

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 14, ISSUE 6 ■ NOVEMBER–DECEMBER 2006

Research Festival PROJECTED GLOBAL IMPACT ON HPV AND CANCER OF “REMARKABLE” VACCINE

by Fran Pollner



Fran Pollner

Douglas Lowy, chief of the Laboratory of Cellular Oncology, NCI, whose two decades of research on the human papilloma virus and collaboration with John Schiller, chief of the neoplastic disease section, culminated in the development of the HPV vaccine

In the most reasonable of all possible worlds, cervical cancer could become history. All that's needed is:

- Worldwide implementation of the HPV vaccination schedule now recommended for 11- and 12-year-old girls
- The replacement of cervical cytologic screening with fast-acting, low-cost HPV DNA testing and appropriate follow-up
- The development of topical microbicides targeting a broad range of HPV types

None of these achievements is beyond reach, investigators agreed at a Research Festival symposium on the pathogenesis and prevention of cervical cancer.

In fact, preventing new cases of

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Research Festival

READING THE TEA LEAVES OF VULNERABILITY: MICROSCOPIC BITS AND PIECES AS PROPHECY

by Dustin Hays

Predicting the future is not a new calling, Abner Notkins observed in opening the NIH Research Festival symposium on predictive medicine. But unlike the predictions of the oracles of antiquity or of new-age fortunetellers—based more in the realms of art or artifice—21st-century predictive medicine is based in science.

Today's oracles, Notkins said, are clinicians who plumb the depths of patients' DNA, RNA, proteins, autoantibodies, and the like to glean potential future health problems—with the objective of countering disease emergence before symptoms appear.

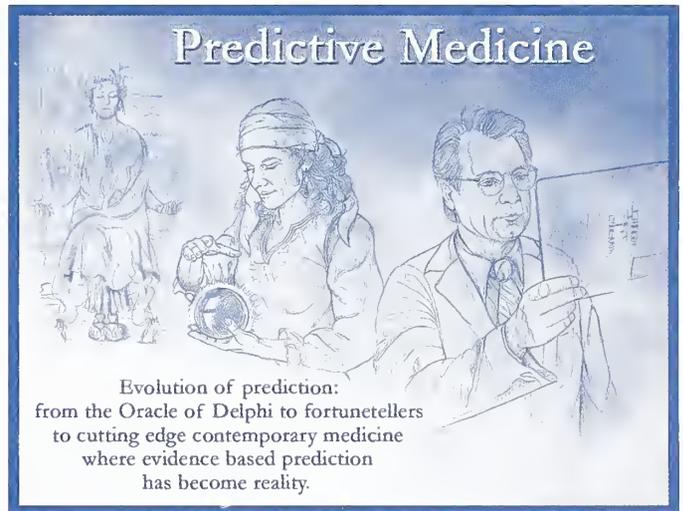
Notkins, chief of the Experimental Medicine Section, NIDCR, was among the symposium's oracles of evidence-based predictive medicine. He focused on the role of autoantibodies in predicting autoimmune disorders.

Joining him were:

- NHGRI Director Francis Collins, who described efforts to elucidate the genetic components of common disease

- Lance Liotta, co-director of the Center for Applied Proteomics and Molecular Medicine at George Mason University, Fairfax, Va. (and former NCI Laboratory of Pathology chief), who presented his research on protein-based predictors to tailor personalized cancer therapy

- Ezekiel Emanuel, chair of the CC Department of Clinical Bioethics, who tempered the momentum toward predictive medicine with some cautionary thoughts



Art by Lydia Kibiuk, ORS

Francis Collins: Genes as Predictors

With the unraveling of the human genome came the revelation that humans are amazingly similar: Roughly 99.9 percent of our DNA base pairs are identical, Collins observed, leaving the scant remaining 0.1 percent to account for our genetic variability and, thus, our varied genetic predisposition to disease.

Great progress has been made in iso-

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SPREADING THE WORD ABOUT TRAINING OPPORTUNITIES AT NIH

"It is as a training ground for young investigators, who have come to Bethesda for their postdoctoral education in research, that the institution has achieved its most singular influence on the progress of American science."

—Lewis Thomas



Michael Gottesman

NIH has traditionally been a training ground for future leaders in biomedical research. Those of us who were trained here and those who have trained many others know that the intramural research program provides talented mentors and research resources that are difficult to match elsewhere.

We also know that the current success and future impact of the NIH intramural program rest on the shoulders of our trainees, who provide a constant infusion of talent, energy, and creativity and do much of the work that powers our scientific productivity.

How can we be assured of continuing to attract the best, the brightest, and the most diverse population of trainees at all levels?

Some Background on New Plans

In the summer of 2004, the scientific directors generated a set of initiatives to improve and highlight various aspects of research at NIH, including our training programs. As a result of these recommendations, a committee co-chaired by Marvin Gershengorn, scientific director of NIDDK, and Jonathan Wiest, training director at NCI, suggested several approaches to improving and communicating training opportunities at NIH.

One major recommendation led to the formation of a steering committee for the newly reorganized Office of Intramural Training and Education (OITE) in the Office of Intramural Research. It is chaired by Eric Green and consists of several scientific directors and training directors.

This group has been extremely active; its first steps were to initiate evaluations of existing programs and to recruit a new director for the office. I am pleased to announce that Sharon Milgram, currently a professor of cell biology as well as postdoc and graduate student training director at the University of North Carolina, will be directing OITE beginning in the spring of 2007.

Reaching Out to Prospective Trainees

Although reorganization, evaluation of existing services, development of new programs, and new leadership may go a long way toward ensuring that NIH training programs retain a pre-eminent role in biomedical research, it has also been recognized that there are many potential trainees who simply know little or nothing about NIH.

Primary efforts have focused on bringing students to NIH who otherwise would not have the chance to visit and see firsthand what NIH has to offer. Two programs have already gotten underway.

The first—the Clinical Investigator Science Training (CIST) program—started four years ago. Under the leadership of Fred Ognibene, the CC's director of medical education, the CIST program has each year brought more than 200 medical students from

all over the country to a two-day symposium at NIH.

These students are all enrolled in highly selective year-off research programs at NIH and elsewhere, supported by NIH, private foundations, and a major pharmaceutical company. By inviting students who have already shown an interest in and talent for medical research, we hope to enrich future medical research training programs at NIH.

The National Graduate Student Research Festival, targeted at graduate students in the last year of their dissertation research, premiered just last month. Graduate students in biomedical research from all the major academic centers in the United States were invited to apply for a trip to NIH.

As detailed in the article on page 9 of this issue of the *Catalyst*, 964 graduate students applied (a substantial percentage of the total senior graduate students in biomedical research in the U.S.!), and 250 were chosen for an all-expense paid trip to NIH, where they presented research posters, heard from our scientific staff, and arranged interviews for potential postdoc positions at NIH.

Both the NIH scientific staff and the future postdocs hailed this event a big success; the majority indicated that they were likely to accept postdoc positions at NIH—whereas few indicated they'd had much knowledge of the intramural program before the opportunity arose to apply for this new graduate student program.

Looking to the Future

Because the selection committee needed to limit the number of participants to 250, many fine applicants who should be outstanding candidates for NIH postdoc positions could not attend this event.

To see whether any of the Research Festival applicants match your program interests, log in to <http://www.training.nih.gov/adminForms/researchfestival/forms/login.aspx> using the credentials you use to access postdoctoral ads. Also, please plan to meet the potential postdocs who attend the second National Graduate Student Research Festival next October.

We are working on many more ways to improve and convey the quality of our training programs: new interdisciplinary and bridge-type programs with well-defined goals, pamphlets advertising the wealth of training experiences at NIH, improved websites, and more mailings to target institutions.

Ultimately, the best way to identify outstanding prospective NIH trainees is for every tenure-track and tenured scientist at NIH to contact their colleagues to invite them to send us their best, brightest, and most diverse candidates. I welcome your ideas about how to get the news out about training at NIH.

—Michael Gottesman

Deputy Director for Intramural Research

*Sigma Xi National Postdoc Meeting, 2006***HOW TO IMPROVE ON A GOOD THING:
ENHANCING THE POSTDOC TRAINING EXPERIENCE**by Rebecca Lipsitz
and Joan P. Schwartz

Want to help your postdoctoral fellows become even more productive?

We got some good tips on how to do that at a recent meeting sponsored by Sigma Xi (the international Scientific Research Society) and the National Postdoc Association. The meeting drew faculty, postdocs, and administrators from around the country.

If you've spoken with your postdoc or faculty colleagues outside NIH, you know that the postdoc training experience varies greatly among institutions. Until recently, most institutions had relatively few stated policies or explicit expectations regarding postdoctoral training. Although some may argue that the flexible nature of postdoc training is the key to intellectual growth, institutions are starting to recognize the advantages of formalizing certain aspects.

Major topics of discussion at the meeting included 1) the desirability of establishing offices on campus dedicated to postdoc professional development and 2) the results of a national postdoc survey to determine the effects of various services and programs on the quality of the postdoc experience.

