosis—and several studies have suggested a link between major depression and low BMD.

To assess the evidence in support of a link between low BMD and depression, Toomey conducted a meta-analysis of data from 16 studies that compared BMD in depressed individuals and nondepressed controls. Some of these studies used DSM (Diagnostic and Statistical Manual of Mental Disorders) criteria to define depression; others relied on less stringent methods, such as the Geriatric Depression Scale, which Toomey says are not as reliable.

BMD values from the antero-posterior spine (AP spine), the total femur, and the femoral neck were analyzed. Overall analysis showed that in all three anatomic areas, BMD was significantly lower in depressed subjects.

When the data were limited to studies that used DSM criteria, BMD values of the total femur and AP spine of depressed patients were even lower than those in the broader analysis described above. There was no similar reduction in the femoral neck BMD in subjects whose depression was diagnosed by DSM criteria. Toomey notes, however, that because this data subset included far fewer subjects, the findings should be interpreted with caution.

In addition, Toomey analyzed a subset of data derived from studies that examined BMD in men and found that only total femur BMD was lower in depressed subjects than in their nondepressed counterparts. No difference was detected in the AP spine or femoral neck BMDs in depressed men versus men without depression. Again, because the numbers were relatively small, Toomey urges caution in interpretation. “We think there probably is some effect in men, but not as large” as that in women, she says.

The results of this meta-analysis do support a correlation between major depression and low BMD, Toomey says, but further studies are required to elucidate the exact nature of the relationship. Toomey's group speculates that people with major depression fail to reach optimal peak bone density, which is usually established by age 30.

Meanwhile, she adds, patients with low BMD might well be screened for depression, and patients diagnosed with depression might well have their BMD evaluated. Toomey starts medical school this fall at the Vanderbilt University School of Medicine in Nashville.

—Dustin Hays

INTERINSTITUTE INTEREST GROUP DIRECTORY

Web Access

Although not all the sites are up to date, nearly all the Interest Groups have websites that can be accessed through <http://www.nih.gov/signs/signs.html>.

MAJOR INTEREST GROUPS

Cell Biology Interest Group

Meeting time: Not specified
Meeting place: Building 32, Library
Contact: Jennifer Lippincott-Schwartz
Phone: 301-402-1010; 301-402-1009
E-mail: <jlippin@helix.nih.gov>
ListServ: subscribe to CELBIO-L

Clinical Research Interest group

Meeting time and place: sponsors CC Grand Rounds once every other month
Contact: Cliff Lane
Phone: 301-496-7196
E-mail: <clane@nih.gov>

Genetics Interest Group

Meeting time and place: Two all-day symposia a year to be announced
Contact: Dan Kastner
Phone: 301-496-8364
E-mail: <kastnerd@mail.nih.gov>
ListServ: subscribe to <GIG-L@list.nih.gov>

Immunology Interest Group

Meeting time: Each Wednesday (except summer), 4:15 pm
Meeting place: Building 10, Lipsett Auditorium
Contact 1: Ron Germain
Phone: 301-496-1904
E-mail: <rgermain@niaid.nih.gov>
Contact 2: Brian Kelsall
Phone: 301-496-7473
E-mail: <bkelsall@niaid.nih.gov>
ListServ: subscribe to IMMUNI-L by joining the interest group at its web site

Molecular Biology/Biochemistry Interest Group

Meeting time and place: No regular meetings. IG heads meet yearly to consider WALS speaker nominations
Contact: Carl Baker
Phone: 301-435-1240
E-mail: <ccb@nih.gov>

Neuroscience Interest Group

Meeting time and place: Check website
Contact 1: Kenton Swartz
Phone: 301-435-5652
E-mail: <swartzk@ninds.nih.gov>
Contact 2: Bruce Cumming
Phone: 402-8097
E-mail: <bcg@lsr.nei.nih.gov>

Structural Biology Interest Group

Meeting time and place (2006-07): Usually 3rd Thursday, 4:00 pm, Building 50, first floor conference room; notices by e-mail and on the SBIG website
Contact 1: Teresa Przytycka
Phone: 301-402-1723
E-mail: <Przytyck@mail.nih.gov>
Contact 2: Doug Sheeley
Phone: 301-594-9762
E-mail: <sheeleyd@mail.nih.gov>
To register for e-mail announcements, join SBIG at <www.nih.gov/signs/sbig>

OTHER INTEREST GROUPS

14-3-3 Proteins Interest Group

Meeting time: Usually the third Wednesday, 4:00-5:00 pm
Meeting place: Building 40, First-floor Conference Room
Contact 1: David C. Klein
Phone: 301-496-6915
E-mail: <kleind@mail.nih.gov>
Contact 2: Surajit Ganguly
Phone: 301-451-6399
E-mail: <ganguly@mail.nih.gov>

Advanced Technologies Interest Group

Meeting time and place: Check the website
Contact: Steven Hausman
Phone: 301-402-1691
E-mail: <hausmans@mail.nih.gov>

AIDS Interest Group

Meeting time and place: Varies
Contact: Fulvia Veronese
Phone: 301-496-3677
E-mail: <veronesf@od.nih.gov>
ListServ: subscribe to AIDSINTG-L

Animal Well-Being Interest Group

Meeting time: quarterly
Meeting place: Building 14G, large conference room; occasionally hosts speakers on campus
Contact: Jim Weed
Phone: 301-435-7257
E-mail: <weedj@mail.nih.gov>

Apoptosis Interest Group

Meeting time: 1st Monday, 4:00 pm
Meeting place: Bldg 49, Room 1 50/59 AB
Contact 1: Richard Youle
Phone: 301-496-6628
E-mail: <youle@helix.nih.gov>
Contact 2: Yves Pommier
Phone: 301-496-5944
E-mail: <yp-ix@nih.gov>

Behavioral and Social Sciences Interest Group

Meeting time: Varies; lecture series
Meeting place: See NIH Calendar of Events
Contact: Ronald Abeles
Phone: 301-496-7859
E-mail: <abeles@nih.gov>

Bioethics Interest Group

Meeting time: 1st Monday (except 2nd Monday following holidays; usually does not meet during summer), 3:00 pm
Meeting place: Natcher, Room D, or Building 31, conference room; check yellow sheet or web site
Contact: Miriam Kelty
Phone: 301-496-9322; 301-229-5639
E-mail: <keltym@mail.nih.gov>
Sign up at <http://
BIOETHICSinterestgroup@list.nih.gov/>

Biomedical Computing Interest Group

Meeting time: 1st three Thursdays, 3:00 pm; 4th Thursday, 5:30 pm (evening socials on 5th Thursdays; dark Aug & Dec)
Meeting place: Building 10, Room 2C116 (Medical Board Room)
Contact 1: Jim DeLeo
Phone: 301-496-3848
E-mail: <jdeleo@nih.gov>
Contact 2: Carl Leonard
E-mail: <cleonard@cc.nih.gov>
ListServe: subscribe to BCIG-L

Biophysics Interest Group

Meeting time and place: Holds seminars and conferences; does not meet regularly
Contact: Peter Basser
Phone: 301-435-1949
E-mail: <pjbasser@helix.nih.gov>

Biosciences Business Interest Group

Meeting time: Monthly, 12:00-1:00 pm
Meeting place: Building 37, 4th Floor Conference Room (4041/4107)
Contact 1: Val Bliskovsky
Phone: 301-435-7249
E-mail: <bliskovv@mail.nih.gov>

Calcium Interest Group

Meeting time and place: Not regularly scheduled at this time
Contact 1: Arthur Sherman
Phone: 496-4325
E-mail: <asherma@nih.gov>
Contact 2: Indu Ambudkar
Phone: 301-496-1478
E-mail: <iambudkar@dir.nidcr.nih.gov>
ListServ: Subscribe to CALCIUM-L

Cancer CAM Research Interest Group

Meeting time and place: Varies
Contact: Jeffrey White
Phone: 301-435-7980
E-mail: <jeffreyw@mail.nih.gov>

Chemistry Interest Group

Meeting time: Periodic seminars
Meeting place: Varies
Contact 1: John Schwab
Phone: 301-594-3827
E-mail: <schwabj@nigms.nih.gov>
Contact 2: Kenneth Kirk
Phone: 301-496-2619

Chromatin and Chromosomes Interest Group

Meeting time: One Tuesday a month, 4:00 pm
 Meeting place: Building 41, Conf. Room
 Contact: David Clark
 Phone: 301-496-6966
 E-mail: <clarkda@mail.nih.gov>

