FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 13, ISSUE 4 ■ JULY–AUGUST 2005

30+ YEARS IN THE LPD: STUDENTS/COLLEAGUES HONOR FRANKLIN NEVA

by Karen Ross

On May 16, NIAID's Laboratory of Parasitic Diseases (LPD) honored its newly retired long-time leader Franklin Neva with a symposium at which Neva's former and current colleagues traced LPD's (and Neva's) history and presented ongoing research. The symposium was organized by LPD Deputy Chief Thomas Nutman, who co-moderated with LPD Acting Chief Alan Sher.

Neva served as chief from 1969 until 1995 and then as head of LPD's Section on Opportunistic Parasitic Diseases. He officially retired in December of 2004, becoming scientist emeritus—and is still a familiar face around the lab.

The Early Days

Karen Ross

Franklin Neva: Scientist emeritus

Ted Nash was Neva's first research fellow. He joined the LPD in 1970, a year after Neva became chief.

In 1969, Nash said, there was very little interest in clinical parasitology at NIH—and the lab was physically scattered, with sections in Georgia and Hawaii, as well as in Bethesda. Moreover, the scientists tended to focus on the biology of individual parasites rather than on parasite-human interactions, recalled Nash, who is now head of the Gastrointestinal Parasites Section.

There was, however, a growing need for a coherent clinical parasitology program because soldiers were returning from the Vietnam War suffering from parasitic diseases.

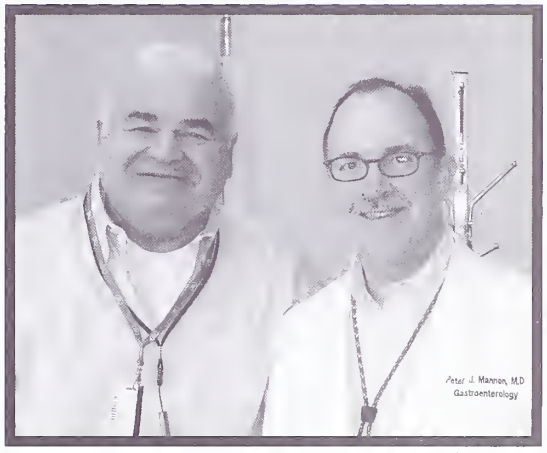
Neva's early training prepared him well to take charge of LPD, said Nash. After medical school and in-

continued on page 4

Translational Research Success Story

CYTOKINES YIELD TREATMENT ADVANCES IN INFLAMMATORY BOWEL DISEASE

by Celia Hooper



Celia Hooper

Warren Strober (left) and Peter Mannon

Increasingly successful treatment of a devastating pair of chronic diseases, Crohn's disease and ulcerative colitis (UC), stands as an elegant demonstration of the bench-to-bedside cooperation that NIH boasts.

Presenting the work of scientists in NIAID's Mucosal Immunity Section of the Laboratory of Host Defense, Peter Mannon and his section chief, Warren Strober, recently described gratifying clinical progress in treating two forms of inflammatory bowel disease (IBD). The pair spoke at NIH's "Demystifying Medicine" course in early May.*

Bedside breakthroughs sprang from the emerging concept of IBD as a Kafkaesque variant on autoimmune disease in which a hyperactive immune system relentlessly and inappropriately reacts not to oneself, but to the next closest thing—the bacteria that make up part of the gut flora. Crossfire from the ensuing battle—and attempts to intervene—wreaks havoc with a patient's gut and other tissues.

By modulating key regulatory cytokines to tone down the reactivity of the immune system, Strober's lab has been able to eliminate IBD in mouse models of the disease—paving the way for translation to humans. Early-stage trials offer some promise of remissions in Crohn's and UC patients.

The Clinical Picture of Crohn's

Crohn's disease, occurring in 40 to 100 of every 100,000 people, is a chronic disease unfolding from inflammation of the gastrointestinal (GI) tract, primarily patches of the small bowel and colon. As Mannon describes it, inflammation of the GI tract can lead to reactions in other tissues, including eye, skin, and bone. Ongoing symptoms may include formation of fistulae and fibrotic obstructions, abdominal pain, nutrient malabsorption, fever, bleeding, oral ulcers, kidney stones, arthritis, uveitis, and a variety of skin lesions.

Data from 1990 put the direct cost of Crohn's at more than $1 billion, with the high toll, Mannon says, reflecting Crohn's tendency to strike young adults and to recur. The disease and the side

continued on page 4

* Webcasts of the course are available at <**http://videocast.nih.gov/PastEvents.asp?c=45**>. Course materials are on the web at <**http://www1.od.nih.gov/OIR/DemystifyingMed/index.html**>.

CONTENTS

The Music of Science Plays On

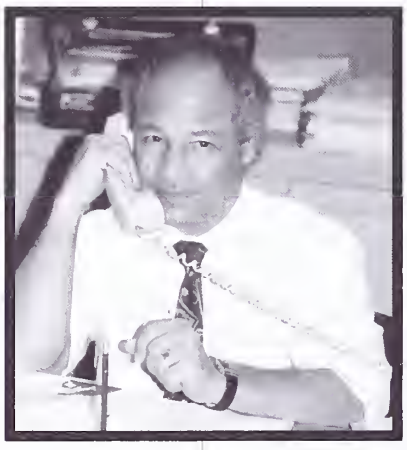
Ralph Isenburg

Lance Liotta, at his going-away party May 11, 2005

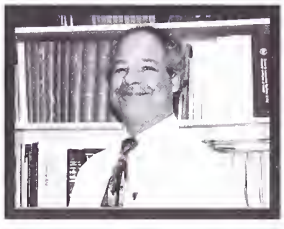
The guest editorial this issue is from Lance Liotta, who launched The NIH Catalyst *in 1993, during his tenure as deputy director for intramural research in the time of Bernadine Healy's NIH directorship. It is only fitting, then, that the departing remarks he delivered at his going-away party at the Cloisters May 11 be adapted to fill this issue's DDIR column.*

A typical statement by the departing person at a going-away party is that this job has been the best years of their career. I cannot make that statement . . . . this has been the *only* job I have had since medical school. I joined the Laboratory of Pathology as a resident in 1976, and because I loved this place so much, and loved the people so much, I stayed ever since.

Over the last three decades, I've learned much from my role models—my co-workers, residents, students, and colleagues. Here are some of the important principles.



Principle 1: It is not enough to believe in a dream. There must be someone who believes in the dreamer. In the beginning of my career, my family and Dr. [Alan] Rabson believed in me—so I began to believe in myself and had the courage to take risks. In 1997, I was privileged to meet Chip Petricoin, and together we proposed our dream of proteomics to NCI. The institute appreciated our dream and helped us create a new clinical proteomics program.



Principle 2: The best way to see your dream realized is to give it away. Transfer the dream to other team members and trainees; let them internalize it, improve on it, and call it their own. This is the secret to germinating a large number of ideas in one's short lifetime.

Principle 3: Taking a risk is the best way to gain security in science. Instead of choosing the popular, safe topic that is in vogue, but will soon be out of vogue, it is smarter to get into new territory, explore beyond the campsite, and discover your own promised land. After all, we really know less than 1 percent about how biology works.

Principle 4: Hire people who are smarter than you and then get out of their way—but continue to lurk in the background and shield them from problems that might distract them. I have been fortunate to work with world-famous pathologists.

Principle 5: Strive to be taken for granted. The best administrative support is invisible. The Laboratory of Pathology has been fortunate to have tireless champions working behind the scenes for its scientific staff—handling the myriad complex personnel activities that come with the territory of the largest lab/branch at NIH and training hundreds of collaborators in the art of laser-capture microdissection and proteomics tecnology.

Principle 6: Publications and patents are not the best way to extend science into the future. The best way is to train and inspire the future scientific leaders and teach them to make your theories and technology obsolete. Our lab's summer student program has literally changed the lives of hundreds of former students who are now physicians and scientists.

* * * * * * * *

When I arrived here as a resident, I viewed the intramural NIH with the deepest reverence—and I still feel the same way. This place has truly been a scientific utopia driven by creative opportunity and freedom, all directed toward the goal of public health benefit. Here, each day, you can wake up to pursue a new idea, try out the idea, and let the data drive the science. Here you have the greatest opportunity to take risks and test grand paradigms. Take advantage of that opportunity and privilege, as I have.