Creating Dedicated Postdoc Offices

Over the past few years, faculty, granting agencies, and postdocs themselves, including the National Postdoc Association, have recommended five specific practices to enhance the postdoctoral experience:

- Funding through individual fellowships
- Increased stipends
- Provision of basic benefits, such as health insurance and retirement benefits
- Opportunities for professional development
- Structured oversight

The establishment of postdoc offices was seen as an important way to accomplish these objectives.

NIH offers two levels of postdoc offices:

- The centralized OIR Office of Intramural Training and Education (OITE) provides a series of NIH-wide career de-

velopment and other training opportunities for all levels of trainee from high school to postdoctoral.

- Fellowship training offices within the individual institutes and centers offer additional IC-specific or science-specific training avenues.

Indeed, the past 10 years have seen a steady growth in these latter offices, to the point that almost every IC with an intramural program also has such an office or, at the very least, a designated training director. These offices have enhanced the training and career development aspects of the Intramural Research Program enormously.



Joan Schwartz,
assistant director, OIR



Rebecca Lipsitz,
former NHLBI postdoc
and current AAAS
fellow in the NIH
Roadmap Office

**From the Source:
Postdoc Survey Results**

Sigma Xi's Geoff Davis, who served as the conference host, presented the results of the recent national Sigma Xi survey. The results are described in detail in "Improving the Postdoctoral Experience: An Empirical Approach" by Davis and can be found at

<<http://postdoc.sigmaxi.org/>>.

The survey was sent to 22,400 postdocs, comprising about 40 percent of the total postdoc population in the United States. The fellows work at 47 different institutions, including NIH. The response rate was 38 percent, and statistical analyses showed no non-response biases.

The survey was designed to determine the extent to which each of the five recommended practices previously cited affects the quality of postdoc experiences and productivity.

Four outcome measures were used: subjective success (respondents' take on their current position), advisor relations, absence of conflict and misconduct, and productivity.

Notwithstanding the observation that postdocs are established professionals with personal responsibility for their own success, survey results supported the added benefit in many outcome measures, including productivity, brought by the provision of structured oversight and professional development opportunities.

Structured oversight includes

- Offering letters that detail salary, benefits, and length of appointment

- Establishing career development plans at the outset of training

- Providing yearly progress reviews

- Creating clear institutional policies on authorship, misconduct, grievance procedures, and intellectual property

- Providing career counseling and placement services

Between OITE and the IC training offices, NIH provides almost all of these, although it is up to the postdoc and mentor to take advantage of them. Career counseling and job placement are the least formalized—we expect mentors to be actively involved, and we know that the training offices do some counseling, but a more structured program has been identified as a need by our incoming OITE director.

Professional development opportunities include training in

- Research ethics
- Writing, speaking, and teaching
- Grant writing
- Lab and project management
- Job negotiations
- Intellectual property issues
- Conflict resolution
- English language skills

as well as the availability of information about nonacademic careers.

Again, NIH offers essentially all of these learning experiences, many free through NIH-wide courses and workshops presented by both OITE and the individual IC offices.

The biggest challenge remains getting our PIs' support for their fellows to participate in them.

PIs argue that it is time out of the lab, away from the bench and their experiments. But the Sigma Xi survey results suggest that these times away actually enhance productivity.

Indeed, according to survey results, "Postdocs reporting the highest levels of oversight and professional development are more satisfied, give their advisors higher ratings, report fewer conflicts with their advisors, and are more productive than those reporting the lowest levels."

That information struck us as the most useful and relevant to NIH postdocs that we gained from the meeting. And we happily pass it on.

We also note that NIH already has a pretty good record for postdoc training: For the past several years, *The Scientist* has consistently awarded recognition to NIH and to some of the individual ICs for being among the "Best Places to Work for Postdocs." ■

TEA LEAVES OF VULNERABILITY

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lating genetic disorders that have a predictable pattern of inheritance, such as cystic fibrosis, but it appears that the familial risks of more common diseases—such as heart disease and depression, which lack a predictable inheritance pattern and vary in severity among individuals—are attributable to genetic variations, mostly single nucleotide polymorphisms (SNPs), scattered among the roughly three billion base pairs in the human genome.

Early attempts to link genetic components to common diseases, Collins said, were akin to a “drunk searching for his keys under a street light—we were looking only in the places where we could see.”

But now, he said, the recently completed Hap Map Project, a multinational effort involving more than 1,000 scientists, has mapped the location of SNPs throughout the human genome and “lit up the street,” providing the power tools to identify weak genetic contributors to common diseases.

Collins cited a few early discoveries attributable to the use of Hap Map data, such as the relationship of a complement factor H gene variant to age-related macular degeneration (AMD)—a leading cause of blindness in the elderly not previously thought to have a strong genetic component. In all, three risk variants have now been identified, accounting for 74 percent of AMD risk.

Similarly, Hap Map data provided the foundation to enable isolation of risk variants for prostate cancer associated with a greater risk among African than European men—which may contribute to the higher incidence of prostate cancer among African-American men.

Collins gave the audience a sense of gene hunting using Hap Map data by profiling the FUSION study, a genome-wide association study aimed at finding weak genetic contributors to type 2 diabetes. The study is a collaboration among four partners—the Keck School of Medicine at the University of Southern California, Los Angeles; the University of Michigan School of Public Health, Ann Arbor; Finland’s National Public Health Institute; and Collins’ intramural research laboratory at NHGRI.

Using the Illumina® 317K platform, which evaluates roughly 317,000 SNPs defined by the Hap Map Project, 1,186 people with type 2 diabetes and 1,171 matched control subjects were

genotyped at the NIH/Johns Hopkins’ Center for Inherited Disease Research in Baltimore to identify gene variants associated with type 2 diabetes.

Among those associations found was a previously identified gene variant called transcription factor 7-like 2 (TCF7L2). Though not conclusive on their own, when FUSION data were combined with data from a similar study conducted by the Diabetes Genetics Initiative of the Broad Institute, Cambridge, Mass., TCF7L2 had the greatest genome-wide significance for type 2 diabetes, with a combined odds ratio of 1.35.

Phase II of the FUSION study will genotype an additional 3,000 patients and controls using the top 1–3 percent of SNPs identified in Phase I.

Collins pointed out that appropriate sampling power is critical to uncover weak heritable links based on SNPs; the rarer the allele, the greater the number of cases that must be genotyped. He anticipates that the Phase II findings will uncover additional, as-of-now elusive, diabetes-susceptibility variants.

“Identifying gene variants such as TCF7L2,” Collins said, “will provide the drug targets of the future for small molecules that go right to the heart of the problem instead of treating some secondary effect.”

Lance Liotta: Proteins as Predictors

Genes can say a lot about an individual’s predisposition to cancer, but they cannot reveal what is happening in cells at the functional protein level, for example, in a tumor, Liotta observed.

He discussed a rationale for using tissue proteomics to subcategorize patients’ tumors based on the activated state of associated tyrosine kinases, corresponding signaling pathways, and the context of the tumor’s microenvironment. Access to this knowledge, he proposed, will allow clinicians to predict patients’ responses to various cancer treatments and to custom-tailor therapies to maximize benefits and minimize side effects.

Liotta noted that anticancer drugs that



Dustin Hays

Francis Collins (left) and Abner Nottkins

target small molecules often work only in a subset of tumors. One such drug, an epidermal growth factor receptor (EGFr) inhibitor called gefitinib, proved effective in 15 percent of nonsmall cell lung-cancer patients enrolled in a clinical trial. By some accounts, those results would constitute a failure—but for the 15 percent in whom the drug worked, it was a success, Liotta said.

He described the use of reverse-phase protein microarrays to assess the activation of signaling pathways in microdissected lung tumor cells taken by core needle biopsy.

This technique can identify which cells in a heterogeneous cell sample are activated by phosphorylation, shedding light

on which pathways may be hyperactivated or suppressed. Hyperactivation of the EGF pathway is believed to contribute to 11–19 percent of non-small cell lung-cancer cases. Protein microarrays can identify patients who fall into this category who may be candidates for EGF-pathway inhibitors.

Liotta is currently collaborating with investigators at NCI and at Northeastern University in Boston to map

phosphorylation sites on the EGF receptors of tumor cells. A new technology called dynamic quantitation using Fourier-transform mass spectrometry enables the investigators to examine patterns of EGFr phosphorylation over time in response to stimulation and to correlate them with interconnected pathways downstream. A prospective clinical trial



Lance Liotta

to evaluate the role these patterns play in association with lung cancer is set to begin early next year.

Abner Notkins: Antibodies as Predictors

Type 1 diabetes patients begin expressing autoantibodies as early as 5–10 years before the clinical onset of disease. Early evidence suggests this phenomenon is also true of many of the 40–80 other autoimmune diseases thus far identified.

Notkins made the case for using autoantibodies as predictors of autoimmune disease and for constructing what he called the “autoantigenome,” which involves the identification and characterization of all the major autoantigens in the most common human autoimmune diseases.

Notkins has been studying autoantigens associated with type 1 diabetes for about 10 years. His prospective studies have revealed that patients with Type 1 diabetes express autoantibodies to one or more proteins—IA-2, GAD₆₅ (glutamic acid decarboxylase) and/or insulin—years before symptoms appear.