Chronobiology Interest Group

Meeting time: 1st Wednesday, almost monthly, 4:00-5:00 pm; check website
 Meeting Place: Building 49, Rm 6A46, or USUHS Rm A2054
 Contact: Steven Coon
 Phone: 301-451-6622
 E-mail: <coons@mail.nih.gov>

Clinical Applications of Stem Cells Interest Group

Meeting time and place: To be announced; see listing for Stem Cell Interest Group
 Contact: Manfred Boehm
 Phone: 301-435-7211
 E-mail: <boehmm@nhlbi.nih.gov>

Clinical Pharmacology Interest Group

Meeting time: 2-3 times a year in conjunction with special lectures in the NIH Principles of Clinical Pharmacology course, 6:30- approx. 7:45 pm
 Meeting place: Building 10, Lipsett Amphitheater
 Contact: Donna L. Shields
 Phone: 301-435-6618
 E-mail: <dshields@mail.cc.nih.gov>

Cognitive Neuroscience Consortium

Meeting time: Every two months, last Wednesday, 4:15 pm
 Meeting place: NSC Building, Conference Room A (starts September 2005; Extramural Program Directors' forum: last Friday every 3rd month, 3:00 pm, NSC Building, Conf. Room 2120, starts October 2005)
 Contact: Emmeline Edwards
 Phone: 301-496-9248
 E-mail: <ee48r@nih.gov>

Cytokine Interest Group

Meeting time: three to four symposia/year
 Meeting place: Varies; one symposium/year at NCI-Frederick
 Contact 1: Thomas Wynn
 Phone: 301-496-4758
 E-mail: <twynn@niaid.nih.gov>
 Contact 2: Daniela Verthelyi
 E-mail: <daniela.verthelyi@fda.hhs.gov>

Data Resources Sharing Interest Group

Meeting time: 4th Wednesday, 3:00-4:30 pm
 Meeting place: Rockledge 1 (6705 Rockledge Dr.), Room 5147
 Contact 1: J.P. Kim
 Phone: 301-435-0679
 E-mail: <jpkim@nih.gov>
 Contact 2: Marilyn Miller
 Phone: 301-496-9350
 E-mail: <millerm@nia.nih.gov>

Dendritic Cell Interest Group

Meeting time and place: TBA
 Contact 1: Uri Lopatin
 Phone: 301-496-8490
 E-mail: <ulopatin@niaid.nih.gov>
 Contact 2: Brian Kelsall
 Phone: 301-496-7473
 E-mail: <bkelsall@mail.nih.gov>

Diabetes Interest Group

Meeting time: ~ Every six weeks, usually Tuesday, usually 3:00 pm
 Meeting place: Building 10, Lipsett
 Contact 1: Eric Liu
 Phone: 301-451-9809
 E-mail: <ericiu@imil.nih.gov>
 Contact 2: Derek LeRoith
 E-mail: <derek@helix.nih.gov>

DNA Repair Interest Group

Meeting time: 3rd Tuesday, 12:30 pm
 Meeting/Videoconference: Natcher, Room J; GRC (Baltimore), Room 1E03; FCRDC, Building 549, Conf. Rm. A; NIEHS (Research Triangle Park, NC) Building 101, Room B200; SUNY, Stony Brook; Univ. of Texas, M.D. Anderson Cancer Center, Smithville, TX; Univ. of Texas, Galveston; Lawrence Livermore National Laboratory, Livermore, CA; Brookhaven National Laboratory, Upton, NY; Univ. of Michigan, Ann Arbor; Univ. of Kentucky, Lexington; Univ. of Pittsburgh, Pittsburgh, PA; Univ. of North Carolina, Chapel Hill, NC; Oregon Health and Science Univ, Portland, OR; Wake Forest Univ., Winston-Salem, NC
 Contact 1: Kenneth Kraemer
 Phone: 301-496-9033
 E-mail: <kraemer@nih.gov>
 Contact 2: Vilhelm Bohr
 E-mail: <vbbohr@nih.gov>

Domestic Violence Research Interest Group

Meeting time and place: To be announced
 Contact: John Umhau
 Phone: 301-496-7515
 E-mail: <umhau@nih.gov>

Drosophila Interest Group

Meeting time: 3rd Tuesday, 1:15 pm
 Meeting place: Building 6B, Room 4B429
 Contact: Jim Kennison
 Phone: 301-496-8399
 E-mail: <James_Kennison@nih.gov>

Drosophila Neurobiology Interest Group

Meeting time: Every other Friday, 12:00 noon (check website for schedule)
 Meeting place: Porter Neuroscience Research Center (Bldg 35), Room BB-1000
 Contact: Chi-hon Lee
 Phone: 301-435-1940
 E-mail: <leechih@mail.nih.gov>

Drug Discovery Interest Group

Meeting time: Usually one Thursday a month, 3:00 pm
 Meeting place: Building 37, 6th-floor conference room
 Contact: John N. Weinstein
 Phone: 301-496-9571
 E-mail: <weinstein@dtpx2.ncifcrf.gov>

Economics Interest Group

Meeting time and place: Varies
 Contact 1: James A. Schuttinga
 Phone: 301-496-2229
 E-mail: <js41z@nih.gov>
 Contact 2: Agnes Rupp
 E-mail: <ar24f@nih.gov>

Emergency Preparedness and Biodefense Interest Group

Meeting time: 1st Thursday, 3:00 pm
 Meeting place: Building 50, ground-floor conference room
 Contact 1: Jeffrey Kopp
 Phone: 301-594-3403
 E-mail: <jeffreyk@intra.niddk.nih.gov>
 Contact 2: Mike Bray
 Phone: 301-451-5123
 E-mail: <mbray@niaid.nih.gov>

End of Life Research Interest Group

Meeting time: 3rd Thursday, 3:00 pm
 Meeting place: NINR Conference Room, 6701 Democracy Blvd., Suite 710
 Contact: Alexis Bakos
 Phone: 301-594-2542
 E-mail: <bakosa@mail.nih.gov>

Epidemiology and Clinical Trials Interest Group

Meeting time and place: Varies (subscribe to ListServ for notices)
 Contact: Martina Vogel-Taylor
 Phone: 301-496-6614
 E-mail: <martinav@nih.gov>
 ListServ: subscribe to Epidem-L at <listserv@list.nih.gov>

Epilepsy Interest Group

Meeting time and place: Seminars and annual Data Blitz session announced by e-mail and on website
 Contact: Michael Rogawski
 Phone: 301-496-8013
 E-mail: <epilepsySIG@nih.gov>

Epigenetics Interest Group

Meeting time: Last Thursday, 3:00 pm
 Meeting place: EPN (6130 Executive Blvd.) Conference Room G
 Contact: Mukesh Verma
 Phone: 301-594-7344
 E-mail: <Vermam@mail.nih.gov>

INTERINSTITUTE INTEREST GROUP DIRECTORY

Flow Cytometry Interest Group

Meeting time: Quarterly, in the morning
 Meeting place: Building 10, Lipsett
 Contact 1: Rajeev Agarwal
 Phone: 301-435-4573
 E-mail: <ragarwal@helix.nih.gov>
 Contact 2: William Telford
 Phone: 301-435-6379
 E-mail: <telfordw@mail.nih.gov>

Fluorescence Interest Group

Meeting time: Usually even Fridays, 4:00 pm; see website; join to receive upcoming events e-mail
 Meeting place: Building 10, usually Room 5N264
 Contact: Jay Knutson
 Phone: 301-496-2557
 E-mail: <jaysan@helix.nih.gov>
 Contact 2: Dan Sackett
 E-mail: <sackettd@mail.nih.gov>

Free Radical Interest Group

Meeting time: Monthly, in conjunction with the Oxygen Club of Greater Washington, D.C., 3rd Friday, 3:00 pm; annual regional symposium and banquet (to be held this year October 12; check website)
 Meeting place: Radiation Biology Conference Room, Building 10, B2.5 level
 Contact: Michael Graham Espey
 Phone: 301-496-7511
 E-mail: <SP@nih.gov>

Genomics and Bioinformatics Interest Group

Meeting time: Usually one Thursday a month, 3:00 pm
 Meeting place: Building 37, 6th-floor conference room
 Contact: John N. Weinstein
 Phone: 301-496-9571
 E-mail: <weinstein@dtpx2.ncicrf.gov>