George Gershwin was asked, "What comes first, the music or the lyrics?" "The money," he answered, referring to the funding from his patrons. In this time of serious NIH fiscal restrictions, many have expressed concern that the music of science will be silenced. I am an eternal optimist. Even if we, as scientists, have to do more with less, a bold creative idea is still the best means to gain funding and move the science to help patients. Do everything to protect that freedom.

—Lance Liotta
Professor of Life Sciences
and Co-Director
Center for Applied
Proteomics
and Molecular Medicine
George Mason University
College of Arts and Sciences
Fairfax, Virginia

NIH Assembly of Scientists Recaps Conflict-of-Interest Work, Sets Up Shop for Continuing Activities and Activism

The Executive Committee of the Assembly of Scientists (AOS) was elected in February of this year and has been working hard to represent the views of NIH scientists. We have worked with representatives of intramural laboratory managers, extramural NIH staff, NIH leadership, and members of professional societies.

The First Five Months: Aims and Accomplishments

The Executive Committee has achieved four objectives, particularly in response to the conflict-of-interest interim final regulations announced in February 2005 (see *The NIH Catalyst,* Special Reference Issue, <**http://www.nih.gov/catalyst/2005/index.html**>.

■ First, we have educated both the NIH community and the public—including the press and politicians—that the charges of conflict of interest against a few scientists do not reflect the overwhelming majority of NIH scientists and employees. We have also spoken out against the interim final regulations, explaining how we view them as onerous, intrusive, and a threat to the ability of the NIH to accomplish its mission.

■ Second, we've encouraged NIH scientists and other employees, as well as professional societies and advocacy groups, to submit any objections they may have to the regulations during the official comment period and to communicate them as well to other interested parties.

■ Third, the Executive Committee proposed an alternative set of regulations designed to prohibit conflicts of interest without jeopardizing NIH recruitment and retention and employee freedom.

■ Fourth, to prepare the way for institutionalizing the Assembly of Scientists to address other important issues related to morale and the quality of life of NIH scientists—including paperwork, resources, and respect— the Executive Committee has devised bylaws and an organizational structure.

Changes in the Air

Along with many other factors, including extensive consultations with and work by Dr. Zerhouni, these activities have contributed to a change in atmosphere and attitude—from one in which NIH scientists were viewed as engaged in unethical practices to enrich themselves to one in which the vast majority are not viewed this way and the regulations are perceived as overbroad and counterproductive.

This change in perception has been the critical prerequisite to generating the momentum to change the regulations.

It is also the impetus for our withdrawing a lawsuit we had launched in April to challenge the regulations. Although we had not considered the lawsuit the preferred option, we had sued because of the impending start of the stock divestiture clock and the statute of limitations that might have negated our right to sue. During the ensuing six weeks, the change in atmosphere and receptivity to our position made it much more likely that a revision approximating our proposal would occur in the policy rather than the legal arena. In addition, the withdrawal of the lawsuit has not foreclosed any rights.

In mid-May, the Committee met with the NIH director to discuss potential revisions in the conflict-of-interest regulations and their future implementation. As a result of that meeting, we have chosen an Executive Committee member to serve on the Implementation Committee, and we look forward to helping ensure that new regulations are implemented in a fair, balanced, and effective manner that does not overwhelm NIH employees with paperwork.

Throughout this process the Executive Committee has been working with the deputy director for intramural research; AOS representatives are now regularly attending the Scientific Directors meetings to enhance communication.

New AOS Bylaws And Work for the Future

Finally, working with legal council, the Executive Committee has drafted new bylaws, which can be viewed at the Assembly web site—

<**http://homepage.mac.com/assemblyofscientists/**>.

These bylaws call for a Council of 24 members, 12 representing institutes and centers and 12 at-large delegates. At least three places will be reserved, one each for a tenure-track investigator, a staff clinician, and a staff scientist. Members of the Council will elect a 10-member Executive Committee and select a chair, deputy chair, secretary, and treasurer, each of whom will serve a one-year term.

Elections for the Council will be held in October 2005, and the newly elected members will begin serving in November.

For consideration, contact the nominating committee, headed by Cynthia Dunbar (<**dunbarc@mail.nih.gov**>; 301-496-1434) and Elaine Jaffe (301-496-0183; <**ejaffe@mail.nih.gov**>). ■

Call for Poster Abstracts for 2005 NIH Research Festival

The 2005 NIH Research Festival is set for **October 18 through October 21.**

NIH and Bethesda FDA/CBER investigators may submit poster abstracts online at <**http://researchfestival.nih.gov**> through July 31. Posters can address any area of research conducted within the NIH Intramural Program, but the Research Festival Organizing Committee—co-chaired this year by scientific directors Sheldon Miller (NEI) and Robert Wenthold (NIDCD)—requests a limit of one poster submission per first author.

The opening plenary session on Tuesday, October 18, at 9 a.m. in Masur Auditorium will feature the high-impact research of four early-career NIH investigators. Their research ranges from the structure of molecules (Susan Buchanan, NIDDK) to gene silencing (Shiv Grewal, NCI) to cell biology (Orna Cohen-Fix, NIDDK) to clinical investigation (Mark Gladwin, NHLBI).

Other events during this 4-day annual showcase of intramural research will include cross-cutting symposia and poster sessions; special exhibits on resources for intramural research; the Job Fair for NIH postdoctoral, research, and clinical fellows; the Festival Food & Music Fair; and the Technical Sales Association scientific equipment tent show.

For a preliminary schedule of events and online poster registration, visit the Research Festival Web site at

<**http://researchfestival.nih.gov**>.

The deadline for online poster submission is July 31. Applicants will receive e-mail confirmation that their abstract has been received and will be notified of acceptance by e-mail in mid-August. For more information about poster registration, contact Paula Cohen, Research Festival Logistics Coordinator, OCPL/OD, at 301-496-1776 or e-mail <**pc68v@nih.gov**>. ■


Karen Ross

Ted Nash


Douglas Seeley

Lou Miller


Karen Ross

Thomas Nutman

Honoring Franklin Neva

continued from page 1

ternship, Neva spent a year and a half (December 1947 to July 1949) in Egypt working at the Naval Medical Research Unit-3 on typhoid fever and schistosomiasis.

Three years of research fellowships at Harvard followed—the first working on rickettsiae with John Snyder and the next two in the lab of John Enders, where he learned techniques of growing viruses in tissue cultures. At this time, he described an exanthem disease (Boston rash) caused by an Echo virus.

After an academic appointment in the lab of Jonas Salk, he returned to Harvard to work in the newly created Department of Tropical Public Health with Tom Weller. It was here in the early 1960s that Weller and Neva isolated and propagated rubella (German measles) virus.

It was also at Harvard that Neva applied tissue culture techniques to the study of intracellular parasites and honed his clinical parasitology skills.

The Neva Decades

Upon his arrival at NIH, Neva consolidated the LPD in Bethesda and emphasized research on the molecular biology of parasites and the human immune response to parasitic infection.

In 1971, he hired Louis Miller, currently head of the Malaria Vaccine Development Branch, who established the malaria research program. Before long, said Nash, "LPD was second to none" in clinical parasitology.

Miller, whose malaria research was a key factor in LPD's rise to preeminence, peppered his talk on malaria–host cell interactions with anecdotes about Neva and the practice of clinical research in the early days of LPD.

People, Places, Parasites

The wide range, both geographic and scientific, represented by the other scientists who described their research at the symposium was a testament to the impact that Neva has had on the field of parasitic diseases.

Some of them—including Peter Weller (Harvard Medical School, Boston), Josh Berman (NCCAM), Gary Weil (Washington University, St. Louis), David Freeman (University of Alabama School of Medicine, Birmingham), Chris Karp (University of Cincinnati), Peter Melby (University of Texas Health Science Center, San Antonio), and Christopher King (Case Western Reserve University, Cleveland)— spent just a few years in the LPD during their training.