He said that the likelihood of developing Type 1 diabetes within five years is 10 percent in the presence of one autoantibody, 50 percent in the presence of two, and 70 percent in the presence of three.

Because the three major autoantigens in type 1 diabetes are associated with vesicles—dense core or synaptic—that carry hormone and neurotransmitter, Notkins hypothesized that there are other still unrecognized autoantigens that are associated with these vesicles.

He and his colleagues have developed a selective screening approach to identify type 1 diabetes-associated autoantigens: They prepared a panel of 56 vesicle-associated proteins, starting with their gene sequences, and then screened each protein with sera from patients with Type 1 diabetes and from control subjects. Both IA-2 and GAD were readily identified as autoantigens, and additional studies now entering a validation phase have revealed several new candidate autoantigens.

As it turns out, type 1 diabetes is not the only autoimmune disease in which autoantibody expression precedes symptoms, Notkins noted. Data from other laboratories indicate that this phenomenon occurs in rheumatoid arthritis, lu-

pus, Addison’s disease, multiple sclerosis, celiac disease, and pemphigus.

Notkins outlined six uses for predictive autoantibodies: 1) to predict the likelihood of developing disease, 2) to estimate the length of the asymptomatic period, 3) to help classify autoimmune diseases, 4) to provide predictive information about disease course, severity, and complications, 5) to serve as a warning to avoid potential disease-triggering factors, and (6) to identify high-risk individuals who might be suitable candidates for therapeutic intervention trials.

The enormous value of autoantibodies as predictive indicators of autoimmune disease, Notkins suggested, warrants screening the entire proteome for autoantigens to create the human “autoantigenome.” Considering the breadth of autoimmune disease, which crosses multiple organ systems, such an endeavor could best be undertaken as a trans-NIH Roadmap project, he said.

Ezekiel Emanuel: Ethical Issues

If the aspirations of predictive medicine are realized, what effects will they have on individuals and on society as a whole? Are there drawbacks to a brand of medicine that seeks to cure disease before it starts?

Yes, there are substantial caveats, Emanuel cautioned. As predictive medicine evolves, it is likely our ability to cure disease will lag behind our ability to detect it. Knowledge is not necessarily a good thing, for example, if one were told to expect a disease for which, at least currently, there is no cure. Predictive medicine, like all medicine, can pose risks to both individuals and society, he observed.

Even as established a procedure as screening mammography can carry undesirable physical and emotional risks for individuals, Emanuel said. The consequences of a breast biopsy following an equivocal mammogram, for instance, range from lymphedema to unnecessary physical and psychological trauma in the approximately 50 percent of women whose biopsies are negative.

There are risks and harms to society as well. Of the two trillion dollars the

United States spends annually on health care, only those spent on vaccines actually save money. Everything else contributes to the steadily rising cost of health care. As of yet, Emanuel noted, there has been no analysis of the cost effectiveness of predictive medicine.

The public’s somewhat ambiguous reception of predictive medicine thus far, he continued, has presented challenges to gauging its overall usefulness. He cited the discovery of *BRCA1/2* mutations, which are linked to both breast and ovarian cancer, as one example. Before the advent of *BRCA1/2* testing, a substantial percentage of women with a family history of breast cancer elected to have prophylactic bilateral mastectomies.

Because women willingly sought such a radical measure in an effort to ward off cancer, it was believed that a genetic test for *BRCA1/2* would instill a sense of hypervigilance among women who tested positive and that they would seek monitoring interventions, such as mammography, in greater numbers.

In fact, however, when a genetic test became available, many women chose not to learn their *BRCA1/2* status, and though mammography rates among those who tested positive did increase—from 49 percent to 61 percent—they did not soar.

As Emanuel pointed out, “...providing predictive tests does not ensure people will adhere to monitoring and preventive interventions.”

Perhaps the most pervasive and difficult to pinpoint undesired consequence of

predictive medicine is captured in the irony that despite the fact that the average lifespan in the United States has increased by seven years since 1960, Americans’ perceived sense of well-being has gone down while health-related anxiety has gone up. Emanuel posed the question: “Why does predictive medicine make us feel worse?”

He suggested that “a heightened consciousness of health might lead to greater self-scrutiny and an amplified awareness of symptoms and feelings of illness” and that “an increasing focus on health issues in the media might create a climate of apprehension, insecurity, and alarm about disease.” ■



Ezekiel Emanuel

HPV VACCINE

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cervical cancer caused by HPV types 16 and 18—which account for 70 percent of cervical cancer cases—is easily envisioned with appropriate use of what NIAID's Carolyn Deal referred to as the "truly remarkable" HPV vaccine invented by Doug Lowy, chief of the Laboratory of Cellular Oncology, NCI, and John Schiller, chief of the Neoplastic Disease Section in that lab.

HPV Vaccine: Plaudits and Limits

This is an "incredibly effective" vaccine, said Deal, chief of the Sexually Transmitted Diseases Branch and the NIAID representative on the HPV Work Group of the CDC Advisory Committee on Immunization Practices.

"Seeing 100 percent efficacy results in a phase III clinical vaccine trial is unique," she said. Because it is thought that "most everyone" will be exposed to this ubiquitous virus, routine immunization, rather than high-risk targeting, makes sense. Moreover, higher antibody titers are generated in preadolescent than in older individuals.

While girls are now the intended recipients of HPV vaccine, the results of ongoing clinical trials to test the efficacy of HPV vaccine in preventing infection in males may some day lead to similar recommendations for boys, Deal added.

Schiller described the research that led to the approval in June of the first HPV vaccine to prevent cervical cancer and genital warts (with another commercial HPV vaccine expected to be submitted for approval by year's end).

Calling the end result a "triumph of modern molecular biology," Schiller nonetheless cautioned against "undue expectations" of the vaccine, which is built around virus-like particles of relevant HPV subtypes.

The vaccine does not protect against infection from several other HPV subtypes, and it is no better than placebo in clearing already existing infection, he said.

However, the protection it does confer is "remarkable"; antibody levels generated are well above those observed after natural infection, and there are no signs of waning protection up to four years now from the time of vaccination.

On the horizon, Schiller said, there may be products with expanded valencies from the HPV manufacturers of the current quadrivalent and bivalent vaccines; an aerosol HPV vaccine; and, to



Fran Pollner

Aiming to bid cervical cancer adieu: (left to right) panel co-chair Doug Lowy, NCI; Chris Buck, NCI; panel co-chair Phil Castle, NCI; Carolyn Deal, NIAID; and John Schiller, NCI

make the vaccine accessible in the developing world, manufacture in emerging countries to decrease the current \$120/dose cost comparable to that eventually secured for the hepatitis B vaccine (from \$80 a dose to 30 cents).

Screening by HPV DNA Testing

Preventing cancer arising from already established HPV 16 and 18 infections and preventing the 30 percent of cervical cancers that arise from other subtypes require screening and prevention programs that "hopefully will shift" from cervical cytology screening to HPV DNA-based testing, Schiller said.

Although routine cervical cancer screening by Pap smear has yielded a 70–90 percent decline in cervical cancer incidence worldwide, it is still the second most common cancer in the world and the cancer whose incidence reflects the greatest disparity among socioeconomic classes.

Moreover, cytologic results are subject to misinterpretation, and the three-tiered approach—Pap smear, followed by biopsy if needed, followed by treatment if needed—is difficult to carry out in developing countries.

A better HPV screening strategy would be noncytological, said Phil Castle, an investigator in the Division of Epidemiology and Genetics, NCI.

Of the 40 mucosal HPV types that in-

fect the lower genital tract, 15 types are carcinogenic, responsible for all cervical cancer. HPV infection that persists carries the risk of evolving into a precancerous state and, ultimately, invasive cancer.

A single HPV DNA test is 95 percent sensitive and reproducible, can predict the risk of precancerous changes 11 years later—a 20 percent risk if HPV 16 and 18 are present at baseline, compared with 0.01 percent if they are not. Although the specificity of a single test falls a little short of that obtained with cytologic testing, "if you're willing to monitor for viral persistence," specificity will soon surpass that from cytology, he said. A low-cost HPV test that yields results in two hours enables same-day testing and treating by cryotherapy, an advantage in low-resource settings where HPV vaccines are not affordable and in any circumstances where multiple doctor visits are difficult.

The idea is to be able to offer a "menu" of approaches to eradicating cervical cancer, based on the social attitudes and resources of any given country, Castle observed.

"From Bench to Bedroom"

The third arm of the strategy to eliminate cervical cancer, said Chris Buck, a postdoctoral fellow in the Laboratory of

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RESEARCH FESTIVAL

DIETARY FATS AND THE NERVOUS SYSTEM

by Fran Pollner

Diets low in omega-3 fatty acids—especially the highly unsaturated docosahexaenoic (DHA)—take their toll on cell signaling, vision, and cognition.

These effects are clearly demonstrated in rat studies and in studies involving patients with Alzheimer's disease and age-related macular degeneration (AMD), panelists reported at a Research Festival symposium on "Regulation of Nervous System Structure and Function by Dietary Polyunsaturated Fatty Acids."