Glycobiology Interest Group

Meeting time and place: Varies
 Contact 1: Diana Blithe
 Phone: 301-435-6990
 E-mail: <blithed@nih.gov>
 Contact 2: John Hanover
 Phone: 301-496-0943
 E-mail: <johnh@intra.niddk.nih.gov>
 ListServ: Subscribe to GLYCO-L@LIST.NIH.GOV

GTP Binding Proteins Interest Group

Meeting time: Irregular
 Meeting place: FAES Social & Academic Ctr.
 Contact: R. Victor Rebois
 Phone: 301-496-9168
 E-mail: <reboisv@nidcd.nih.gov>

Handheld Users Group (HUG)

Meeting time and place: check the website
 Contact: Ben Hope
 Phone: 301-594-6473
 E-mail: <tallguy@nih.gov>

Hard Tissue Disorders Interest Group

Meeting time: Day varies, 9:30 am
 Meeting place: Building 30, Room 117
 Contact: Pamela Robey
 Phone: 301-496-4563
 E-mail: <probey@dir.nidcr.nih.gov>
 Contact 2: Michael Collins
 Phone: 301-435-1689

Head and Neck Cancer Interest Group

Meeting time and place: To be announced
 Contact 1: Wendy Weinberg
 Phone: 301-827-0709
 E-mail: <weinberg@cber.fda.gov>
 Contact 2: Carter Van Waes
 Phone: 301-402-4216
 E-mail: <vanwaesc@nidcd.nih.gov>

Health Services Research Interest Group

Meeting time: Quarterly (day, time, and place to be announced);
 Contact: Jack Stein
 Phone: 301-443-4060
 E-mail: <js413y@nih.gov>

HIF (Hypoxia Inducible Factor) Interest Group

Meeting time: Quarterly
 Meeting place: Building 10, Hatfield 2-3750
 Contact: Tawnya McKee
 Phone: 301-846-1943
 E-mail: <mckee@ncicrf.gov>
 Website: <<http://ccr.cancer.gov/faculties/faculty.asp?facid=457>>

History of Biomedical Research Interest Group

Meeting time: Second Tuesday, 1:00 pm
 Meeting place: Varies; check web site
 Contact 1: Office of NIH History
 Phone: 301-496-6610
 Contact 2: Buhm Soon Park
 E-mail: <parkb@od.nih.gov>

HTS Assay Development Interest Group

Meeting time and place: Varies; check website
 Contact 1: Ingrid Li
 Phone: 301-443-1421
 E-mail: <ili1@mail.nih.gov>
 Contact 2: James Ingles
 Phone: 301-496-7029
 E-mail: <jinglese@mail.nih.gov>

Image Processing Interest Group

Meeting time and place: Distributed by e-mail and on <image.nih.gov>
 Contact 1: Benes Trus
 Phone: 301-496-2250
 E-mail: <Benes_Trus@nih.gov>
 Contact 2: Matt McAuliffe
 Phone: 594-2432

Infectious Disease Imaging Interest Group

Meeting time: 1st or 2nd Tuesday, 4:00 pm (check website)
 Meeting place: Building 10, Doppman Conference Room
 Contact: Mike Bray
 Phone: 301-451-5123
 E-mail: <mbray@niaid.nih.gov>

Integrative Neural-Immune Interest Group

Meeting time and place: To be announced
 Contact: Socorro Vigil-Scott
 Phone: 301-496-9255
 E-mail: <vigilscs@mail.nih.gov>

Integrative Neuroscience Interest Group

Meeting time: Alternate Thursdays, 4:00 pm
 Meeting Place: Building 49, Room 1A51
 Contact: Bruce Cumming
 E-mail: <bgc@lsr.nei.nih.gov>

Inter-Agency Image-Guided Interventions Group

Meeting time: Monthly, 4th Tuesday, 3:30 pm
 Meeting Place: NIBIB, 6707 Democracy Blvd, Bethesda, Suite 200, Room 223
 Contact: Theresa Smith
 Phone: 301-451-4784
 E-mail: <smiththe@mail.nih.gov>

In Vivo NMR Interest Group

Meeting time: Varies
 Meeting place: Building 10, Room B1N256
 Contact: Jeff Duyn
 Phone: 301-594-7305
 E-mail: <jhd@helix.nih.gov>

Knowledge Management Interest Group

Meeting time and place: Announced prior to each meeting
 Contact 1: Geoffrey Marsh
 Phone: 301-594-9683
 E-mail: <geoff@mail.nih.gov>
 Contact 2: Paul Beatty
 E-mail: <pbeatty@mail.nih.gov>

Lab Managers Interest Group

Meeting time: 2nd Thursday, noon
 Meeting place: Building 40, Conference Room 1203
 Contact: Dawn A. Walker
 Phone: 301-402-7149
 E-mail: <walkerd@exchange.nih.gov>

Lambda Lunch (Bacterial and Phage Genetics)

Meeting time: Each Thursday, 11:00 am
 Meeting place: Building 37, Room 6107/6041
 Contact: Susan Gottesman
 Phone: 301-496-3524
 E-mail: <susang@helix.nih.gov>
 Contact 2: Robert Weisberg
 E-mail: <rweisberg@nih.gov>
 Anonymous FTP site: FTP.CU.NIH.-GOV directory "LAMBDA_LUNCH"

Light Microscopy Interest Group

Meeting time: Monthly, Tuesday, noon
 Meeting place: Building 10, Room 4B51
 Contact: James McNally
 Phone: 301-402-0209
 E-mail: <mcnallyj@mail.nih.gov>
 Contact 2: Christian Combs
 Phone: 301-496-0014

Mass Spectrometry Interest Group

Meeting time: 1st & 3rd Thursday, 10:30 am (check website)
 Meeting place: Building 10, Room 7S235
 Contact: Dawn Maynard
 Phone: 301-402-6622
 E-mail: <maynardd@mail.nih.gov>

Membrane Microdomains Interest Group

Meeting time: 1st Tuesday, 1:00 pm
 Meeting place: Building 10, Room 9C209
 Contact: Paul Roche
 Phone: 301-594-2595
 E-mail: <rochep@pop.nci.nih.gov>

Membrane Protein Interest Group

Meeting time: Usually one Wednesday a month, 1:00 pm; check website: <http://www.nih.gov/signs/mpig>
 Meeting place: Building 5, Room 127
 Contact: Reinhard Grisshammer
 E-mail: <rkgriss@helix.nih.gov>

Microarray Users Group

Meeting time and place: Usually first Wednesday; Journal Club meets weekly or bimonthly, as the group decides
 Meeting place: Varies
 Contact: Katherine Peterson
 Phone: 301-402-5678
 E-mail: <peterstonk@nei.nih.gov>

Mitochondria Interest Group

Meeting time: 1st Monday, 3:00 pm (excluding federal holidays)
 Meeting/BREEZE WEB-conference: Building 2 Conference Room or other NIH campus sites; recent nodes for group viewing include NIEHS, Research Triangle Park, NC; GRC, Baltimore; VA Hospital, Cleveland; Podell Auditorium, Beth Israel Medical Center, NYC; Baylor Univ., Texas; Louisiana State University Health Science Center
 Contact 1: Steve Zullo
 Phone: 301-435-2810
 E-mail: <zullo@helix.nih.gov>
 Contact 2: Salvatore Alesci
 E-mail: <alescis@mail.nih.gov>
 Contact 3: Nadja Souza-Pinto
 E-mail: <souzan@mail.nih.gov>

Molecular and Functional Optical Imaging Interest Group

Meeting time: 2nd Wednesday, 12:00 noon
 Meeting place: Building 10, Room B3MB-38 (2.5 level, B-wing)
 Contact 1: Amir Gandjbakhche
 Phone: 301-435-9235
 E-mail: <amir@helix.nih.gov>
 Contact 2: Abby Vogel
 Phone: 301-402-0648
 E-mail: <vogelab@mail.nih.gov>

Molecular Modeling Interest Group

Meeting time: See <http://mmignet.nih.gov>
 Meeting place: Building 12A, conf. rooms
 Contact: Peter Steinbach
 Phone: 301-496-1100
 E-mail: <steinbac@helix.nih.gov>

Mood and Anxiety Disorders Interest Group

Meeting time: Tuesday, noon, 12-18 times a year
 Meeting place: Varies (once speakers are set, the IG schedule is sent out to members and interested persons)
 Contact: Holly Giesen
 Phone: 301-435-8982
 E-mail: <giesenh@mail.nih.gov>