Others, such as Eric Ottesen (Emory University, Atlanta), were part of LPD for decades but then moved elsewhere.

Still others, such as Amy Klion, David Sacks, and Tom Wellems, are current NIAID researchers.

And representing two of the many scientists the world over with whom Neva collaborated were Barbara Herwaldt (CDC) and Edgar Carvalho (Universidade Federal da Bahia, Salvador, Bahia, Brazil). The parasites they study include single-celled organisms, such as Plasmodium (the malaria agent), Leishmania, and Cyclospora; and worms, such as schistosomes, strongyloides, and filariae.

Projects

They work at the bench, at the bedside, in the field, and everywhere in between. Weller studies the molecular function of eosinophils, immune cells that are critical for fighting parasitic infections but that also contribute to airway inflammation in people with asthma.

Ottesen is working on a campaign to eliminate lymphatic filariasis by treating the entire at-risk population in Africa with parasite-killing drugs.

Herwaldt is a detective: She helped pinpoint raspberries from Guatemala as the source of Cyclospora that sickened people in the United States in 1996.

Praise

All of them talked about how Neva's insights and enthusiasm had inspired their research. Weil, who works on the diagnosis and treatment of filaria infection, said he had Neva's scientific spirit in mind when he developed an overseas research program for Washington University medical students.

Sacks stressed Neva's generosity, noting he was allowed to experiment with Neva's precious collection of Leishmania strains, even when he was a very inexperienced member of Neva's lab.

Ottesen emphasized Neva's leadership—of people and of projects.

Miller urged Neva to continue to be a frequent visitor. "The young people need you," he said, "and a few of us old guys also love to talk to you." ■

Cytokines Advance IBD Treatment

continued from page 1

effects of standard treatments—corticosteroids, 5-aminosalicylic acid (5-ASA), and immunomodulators such as azathioprine and methotrexate—often make work impossible and life miserable. Up to 74 percent of patients eventually need surgery to clear gut obstructions and other complications. Repeated removal of segments of the small bowel in turn may lead to additional nutrient absorption problems.

The Clinical Picture of UC

Similarly disabling, chronic, and relapsing, UC is an inflammation of the lower reaches of the bowel, from the distal rectum up into parts of the colon. Continuous rather than patchy in its distribution, UC affects only the lining of bowel, without forming fistulae knotting into other tissues. Mannon says the onset of UC tends to be more abrupt than Crohn's, but many of the general symptoms are similar, including diarrhea, pain, and weight loss. Proctitic symptoms, such as rectal pain, urgency, and bloody stools, are more prominent in UC; affected tissues outside the GI system include the eye, skin, joints, and liver. Patients are at risk for colon cancer and inflammation of the biliary system. Two-thirds will develop chronic relapsing disease, and 40 percent will undergo surgery for UC. Current treatments include topical and oral 5-ASA, corticosteroids, and immunomodulators.

From Mouse Models of IBD . . .

A view of IBD as an immune disorder began to emerge 30 years ago. In the past decade, Strober's lab developed animal models that greatly refined that view, framing Crohn's as a Th1-mediated immune disease heavily influenced by IL-12, and UC as a Th2-like disease (like but not identical to a Th2-mediated response) heavily affected by IL-13. In both, inflammatory cells in the gut churn out their respective cytokines in response to normal gut flora.

Gut bacteria were first implicated as immune system provocateurs by the fact that germ-free animals could not be induced to develop IBD, no matter what immune system genetic lesion researchers visited upon them. But IBD can be induced via gene manipulations in animals that harbor any of a large number of different gut bacteria or are exposed to muramyl dipeptide, a component of some bacterial coats. Strober says that

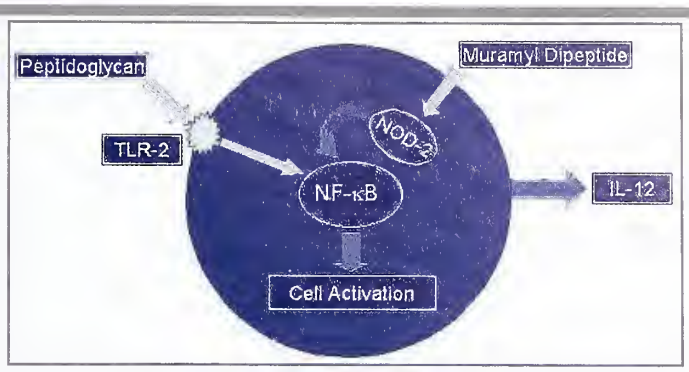


Fig. 1-NOD2, a Negative Regulator of Peptidoglycan-Induced IL-12: NOD2 mutations lead to excessive IL-12-induced Th1 responses and the inflammation of Crohn's disease

most of the thousands of antigens of the gut flora are benign—but the species that can potentially trigger IBD "may number in the hundreds and may vary from individual to individual," so that identifying the exact culprits for a particular IBD patient is nearly impossible.

Strober's lab used knockout mice to piece together the hypotheses that Crohn's disease (see Fig. 1) involves various cytokines and NF-κB, NOD-2, and TLR-2, with dysregulation of IL-12, IFN-γ, and TNF-α. Strober's murine model of UC uses oxazolone (4-ethoxymethylene-2-phenyl-2-oxazolin-5-one)—a contact-sensitizing agent applied to the rectum. Much like an adjuvant in a vaccine, the chemical spurs the immune system to respond to the flora that line the lower reaches of the bowel. The treated mice exhibit UC-like symptoms, microscopic pathology, and changes in cytokines.

Strober's group was able to block colitis symptoms by neutralizing IL-13 or thwarting presentation of antigen through interference with CD1 on natural killer T (NKT) cells. They now see UC as a Th2-like inflammation with IL-13 playing the lead role (see Fig. 2).

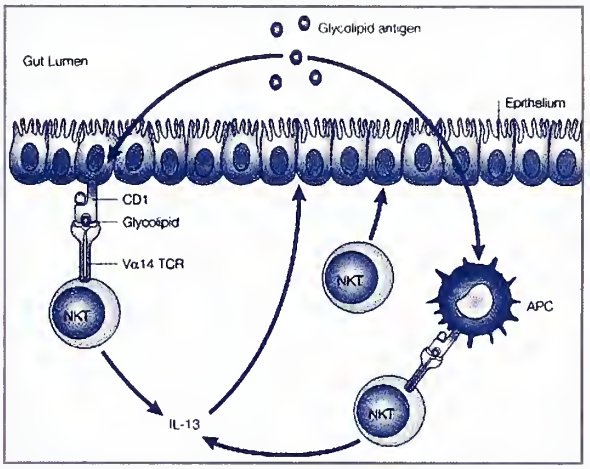
. . . To Clinical Trials of Cytokines

Crohn's: Strober says studies of cells from Crohn's patients confirmed that immune cells in the gut mucosa secrete increased amounts of IL-12 and other effector cytokines, including IFN-γ and TNF-α. He believes IL-12, the master cytokine of Th1 T-cell differentiation, drives the hyperactive immune response in Crohn's.

Based on these and other studies, physicians in the past few years have been using infliximab, an anti-TNF-α monoclonal antibody, to treat Crohn's, enlarging the percentage of patients with remissions and launching a new era of increasingly focused immune therapies. Other agents under investigation promise to increase the frequency, durability, and extent of response, while reducing side effects, Mannon says. These include IL-10; ISIS-2302 (an antisense oligonucleotide to ICAM-1); an anti-IL-6 receptor monoclonal antibody; thalidomide; granulocyte and granulocyte-macrophage colony-stimulating factor (G-CSF/GM-CSF); and anti-IFN-γ.

An NIH study group that includes Strober, Mannon, and Ivan Fuss completed a pilot phase 2 trial that tested an antibody against IL-12 in adult patients with active Crohn's disease. The multicenter, randomized, controlled, double-blind trial of 80 patients included 63 who received human monoclonal antibody directed against the p40 subunit of IL-12. The group tested two dose levels and two admin-istration schedules for seven injections of antibody. The treatment was well tolerated, and one of the schedules for the higher dosage led to significant responses and remission of disease compared with placebo (*NEJM* 351:2069-2079, 2004).