The absence of omega-3 fatty acids from the diet results in the replacement of DHA by docosapentaenoic acid (DPA) omega-6, observed Norman Salem, Jr., chief of the Laboratory of Membrane Biochemistry & Biophysics, NIAAA, and of the Section on Nutritional Neuroscience.

"They're both long-chained and they're both PUFAs [polyunsaturated fatty acids], but there is a difference in structure at the atomic level that causes major physiologic differences. It's one of the most amazing things I've ever seen in biology—and that's why I've been working on this for decades."

That one structural difference manifests itself in olfactory deficits, an inability to remember an escape route, and neuroanatomical defects such as decreased neuron size and density and impaired dendritic tree development in the DHA-deprived cohort of rats fed otherwise-identical diets.

The bottom-line explanation for these findings, "we think," Salem said, is disrupted regulation of G protein-coupled receptor signaling (GPCR).

Drake Mitchell, acting chief of the Section on Fluorescence Studies, bolstered the GPCR signaling hypothesis with his report on a series of rat studies in which

the replacement of omega-3 PUFA with omega-6 PUFA disrupted regulation of GPCR signaling, membrane composition, and visual responses in the retina.

Human retinal health and disease, said John Paul SanGiovanni, staff scientist in the Clinical Trials Branch, NEI, and project officer of the Age-Related Eye Disease Study 2 (AREDS2), are intimately connected to the level of dietary intake of long-chain PUFAs, specifically the omega-3 fatty acids DHA and EPA (eicosapentaenoic acid).

Findings from NEI's first AREDS trial and other studies examining the relationship of dietary omega-3 long-chain PUFA and the likelihood of having the neovascular form of AMD, which accounts for most AMD-related vision loss, SanGiovanni said, are "consistent"—decreasing risk with increasing intake.

In the NEI study, involving 658 participants with neovascular AMD and 1,080 AMD-free healthy control subjects, those consuming the highest amounts of DHA had a 50 percent decreased risk of having neovascular AMD relative to peers reporting the lowest levels of DHA intake. Other NEI findings include a protective effect of EPA on progression to central geographic atrophy and vision loss, and a synergistic protective effect of aspirin with either DHA or EPA on prevalence and incidence of sight-threatening AMD.

A newly launched phase III clinical trial—AREDS2—will enroll 4,000 AMD patients and assess the value of dietary



Fran Pollner

Counting the praises of omega-3: (left to right) Drake Mitchell, NIAAA; panel chair Norman Salem, NIAAA; Stanley Rapoport, NIA; and John Paul SanGiovanni, NEI

DHA and EPA in addition to the antioxidant regimen tested in the earlier AREDS trial, SanGiovanni noted.

Brain AA findings in a rat model of neuroinflammation—elevated AA release from and reincorporation into brain phospholipids and increased brain activity in phospholipase A2 in rats subjected to lipopolysaccharide infusion—provided a basis for ongoing studies in patients with Alzheimer's disease and healthy control subjects.

Stanley Rapoport, chief of the Brain Physiology and Metabolism Section, NIA, reported PET imaging data on increased incorporation of intravenously injected radiolabeled AA from plasma into the brain regions of Alzheimer's disease patients where brain blood flow was reduced.

Related findings include the fact that lithium and other agents used to treat bipolar disorder decrease AA turnover in rat brain phospholipids, as well as brain phospholipase A2 activity, Rapoport said. He noted that increased AA incorporation from plasma on PET may be used as a marker of neuroinflammation in Alzheimer's disease and conditions such as AIDS dementia and multiple sclerosis. ■

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Cellular Oncology, NCI, is the development of topical microbicides targeting a broad range of sexually transmitted HPV types. This is an especially important goal given that condoms offer no more than 70 percent protection against HPV, Buck noted.

Buck described his work using HPV pseudoviruses to screen compounds for their inhibitory potential. The most promising agent yet tested is a sulfated polysaccharide called carrageenan that is "commercially ubiquitous," he said, pointing out that among the products

in which it is an ingredient are several personal lubricants intended for sexual use. Carrageenan was highly inhibitory to all genital HPV types tested.

Carrageenan is currently in clinical trials as a topical microbicide against HIV—and "HPV has been found to be a thousand times more susceptible to carrageenan" than either HIV or HSV, he said.

The agent blocks the binding of fluorescently tagged HPV 16 capsids to cells at doses that also inhibit infectivity, he said, noting that it is so "extraor-

dinary potent that it not only prevents virion-to-cell attachment but also inhibits post-attachment events, raising the possibility of postcoital application."

The degree of personal control such an agent would offer to women is obvious, Buck observed, calling the translation of this particular research effort "from bench to bedroom."

However, although the agent works very well "in a dish and in a mouse genital challenge model," Buck said, it remains for clinical trials to establish true safety and efficacy. ■

LOOKING FOR THE BEST ENDING TO A MAJOR ANTI-HIV SUCCESS STORY

by Fran Pollner

When it comes to reducing the rate of mother-to-child HIV transmission, the elusive perfect is not the enemy of the good; nonetheless, investigators would like to better define and minimize the risk, however small it may currently be, of genetic damage or mitochondrial dysfunction in fetuses and infants exposed to antiretroviral therapy.

To that end, NIEHS and the National Toxicology Program (NTP) have been examining the mitochondrial and potential carcinogenic effects of zidovudine (AZT), the first FDA-approved anti-HIV agent, and other nucleoside reverse transcriptase inhibitors (NRTIs); and NICHD, in collaboration with NIAID, NIDA, NIMH, NIDCD, and NHLBI, has launched the Pediatric HIV/AIDS Cohort Study (PHACS) to assess the long-term safety of fetal and infant exposure to prophylactic antiretroviral therapy.

According to John Bucher, deputy director of the Environmental Toxicology Program, NIEHS, and chair of the NIH Research Festival symposium on the benefits and risks of antiretroviral therapy in preventing mother-to-child HIV transmission, antiretroviral HIV regimens are among NTP's top targets of investigation today (cell phone radiation and dietary supplements are two others).

Three NIEHS scientists reported recent findings:

- William Copeland, of the Laboratory of Molecular Genetics, reported on the propensities of NRTIs to induce disruption of mitochondrial DNA replication through inhibition of DNA polymerase- γ .

A new NTP study, he said, establishes mitochondrial DNA damage in mouse-pup hearts from perinatal exposure to two NRTIs—AZT and 3TC. A possible cascade of NRTI-induced oncogenic events starts with the inhibition of thymidine kinase 2 and DNA polymerase- γ and potentially culminates in activated protooncogenes and cancer.

- Robert Sills, of the Laboratory of Experimental Pathology, elaborated on AZT-induced lung tumors in mice after in utero exposure. Mutations in the *K-ras* oncogene and P53 tumor-suppressor gene were among the findings reported in mouse lung tumors.

- Kristine Witt, of the Environmental Toxicology Program, noted that NTP studies revealing chromosomal damage

in mouse pups were designed to echo human therapeutic levels of AZT. Transplacental exposure alone to low-dose AZT (50 mg/kg) is associated with a 10-fold increase in micronucleated reticulocytes—a standard biomarker of chromosomal damage—in newborn pups.

"These were the findings," she said, "that prompted human studies"—studies in which the frequency of micronucleated reticulocytes in 13 infants exposed

prenatally to AZT was 10-fold that found in cord blood of control subjects and in three infants whose HIV-infected mothers had received prenatal antiretroviral therapy that had not included AZT. "Transplacental AZT is genotoxic to erythrocytes," Witt remarked.

Whether findings of this sort have any long-term clinical consequences, however, remains to be determined.

In addition to transplacental exposure to maternal treatment for HIV during pregnancy and at labor and delivery, infants of HIV-infected mothers also receive prophylactic antiretroviral therapy for the first six weeks of life. About 6,000 to 7,000 HIV-infected women give birth annually in the United States.

The most salient consequence of this treatment is that most offspring of HIV-infected mothers are now shielded from the ravages of HIV infection, a resounding public health success story, observed Lynne Mofenson, chief of the Pediatric and Adolescent AIDS Branch, NICHD, and executive secretary of the PHS committee that issues guidelines for HIV/AIDS treatment and prevention of transmission in pregnancy.

Indeed, mother-to-child transmission rates have decreased from 25 percent to 1 percent or less with the use of combination antiretroviral therapy.

Mofenson noted, however, that the long-term clinical effects of in utero exposure to these drugs is unknown, as combination regimens have been used for only 8 to 10 years, and the data on



Fran Pollner

Prospecting for the best regimens: (left to right) William Copeland, NIEHS; Lynne Mofenson, NICHD; Kristine Witt, NIEHS; Robert Sills, NIEHS; and panel chair John Bucher, NIEHS

mitochondrial dysfunction and genetic toxicity are concerning.

This concern, she added, informs the recommendation for long-term follow-up of uninfected children born to HIV-infected mothers who receive such drugs during pregnancy.

French studies have suggested that in utero antiretroviral exposure may rarely be associated with development of symptoms (primarily neurologic) of mitochondrial dysfunction in young HIV-exposed but uninfected infants; two deaths in the perinatal period in children with such findings have been reported. Other studies in the United States and Europe have not observed these findings, she said, but large numbers of children need to be followed to detect a rare event.