Motility Interest Group

Meeting time and place: Varies
 Contact: Jim Sellers
 Phone: 301-496-6887
 E-mail: <sellersj@nhlbi.nih.gov>

Mouse Club

Meeting time: 1st Tuesday, 4:00 pm
 Meeting place: Building 6A, Room 4A05
 Contact: Heiner Westphal
 Phone: 301-402-0545
 E-mail: <hw@mail.nih.gov>

Muscle Interest Group

Meeting time: Irregular
 Meeting place: Building 40, Room 1203 or 1205
 Contact: Andres Buonanno
 Phone: 301-496-0170
 E-mail: <buonanno@mail.nih.gov>

Nanotech/Nanomedicine Interest Group

Meeting time and place: TBA
 Contact 1: Kuan Wang
 Phone: 301-496-4097
 E-mail: <rwangk@dmil.nih.gov>
 Contact 2: Jeffrey Forbes
 E-mail: <forbesj@mail.nih.gov>

Neuroinformatics Interest Group

Meeting time and place: To be announced
 Contact 1: Michael Huerta
 Phone: 301-443-3563
 E-mail: <mhuert1@mail.nih.gov>
 Contact 2: Barry Davis
 Phone: 301-402-3464
 E-mail: <barry_davis@nih.gov>

Pain Interest Group

Meeting time: 2nd Tuesday, 3:30 pm
 Meeting place: Building 30, Room 117
 Contact: Michael Iadarola
 Phone: 301-496-2758
 E-mail: <miadarola@dir.nidcr.nih.gov>

PET Interest Group

Meeting time: Friday, 2:00 pm; see website for seminar listing
 Meeting place: Building 10, Room 1-5674
 Contact: Peter Herscovitch
 Phone: 301-451-4248
 E-mail: <herscovitch@nih.gov>

****Phage-Tech Interest Group**

Meeting time and place: Varies
 Contact 1: Dean Scholl
 E-mail: <dscholl@mail.nih.gov>
 Contact 2: Carl Merrill
 E-mail: <merrilc@mail.nih.gov>
**** Last year's listing—not verified or updated**

Pharmacogenetics Interest Group

Meeting time: Last Thursday, 3:00-5:00 pm
 Meeting place: Rockledge 2 or Natcher (members informed by e-mail)
 Contact: Pothur Srinivas
 Phone: 301-435-0550
 E-mail: <srinivap@mail.nih.gov>

Pigment Cell Research Interest Group

Meeting time: Monthly, usually 3rd Thursday, 12:30-2:00 pm; yearly day-long meeting most years; check the website
 Meeting place: Bldg 49, Conf. Room 1A51
 Contact 1: Marjan Huizing
 Phone: 301-402-2797
 E-mail: <mhuizing@mail.nih.gov>
 Contact 2: Tom Hornyak
 Phone: 301-451-1926

Polyunsaturated Lipid Function Interest Group

Meeting time: Usually 1st Wednesday, as announced (resuming in September), 1:30 pm
 Meeting place: 5626 Fishers Lane, Conference Room 3N-25, Rockville, MD
 Contact: Norman Salem
 Phone: 301-443-2393
 E-mail: <nsalem@niaaa.nih.gov>

Prostate Cancer Interest Group

Meeting time: Monthly, Friday, 4:00 pm
 Meeting place: Bldg. 10 CRC, Room 2-3750
 Contact: Marston Linehan
 Phone: 301-496-6353
 E-mail: <linehanm@mail.nih.gov>

Protein Trafficking Interest Group

Meeting time: 2nd Tuesday, 3:30 pm
 Meeting place: Building 50, Room 2328
 Contact 1: Manu Hegde
 Phone: 301-496-4855
 Email: <hegder@mail.nih.gov>
 Contact 2: Peng Loh
 Phone: 301-496-3239

Proteomics Interest Group

Meeting time: 1st Friday seminars
 Meeting place: Building 50; check website; join listserv to receive seminar notices
 Contact: Sanford Markey
 Phone: 301-496-4022
 E-mail: <markeys@mail.nih.gov>

RNA Club

Meeting time: 1st Tuesday (except August), 4:00 pm
 Meeting place: Building 41, Room C509
 Contact: Rich Maraia
 Phone: 301-402-3567
 E-mail: <maraiar@mail.nih.gov>

INTERINSTITUTE INTEREST GROUP DIRECTORY

Scientific Integrative Medicine Interest Group

Meeting time and place: TBA; lectures planned; website under construction
 Contact 1: David Goldstein
 Phone: 301-496-2103
 E-mail: <goldsteind@ninds.nih.gov>
 Contact 2: Eleanor Hanna
 E-mail: <hanna@mail.nih.gov>

Signal Transduction Interest Group

Meeting time: Alternate Wednesdays, 5:00 pm
 Meeting place: 5 Research Court, Conf. Room
 Contact 1: John Northup
 Phone: 301-496-9167
 E-mail: <drjohn@codon.nih.gov>
 Contact 2: James Battey
 Phone: 301-402-0900

Stem Cell Interest Group

Meeting time and place: Monthly seminars to rotate through Baltimore, Bethesda, and Frederick campuses; check website
 Contact 1: Nadya Lumelsky
 Phone: 301-451-9834
 E-mail: <nadyal@nidcr.nih.gov>
 Contact 2: Colin Stewart
 Phone: 301-846-1755
 E-mail: <stewartc@ncifcrf.gov>
 Contact 3: Manfred Boehm
 Phone: 301-435-7211
 E-mail: <boehmm@nhlbi.nih.gov>

Stroke Branch Interest Group/Seminar Clinical Stroke Rounds (year-round)

Meeting time: Wednesdays, 8:30 am
 Meeting place: Suburban Hospital or Washington Hospital Center
Stroke Branch Seminars (September through May)
 Meeting time: Thursdays 4:00 pm
 Meeting place: Suburban Hospital Auditorium
 Contact 1: Jose Merino
 Phone: 301-435-9321
 E-mail: <merinoj@ninds.nih.gov>
 Contact 2: John Kylan Lynch
 Phone: 301-451-7968
 E-mail: <LynchJ@ninds.nih.gov>

Synaptic and Developmental Plasticity Interest Group

Meeting time: Tuesday, every other month, 11:00 am
 Meeting place: Building 35, Room BB1000
 Contact: Bai Lu
 Phone: 301-435-2970
 E-mail: <bailu@mail.nih.gov>

Systems Biology Interest Group

Meeting time: 1st Thursday, 2:00 p.m., monthly seminars
 Meeting place: Berlioner Room, Building 10, Room 7S235
 Contact 1: David Balshaw
 Phone: 919-541-2448
 E-mail: <balshaw@niehs.nih.gov>
 Contact 2: Eric Billings
 Phone: 301-496-6520
 E-mail: <billinge@nhlbi.nih.gov>

Technology Transfer Interest Group

Meeting time: 1st Tuesday, 3:00 pm
 Meeting place: 6011 Executive Blvd., suite 325
 Contact 1: Kate Sinclair Dunn
 Phone: 301-435-2813
 E-mail: <sinclairk@mail.nih.gov>
 Contact 2: Brian Stanton
 Phone: 301-435-4074
 E-mail: <bs66d@nih.gov>

Therapeutic Oligonucleotides Interest Group

Meeting time: Last Thursday, 4:00 pm
 Meeting place: Building 10, Room 2C116 (Medical Board Room)
 Contact: Yoon Cho-Chung
 Phone: 301-496-4020
 E-mail: <chochuny@mail.nih.gov>

Tobacco and Nicotine Research Interest Group

Meeting time: 4th Wednesday, every other month, 2:00 pm (next meeting is July 27)
 Meeting place: 6701 Rockledge Dr., Rooms 8115/8119, Rockledge 2 Building
 Contact: Geraldine Anderson
 Phone: 301-589-4020
 E-mail: <ganderson@consultinggroup.com> or <andersong@mail.nih.gov>

Transcription Factor Interest Group

Meeting time: 1st Thursday (except July-Sept.), 2:00 pm
 Meeting place: Building 50, ground-floor Conference Room (Room 1227)
 Contact 1: Stoney Simons
 Phone: 301-496-6796
 E-mail: <steroids@helix.nih.gov>
 Contact 2: Uli Siebenlist
 Phone 301-496-8917
 ListServ: subscribe to TFACTORS