Mannon was impressed that the patient response was as good as or better than that with infliximab. He suspects it would be possible to obtain even better results with refinements in dosing and maintenance regimens. "It's a very promising approach," Mannon says. The pharmaceutical company that owns rights to the drug is examining application to other diseases. NIH investigators have started a pilot phase 2 study of G-CSF as another approach to down-modulating IL-12 and perhaps inducing T-regulatory cells in Crohn's patients.



Figures courtesy oif Warren Strober

Fig. 2-NKT Cells and IL-13 In Experimental and Human Ulcerative Colitis

Ulcerative Colitis: Investigational approaches to treating UC include:

- Dietary supplements and probiotics ingested to alter the gut flora
- Granulocyte pheresis
- Topical epithelial growth factor
- Anti-IL-13 agents
- Anti-CD3 and anti-IL-1

Strober says that one of the most promising investigational drugs for UC, IFN-β, may work in accordance with his lab's model—by blocking NKT cell activity, thereby curtailing IL-13 production. Mannon says the group has now recruited more than half of the patients needed for its pilot phase 2 study of IFN-β. A UC patient in the open-label trial describes prolonged periods without disease relapse, and Mannon says the early results are "very encouraging."

Strober would like to see the development of a UC therapy based on more direct, specific inhibition of IL-13. Mannon sees the future of UC treatment in detailed, individualized understanding of each patient's dysfunctional immune relationship with his or her gut flora. Treatment would be targeted to identified patient subsets; a lab test would predict relapse risk, informing decisions for early intervention.

Beyond IBD

Strober and Mannon believe concepts emerging from their work may have application beyond IBD. Intervention against IL-12—also at work in rheumatoid arthritis, multiple sclerosis, and psoriasis—might be effective in suppressing these other Th1 immune-mediated diseases.

Based on observations of Th2-like aspects of UC, investigators are looking at the involvement of IL-13 in allergic reactions and asthma. But UC's most important lessons may be more conceptual, Mannon says, as it involves a distinctive interplay of cytokines and cells at work. The tiny population of NKT cells that manage to cause such a large immune malfunction offers "a real opportunity to target therapy not broadly, but to a very specific population of immunocytes that seem to be the bad actors," Mannon says, emphasizing the importance of focusing therapy on more upstream factors in the cascade of cytokines in immune responses. ■

Postbac Poster Day, May 5, 2005: A Small Sampler

HIV, Stroke, Dengue Among Targets of Postbac Research

by Aarthi Ashok and Annie Nguyen

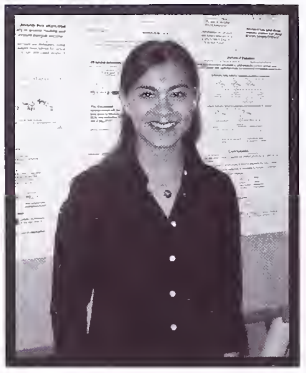
From Virus to Vaccine: Creating a Live Attenuated Vaccine for Dengue, Type 2

Caroline Agrawal, Boston University. Preceptors: Steve Whitehead and Joseph Blaney, NIAID, Laboratory of Infectious Diseases

Dengue is a mosquito-borne virus with serotypes 1, 2, 3, and 4, which are prevalent in most of the tropical areas of the world. Dengue causes a flu-like illness that can result in severe or fatal complications when a previously infected individual encounters a secondary infection with a different serotype of the virus. No effective vaccines are currently available.

Agrawal was interested in designing a live attenuated vaccine strain of dengue virus in the laboratory primarily because of its immediate clinical applications. She adopted a reverse genetics approach, using PCR mutagenesis to modify the genome of a dengue serotype 2 strain in order to attenuate the virus.

She has been able to design two candidate vaccine strains: a dengue type 2 strain with a 30-nucleotide deletion in the 3'-UTR sequence (D-30) and a 3-nucleotide deletion in the NS3 viral protein that has both helicase and protease activities; and a dengue type 2/4 chimera that has the structural protein of a type 2 strain in a type 4 background in addition to two point substitutions in the NS5 polymerase protein.



Aarthi Ashok

Caroline Agrawal

The ability of these candidate vaccine strains to grow in Vero cells, the intended vaccine production cell line, was then assessed. Although the type 2/4 chimera candidate grew efficiently in these cells, Agrawal and colleagues were surprised to find that the type 2 D-30 strain with the single amino acid deletion in NS3 was unable to grow in these cells. Agrawal is currently exploring the possible reasons for this surprising finding.

In future studies, the candidate strains will be injected directly into human liver tumor cells in SCID mice to assess their level of attenuation. If these candidate strains show promise in the rodent model, they will be used to vaccinate rhesus monkeys prior to challenge with wild-type virus. The titer of neutralizing antibody in these monkeys and the development of significant viremia or side effects will be closely monitored. If these strains are attenuated in monkeys, they will be included in a tetravalent dengue vaccine formulation to be used in human clinical trials.

Agrawal plans to continue to study viruses during her graduate education at Duke University in Chapel Hill, N.C.

—Aarthi Ashok

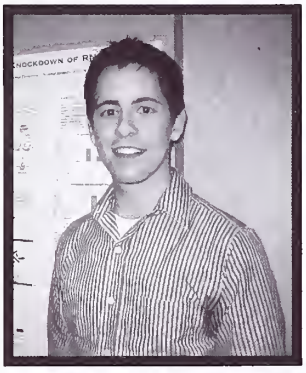
RNase H1 and Cell Viability: In vitro RNAi Knockdown of Rnase H1

Robert C. Wirka, University of Wisconsin, Madison. Preceptor: Robert Crouch, NICHD, Laboratory of Molecular Genetics

Ribonucleases H (RNases H) are important enzymes required for the removal of RNA in the RNA-DNA hybrids formed during DNA replication in eukaryotic cells and during the conversion of the viral RNA genome to DNA during HIV replication. In the latter case, the virally encoded reverse transcriptase (RT) contains the RNase H activity.

Wirka was interested in studying the function of RNase H1 during normal cell growth and proliferation. Previous experiments in their lab had shown that RNase H1 gene knockout deprives mice of the ability to replicate mitochondrial DNA and is thus lethal.

Because cells from these mice could not be grown up to examine any cellular defects, Wirka decided to knock out RNase H1 function using siRNA. To this end, he constructed a RNase H1-GFP fusion construct that was transfected into human osteosarcoma cells by electroporation. He also co-transfected this construct with various anti-RNase H1 siRNAs and quantified the knockdown of expression by FACS analysis.



Aarthi Ashok

Robert Wirka

Wirka was able to obtain specific knockdown of RNase H1 expression using this system, with siRNA electroporation efficiencies estimated at 99 percent, RNase H1-GFP knockdown at about 70 percent, and construct transfection efficiencies at about 70 percent.

He plans to continue using and optimizing this siRNA strategy to knock down expression of endogenous RNase H1 in untransfected human osteosarcoma cells. Using RT-PCR and Western blot analysis, he hopes to determine the efficiency of knockdown of RNase H1 expression in these cells.

RNase H is critical for the production of infectious HIV and is therefore an excellent target for therapeutic drugs, Wirka notes. This research, he says, may inform the development of HIV RNase H drugs that are extremely specific for the viral enzyme.

"This has been an excellent experience for me," says Wirka, who hopes to remain involved in research during his clinical training at The Cleveland Clinic Lerner College of Medicine.

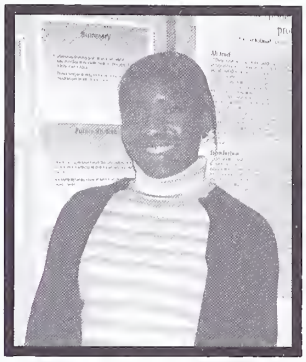
—Aarthi Ashok

NCCAM Launches Free Online CME Series

NCCAM has launched a new online Continuing Education Series in complementary and alternative medicine (CAM). This user-friendly seminar series offers health-care professionals and the public the opportunity to learn more about CAM therapies and the state-of-the-science about them through video lectures by experts in their fields. Health-care professionals can earn CME credits; the course is free and can be found at **<http://nccam.nih.gov/videolectures>**.

