FOSTERING COMMUNICATION AND COLLABORATION

# The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 5, ISSUE 2 ■ MARCH–APRIL 1997

## NIMH OFFERED 77 MANEUVERS TO REACH BALANCE

Congress attached a long string to its 1994 appropriations for NIH—a directive that NIH appraise the size, quality, and cost of its entire intramural program.

The first order of business was an NIH-wide scan by a committee headed by Paul Marks (Memorial Sloan-Kettering Cancer Center) and Gail Cassell (University of Alabama). The next level of scrutiny fell on individual institutes, and the first institute to go under the microscope was NCI, which, under a new director, has been undergoing extensive reorganization since the report of the ad hoc working group to review the NCI IRP was delivered in June of 1995.

Now a second institute has been dissected. After 10 months of deliberations, including soliciting and reviewing confidential letters from IRP scientists and staff of NIMH, a 17-member outside panel—chaired by Herbert Pardes, dean of the faculty of medicine and chairman of psychiatry at Columbia University College of Physicians and Surgeons and a former NIMH director—has delivered its report.

Called *Finding the Balance*, the report opens in no uncertain terms: "Faced with an explosion in knowledge, rapid changes in technology, and increasing complexity of research questions, the infrastructure and organization that have served the [NIMH] IRP so well in the past are no longer sufficient to guarantee high quality science."

Nonetheless, the panel found a "powerful rationale for [NIMH's] continued existence . . . provided the research is of the highest quality" and offered 77 recommendations. Salient

*continued on page 3.*

> "WITHOUT TECH TRANSFER, WE WOULDN'T HAVE CHAPS OR THE AIDS TEST OR SO MANY OF THE BENEFITS TO THE PUBLIC HEALTH THAT COME FROM THESE DISCOVERIES. IT'S AN INHERENTLY GOOD THING TO DO."
> —*Maria Freire, OTT*

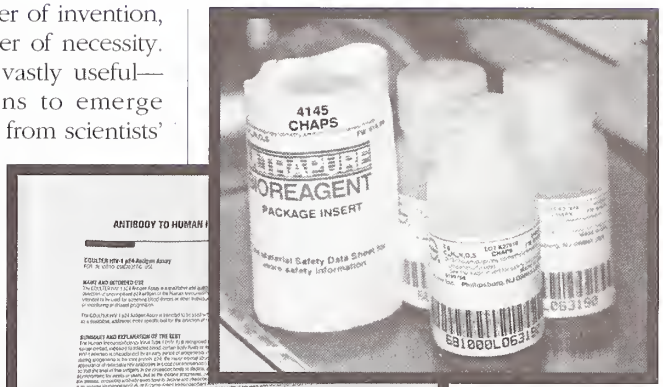
## NIH INVENTIONS: FROM THE SUBLIME TO THE UBIQUITOUS

*by Fran Pollner*

If necessity is the mother of invention, NIH may be the mother of necessity.

Some of the most vastly useful—and lucrative—inventions to emerge from NIH research sprang from scientists' need to advance their own research, to take their experiment to the next step. The results of their efforts, naturally enough, were laboratory tools appreciated by scientists the world over.

Thus, the value of an NIH-patented zwitterionic detergent, popularly known as CHAPS, has not diminished since its market debut in 1981. In fact, it's one of a fairly exclusive club of top moneymakers for the Public Health Service, defined as a PHS-invented commercialized product that exceeds $100,000 in annual sales. In 1995, 28 inventions fit that category (see "Inventions" chart, page 6).




Fran Pollner

*Two of many standout NIH inventions: an HIV antibody test kit (left) and CHAPS.*

At a price of $48.40 for a 5-g bottle (at the NIH Self-Service store), CHAPS is clearly not a high-tech, high-ticket item. But it is a high-volume item. Zwitterionic agents, which bear both positive and negative charges, enable the release of biochemically active proteins from cellular membranes without disrupting the proteins' chemistry, composition, or structure. This makes CHAPS a crucial tool in protein purification.

"It's used in almost every laboratory in the world that does basic biological research," said Maria Freire, director of the NIH Office of Technology Transfer. But, she adds, "I don't think people realize it's an NIH invention."

To stoke the tech-transfer fires of the ICD scientific directors, Freire brought a carton of NIH inventions to the directors'

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### CONTENTS

# REVIEWING AND REINVIGORATING INTRAMURAL RESEARCH

Michael Gottesman

We are now close to the third anniversary of the release of the Marks-Cassell external advisory committee report on intramural research programs at NIH. We have implemented most of the report's recommendations—complying with the advice, for example, to strengthen our Boards of Scientific Counselors (BSC) review system and tenure process—and are now in the midst of the more detailed reviews of each individual intramural program mandated by the Marks-Cassell report. The purpose of these reviews is to help revitalize our venerated intramural research and training programs. Here's a midcourse update on this continuing endeavor.