Additionally, there have been reports suggesting that mild, persistent, but clinically insignificant, hematologic abnormalities may be associated with antiretroviral exposure in HIV-exposed uninfected infants. Similar findings have been reported regarding asymptomatic, mild echocardiographic abnormalities.

Mofenson noted that the PHACS study will provide systematic follow-up of several thousand antiretroviral-exposed infants, with a focus on growth, metabolic, cardiac, and neurologic/neurodevelopmental evaluations. The study, she said, should provide more answers and perhaps clues to which combination regimens may have the fewest risk of long-term adverse effects. ■

GRADUATE STUDENTS SHOWCASE THEIR RESEARCH AT NIH —AND THINK ABOUT COMING BACK FOR POSTDOC TRAINING

by Patricia Sokolove

NIH hosted its first annual National Graduate Student Research Festival, and by all accounts it was a great success.

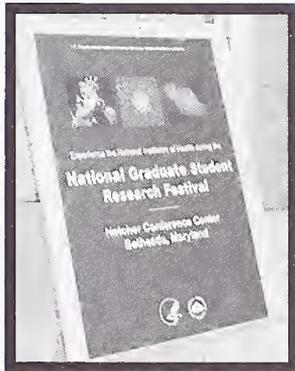
The objective was to increase awareness among graduate students throughout the United States that NIH is a highly desirable postdoc training site—and to pave the way for the recruitment of outstanding postdocs.

Advanced graduate students in training around the country were invited to apply to attend and present a poster at the festival; 964 sent in applications.

More than 90 NIH investigators participated in the review process. The material evaluated included an abstract describing the applicant's research, a cover letter, a letter of reference from the dissertation advisor, and the applicant's *curriculum vitae*. An overall assessment of the fit between the applicant's interests and the NIH mission completed the review.

The 250 most highly ranked applicants were invited to attend the festival.

Festival participants spent the better part of two days on the NIH Bethesda campus, presenting their work in poster format; interviewing with NIH investigators regarding potential postdoctoral positions; and attending sessions focused on how NIH works, the role of NIH postdoctoral training in the career paths of former NIH trainees, and the scope of NIH intramural science. NIH covered all participant costs.



Natcher served as the site of the first National Graduate Student Research Festival, held October 12 and 13

Both the graduate students and NIH investigators had overwhelmingly positive reactions to the festival: 97 percent of respondents to a participant survey said they would recommend the Graduate Student Research Festival to their colleagues; 71 percent said that were an offer to be made, they were likely or very likely to accept a postdoctoral position at NIH.

Michael Lenardo, a senior investigator in the Laboratory of Immunology, NIAID, was so enthusiastic, he dispatched a post-festival accolade to the festival organizing committee:

"I want to tell you how spectacular the research festival for graduate students was last week. I interviewed 12 students who expressed interest in my lab and they were terrific.

"Also, I talked to another 15 or so at the lunch and the poster sessions, and it was amazing that only one of all of these students had ever been to the NIH before.

"There was no doubt that they all had a much better appreciation of the institution and were quite excited by the intramural program. They seemed to enjoy the festival tremendously.

"For me personally, it was a very efficient and cost-effective way to interview some outstanding postdoc prospects, and it will be difficult to choose one from the bunch I saw."

Planning for the second annual festival is underway. ■



Terry Moody

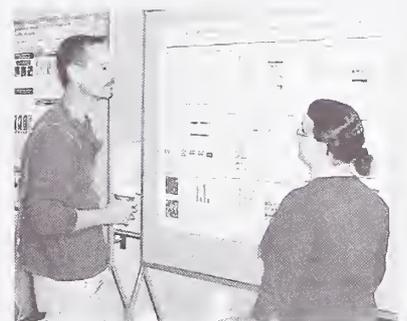
Stephen Leppla, senior investigator, Laboratory of Bacterial Disease, NIAID (third from left), hosts a table of festival participants at a lunch to introduce them to NIH fellows and investigators



Janell Hill, of Howard University, Washington, D.C., describes her work on CHEK2, a protein kinase involved in cell-cycle control. Abolition of CHEK2 function increases the risk of breast cancer; Hill is looking specifically at CHEK2 mutations in African-American families



Michelle Demory (right), of the University of Virginia, Charlottesville, explains her findings regarding the translocation of the epidermal growth factor receptor to the mitochondria, a process that may be associated with poor breast cancer prognosis; among the listeners are Stephanie Dance (far left) of Wake Forest University, Winston-Salem, N.C., and Eva Mezey (3rd from left), senior investigator, Adult Stem Cell Unit, NIDCR



Rebecca Cerio, of the University of Wisconsin-Madison, discusses her research on the role of multiprotein complexes in the inhibition of apoptosis with Tom Kristie, senior investigator, Laboratory of Viral Diseases, NIAID

Photos by Terry Moody

THE ROAD LESS TRAVELED

Ed note: The following commentaries on current regulations regarding official travel by NIH employees represent the views of the authors and appear here under the auspices of the NIH Assembly of Scientists, which has been accorded a standing ViewPoint space in The NIH Catalyst. Individuals who wish to write a column should contact a member of the ViewPoint editorial board (Abner Notkins, Harvey Alter, Edward Korn, Alan Schechter, Joshua Zimmerberg).

In this the winter, spring, summer, and fall of our discontent since implementation of the HHS interim final guidelines, there has been a retrenchment towards rationality, and some of the most egregious restrictions have been removed in the final guidelines. In particular, academic freedom has been restored in large measure and severe stock-divestiture rulings have been rescinded.

Nonetheless, the final HHS guidelines have provisions that continue to sap morale on campus and that serve as a deterrent to recruitment and retention. These include restrictions on paid consultation with industry and restrictions on travel, wherein DHHS appears to have more stringent guidelines than any other federal agency. This article will deal only with issues related to travel.

Word has trickled down that one of the foundations for these travel prohibitions is that "scientists travel too much." While it is true that scientists travel to meetings and to other academic institutions with some frequency, that is because it is in the very nature of science to stay abreast of the latest developments in one's field, to disseminate one's own findings, and to exchange ideas in person with collaborators and potential collaborators. In essence, meeting travel is intrinsic to good science.

Perhaps the most contentious issue is that NIH employees on approved official duty can take only two days annual leave in conjunction with any single meeting and are limited to six such days per year—unless they get an exception that can be granted only by the NIH director.

Further, if official travel is supported by an outside source, no personal leave can be taken unless an explicit exception is granted directly by the director of NIH.

Until recently, business-class travel was prohibited in most circumstances, even if paid by an outside source—suggesting that the ruling was not predicated on budgetary concerns, but rather over concern that an NIH employee might be unduly influenced by this perceived "perk."

In a recent HHS ruling, business-class travel now can be approved in a broader context, but only with written justification, several layers of review, and the personal signature of the NIH director.

The ruling stipulates that the director cannot delegate this signatory authority.

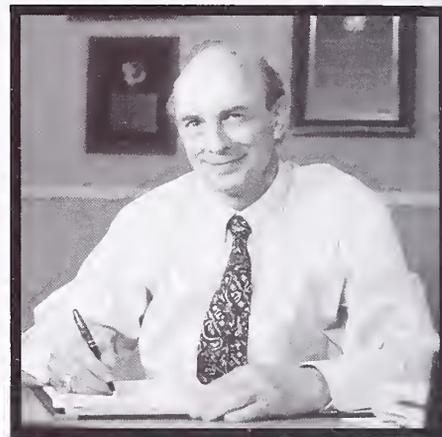
In essence, by allowing one to travel on official duty, the government becomes able to prescribe not only what one does during the official activity, but also before and after that activity. It is akin to saying that because the government pays one's salary, it can regulate what activities one performs beyond the paid work schedule, including weekends and holidays.

Whether HHS has the constitutional authority to exercise such overarching control of one's personal time can be questioned, but my concern is not in the legalities but in the realities and in the now widely held perception that NIH scientists have lost some of the basic freedoms available to almost all other scientists in both the public and private sectors. This perception is damaging to NIH on many levels and, in the competition for high-level scientists, certainly places NIH at a disadvantage.

The HHS presumption that NIH scientists will take unfair advantage of the system to obtain paid vacation travel misses an important point. The critical decision should be whether or not the travel/meeting is a legitimate activity that fosters NIH science and brings value to job performance. This decision is part of the approval process for any NIH travel activity whether it is paid for by the government or by an outside sponsor. If the activity is deemed ethical and relevant to the HHS mission and approval is granted, then the government should have no further right to dictate the status of annual leave attached to that activity.

Most scientists give the government a huge number of unremunerated hours. This is not generosity on the part of scientists; it is what is necessary to get the job done. To have these "donated" hours rewarded by travel policies that control personal time is reprehensible; when the government is not paying for the travel, it is also incomprehensible.

The recent loosening of restrictions to allow the NIH director to make limited exceptions for personal leave or business-class travel does not address the fundamental issue and source of discontent. From a practical standpoint, the right to grant exceptions requires that scientists prepare written justification,



Harvey Alter

that a new mini-bureaucracy be established to review these justifications, and that the NIH director personally sign each approval or denial. It seems inane to have the director of NIH spend even a moment of his or her time on such mundane matters when issues of great magnitude confront that office in unending succession.