Glycodendrimers: Novel Inhibitors of HIV-1 Infection

Benitra Johnson, South Carolina State University, Orangeburg. Preceptors: Robert Blumenthal and Anu Puri, NCI, Laboratory of Experimental and Computational Biology



Annie Nguyen

Benitra Johnson

Glycodendrimers are synthetic multivalent carbohydrate conjugates derived from analogous moieties found on cell membrane surfaces; they play a role in the binding interactions of certain pathogens with mammalian cells.

Previous studies have shown that glycodendrimers inhibit viral entry into host cells.

Johnson carried out experiments using a reporter-gene–based assay to measure the effectiveness of a novel glycodendrimer in blocking HIV-1 infectivity.

Successful viral entry and integration into the host cell's genome leads to the expression of the luciferase reporter gene; quantification of luciferase luminescence serves as an indirect measure of HIV infection. Preliminary data, Johnson reported, indicate that glycodendrimers effectively inhibit HIV-1 entry.

Although the mechanism of inhibition remains unknown, Johnson offers two possible hypotheses: There may be some form of modulation of the virus-cell interaction and/or there may be some interaction between the glycodendrimers and the host cell, leading to altered cell physiology and abortion of infection.

Continuing glycodendrimer research, she says, may lead to additional avenues to counter HIV, which persists despite the expanding marketplace of antiviral agents.

Johnson is contemplating applying to medical school.

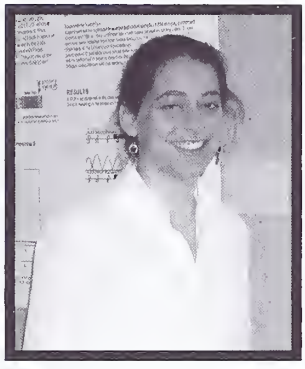
—Annie Nguyen

Magnetic Resonance Imaging in Experimental Cerebral Ischemia

Naomi Lewin, University of Maryland, College Park. Preceptor: Lawrence Latour, NINDS, Stroke Branch

The aim of Lewin's research is to develop noninvasive MRI techniques to track cerebral changes in animal models of stroke throughout the course of stroke induction and recovery.

Stroke is induced in the rat by inserting a silicon-coated suture into the middle cerebral artery; the suture is removed after a given amount of time.



Annie Nguyen

Naomi Lewin

The acute phase of stroke is characterized by cell death resulting from ischemia, or decreased blood flow, either by direct or indirect causes such as apoptosis and inflammation.

Two MRI techniques were used to observe neurological damage in rats. Perfusion-weighted MRI using gadolinium contrast agent reveals light regions on the mean-transit-time map that signify decreased blood flow—which is interpreted to reflect areas at risk for damage.

In addition, diffusion-weighted MRI, in which light regions indicate areas of cell death and cell swelling, delineate actual lesions.

Lewin noted that the use of both MRI techniques is better than either alone in tracking and interpreting the course of ischemia and cell death in the lab and in the clinical setting.

Lewin's lab aims to investigate potential markers of cerebral damage in rats and then translate the findings to human diagnosis. Ultrasmall superparamagnetic iron oxide particles are among markers of inflammation under investigation.

Lewin plans to continue research in neuroscience as part of an MD/PhD program at the Weill Medical College of Cornell University in New York City, which she will enter this fall.

—Annie Nguyen

'O Pioneers!'

The first annual NIH Director's Pioneer Award Symposium takes place on Thursday, September 29, 2005, in Masur Auditorium.

The event will feature talks and a roundtable discussion by the inaugural group of Pioneer Award recipients, selected in 2004, as well as the announcement of the 2005 awardees. The day begins with opening remarks by NIH Director Elias Zerhouni at 8:15 a.m. and ends with an informal reception at 3:00 p.m.

Slated to speak on their exceptionally creative and innovative approaches to major biomedical research challenges are:

- Larry Abbott, Ph.D., Brandeis University, Waltham, Mass. (Mathematical Modeling of Neural Systems)
- George Q. Daley, M.D., Ph.D., Children's Hospital, Boston/Harvard Stem Cell Institute, Boston (Stem Cell Biology)
- Homme W. Hellinga, Ph.D., Duke University Medical Center, Durham, N.C. (Protein Design and Synthetic Biology)
- Joseph (Mike) McCune, M.D., Ph.D., Gladstone Institute of Virology and Immunology/University of California, San Francisco (HIV Pathogenesis)
- Steven L. McKnight, Ph.D., University of Texas Southwestern Medical Center, Dallas (Biochemistry)
- Chad Mirkin, Ph.D., Northwestern University, Evanston, Ill. (Nanotechnology and Chemistry)
- Rob Phillips, Ph.D., California Institute of Technology, Pasadena (Applied Physics)
- Stephen R. Quake, D.Phil., Stanford University, Stanford, Calif. (Bioengineering and Biophysics)
- Sunney Xie, Ph.D., Harvard University, Cambridge, Mass. (Cellular Imaging and Single Molecule Approach to Biology)

For the tentative agenda, see **<http://nihroadmap.nih.gov/pioneer/symposium2005/>**.

Attendance is free, and there is no need to register. For an overview of the Pioneer Award and its place on the NIH Roadmap, see **<http://nihroadmap.nih.gov/pioneer>**.

Interinstitute Interest Group Directory

Web Access

Although not all the sites are up to date, nearly all the Interest Groups have web sites that can be accessed through <http://www.nih.gov/sigs/sigs.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: Phil Murphy
Phone: 301-496-8616
E-mail: <pmurphy@niaid.nih.gov>
Contact 2: Rachel Caspi
Phone: 301-435-4555
E-mail: <rcaspi@helix.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: 301-496-2078
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 (2005-06): Usually 3rd Thursday, 4:00 pm, Building 50; notices by e-mail and on the SBIG website
Contact 1: Susan Buchanan
Phone: 301-594-9222
E-mail: <skbuchan@helix.nih.gov>
Contact 2: Doug Sheeley
Phone: 301-480-3659
E-mail: <sheeleyd@mail.nih.gov>
To register for e-mail announcements, join SBIG at <www.nih.gov/sigs/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: Surajit Ganguly
Phone: 301-451-6399
E-mail: <gangulys@mail.nih.gov>
Contact 2: David C. Klein
Phone: 301-496-6915
E-mail: <kleind@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: varies, approximately quarterly
Meeting place: Building 14G, large conference room; occasionally hosts speakers at Natcher
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: Building 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: <yp4x@nih.gov>

Behavioral and Social Sciences Interest Group
Meeting time: Varies; mainly sponsors 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
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
Phone: 301-496-0191
E-mail: <cleonard@cc.nih.gov>
ListServe: subscribe to BCIG-L

Biomedically Enabling Sciences and Technologies (BEST) Cluster
Meeting time and place: As needed, for the heads of its member IGs (Biomedical Computing IG, Advanced Technologies IG, Knowledge Management IG, Handheld Users Group, and Microarray Users Group)
Contact: Mohammad Al-Ubaydli
Phone: 451-6716
E-mail: <alubaydl@ncbi.nlm.nih.gov>
Web address: <http://www.nihbest.org>

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@pop.nci.nih.gov>
Contact 2: Gil Ben-Menachem
E-mail: <gilben@mail.nih.gov

Birth Defects and Teratology Interest Group
Meeting time: Quarterly seminars
Meeting place: Videoconference between Bethesda and Research Triangle Park, N.C.
Contact: Megan Adamson
Phone: 301-443-4354
E-mail: <madamson@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: <asherman@nih.gov>
Contact 2: Indu Ambudkar
Phone: 301-496-1478
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: 301-496-8293
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 Immunology Interest Group
Meeting time: Monthly, last Wednesday, noon
Meeting place: Building 10, Room 9S235
Contact: Oral Alpan
Phone: 402-3447
E-mail: <oalpan@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>

Cultural and Qualitative Research Interest Group
Meeting time: Usually second Thursday every other month (next meeting is September 15), 3 pm
Meeting place: As announced
Contact 1: Sabra Woolley
Phone: 301-435-4589
E-mail: <woolleys@mail.nih.gov>
Contact 2: Simon Craddock Lee
Phone: 301-496-2794
E-mail: <leesi@mail.nih.gov>