Tumor Angiogenesis & Invasion Working Group

Meeting time and place: Posted at website
 Contact 1: William Figg
 Phone: 301-402-3622
 E-mail: <wdfigg@helix.nih.gov>
 Contact 2: Steven Libutti
 Phone: 301-496-5049

Viral Hepatitis Interest Group

Meeting time: 2nd Monday, 4:15 pm
 Meeting place: Building 10, Room 9S235 (Bunim Room)
 Contact: Barbara Rehermann
 Phone: 301-402-7144
 E-mail: <barbarar@intra.niddk.nih.gov>

Virology Interest Group

Meeting time: 1st Thursday, 12:00 noon; minisymposium in November
 Meeting place: Building 4, Room 433
 Contact 1: Alison McBride
 Phone: 301-496-1370
 E-mail: <amcbride@nih.gov>
 Contact 2: Carolyn Wilson
 E-mail: <wilsonC@cber.fda.gov>
 ListServ: Contact <CBuckler@nih.gov>

Washington Area NMR Interest Group

Meeting time: Three times a year, generally in December, February, and May
 Meeting place: Building 5, Room 127, or the Cloister (Building 60) Lecture Hall
 Contact: Robert Tycko
 Phone: 301-402-8272
 E-mail: <robertty@mail.nih.gov>

Washington Area Yeast Club

Meeting time: 2nd Wednesday, 4:30 pm
 Meeting place: Building 6A, Room 4A05
 Contact 1: Reed Wickner
 Phone: 301-496-3452
 E-mail: <wickner@helix.nih.gov>
 Contact 2: Alan Hinnebusch
 Phone: 301-496-4480
 E-mail: <ahinnebusch@nih.gov>

Women's Health Special Interest Group

Meeting time: One Friday a month, September through May, 11:30 am-12:30 pm
 Meeting place: Building 1, Wilson Hall; upcoming meetings/seminars posted at website and announced through WHSIG list and NIH staff list e-mails
 Contact: Vicki Malick
 Phone: 301-496-7989
 E-mail: <malickv@mail.nih.gov>

X-ray Diffraction Interest Group

Meeting time and place: See biweekly newsletter: <<http://mc1.ncifcrf.gov/nihxray/>>
 Contact: Fred Dyda
 Phone: 301-402-4496
 E-mail: <fred.dyda@nih.gov>

Zebrafish/Xenopus Interest Group

Meeting time and place: Monthly, rotating through participating labs; space is limited
 Contact: Tom Sargent
 Phone: 301-496-0369
 E-mail: <sargentt@mail.nih.gov>

IGS ON THE HORIZON

Neurodevelopmental Disorders Interest Group

This group has not yet met, but these are its plans:
 Meeting time: Monthly on a Monday, TBA
 Meeting place: Building 10, Room 4N222
 Contact 1: Audrey Thurm
 E-mail: <athurm@mail.nih.gov>
 Contact 2: Teresa Huggins
 E-mail: <teresaHuggins@mail.nih.gov>

R Users Group

Contact: Terry Cox
 Phone: 301-496-1331
 E-mail: <TAC@NEI.NIH.GOV>

Considering starting a new Interest Group? Contact Sandeep Nair: <snairs@od.nih.gov>. Need to correct your group's listing? Contact CIT's web publishing group:

<publish@cit.nih.gov>.

PIGMENT CELL INTEREST GROUP—A PORTRAIT

When an immigration officer at Dulles Airport recently asked a French graduate student what she was working on at NIH, she happily responded: "Studying the biology of pigment cells!" The officer shot back: "Do we really need French people for doing this?"

One might as well ask, do we really need pigment cell research at NIH? The answer is a resounding "Yes!" Pigment cells are not only for the fashion-conscious. We need them in the eye for vision. We need them—and this may come as a surprise—in the inner ear for hearing.

Their abnormalities can point to systemic disorders or lead to life-threatening melanomas. They are model cells for a host of basic studies—in developmental biology, cell biology, immunology, genetics, biochemistry, and more. They have yielded insights into G-coupled signaling pathways, intracellular transport, cell-lineage specification, and malignant transformation.

Pigment mutations in mice, which occur in more than 100 different genes, were among the first to be mapped in the genome.

In short, pigment cells are important.

Some Pigment Cell Basics

But what exactly are pigment cells? There are many types and many different colors in animals. The major type in mammals is the melanocyte, which is derived from the neural crest. Its pigment—melanin—is a biopolymer that is synthesized through a series of catalytic steps starting with the conversion of the amino acid tyrosine to dihydroxyphenylalanine by a copper-binding enzyme called tyrosinase.

Melanin comes in two versions: black eumelanin and yellow pheomelanin. Both versions are made in membrane-bound intracellular organelles called melanosomes.

Not every cell that contains melanosomes is a melanocyte, however, because melanocytes can transfer their melanosomes to other cell types that are not capable of producing melanin themselves. In human skin, for instance, melanosomes are transferred from melanocytes to keratinocytes and into hair shafts; in birds, they are found in feathers.

Melanocytes are present in the iris, which serves as an aperture to regulate

the depth of focus and the amount of light that enters the eye. A reduction in iris pigmentation leads to blurred vision. Melanocytes are also found in the choroid behind the retina, where they serve to block the passage of light to deeper tissues.

Between retina and choroid, there is yet another layer of pigment cells, called the retinal pigment epithelium, that regulates the development of the eye in the embryo and the physiology of photoreceptor cells in the adult.

In the inner ear of mammals, melanocytes are found in a portion of the wall of the cochlear duct, where they regulate the ionic composition of the endolymph and ensure that auditory hair cells function normally.

Typically, there are three possible consequences of melanocyte misconduct: Their numbers can change, the amount and quality of pigment can change, or the cells can become malignant. Malignant potential is what makes melanocyte pathology a major health burden for humans. In the United States alone, more than 60,000 new melanoma cases are projected to arise this year—yet preventing melanoma is entirely feasible. For more information on melanoma, go to

<<http://www.cancer.gov/cancertopics/types/melanoma>>.

Pigment Cell Research at NIH

Over the years, the NIH Intramural Research Program has become one of the premier centers for pigment cell research worldwide. At least six institutes have active programs in this field, rang-

ing from developmental biology to organelle and melanin biosynthesis to tumor biology, immunology, and epidemiology.

Last year, NIH hosted the International Pigment Cell Congress, chaired by Vincent Hearing, NCI. The meeting focused on human pigmentary diseases and attracted more than 400 attendees from all over the world.

In 2001 and again in 2004, two consecutive meetings of the Development Group of the International Federation of Pigment Cell Societies met on campus at the Cloisters. Co-chaired by NHGRI's William Pavan, they each drew more than 50 participants and generated a great deal of excitement.

The Pigment Cell Interest Group enables dynamic interactions among many labs both inside and outside NIH. This active group usually meets on the third Thursday of the month at 12:30 in the conference room of Building 49.

Each month, one of the many member labs presents its hottest results and discusses future approaches. In addition, students and postdocs have the opportunity to present practice talks for upcoming national or international meetings.

We welcome new members. Find out more about this group—and join up—at

<http://tango01.cit.nih.gov/sig/home.taf?function=main&SIGInfo_SIGID=76>.

—Heinz Arnheiter
Senior Investigator

Mammalian Development Section
Laboratory of Developmental Neurogenetics
NINDS

NEW WEBSITE OFFERS PATHWAYS TO TRANS-NIH IMMUNOLOGY RESEARCH



A new website that provides a single point of access to campus-wide intramural immunology research is now available at

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

This site is the fruit of more than a year's work by the NIH immunology steering committee. It contains

- A searchable faculty directory of more than 150 immunology labs at NIH
- A history of immunology in the intramural research program
- Useful links, including publicly accessible webcast archives of NIH immunology research seminars by invited and internal speakers dating back four years. ■

PEOPLE

RECENTLY TENURED

Alan DeCherney received his M.D. degree from Temple University School of Medicine, Philadelphia, in 1967. He received additional training at the Lister Institute in London, the University of Pittsburgh, and the University of Pennsylvania in Philadelphia and held high-ranking academic positions at Yale University School of Medicine in New Haven, Tufts University School of Medicine in Boston; and the David Geffen School of Medicine, University of California at Los Angeles, before joining NIH in 2006 as chief of the Reproductive Biology and Medicine Branch, NICHD. He is also a member of the Institute of Medicine of the National Academies.