In August of 1995, a committee chaired by Michael Bishop (UCSF) and Paul Calabresi (Brown University) completed their analysis of the NCI intramural program. Their far-reaching revitalization plans included reorganizing the NCI IRP so that division directors did not divide their time between intramural and extramural responsibilities, some consolidations at the Frederick Cancer Research Facility, restructuring of the NCI BSC review system to make the process more vigorous, reducing the percentage of the NCI budget devoted to intramural research, and establishing budgets for individual principal investigators (tenured and tenure-track). All of these recommendations have been implemented.

In January of 1997, a committee chaired by Herb Pardes (Columbia University) released its report on the NIMH IRP. Its recommendations are discussed in detail in this issue of *The NIH Catalyst.* Some of the major ones include restructuring NIMH labs and branches to maximize research and training opportunities for fellows and principal investigators and new recruitment—including the appointment of a permanent scientific director, which NIMH has not had for four years. The Pardes report also recommends that research at St. Elizabeth's be phased out as appropriate replacement facilities on the Bethesda campus become available. This report has been enthusiastically received by Steve Hyman, director of NIMH, and should be implemented within the next year or so.

To speed the review process a bit, we are now embarking on the simultaneous scrutiny of several IRPs. The current plan is to develop, in consultation with the institute directors, review groups consisting of the chair of the BSC, a representative from the institute's National Advisory Counsel, a representative from the Advisory Committee to the Director of NIH, and subject-matter experts, including both clinical and basic researchers.

Such committees have been established for NIA, NIAMS, NIDA, and NIAAA, and each committee met for the first time earlier this year to initiate the review process for their respective IRPs. Reviews of NEI and NHLBI are in the early planning stages, and those of all of the remaining IRPs will follow within the next year.

Although each intramural program has specific problems and issues to be discussed, there are also certain overarching concerns that are currently not covered by our other intramural review processes. Our BSC reviews focus on the merit of individual scientific programs. Our five-year reviews of the scientific directors specifically address leadership skills. The new intramural reviews will look at the effectiveness of the BSC reviews, the organization of the programs (at the level of labs and branches), the laboratory facilities and physical location of the program (several of the programs currently under review are mostly sited off-campus), the balance between clinical and laboratory-based research, the balance between intramural and extramural funding, and the quality of training, mentorship, and career development within the program.

IF THE SUCCESS OF THE REVIEWS OF NCI AND NIMH IS ANY GUIDE, THESE REPORTS WILL GENERATE SWEEPING CHANGES, IMPROVING OUR ORGANIZATION AND INFRASTRUCTURE AND CREATING EXCITING NEW RESEARCH ON THE NIH CAMPUSES.

These committees will meet approximately four times over about eight months to develop recommendations for consideration by the NIH leadership. Staff of each institute will be contacted for comments about various aspects of intramural research, either written or presented orally to the committees. There will be a report on each program to the Advisory Committee to the NIH Director, and each institute will be expected to develop appropriate implementation plans. If the success of the reviews of NCI and NIMH is any guide, these reports will generate sweeping changes, improving our organization and infrastructure and creating exciting new research on the NIH campuses.

I welcome your ideas about the review process and would especially like to hear about issues you think should be covered during these reviews. This issue of *The Catalyst* has a "call for catalytic reactions" devoted to intramural review; alternatively, you can send your thoughts to me by e-mail at <mgottesman@nih.gov>.

*Michael Gottesman*
*Deputy Director for Intramural Research*

**77 Maneuvers**
*continued from page 1.*

among them are the need to recruit a permanent scientific director, emphasize more translational and clinical research, and foster a greater spirit of cooperation and collaborative research among the various components without stifling the autonomy of independent investigators.

Neither the overall NIMH budget nor the proportion devoted to the intramural research program would need alteration to respond to the recommendations, the panel determined, but it advises that the scientific director have a discretionary fund, that resource distribution within the IRP be more firmly rooted in scientific merit rather than "history," and that the fees the IRP pays to use the Clinical Center be reduced. A summary follows.

**Leadership**
NIMH, which has not had a permanent scientific director since 1993, must fill that position with an individual with outstanding credentials and track record. The permanent scientific director, together with a newly recommended ad hoc planning group should develop a long-term agenda—and then restructure the IRP to fulfill that agenda. The scientific director should have a discretionary fund to facilitate shaping the IRP's scientific directions.