Cytokine Interest Group
Meeting time: three to four symposia/year
Meeting place: Varies; one symposium/year at NCI-Frederick
Contact 1: Robert Seder
E-mail: <rseder@mail.nih.gov>
Phone: 301-594-8483
Contact 2: Tom Wynn
E-mail: <twynn@niaid.nih.gov>

Dendritic Cell Interest Group
Meeting time and place: TBA
Contact: Uri Lopatin
Phone: 301-496-8490
E-mail: <uri@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: Renee Rabben
Phone: 301-496-6289
E-mail: <ReneeR@intra.niddk.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
Contact 1: Kenneth Kraemer
Phone: 301-496-9033
E-mail: <kraemerk@nih.gov>
Contact 2: Vilhelm Bohr
E-mail: <vbohr@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 (starting September 9)
Meeting place: Porter Neuroscience Research Center (Bldg 35), Room BB-1000
Contact: Benjamin White
Phone: 301-435-5472
E-mail: <WhiteB@intra.nimh.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@dtpax2.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, 4:00 pm
Meeting place: Building 50, ground-floor conference room
Contact 1: Jeffrey Kopp
Phone: 301-594-3403
E-mail: <jeffreyk@building10.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: Natcher, room as available
Contact: Alexis Bakos
Phone: 301-594-2542
E-mail: <bakosa@mail.nih.gov>

Interinstitute Interest Group Directory

Endocrinology Interest Group **
Meeting time and place: Varies
Contact 1: George Chrousos
Phone: 301-496-5800
E-mail: <George_Chrousos@nih.gov>
Contact 2: Phil Gold
Phone: 301-496-1945
** ***Last year's listing-not verified or updated***

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, monthly, 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>

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 July 29; check the web site)
Meeting place: Radiation Biology Conference Room, Building 10, B2.5 level
Contact: Michael Graham Espey
Phone: 301-496-7511
E-mail: <SP@nih.gov>

Gene Therapy Interest Group
Meeting time: 2nd Thursday, 2:00 pm
Meeting place: Building 10, Lipsett Auditorium
Contact: Fabio Candotti
Phone: 301-435-2944
E-mail: <fabio@nhgri.nih.gov>
Contact 2:Robert Kotin
E-mail: <kotinr@nhlbi.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@dtpax2.ncifcrf.gov>

Glycobiology Interest Group
Meeting time and place: Varies
Contact: Diana Blithe
Phone: 301-435-6990.
E-mail: <blithed@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: 301-496-4913

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 1: Emily DeVoto
Phone: 301-496-6615
E-mail: <DeVotoE@od.nih.gov>
Contact 2: Jack Stein
Phone: 301-443-4060
E-mail: <js413y@nih.gov>

HIF (Hypoxia Inducible Factor) Interest Group
Meeting time: Last Thursday, 11:30 am–1:00 pm
Meeting place: Building 10, Hatfield 2-3750
Contact: Tawnya McKee
Phone: 301-846-1943
E-mail: <mckee@ncifcrf.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: Victoria Harden
E-mail: <hardenv@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 Inglese
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

Integrative Neural-Immune Interest Group
Meeting time and place: To be announced
Contact: Socorro Vigil-Scott
Phone: 301-496-9255
E-mail: <sv53s@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: To be announced
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: Jeff Kowalak
Phone: 301-496-4242
E-mail: <jkowalak@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/sigs/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: <petersonk@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: 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>

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@helix.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@helix.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: 1st Tuesday, 3:00 pm
Meeting place: Building 30, Room 117
Contact 1: Raymond Dionne
Phone: 301-496-0294
E-mail: <rdionne@dir.nidcr.nih.gov>
Contact 2: Michael Iadarola
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 Merril
E-mail: merrilc@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 (journal club; 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: Carl Baker
Phone: 301-496-2078
E-mail: <ccb@nih.gov>

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: <hannae@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

Interinstitute Interest Group Directory

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@intra.niddk.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: John Kylan Lynch
Phone: 301-496-1187
E-mail: <LynchJ@ninds.nih.gov>
Contact 2: Zurab Nadareishvili
Phone: 301-496-6231

Synaptic and Developmental Plasticity Interest Group
Meeting time: Tuesday or Wednesday, every other month, 11:00 am
Meeting place: Building 35, Room 1BB1000
Contact: Bai Lu
Phone: 301-435-2970
E-mail: <bailu@mail.nih.gov>

Systems Biology Interest Group
Meeting time: Quarterly seminars; less formerly, most first Thursdays, 1:00 p.m.
Meeting place: Natcher, Room 2AS10
Contact 1: David Balshaw
Phone: 919-541-2448
E-mail: <balshaw@niehs.nih.gov>
Contact 2: Martin Meier-Schellersheim
Phone: 301-496-5046
E-mail: <mms@niaid.nih.gov>

Technology Transfer Interest Group
Meeting time: First Tuesday each month, 3:00 pm
Meeting place: 6011 Executive Blvd., suite 325
Contact 1: Robert Baughman
Phone: 301-496-1779
E-mail: <baughmar@ninds.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: <cyc12b@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: 6001Executive Blvd., Room 3103
Contact: Ruth Stadius
Phone: 240-632-5620
E-mail: <stadiusr@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 1: Edward Doo
Phone: 301-451-4524
E-mail: <dooe@niddk.nih.gov>
Contact 2: Barbara Rehermann
Phone: 301-402-7144
E-mail: <barbarar@intra.niddk.nih.gov>

Virology Interest Group
Meeting time: 4th Tuesday, 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: <robertt@niddk.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 and place: Usually one Friday a month, 11:30 am–12:30 pm
Meeting place: Varies, but usually in Building 1, Wilson Hall; see website (<www4.od.nih.gov/orwh>) for upcoming lectures
Contact: Vicki Malick
Phone: 301-496-7989
E-mail: <malickv@od.nih.gov>

X-ray Diffraction Interest Group
Meeting time and place: See biweekly newsletter: <http://mcl1.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

Flow Cytometry Interest Group
Contact 1: Rajeev Agarwal
Phone: 301-435-4573
E-mail: <<ragarwal@helix.nih.gov>>
Contact 2: William Telford
E-mail: <wt40b@nih.gov>

Mood and Anxiety Disorders Interest Group
Contact: Holly Giesen
Phone: 301-435-8982
E-mail: <giesenh@mail.nih.gov>

This group will meet regularly September through early May in conjunction with a Distinguished Lecturers series, typically held on Tuesdays at noon in one of the larger auditoriums on campus. Other lectures featuring intramural speakers are held in the Building 15K conference room. Discussion and meeting follow.

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

Considering starting a new Interest Group? Contact* Celia Hooper: *<hooperc@od.nih.gov> or fax: 301-402-4303. Need to correct your group's listing? Contact CIT's web publishing group: <publish@cit.nih.gov>.

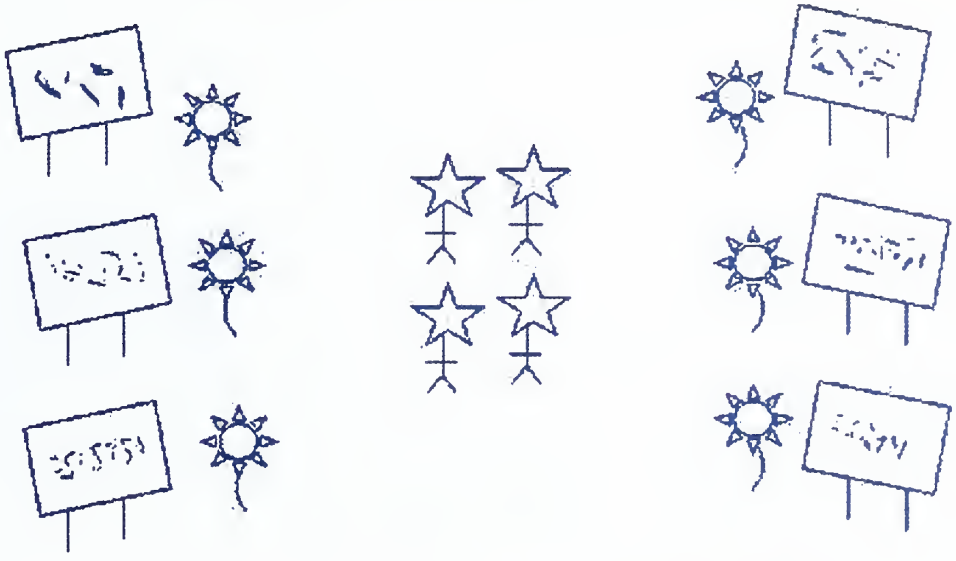
Commentary

Why a Postdoc's Life Reads like a Bad Jane Austen Novel (if she had written one)