Some may view business-class travel as a perk, but anyone who has traveled overnight in coach class to attend a meeting or give a talk on arrival knows the physical and mental exhaustion that greatly diminishes the activity that was the very purpose of the trip. Again, the focus should be on the nature of the activity and not on the mode of travel or the personal leave associated with the travel. Emphasis on the latter trivializes the purpose of the approved travel and disrespects the traveler's intentions.

Abuse of travel is of course possible, but sweeping restrictions, such as those currently in place, punish everyone and still do not prevent occasional abuse. Instead, they create an atmosphere of distrust that impinges on morale and has more far-reaching consequences for NIH than does a rare case of system abuse.

Overzealous HHS reactions have sent messages throughout academia and industry that NIH, as great as it is, is no longer an environment conducive to unfettered science. The retention and recruitment of scientists is what is at stake in these deliberations over individual rights and, in their impingement, the scientific mission of HHS suffers.

It is hoped that "the road less traveled" could again mean what it has always meant to NIH—"to go where others have not gone"—rather than the current meaning—"not to go because you are not allowed."

—Harvey J. Alter

Chief, Infectious Diseases Section
Department of Transfusion Medicine, CC

TRAVEL: TIME TO CHANGE THE REGULATIONS

We have all been frustrated by the regulations restricting annual leave during travel on official duty, especially for foreign trips. The rationale for such restrictions is that NIH scientists must not exploit, or even appear to exploit, their government position for personal vacation. Taxpayers' money is not earmarked for government employees' annual leave.

Recently, the rules have been somewhat relaxed, and it is now possible to take up to two days annual leave three times a year in the context of foreign official-duty travel (with extensions possible if an extension is granted by the NIH director).

Although a step in the right direction, the regulations are still too restrictive. Rules must make sense and must not create more problems than they solve. Even amended, the current travel regulations imply that we law-abiding scientists have illicit intentions and need punitive rules to preserve our innocence.

Earned annual leave should be independent of professional choices for attending scientific meetings or accepting lecture invitations. If a meeting is inappropriate to attend for whatever reason, it is inappropriate whether or not we

take annual leave, at our expense, associated with the meeting.

Why would NIH control our annual leave to create standards for meetings we attend? Are they not independent variables?

The current travel regulations imply that we might attend poor scientific meetings at government expense to pay for our annual leave travel. In fact, as the rules currently read, they could discourage scientists from attending important scientific meetings that happen to be very far away and of short duration. In order to extend the professional travel, seminars are often arranged at institutions where we have colleagues in the area and these may be of dubious scientific necessity.

That we are routed through Washington on trips to several meetings that take place a week apart in adjacent countries overseas, or the suggestion that we go to a meeting, return home, and go back to the meeting place for annual leave is, of course, ridiculous.

My extramural colleagues at universities who also depend on NIH funding are flabbergasted at our travel regulations. They scratch their heads in bewilderment when I cancel or refuse in-



Fran Pollner

Joram Piatigorsky

vitations or when they watch me agonize over finding appropriate ways to reconcile a normal life with abnormal rules.

Enough said. I doubt that anyone reading this plea for reason needs more explanation. How can we expect to be respected as an institution or to appear ethical when we establish regulations that suggest that we are less than honest scientists who are serious about our work?

—Joram Piatigorsky
Chief, Laboratory of Molecular
and Developmental Biology, NEI

Applications Due For PRAT 2007

The NIGMS Pharmacology Research Associate (PRAT) program is accepting applications for positions to begin October 2007.

This competitive research fellowship program supports training at NIH or FDA laboratories for postdoctoral candidates and focuses on the pharmacological sciences and related research areas.

PRAT fellowships are three-year appointments that include competitive salaries as well as supply and travel funds to support research in preceptors' laboratories.

Applicants must identify a preceptor in their application. Preceptors may be any tenured or tenure-track scientist at NIH or FDA who has agreed to host the applicant.

Postdoctoral fellows who have more than one year of research experience at NIH or FDA are not eligible. Applications must be received by **December 15, 2006**.

For more information or application materials, contact the PRAT program assistant at 301-594-3583 or

<mailto:prat@nigms.nih.gov>

NIH-Duke Clinical Research Program

Applications are being accepted for the 2007–2008 NIH-Duke Training Program in Clinical Research. Designed primarily for physicians and dentists who desire formal training in the quantitative and methodological principles of clinical research, the program calls for part-time study, allowing students to integrate their academic with their clinical training.

Courses are offered at the NIH Clinical Center via videoconference. Credit earned may be applied toward satisfying the degree requirement for a Master of Health Sciences in Clinical Research from Duke University School of Medicine in Durham, N.C.

Applications are available in the Office of Clinical Research Training and Medical Education, Building 10, Room B1L403. Additional information on coursework and tuition costs can be found at

<http://tpr.mc.duke.edu>.

Interested individuals should check with their institute or center regarding funding for participation in this program.

The deadline for applying is March 1, 2007. Successful applicants will be notified by July 2, 2007. ■

Pulmonary Hypertension Two-Day Meeting

A meeting on "The Evolution of Pulmonary Hypertension: Emerging Diseases and Novel Therapeutics" will be held **December 7–8, 2006**, in the Natcher Conference Center.

Sponsored by NHLBI, the OD Office of Rare Diseases, and the CC Critical Care Medicine Department, the meeting will focus on the pathobiology, pathogenesis, and therapy of pulmonary hypertension.

For more information, visit
<<http://www.strategicresults.com/ph>>.

THE CATALYST NEEDS YOU

The NIH Catalyst is looking for a few good writers: Contribute your time writing stories for the Catalyst based on your interviews with NIH researchers and your notes covering NIH meetings and lectures. In exchange, you hone your science journalism skills and build a portfolio of published bylined articles. Call 301-402-7248 or e-mail catalyst@nih.gov.

RECENTLY TENURED

Munira A. Basrai received her Ph.D. from the University of Tennessee, Knoxville, in 1992. She pursued her postdoctoral studies at The Johns Hopkins School of Medicine, Baltimore. She joined NCI in 1998 as a tenure-track investigator in the Genetics Branch and is currently a senior investigator in that branch.

Aneuploidy is a hallmark of cancer cells. Defects in mechanisms that ensure high-fidelity chromosome transmission contribute to aneuploidy.

Our research focuses on defining the molecular determinants of chromosome segregation and cell-cycle checkpoint responses in the budding yeast, *Saccharomyces cerevisiae*, and the human orthologs of these determinants.

The high degree of conservation between yeast and human genes makes *S. cerevisiae* an attractive model system to elucidate how the failure of chromosome segregation mechanisms may give rise to diseases in humans.

We have two research projects: 1) mechanism of faithful chromosome transmission and cell-cycle checkpoint function, and 2) identification and characterization of small open reading frames (sORFs).

Our major research efforts are focused on the first project, in which we have used genetic screens and a colony color assay for chromosome loss to establish that mutations or deletions in *S. cerevisiae* *SPT4* and *NUPI70* lead to defects in chromosome-transmission fidelity and integrity of the kinetochore (centromere DNA and associated proteins).

We determined that Spt4p is a novel component of centromeric and heterochromatic chromatin and is required for localization of Cse4p, the evolutionarily conserved centromeric histone H3 variant (CENP-A) in *S. cerevisiae*. Our results have shown that restricting the localization of Cse4p to centromeric DNA is essential for high-fidelity chromosome transmission. Overexpression and mislocalization of CENP-A has been observed in colorectal cancer cell lines.

In collaborative efforts with NCI's Natasha Caplen and Anna Roschke, we

are doing RNAi experiments to determine if human *SPT4* plays a role in genome stability and CENP-A localization in mammalian cells.

In a cross-species approach, we have shown that the yeast mutant phenotypes are functionally complemented by a human homolog of *SPT4*.

Our current research is focused on understanding how *SPT4*, *CSE4*, and other factors contribute to chromosome-transmission fidelity in both yeast and humans, with the goal of understanding chromosomal aneuploidy, which is observed in essentially all sporadic tumors.

In addition to the kinetochore, checkpoints regulate progression through mitosis by halting the cell cycle in response to defective kinetochore function.

In collaboration with Richard Wozniak, University of Alberta, Edmonton, and Forrest Spencer, Johns Hopkins School of Medicine in Baltimore, we established that the evolutionarily conserved Nup170p is a specialized component of the nucleopore complex (NPC), with roles in kinetochore function and checkpoint regulation via its association with Mad1p.

Our studies demonstrate that the Nup170p complex associates with spindle checkpoint proteins Mad1p and Mad2p in *S. cerevisiae*. Similar observations have since been made by other investigators in other systems, including humans.

Our novel findings that *S. cerevisiae* Mad1p and Mad2p are localized to the NPC prompted us to investigate the localization of another spindle checkpoint protein, Bub3p. We designed a novel genetically engineered reporter strain and showed preferential enrichment of Bub3p at defective kinetochores.

Enrichment of a spindle checkpoint protein at kinetochores upon checkpoint activation had not previously been reported in *S. cerevisiae*.

We are currently investigating the molecular mechanisms for spindle checkpoint activation and how cells resume

cell-cycle progression when the checkpoint activation response is fulfilled.