I am in the process of establishing the Section on Implantation and Oocyte Physiology within the Reproductive Biology and Medicine Branch. This section will conduct patient-oriented research in such reproductive problem areas as infertility, recurrent pregnancy wastage, and failed treatment modalities.

A major effort will be to serve as a "court of last resort" for patients with a history of multiple fertility treatment failures. In addition to the intensive evaluation of these patients, the section will also explore why, in the absence of fertility problems, the rate of loss of fertilized eggs is so high. Among fertile couples seeking to become pregnant, 80 percent of ovulated eggs are fertilized, yet only 20 percent of these result in live births—almost half are lost between conception and the next menstrual period, and another 20 percent end in later spontaneous abortions.

We have plans to establish a Center of Excellence for Recurrent Pregnancy Loss that will focus on basic immunologic and clinical investigation. Two tenure-track investigators will be recruited to conduct research concentrating on implantation and oocyte physiology.

There are also plans to expand existing branch programs in endometriosis, fibroids, premature ovarian failure, receptor physiology, endocrine diseases such as Cushing's syndrome, and neuroendocrinology.

Phillip Dennis received his M.D. and Ph.D. degrees from New York University School of Medicine in 1991 and 1992, respectively. He completed an internal medicine residency and medical oncology fellowship, and, with Michael Kastan, a postdoctoral fellowship focusing on molecular control of apoptosis, all at Johns

Hopkins University in Baltimore. He joined NCI in 1999 as an investigator in the Developmental Therapeutics Department and is now a senior investigator and leader of the Signal Transduction Section in the Medical Oncology Branch, NCI.

Lung cancer is the number-one cause of cancer-related death across the world and is most commonly associated with smoking. My work has focused on signal transduction pathways that promote lung tumorigenesis and the therapeutic resistance of established cancers.

Although my group has investigated many signaling pathways that contribute to the resistance of lung cancer cells to therapy, we are currently focused on one pathway, the PI3K/Akt/mTOR

pathway. Our body of work over the past few years has established that activation of the PI3K/Akt/mTOR pathway is important at the earliest and latest stages of lung cancer.

For example, tobacco components activate this pathway and promote a partially transformed phenotype in normal human epithelial cells. Increased activation of the pathway occurs with phenotypic progression of preneoplastic lesions. Moreover, inhibitors of the pathway such as the mTOR inhibitor rapamycin prevent tobacco carcinogen-induced lung tumors in two murine model systems.

Most lung cancer cell lines have constitutive activation of the pathway and depend on the pathway for survival; similarly, agents that inhibit the pathway also cause the death of lung cancer cells and increase the efficacy of chemotherapy or radiation therapy.

Most recently, we showed that Akt activation is indicative of a poor prognosis for all stages of lung cancer patients, but especially those with Stage I disease and/or tumors of less than 5 cm.

Our current studies focus on the mechanisms by which tobacco components signal through nicotinic receptors to the PI3K/Akt/mTOR pathway; to that end, we are creating new transgenic and knockout mouse models that will allow us to dissect the role of individual pathway components in tobacco-induced tumorigenesis.

We are also working on two approaches to develop inhibitors of the PI3K/Akt/mTOR pathway in lung cancer. First, we have used molecular modeling to guide

the synthesis and characterization of lipid-based inhibitors of Akt called phosphatidylinositol ether lipid analogues (PIAs). We have identified the spectrum of activity of PIAs and molecular correlates of response to PIAs; we have also performed microarray analyses to identify changes in gene expression that are associated with PIA administration and have identified several genes that could serve as biomarkers in clinical trials. Indeed, PIAs have been identified as candidates for limited exploratory human trials to test the effects of low doses (so-called Phase 0 trials).

The second approach to inhibit the pathway is to test off-the-shelf drugs that are FDA approved for other indications—this approach could expedite the drug-development process.

We recently identified HIV protease inhibitors (HIV PI) as inhibitors of Akt that have a wide spectrum of activity and exert dose-dependent toxicity on all cell lines in the NCI60 cell line panel. A Phase I dose-escalation trial of the HIV PI nelfinavir in cancer patients is planned.

We perform all of our pre-clinical studies with an eye toward clinical translation to new therapies for lung cancer patients. Inhibitors of the PI3K/Akt/mTOR pathway hold the promise of clinical benefit for those at risk of developing lung cancer and for lung cancer patients who need better therapeutic options.

Steven Hou received his Ph.D. from the University of Chicago in 1994 and did his postdoctoral research in the laboratory of Norbert Perrimon at Harvard Medical School in Boston. He was recruited to the Laboratory of Immunobiology, NCI, in September 1997 as a tenure-track investigator and is currently a senior principal investigator at the Mouse Cancer Genetics Program, NCI.

My group has played a major role in developing the *Drosophila* model of the JAK/STAT and JNK/JUN signal-transduction pathways and is currently focused on these pathways' functions in stem cell regulation and animal aging in model organisms.

My research at NCI has three stages:

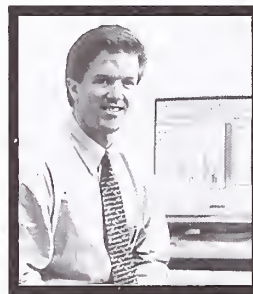
■ Developing the *Drosophila* model of the JAK/STAT and JNK/JUN signal-transduction pathways

I identified the *Drosophila* *stat* and *jun* genes' mutations in the course of my postdoctoral research. During the first few years at NCI, my group concentrated on identifying components of the JAK/STAT



Fran Pollner

Alan DeCherney



Phillip Dennis

and JNK/JUN signal-transduction pathways.

We conducted a large-scale transposon P-element-mediated gene disruption screen, which enabled us to identify 900 different gene mutations (*Genetics* **163**:195–201, 2003). From that screen, we identified a receptor for the JAK/STAT signal-transduction pathway (*Genes Dev.* **16**:388–398, 2002); we also found that the JAK/STAT pathway and cyclin D/Cdk4 cooperatively regulate tumor development in the fly blood and eye (*Dev. Cell* **4**:179–190, 2003). In the JNK/JUN signal-transduction pathway, we cloned a new multidomain scaffolding protein (*Mol. Cell. Biol.* **22**:1792–1803, 2002).

■ Elucidating functions of the JAK/STAT and JNK/JUN signal-transduction pathways in stem cell regulation and animal aging

In a genetic screen for mutations that interact with the JAK/STAT signal-transduction pathway in regulating male germ-line stem cell (GSC) fates, we identified a small GTPase Rap guanine nucleotide exchange factor (Gef26) from our library of P-element mutations.

We demonstrated that the Rap-GEF/Rap signaling controls stem cell anchoring to the niche through regulating DE-cadherin-mediated cell adhesion (*Dev. Cell* **10**: 117–126, 2006).

We also found that the *Drosophila* homologue of the Birt-Hogg-Dubé (BHD) syndrome tumor suppressor functions downstream of the JAK/STAT and Dpp/TGF- β signal transduction pathways and regulates male GSC maintenance (*Oncogene* Apr 24, 2006, Epub ahead of print).

These findings suggest that the BHD protein may regulate tumorigenesis through modulating stem cells in humans.

The JNK/JUN signal-transduction pathway regulates stress response and lifespan in the fly. We screened the P-element mutants, either generated by us or obtained from the public stock centers, and identified 40 long-lived mutants.

We are currently exploring the molecular mechanism of how these new mutants and the JNK signaling pathway cooperatively regulate fly lifespan.

■ Exploring stem cell regulation and animal aging in mice

We are applying knowledge gained from the *Drosophila* systems to study stem cell regulation and animal aging in the mouse system.

There are two mouse orthologs of

Gef26—RapGEF1 and RapGEF2. We are in the process of generating the conditional knockout mice of the RapGEF1 and RapGEF2 genes.

We are also developing cell-labeling systems to specifically label stem cells and cancer stem cells in mice.

The powerful genetic manipulations available in *Drosophila* enable us to dissect the molecular mechanism of stem cell regulation and animal aging. Extending the findings in the fly system to the mouse system will enable us to develop better human disease models.

Our studies using both systems will not only lead to an enhanced biological understanding of stem cell regulation and animal aging but may also provide new targets for treating relevant human diseases.