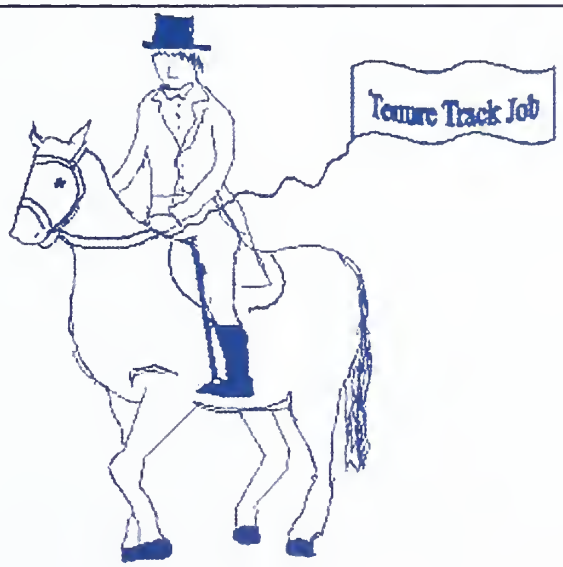
by Fatima Husain, NIDCD

Class distinctions rule: 1 hour of PI work = 20 hours of Postdoc = 40 hours of Postbac; calculate authorship accordingly

At conferences, the PIs congregate with other PIs and the Postdocs stand by their posters like so many wallflowers waiting to be asked to dance



All Postdocs are waiting for a Mr. Darcy to come swooping in with a tenure job and rescue them from their moribund lives as lab rats



People

Recently Tenured

Kyung Lee *received his Ph.D. in 1994 from the Department of Biochemistry at the Johns Hopkins University in Baltimore. He then worked with Raymond Erikson at Harvard University in Cambridge, Mass., as a postdoctoral fellow and studied in the fields of cellular proliferation and mitotic controls. In 1998, he joined NIH as a tenure-track investigator in the Laboratory of Metabolism at NCI and is now a senior investigator and head of the Chemistry Section.*

Fran Pollner

Kyung Lee

During the eukaryotic cell cycle, reversible protein phosphorylation by protein kinases is a fundamental regulatory mechanism. The G/M phases of the cell cycle comprise a series of regulatory biochemical steps and coordinated cellular events that ensure the faithful partitioning of genetic and cytoplasmic components.

It is now clear that, in addition to the much-studied cyclin-dependent protein kinases, the polo subfamily of serine/threonine protein kinases (collectively, polo-like kinases, or Plks) plays a pivotal role in regulating various mitotic events. Plks cooperate with a master cell-cycle kinase, Cdc2, to bring about essential mitotic events at mitotic entry; Plks also regulate pathways leading to the inactivation of Cdc2 at mitotic exit.

Loss or depletion of Plks activity in various organisms results in mitotic arrest followed by cell death, suggesting that the function of Plks is essential for mitotic progression in all eukaryotic organisms.

Using both budding yeast and cultured mammalian cells, my laboratory has investigated the mitotic functions of Plks. We have shown that the polo-box motif, which resides in the C-terminal noncatalytic domain, is essential for the localization of both budding yeast polo kinase Cdc5 and mammalian Plk1 to specific subcellular structures.

In line with this notion, mutations of the polo-box of either Cdc5 or Plk1 in its native organism abolished the function of these enzymes and induced mitotic arrest, indicating that polo-box–dependent subcellular localization is critical for the mitotic functions of these enzymes.

One of the critical events that budding yeast polo kinase Cdc5 mediates is mitotic entry, a process that requires activation of Cdc28 (homolog of mammalian Cdc2). We set out to clarify the molecular mechanisms of Cdc5 regulation of this event.

Studies have shown that Swe1 (ortholog of mammalian Wee1) inhibits mitotic entry by negatively regulating Cdc28. We found that Cdc5 directly phosphorylates and downregulates Swe1, thus permitting the activation of Cdc28 and thereby mitotic entry. The conserved polo-box domain of Cdc5 appeared to play a crucial role for this biochemical step by targeting the catalytic activity of Cdc5 to its substrate Swe1.

Similar regulation occurs in human cells, where downregulation of Wee1 by Plk1 is critical for entry into mitosis. These findings demonstrate the importance of the polo-box domain for specifically targeting the Plks to their substrates through protein-protein interactions.

Dynamic subcellular localization and the multitude of Plks functions predict that the polo-box interacts with multiple cellular proteins at specific stages of the cell cycle. To gain a deeper understanding of the function of the polo-box, we have been focusing on the identification of novel polo-box–binding proteins in cultured mammalian cells.

From a yeast two-hybrid screen using the polo-box domain of Plk1 as bait, we isolated a novel kinetochore protein that we termed PBIP1 (polo-box interacting protein 1). Consistent with the two-hybrid analyses, PBIP1 interacted with endogenous Plk1 in vivo under physiological conditions.

Preliminary characterization of PBIP1 suggested that it is a kinetochore-specific mitotic inhibitor that is phosphorylated and degraded by Plk1. Expression of the nondegradable PBIP1 lacking the Plk1-dependent phosphorylation sites induced a mitotic arrest, indicating that degradation of PBIP1 is required for proper mitotic progression.

Intriguingly, PBIP1 interacted with cellular proteins whose deregulation is implicated for tumorigenesis, suggesting that the Plk1-dependent downregulation of PBIP1 may contribute to the development of cancers in humans. In line with these observations, Plk1 was both upregulated and multiply mutated in about 80 percent of human cancers.

Our recent results raise the possibility that PBIP1 is a novel tumor suppressor. Precocious degradation of PBIP1 by deregulated Plk1 activity may lead to chromosome missegregation and genomic instability, thus promoting tumorigenesis. We expect that understanding Plk1-dependent PBIP1 regulation may provide new insights into how Plk1 deregulation promotes cancers in humans and how to approach the development of anti-Plk1 therapeutic agents.

Francesco Marincola *received his MD from the University of Milan (Italy) in 1978 and completed a general surgery residency at Stanford University (Stanford, Calif.) in 1990. He joined the Surgery Branch, NCI, in 1990 as an immunotherapy fellow and subsequently became a surgical oncology fellow. In 1993, he was appointed to the staff of the Surgery Branch; in 2001, he assumed two additional positions—director of the Immunogenetics Program in the Clinical Center Department of Transfusion Medicine and director of the HLA laboratory.*

Fran Pollner

Francesco Marincola

Since my immunotherapy fellowship in 1990 with Steve Rosenberg in the NCI Surgery Branch, I have been intrigued by the rare yet overwhelming observation of dramatic tumor regressions mediated by immune manipulation with the systemic administration of interleukin-2 (IL-2)—with or without tumor-infiltrating lymphocytes. When the fellowship ended, I agreed to continue in the staff of the Surgery Branch to work on the identification of the algorithm regulating tumor rejection in humans exposed to this kind of therapy.

As the tumor antigens (TA) recognized by lymphocytes became molecularly characterized in the '90s, TA-specific vaccines were developed that yielded the unprecedented opportunity to study tumor-host interactions specific to a unique TA and in some cases to a specific TA-human leukocyte antigen (HLA)-specific combination. This ability to minimize experimental variables in humans simplified the study of the effect of immunization in clinical trials.

We discovered that TA-specific immunization can reproducibly induce cytotoxic T cells (CTL) in patients that are capable of recognizing tumor cells. In addition, we observed that the CTL induced by vaccines localized at tumor sites, where they recognized tumor cells and produced cytokines such as IFN-γ.