The second project is a pioneering effort aimed at defining and characterizing previously nonannotated sORFs (<100 a.a.) in *S. cerevisiae*. We undertook the first functional studies of sORFs in any system and showed that there may be at least 299 sORFs in *S. cerevisiae*.

In collaboration with Jef Boeke (Johns Hopkins), Ronald Davis (Stanford University, Stanford, Calif.), and Michael Snyder (Yale University, New Haven, Conn.), we made gene deletion strains for 148 sORFs. About 75 percent of the sORFs are evolutionarily conserved, and several of the sORFs are required for genome stability.

As the databases expand, we propose to establish the presence of additional sORFs and investigate their molecular role in both protein coding and noncoding functions.

Dennis Drayna received his Ph.D. from Harvard University in Cambridge, Mass., in 1981. After 15 years in the California biotechnology industry, he came to NIH in 1996 under the Visiting Investigator Program at NHGRI. In 1997, he joined NIDCD, where he is currently the acting chief of the Section on Systems Biology of Communication Disorders in the Laboratory of Molecular Genetics.

Over the past 20 years, the goal of my research has been to understand how genetic variation in humans contributes to disease.

Although the disorders we study are quite diverse, our projects are unified by a common set of technologies and by the statistical analysis methods and intellectual framework of human genetics.

We use traditional genetic-linkage methods in families as well as population-based association studies, with the goal of identifying specific genetic variants in individual genes that underlie complex disorders, that is, disorders with both genetic and nongenetic causes.

Stuttering, a common speech disorder that can have profound quality-of-life and economic consequences, is a



Munira A. Basrai



Dennis Drayna

major focus of our lab. Many studies have supported the view that this disorder can have genetic underpinnings, and about half of all affected individuals have a family history of stuttering.

However, the disorder does not display a clear pattern of inheritance, and it has many characteristics, such as a high rate of spontaneous recovery in children, that make genetic analysis difficult.

To overcome these difficulties, we have worked in two specialized populations. The first of these is centered in Pakistan, where traditional marriage patterns, involving unions between cousins, prevail.

Such inbreeding can increase the frequency of some types of genetic disorders, and we have identified many highly inbred families with a high density of individuals who stutter.

Our studies have shown that a gene on chromosome 12 appears to be responsible in a significant fraction of these families, and we are currently focused on identifying that gene.

We have also discovered several families in the Republic of Cameroon, in equatorial West Africa, in which stuttering is transmitted as an apparently simple autosomal dominant trait. Several of these families are quite large, containing over 100 individuals, roughly half of whom stutter as adults.

Our preliminary results suggest a gene on chromosome 1 is responsible in at least one of these families, and we are currently narrowing down the location on the chromosome in which this gene resides.

My lab is also studying deficits in the sense of taste. We previously focused on the inability to taste the substance phenylthiocarbamide (PTC), which is intensely bitter to three-quarters of the world's population (including myself), but essentially tasteless to the remainder of the population.

This bitter-taste deficit has served for many decades as a classroom example of a human Mendelian trait. We discovered that this deficit is caused by alterations in the bitter-taste receptor gene T2R38.

Remarkably, the non-taster allele represents almost half of all the copies of the gene in humans worldwide. We showed that this is due to balancing natural selection, which maintains both

the taster and non-taster alleles at high frequency.

Because our sense of bitter taste serves to protect us from toxic substances produced in plants (which are typically bitter), the selective force that maintains the non-taster allele is something of a puzzle.

We've hypothesized that the non-taster form of this taste receptor serves as a perfectly functional receptor for some other toxic bitter substance not yet identified.

We have also performed population genetic studies of variation in all of the human bitter- and sweet-taste receptor genes and shown that these genes are unusually polymorphic in their coding sequences.

We are currently exploring how this genetic variation affects taste perception of a wide variety of substances.

Mario Roederer received his Ph.D. in biology in 1988 in the laboratory of Robert Murphy at Carnegie Mellon in Pittsburgh. He did his postdoctoral training with Leonard Herzenberg at Stanford University, Stanford, Calif., and became a tenure-track investigator at the Vaccine Research Center, NIAID, in 2000. He is currently a senior investigator, leading the ImmunoTechnology Section in the Laboratory of Immunology, VRC.

A major goal of our laboratory is to identify the types of immune responses that may predict vaccine-generated protection or elucidate the pathogenesis of infections.

To this end, we are working on technology development (multicolor flow cytometry), human immunology (HIV disease and vaccines), and nonhuman primate models of HIV.

The original impetus for much of this work came from a study involving HIV-infected individuals in whom we characterized a selective loss of naïve CD4 and CD8 T cells during chronic disease. This fundamental change in the immune system had been largely unrecognized because of the inadequacy of extant technology to discriminate T-cell subsets.

The recognition that T cells were far more complex than envisioned led us

to develop the technology—the hardware, software, and chemistry—we needed to identify and characterize these cells.

The current incarnation of that technology includes our 18-color flow cytometers (sorters and analyzers), which accord us the ability to discriminate as many as 18 different cell-associated markers.

Not only can we identify fine T-cell subsets (for example, by differentiation or activation) but we can also simultaneously interrogate different functions, such as cytokine and chemokine profile, on a cell-by-cell basis.

Perhaps not surprising, we found that immune responses to antigenic challenge are highly complex, with a dozen or more functionally defined subsets of CD4 or CD8 T cells, each associated, for example, with a unique combination of cytokines.

In collaboration with other sections of the Laboratory of Immunology, we are identifying selective subsets of these functional states that are associated with good clinical prospects—indeed, the “best” T cells appear to be those that simultaneously make many functions at once. We are now focusing on understanding what makes these cells different from other antigen-specific T cells.

Finally, working with the nonhuman primate model for HIV, we recently demonstrated that the acute phase of SIV infection is accompanied by an enormous destruction of the memory CD4 compartment, a destruction that predicts subsequent progression during chronic disease.

Furthermore, we showed that vaccination against SIV could ameliorate this destruction, resulting in significantly increased life expectancy for the animals.

We are now seeking to identify which vaccine-induced T-cell responses accounted for the protection during acute infection and to identify the mechanism of this protection.

Our continuing efforts include developing new models for understanding the generation and efficacy of vaccine-induced immune responses and expanding our arsenal of research tools.

continued on next page



Mario Roederer

RECENTLY TENURED

Yun Wang received an M.D. degree in 1979 from the National Defense Medical Center in Taiwan and a Ph.D. in pharmacology from the University of Colorado in 1986. He came to the Molecular Neuropsychiatry Branch, NIDA, in 1997 and is now chief of the Neural Protection and Regeneration Section.

Our laboratory uses animal models of neurodegenerative disorders to identify and study genes and compounds with neural protection and repair capabilities.

In particular, we are focusing on three models:

■ Acute and chronic methamphetamine (Meth) exposure (drug toxicity)

■ 6-Hydroxydopamine-lesioning of substantia nigra (Parkinson's disease)

■ Middle cerebral artery (MCA) occlusion (stroke).

We also use primary neuronal cultures derived from mouse and rat embryonic tissue for in vitro work.

We target three common pathways of



Yun Wang

degeneration and death: free radical toxicity, excitotoxicity, and apoptosis.

In the past few years, we have demonstrated the protective and regenerative properties of TGF- β family members, in particular, glial cell line-derived neurotrophic factor (GDNF).

For example, we reported that GDNF receptor- α 1 (GFR α -1) mRNA is upregulated in brain after cerebral ischemia and that intracerebral administration of GDNF potently protects against cerebral infarction induced by MCA occlusion in rodents.

In addition, we found that GDNF counters the increase in nitric oxide that accompanies MCA occlusion and subsequent reperfusion. This neuroprotective effect is greatly suppressed in GFR α -1 \pm animals.

These data provided the first evidence that GDNF has a neuroprotective effect in the context of brain ischemia.

We also found that intranigral transplantation of fetal ventral mesencephalic tissue and nigrostriatal bridge admin-

istration of GDNF restore striatal dopamine input in hemiparkinsonian rats.

These results indicate that combinations of trophic factors and fetal nigral bridge transplants can restore the nigrostriatal dopamine pathway in Parkinsonian rats and thus may have clinical implications for fetal transplant surgery in human Parkinson's disease.

Finally, our laboratory found that Meth potentiates ischemic brain injury in mice. We found that pretreatment with Meth increases ischemia-induced cerebral infarction, potentiates the expression of p53 mRNA in the ischemic mouse brain, and decreases GDNF levels in ischemic striatum; conversely, intracerebral administration of GDNF before ischemia protects against Meth toxicity.

In sum, our data indicate that Meth can exacerbate ischemic insults in brain through the inhibition of GDNF-mediated pathways.