Steven Hou

Stan Lipkowitz received his M.D. and Ph.D. degrees from Weill Medical College of Cornell University in New York in 1984. After clinical training in internal medicine at The New York Hospital, he came to NCI as a medical oncology fellow. After completing a postdoctoral fellowship in the laboratory of Ilan Kirsch, he joined the Genetics Branch as a tenure-track investigator in 1997. In 2003, he moved to the Laboratory of Cellular and Molecular Biology, where he is currently a senior investigator.

My laboratory studies signal-transduction pathways that regulate growth and programmed cell death in epithelial cancer cells, with a focus on breast and ovarian cancer. We have three projects:

1) The function of Cbl

proteins. Human epithelial malignancies frequently display deregulated tyrosine kinase activity. Understanding the mechanisms that regulate signaling by these kinases should uncover new ways to inhibit cancer cell growth. We are investigating the function of Cbl proteins, a family of proteins that regulate tyrosine kinase activity. Cbl proteins belong to the RING finger class of ubiquitin protein ligases (E3s) and function as E3s for activated tyrosine kinases.

My group cloned two of the three mammalian Cbl genes. We have focused primarily on the activated epidermal growth factor receptor (EGFR) as a model substrate for Cbl proteins and have shown that all mammalian Cbl proteins mediate

ubiquitination and degradation of the activated EGFR. Furthermore, the Cbl proteins, as well as other components of the signaling complex, are degraded upon activation of the EGFR. Thus, Cbl proteins mediate degradation of the active EGFR signaling complex.

In collaboration with Allan Weissman, of the Laboratory of Protein Dynamics and Signaling, NCI, we have demonstrated that Nedd4 and Itch, two HECT E3s, target Cbl proteins for degradation. Thus, there is likely to be a network of regulation of E3s by other E3s.

Ongoing work is focused on understanding the biochemical and physiologic functions of the three mammalian Cbl proteins in epithelial cells and elucidating the differences in their specificity and/or function.

2) The function of death receptors

in epithelial cancer cells. Cancer cells avoid apoptosis by a variety of genetic and epigenetic mechanisms. We are investigating the induction of apoptosis by activation of death receptors for the ligand TRAIL in breast and ovarian cancer cells. Our goal is to selectively trigger apoptosis in the cancer cells.

My group has shown that most breast and ovarian cancer cell lines are resistant to the induction of apoptosis by TRAIL, the ligand for the death receptors DR4 and DR5. We have demonstrated that resistance to TRAIL-induced apoptosis can be overcome by co-cubation of the cells with chemotherapeutic agents, semisynthetic

retinoids (such as 4HPR), or molecularly targeted agents (such as EGFR or ErbB-2 inhibitors).

These observations are particularly important because agonists for the TRAIL receptors are being tested in patients with cancer. Our results suggest that many cancers will be resistant to these agents when they are used alone. Predicting and overcoming this resistance will be essential to the

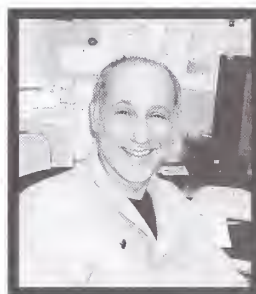
clinical success of these agents.

Our current work utilizes biochemical and genetic approaches to identify mechanisms that regulate the induction of death by TRAIL ligand in breast and ovarian cancer cells.

3) The assessment of molecular effects of targeted therapy in cancer patients.

It is critical to assess the action of new therapeutic agents on the predicted targets in the tumor in order to correlate the molecular function of these agents with clinical outcomes.

In collaboration with Sandra Swain, of



Fran Pollner

Stan Lipkowitz

RECENTLY TENURED

the NCI Medical Oncology Branch, we investigated the biochemical consequences of EGFR inhibition in breast cancer patients treated with the small-molecule EGFR inhibitor erlotinib. We were able to demonstrate effects of the inhibitor on EGFR signaling in biopsies of both surrogate and tumor tissue that expressed EGFR.

Using this pilot study as a template for the design of future studies, we will assess the biochemical effects of other molecularly targeted agents in breast cancer patients—particularly those that are relevant to our own research, such as EGFR inhibitors and agents that activate the TRAIL receptors.

Daniel Masison received his Ph.D. in biomedical sciences from the University of Massachusetts Medical Center, Worcester, in 1993, after which he joined the Laboratory of Biochemistry and Genetics, NIDDK, as a postdoctoral fellow. He became a tenure-track investigator in 1998 and is currently a senior investigator in that lab.

My research focuses on how protein chaperones and their co-chaperone partners affect propagation of the yeast [PSI] prion, an infectious amyloid form of a cytosolic protein. Amyloid is a fibrous protein aggregate that self-assembles like a crystal, converting the soluble protein into the non-native amyloid form as it joins the fiber. Amyloid accumulation is associated with tissue pathology in many disorders, including type 2 diabetes, Alzheimer's disease, and prion diseases. Prion diseases are the only infectious amyloidoses. What makes them infectious is unknown.

Prion particles, or "seeds," must replicate to be infectious or maintained in a growing yeast population. My isolation of an Hsp70 mutant that impairs [PSI] propagation led to our discovery that Hsp70 influences this replication and, thus, prion infectivity.

Hsp70 is a ubiquitous and essential chaperone that helps proteins adopt and maintain their native conformations. Because Hsp70 is important in many processes during which proteins are incompletely folded, such as translation, its activity is highly regulated by many co-chaperones. We found that modifying such co-chaperones could alter prion propagation by affecting Hsp70 activity in defined ways—which revealed how the mutant Hsp70's reaction cycle was altered.



Fran Pollner

Daniel Masison

Although the mutant Hsp70 is incompatible with prion propagation, it has no overt effect on cell growth or stress protection, pointing to Hsp70 as a target for therapeutic treatment of amyloidoses. To this end, we are looking to identify compounds that alter Hsp70 function in a way similar to the mutation.

We also discovered that the small molecule guanidine, known for over 20 years to be a potent yeast prion-curing agent, acts specifically by inactivating Hsp104, another chaperone important for yeast prion replication. Hsp70 and its co-chaperones are components of the Hsp104 chaperone machinery, and our continuing studies are uncovering how this machinery acts to influence amyloid-forming and amyloid-eliminating processes as well as cell growth and stress protection.

Hsp70 is also a component of the Hsp90 chaperone machinery, which assists folding of many "client" proteins, in particular signaling and transcription factors. Our studies identified novel functions for several Hsp90 co-chaperones in the regulation of Hsp70 and Hsp90. In addition to uncovering differences in chaperone activities for cellular and prion functions, this work identified the Hsp90 co-chaperones as factors involved in yeast prion propagation and provided the first functional evidence for some of their specific activities in vivo.

We also developed yeast systems wherein we can replace various chaperone components with those from any species. We found that mammalian counterparts supported growth and prion propagation, which demonstrates their utility as models for studying human chaperone/co-chaperone functions and for screening for compounds effective against them.

Using one such system, we discovered functional distinctions between the nearly identical constitutive and stress-inducible mammalian Hsp70s, which implies that optimal stress protection requires a function lacking in Hsp70 isoforms expressed during non-stress conditions.

Our ability to identify chaperone defects that do not affect cell growth and metabolism is allowing us to make significant innovative contributions to the understanding of the functions of the chaperones and their co-chaperones.

Although we are primarily focused on how protein chaperones interact with each other and with amyloid to better define how they affect amyloid propagation at a molecular level, our studies are also helping us understand how chaperones function both independently and as collaborators in general aspects of protein folding.

John Tisdale received his M.D. degree from the Medical University of South Carolina in Charleston in 1990. He completed an internal medicine residency at Vanderbilt University Medical Center in Nashville and then trained in hematology in the Hematology Branch, NHLBI, where he served as a postdoctoral fellow under the mentorship of Cynthia Dunbar. He joined the Molecular and Clinical Hematology Branch of NIDDK in 1998 and is currently a senior investigator in that lab.



Fran Pollner

John Tisdale

The description of sickle cell anemia (SCA) as a "molecular disease" by Linus Pauling over a half-century ago generated hope for a new era of molecular medicine. The defect was later traced to a single substitution at the sixth position of the β -globin chain of the hemoglobin (Hb) tetramer, resulting in an abnormal Hb among the erythroid progeny of hematopoietic stem cells (HSCs).

Our group focuses on HSC-based therapeutic approaches through the development of methods for transplantation of normal donor-derived HSCs or genetically modified patient-derived HSCs.

Though the curative potential of allogeneic HSC transplantation has been established in a select group of children with SCA, procedural toxicities limit this approach.