Such interactions, however, were not sufficient to induce tumor regression. In addition, we observed that the level of expression of TA or HLA molecules re-

sponsible for the presentation of the TA to CTL did not predict response, suggesting that other factors modulate immune responsiveness at the tumor site.

The development of high-resolution molecular testing of HLA molecules, using high-throughput sequencing technology, was critical in these early vaccine studies and was made possible by Harvey Klein in the CC Department of Transfusion Medicine (DTM), who offered me a joint appointment as director of the HLA Laboratory in addition to my original appointment in the NCI Surgery Branch.

We employed a novel strategy to analyze T cell localization at tumor sites during immunization and the interactions of T cells with their target (the HLA-TA combination): With multiple fine-needle-aspiration biopsies, we could monitor tumor-host interactions in the target tissue ex vivo while leaving the tumor in situ, allowing us to follow the natural history of the disease and serially evaluate response to therapy.

In 2000, Ena Wang in my laboratory developed and validated a technique for RNA amplification that allowed the use of very small amounts of starting RNA (obtained from fine-needle aspirates) in the study of tumor-host interactions in conjunction with high-throughput technologies such as microarrays. This research expanded our ability to monitor immune responses during immunization and other immune therapies.

These original studies suggested that the tumors most likely to respond to immunotherapy are characterized by an immunologically active (chronically inflamed) transcriptional profile. When successful, immune therapy—whether TA-specific immunization or the systemic administration of immune stimulants such as IL-2—acts by turning a chronic inflammatory process into an acute one quite similar to that observed by others in the context of acute transplant rejection.

Subsequently, Monica Panelli, also in my group, compared fine-needle aspirates obtained before and during IL-2 therapy and showed that this cytokine acts by inducing a general inflammatory process at the tumor site. This inflammatory process activates innate effector mechanisms in mononuclear phagocytes and natural killer cells and induces activation of antigen-presenting cells and production of chemoattractants capable of recruiting and activating T cells at the tumor site.

In 2001, Klein invited my group to develop the Immunogenetics Program in the DTM. We are now developing high-throughput, hypothesis-searching tools for the direct ex vivo analysis of tumor-host interactions during vaccine therapy. Our aim is to identify factors predictive of the immune responsiveness of patients and/or their tumors.

These tools include the combined analysis of DNA, RNA, and protein to identify genetic and epigenetic differences between patients who do and do not respond to therapy.

Using affordable, custom-made oligonucleotide-based chips, we are developing high-throughput screening tools to analyze cytokine polymorphisms and test whether genotype can be linked to phenotypic responses and to clinical parameters. We are also continuing to improve our proteomics and functional genomics tools for the global assessment of patients' response to treatment during clinical trials.

Mahendra Rao

Mahendra Rao *completed his medical training at Bombay University in India in 1983 and received his Ph.D. from the California Institute of Technology in Pasadena in 1991. After postdoctoral training with Story Landis, then at Case Western Reserve University in Cleveland, and David Anderson at the California Institute of Technology, he joined the Department of Neurobiology and Anatomy at the University of Utah School of Medicine in Salt Lake City in 1994. In 2001, he joined NIA as chief of the Stem Cell Biology Unit in the Laboratory of Neurosciences. He is currently also an adjunct associate professor at the National Center for the Biological Sciences in Bangalore, India, and holds a joint appointment as an associate professor at Johns Hopkins University, Baltimore.*

At both the University of Utah and NIA, my laboratory has focused on understanding how embryonic and adult stem cells self-renew and differentiate. Our early work with fetal and adult neural stem cells revealed that they change over time with respect to their self-renewal capabilities, expression of markers, positional information, and differentiation ability.

We then showed that stem cells do not differentiate into fully mature cells directly but do so by first generating intermediate precursors, which we termed lineage-restricted precursors. We subsequently isolated specific lineage-restricted precursors and showed that they play an integral part in the normal process of development. Indeed, their action at specific stages can explain the effects of many genes.

Our ability to identify specific populations of cells allowed us to use the large-scale analytical procedures—such as massively parallel signature sequencing, microarray, and EST scan—developed at NIH and elsewhere to identify novel genes and new signaling pathways that regulate self-renewal. Using such methods, we were able to cross-correlate information to obtain a global view of cell function and start to identify context-dependent and cell type–specific signaling pathways. For example, we identified Lin41 as a microRNA-regulated gene that is important in regulating embryonic stem-cell self-renewal.

In the past couple of years, we have extended this strategy to examine human embryonic stem-cell populations—with equally exciting results. Most of our findings have followed as a logical consequence of the key observation that all stem-cell populations generate differentiated progeny by first generating more restricted precursors.

For example, based on our initial finding, we were able to hypothesize and then confirm that repair in the adult nervous system likely involves a larger role for restricted progenitors than for true multipotent stem cells.

This result has important implications for both embryonic stem-cell and neural stem-cell biologists. It suggests both that stem-cell populations need to be differentiated prior to implantation and that for specific diseases, subsets of cell types may be more important—glial for glial disorders and neuronal cells for diseases that include neuronal loss.

We then proceeded with transplant experiments using rodent models of Parkinson's disease and spinal cord injury to show that these restricted precursors have a therapeutic benefit. This opened up an entirely new field of endeavor, new collaborations, and interactions with new colleagues.

I have benefited enormously from the efforts and intellectual input of people in my own laboratory and from Mark Mattson and other colleagues in the Laboratory of Neurosciences—and from NIA and NIH resources and infrastructure that allow relatively small laboratories to undertake large-scale analyses.

In the coming years, I hope to build on the wealth of information we have generated to begin to understand how stem cells maintain their self-renewal capability and avoid senescence. Further, comparisons across species will allow us to determine what common and/or distinct mechanisms of self-renewal have evolved over time. ■

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...

- Yoga Therapy
- CRADA Country
- More Bench To Bedside

Kid's Catalyst: Worth Its Weight in Gold—Eureka! Part 1

One day about 2000 years ago, the Greek King Heiro wanted a new crown. So he weighed out some gold, gave it to his local crown-making craftsperson, and soon had a shiny new diadem. But something made King Heiro suspicious. Convinced he had been cheated out of some of his gold, he asked around for help on how to prove it.

The problem eventually came to a very clever guy named Archimedes (you'll hear his name many times again in your travels!). Bright as he was, this one had him stumped. How to prove the crown wasn't 100 percent gold? After days of contemplation, he finally took a break. What does a frustrated scientist do to relax? Take a bath.

Archimedes stepped into his tub and the very same thing happened then as would happen now if you got into a tub full of water: It would overflow. So with water spilling all over the place, the solution to the problem hit him. He was so excited that he was crying "Eureka!" (Greek for "I have found it") out the door, through the streets, and to the king. (In his glee, he apparently forgot his robe, guaranteeing that this would be the stuff of legend!)

So how did Archimedes figure it out? Here's what he knew: the weight of the crown and what the crown was allegedly made from. He placed the crown into a vessel full of water to see how much water overflowed. Then he did the same with the same amount weight-wise of gold. Even though the crown was the same weight as the gold, it displaced a different amount of water. The king had his proof, the crown maker got his just reward, and Archimedes put his robe on.

Now you don't need gold crowns lying around to test the volume of irregularly shaped objects, and you certainly don't need anything more than a carefully-made scale to tell that two things shaped the same are made out of different materials.

Next issue we will take a bunch of pennies and prove that not all pennies are created equal using a surprisingly accurate home scale. Maybe you can work on that problem in the meantime, but here's a hint: Compare U.S. pennies made before and after 1982. You'll be surprised!

—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>

Publisher
Michael Gottesman
Deputy Director
for Intramural Research, OD

Editor
John I. Gallin
Director, NIH Clinical Center

Scientific Editor
Celia Hooper

Managing Editor
Fran Pollner

Copy Editor
Shauna Roberts

Contributing Writers
Aarthi Ashok
Annie Nguyen
Karen Ross
Jennifer White

U.S. Department of Health and Human Services
National Institutes of Health
Building 2, Room 2E26
MSC 0235
Bethesda Maryland 20892

Official Business
Penalty for Private Use $300

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

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