We are currently studying the protective and regenerative mechanisms of bone morphogenetic proteins, purinergic compounds, and antioxidants after methamphetamine intoxication and in parkinsonian animals. ■

RELAY REPLAY



Carol Regan

Totally Tubular: With Olympian grace and lots of spirit, more than 500 NIHers donned running shoes and shorts and sprinted around the campus on a glorious September day to participate in the annual Institute Challenge Relay Race. Pictured above, dressed as tubes, the "ECCENTRIFUGES" came in 30th in a field of 107 NIH teams; from the Laboratory of Cellular and Molecular Biology, NCI-CCR, they are (left to right) postdoc Mirikka Janka-Juntilla, postdoc Frank Comer, postdoc Lakshmi Balagopalan, postbac Rishi Surana and postdoc Kelsie Bernot. Check out team standings to the right and continued on next page.

Place	Name	Time
1	Proud Snail Hunters	13:59
2	Bolting Electrons	14:25
3	Wurtz Possible Runners	14:34
4	Catch Me If You Can	14:51
5	Blair Swift Project	15:03
6	Asthma Attacks	15:13
7	Figg Leaf	15:14
8	The Nitros	15:20
9	Roundabouts	15:22
10	Atroglide	15:30
11	Fruits and Nuts	15:37
12	Run for Fun	15:49
13	Natural Winner Cells	15:52
14	Waisted Kinetics	15:54
15	Running Buffers	16:01
16	Running Averages	16:02
17	Racy Ears	16:03
18	Big and Benign	16:10
19	Lethal Factors	16:15
21	Running Without Sox2	16:25
22	CD Four Runners	16:25
23	5' RACERs	16:35
24	V "Eye" P	16:39
25	Mobile Side Chains	16:39
26	FIC Globe Trotters	16:40
27	Eye aei aei	16:40
28	The First Shall Be Lasp and the Lasp Shall...	16:42
29	Cancer Crusaders	16:43
30	Eccentrifuges	16:46
31	The Uncatchable Catchables	16:47
32	Clinic 8 Velocity Raptors	16:51

DEMISTIFYING MEDICINE FOR PH.D.s, 2007

The Demystifying Medicine course will be held every Tuesday from **January 9 to May 7**, 4:00 to 6:00 p.m. in the Building 50 ground-floor auditorium. All presentations will be videocast and archived.

For academic credit, register with FAES: <http://www.faes.org>; otherwise, register at the Listserv: <http://list.nih.gov/archives/demystifyingmed.html>.

The schedule can also be seen at <http://www1.od.nih.gov/oir/DemystifyingMed/index.html>.

33	Oxidative Stress	16:53
34	Kiss Meiosis Again	16:53
35	Inverse Insertions in the ARS	16:57
36	Grim Reapers	17:04
37	Uncoupled Expectations	17:06
38	Apoptotic Buddies	17:07
39	Anaphylactic Socks	17:08
40	Clathrin Zeta-Jone	17:09
41	The Smooth Pursuers	17:14
42	Harmful Hooligans	17:18
43	LEC Wild Types	17:19
44	Signal 2	17:21
45	Free Radicals	17:22
46	Long-Legged Crazy Mental Runners	17:25
47	Killer T-Cells	17:28
48	Retinal Degenerates	17:28
49	BRATS	17:30
50	Micro-Hurrays	17:33
51	Poxjox	17:35
52	Francesca and the Fast-Footed	17:35
53	Assay Kickers	17:40
54	Around the World in 5 NIHers	17:41
55	Supersonic Pancakes	17:42
56	smORFs	17:50
57	Distortion Products	17:51
58	I Zinc I Can	17:54
59	Resting Zone	17:55
60	Isotopes	17:58
61	Eyes on the Prize	18:00
62	Catechol-O-Methyltransfer Racers	18:01
63	Unnamed Commandes	18:04
64	Extramuruns	18:04
65	Fantastic Five	18:06
66	Silvo Bullets	18:13
67	Decibells	18:14
68	The Protein Traffickers	18:18
69	Team M	18:23
70	CCR Screammers	18:23
71	eNIGMaS	18:25
72	C uS Run	18:32
73	Direct Insertions in the ARS	18:35
74	The Runners Up	18:38
75	Spin Doctors	18:39
76	All ears, no legs	18:43
78	Metastasizers	18:44
79	Cytopathic Slugs	18:44
80	Ashmatics	18:45
81	Let's Move and Shake our Histones	18:48
82	Not the Machine	18:48
83	Drug Runners	19:07
84	Feets of Prevention	19:09
85	Bad Breath All Stars	19:16
86	CIT Trotters	19:22
87	In the Red	19:22
88	Cells R us	19:22
89	Brain Cramps	19:53
90	Pacemakers	20:00
91	Eye Run Fast	20:06
92	Scintilla of Redoubt	20:10
93	Last Minute	20:13
94	Half-Athlons	20:20
95	Paper Tigers	20:24
96	E eye E eye Oh	20:24
97	Nutso Fast	20:27
98	6Immobilized Cube Creatures	20:37
99	Hartinger's Harrs	20:41
100	We'll Run for Chocolate	20:55
101	Librarians Locos	21:08
102	PDS Packers	21:33
103	Carcinogens	21:35
104	Team E	22:00
105	Access Denied	22:56
106	They Masters	22:58
107	Eye Team!	23:27

Date	Speakers	Subject
January		
9	John Coffin (NCI) Lori Wiener (NCI) Lauren Wood (NCI)	HIV: new clinical and basic problems arise from success
16	Anthony Fauci (NIAID) Jeffery Taubenberger (NIAID)	Emerging and re-emerging infectious diseases: challenge to global health
23	Roger Glass (FIC) Albert Kapikian (NIAID)	Enteric infections: deadly challenges at all ages
30	Richard Johnson (Johns Hopkins) Ramanujan Hegde (NICHD)	Prions: biology and diseases
February		
6	John Schiller (NCI) Herbert Kotz (NCI) Christina Annunziata (NCI)	Human papilloma virus: cervical cancer and prevention by vaccination
13	John Gallin (CC) and colleague	Chronic granulomatous disease: phagocytes misbehave
20	Gabor Illei (NIDCR) Rachel Caspi (NEI)	Autoimmune disease: lupus erythematosus, scleroderma
27	John Hardy (NIA) Katrina Gwinn-Hardy (NINDS)	Dementias: losing one's mind in the genomic era
March		
6	Toren Finkel (NHLBI) Richard Cannon (NHLBI)	Coronary heart disease: a major killer
13	Owen Rennert (NICHD) Alan DeCherney (NICHD)	Infertility and assisted reproduction: clinical and basic advances
20	Peter Jahrling (NIAID) John Robbins(NICHD)	Agents of potential bioterrorism: small pox, anthrax
27	Elias Zerhouni (OD) Sriram Subramaniam (NCI)	Imaging: frontier for 3D and 4D study of organs and cells
April		
3	Henry McFarland (NINDS) and colleagues	Multiple sclerosis: an immune challenge
10	Michael Gottesman (NCI) Win Arias (NICHD)	ATP binding cassette proteins: expanding scope of their diseases
17	Phillip Gorden (NIDDK) David Harlan (NIDDK)	Diabetes: new clinical and basic dimensions (obesity, immunity, cancer)
24	Jack Liang (NIDDK) and colleagues	Hepatitis C: comes of age globally and in culture
May		
1	Joseph Apud (NIMH) and colleagues	Schizophrenia (the "shattered mind" disease): clinical and basic aspects
7	Finale: What does the future hold for Ph.D. postdoctoral fellows? Participants to be named.	

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...

- Biophotonic Imaging
- IRP Research Roundup
- Women's Health Fellowship

Kids' Catalyst Before Your Eyes: Changing Colors

It's fall, and all around you leaves are falling and changing in a magnificent display of colors.

Even though most of the flowers are gone now, you can probably find a few for our current experiment—which will play a little trick on your eyes at the same time it sweetly illustrates how we perceive color.

For our series of colorful experiments, you will need some flowers, some sugar, an eye dropper, and red, blue, and yellow food coloring.

Experiment 1: Your supplies are a white rose or carnation and red food coloring. Put the flower in about an inch of water and add 7 to 10 drops of the food coloring. Depending on how healthy the flower is and how long the stem is, in about half an hour you will begin to see spots on the flower that are the same color as the water. So you can very easily turn that white rose to red!

Experiment 2: Now try a yellow rose and blue food coloring. If you put a yellow rose into blue water, what do you think will happen? From a distance, that flower may look green, but if you look more closely, you'll see blue spots on a yellow background. Is this what green looks like if you peer really closely? See what happens with a "sweet" side experiment, using colored sugar.

Experiment 3: Create two piles of sugar, say a tablespoon each. Add yellow food coloring to one pile and blue to the other, adding a drop at a time and mixing thoroughly until you get the desired color (you don't want to add too much coloring because it will dissolve the sugar). Now take equal amounts of yellow sugar and blue sugar and mix them together. (No tasting, please, unless you want to change the color of your tongue, too!) Green, right? But just like with the yellow rose, only from a distance. The closer you look, the more clearly you can see the constituent parts. Try this with other colors.

You can also test this with a nonpermanent green highlighter. Draw a line on paper (filter paper, if you have it, but loose-leaf paper and even tissue paper will work) and dip the end in water. As the water creeps up the paper, it will separate the green into other colors—yellow and blue.

So if you have a bunch of white roses you wish were red, plain sugar you wish were green, or want to see what blue can do, now you know!

—Jennifer White



The *NIH Catalyst* is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2E26, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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