The development of conditioning regimens for graft-specific tolerance in the absence of conventional bone marrow-ablative chemoradiotherapy may allow extension of this approach to adults.

We and others have demonstrated the ability to achieve engraftment of allogeneic HSCs without the need for toxic ablative conditioning, yet full engraftment using intensive immunosuppression appeared to result from a donor T cell-mediated immune response and was associated with significant complications.

We therefore sought to develop a transplantation regimen for adults with SCA for which engraftment does not depend on such alloreactivity. We explored low-dose radiation and the immunosuppressant

rapamycin to induce tolerance *in vivo* in a murine HSC transplantation model and achieved phenotypic correction in a murine model of SCA, even with only moderate donor engraftment (mixed hematopoietic chimerism).

Based on these findings, we initiated a clinical trial of this novel transplantation approach in adults with severe SCA; initial results in the first three patients are encouraging, and our data support mixed hematopoietic chimerism as a reasonable goal for HSC transplantation in SCA.

For those lacking a suitable sibling matched donor, the permanent integration of potentially therapeutic genes into primary autologous HSCs using retroviral vectors remains a viable alternative.

Despite successful high-level gene transfer to murine HSCs and human progenitors *in vitro*, poor transgene expression and extremely low gene-transfer efficiency were observed in early human clinical trials. Our team and others have made significant progress over the past decade, with marking levels of 10 percent or higher at the HSC level now attainable in large animals.

Given the toxicity of myeloablative irradiation currently used in our animal models, we have focused our recent efforts on determining the degree of host conditioning required to achieve moderate-level engraftment of genetically modified cells.

Until recently, the desired attainment of erythroid-specific expression of the transferred globin gene had been problematic. Lentiviral vector systems, however, now permit the incorporation of large-globin locus control region elements in viral vectors—a development that enabled Michel Sadelain and his colleagues at the Memorial Sloan-Kettering Cancer Center in New York to achieve for the first time regulated human β -globin expression sufficient to revert the phenotype in a murine model of β -thalassemia.

In collaboration with the Sadelain group, we have now established a preclinical, large-animal model for lentiviral globin gene transfer.

Using a VSV-G pseudotyped, modified HIV-1–based vector, high gene-transfer rates to HSCs are achievable, with human β -globin expression of greater than 50 percent among erythroid progeny generated *in vitro*.

Transplantation studies in two rhesus macaques demonstrated human β -globin expression at greater than 10 percent early post-transplantation, with stabilization, albeit at lower levels, long-term.

Follow-up of these and other animals with clonal tracking of HSC progeny by

integration site analysis will permit assessment of the safety of this approach, and the model will be used to support eventual clinical application in disorders of globin synthesis.

Nan-ping Weng graduated from Shanghai Medical College, Fudan University (former Shanghai First Medical College), Shanghai, China, in 1984. He received his Ph.D. in immunology from Baylor College of Medicine, Houston, in 1993 and did his postdoctoral training at the Experimental Immunology Branch, NCI. In 1997, he became a tenure-track investigator in the Laboratory of Immunology, NIA, where he is currently a senior investigator in the Lymphocyte Differentiation Unit.

Immunological memory, a hallmark of immune response, is characterized by a rapid and robust response to subsequent encounters of a previously experienced antigen.

This memory, housed in long-lived T and B lymphocytes, serves as the physiological basis for vaccination and immunization. Despite advances in the field, the molecular mechanisms underlying immunological memory have only begun to be understood.

My laboratory seeks to elucidate the mechanisms of memory T cell generation, response, and aging. Specifically, we have focused our efforts on three areas: 1) identifying and characterizing differentially expressed genes in memory T cells, 2) determining the epigenetic basis for differential gene expression in memory T cells, and 3) exploring the molecular and cellular alterations of memory T cells with aging.

The pattern of gene expression and silencing defines the cellular characteristics and functions. Thus, one of our major research goals is to identify genes that are differentially expressed in memory T cells and to further characterize the roles of those genes in the generation, function, and homeostasis of memory T cells.

Using DNA microarray technology, we have analyzed and compared gene-expression profiles of human and mouse naïve and memory CD4 T cells and human naïve and memory CD8 T cells.

We have identified dozens of genes that are differentially expressed in memory CD4 and CD8 T cells in both human and mouse.

We have used mouse models that lack expression of these differentially expressed genes to further examine their role in

memory T cell formation and response.

Prospecting for the molecular basis of differential gene expression in memory T cells, we investigated the contribution of chromatin structure—particularly the modification of histone—in the regulation of gene expression in memory T cells. We found that acetylation levels of histone H3 lysine 9 (H3K9) are higher in memory CD8 T cells than in naïve cells in both resting and activated states.

Furthermore, we found that higher H3K9 acetylation levels were detected in resting memory cells, *prior* to their activation, for those genes that were differentially expressed after activation—indicating that hyperacetylation of histone H3K9 may play a role in the selective and rapid gene expression of memory CD8 T cells.

We are now extending analysis of histone H3K9 acetylation and other histone modifications to a genome-wide scale in parallel with genome-wide gene expression analysis. We hope such analyses will provide a genome-wide account of histone modification and gene expression in memory T cells.

Immune functions decline with age, with a resulting increase in infection-related morbidity and mortality in the elderly. We are interested in age-associated changes of memory T cell function and replicative lifespan.

It is known that short telomeres curtail cellular replication; not known is the *in vivo* rate of telomere attrition and whether *in vivo* T cell telomerase activity declines with age. A major research goal in my laboratory is to understand the role of telomere length and telomerase activity in memory T cell function and replicative lifespan and to investigate age-related changes in their regulation.

Currently, we are using human primary T cells (normal cells directly isolated from blood, as opposed to T cell lines) for molecular and cellular analyses and longitudinal studies to elucidate the changes of T cell function with aging.

We anticipate that knowledge derived from these experiments will further our understanding of the mechanisms of memory T cell formation, response, and age-associated functional decline. This understanding is essential for the rational design of vaccines to protect against infectious diseases and to develop strategies to combat cancer and autoimmune diseases in both the general and elderly populations. ■



Nan-ping Weng

Kids' Catalyst: Finding Magnetic North

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...

- Systems Biology
- Nobel Experience For GPP Students
- Sigma Xi Survey

Sometimes it's not so easy to find your way. Whether you live in the city or the country—or have a bike or a new car that talks to a satellite—sometimes you can get a little turned around.

There are many guides to finding your way—maps, stars, street signs, or just asking for directions. But if you really want to know in which way you're pointing, look no further than the earth itself, and a compass.

You can make your own compass at home. You'll need a magnet (refrigerator magnets work, and the magnets typically found in home science kits work even better), a sewing needle, a few inches of office tape (or a cork; see below), a large nonmetallic bowl, and enough water to fill the bowl.

Put the needle on a flat surface, with the eye toward you; then stroke it with the magnet, going from the eye to the tip (always the same direction). How many strokes depends on the strength of your magnet, but about 20 should suffice. Now you have a magnetized needle.

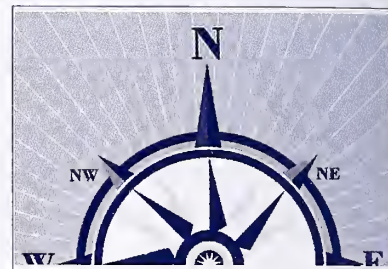
You can place the magnetized needle on a piece of cork or encase it in office tape and then place it in the water and watch how it floats. (Although the needle will float on top of water on its own due to surface tension, it may take longer; making a tape pontoon for the needle is perhaps the most practical approach—it has the added benefit of protecting fingers from the needle's sharpness and making the needle easier to find if it is dropped.)

Once the needle is ensconced and floating on the surface, where do you think the tip will point? If you guessed North, you're right—and not just any North, but magnetic North—just the same as any compass.

What if you're in space? Or in the Southern Hemisphere? Or live 100 years in the past or in the future? The fun thing about magnetic North is that it's always changing relative to itself and to where you are, so it's very important to keep up on your declination and inclination toes—but that is for you to look up!

By the way, please note: Our home-made magnetic needle will work only in still water, so its use outdoors is limited. But indoors, it's not only a compass, but can be turned into a game as well. You can make however many tape-encased magnetized needles as you have friends at your house. You can chase the needles around with your magnets—they will go wherever the magnet does—and have races and other rivalries with your friends.

—Jennifer White



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