In what some early responses to the report suggest is one of its more eye-catching recommendations, the panel advises that a portion of that fund be allocated to laboratory and branch chiefs to enable them to "encourage thematic integration" within their group. The chiefs should coordinate, rather than direct, individuals and groups of researchers. This approach, the panel suggests, would correct past shifts in the balance toward the particular scientific interests of the chief.

Only rarely should a basic scientist be placed in a clinical laboratory, and then with extreme care, lest the basic scientist become isolated. Collaboration among basic and clinical scientists is not dependent on their residing in a common lab, the panel maintains.

**Quality of Science**
The panel calls for rigorous BSC review of chiefs and independent investigators as critical to the restoration of high-quality science in the IRP and advises an "arm's-length relationship" between the scientific director and the BSC. The recommended components of the "stewardship" evaluations of the scientific director and lab and branch chiefs are quality of science, scientific vision, relevance of projects to the laboratory or branch overall and to the IRP mission, and use of special IRP resources, as well as mentoring and administration abilities.

There should be two distinct sets of recommendations by the BSC in each chief's review: one regarding resource allocations based on the review of the science, the other regarding the status of the individual (reappointed, promoted, demoted) based on the stewardship review. There should also be set procedures for downsizing or closing labs with severe deficiencies. Appeals of negative reviews ought to be handled within the current review cycle.

**Recruitment, Retention, and Retirement**
Regarding recruitment, the panel observes that a marked preponderance of "homegrown" IRP scientists has led to "insularity" and "fiefdoms," a situation that should be corrected by efforts to recruit externally and by encouraging individual research pursuits.

Regarding retention, the panel faults the IRP for not exploiting available incentives to retain valued tenured scientists, noting, for instance, that although retention bonuses of up to 25% of base salary are possible, "only one tenured scientist at NIMH is currently receiving a retention bonus."

The panel outlines several mechanisms for shifting senior scientists out of positions for which others become better suited—so-called "graceful exit pathways."

**Training and Mentoring**
The report presents quotes from the confidential letters of IRP staff solicited by the panel during its review. Perhaps the most scathing published comments accompany the panel's deliberations on the issue of mentoring: "Young scientists are being employed as pawns in the game of obtaining recognition, resources, and influence instead of being mentored."

The panel's detailed recommendations to upgrade the quality of the IRP fellowship program reflect its concern that NIH overall, as well as NIMH in particular, be competitive in attracting excellent postdoctoral candidates; that the focus of fellowships be on training, rather than technical support; and that the training, including experience in "teaching and grantsmanship," equip fellows to be competitive in their search for positions after they leave NIH.

Recognizing that intensified mentoring will necessarily cut into the research time of the mentors, the panel suggests that mentors be rewarded with more fellows or more flexibility in hiring support staff.

**Clinical Research**
"Revitalization of clinical research efforts is critical," the panel says, and should be a "special focus of the NIMH IRP, particularly since clinical research is threatened in the extramural community."

Noting that NIMH is the third largest institutional contributor to the Clinical Center budget (after NCI and NHLBI), expending about 22% of its own budget for use of the Clinical Center, the panel points to a "growing consensus . . . that the charges to the NIMH IRP are excessive." It recommends lowering them to reflect lower utilization by NIMH clinical research patients of such high-cost services as surgery and intensive care.

The panel advocates the consolidation of all NIMH clinical research programs, which, in practical terms, would mean bringing onto the Bethesda campus the clinical neuroscience program now housed at St. Elizabeth's Hospital in Washington. ■

## *Two Thumbs Up*

NIMH Director Steve Hyman can point to nothing within *Finding the Balance* to dim his enthusiasm for what he calls an "extremely thoughtful and constructive report that will help the scientific director renew the program and empower young and mid-career investigators—while retaining the benefits of the lab structure."

Some of the review panel's "noncontroversial, important, and timely" suggestions have already been implemented by the acting scientific director, Susan Swedo, he notes, including reduction in size of the largest labs.

He expects the report's greatest impact will be felt where it's most needed but most difficult to quantify—on morale. "The intramural program has felt beleaguered, and morale has been low," partly due to the lack of a permanent scientific director, he says. "Now we will fill that position with an outstanding individual and proceed to implement the core of the report." Hyman predicts a return to a state of excellence, in both morale and science.

Candidates for the scientific director position were being interviewed as *The Catalyst* went to press. ■

# Catalytic Reactions

*Below are comments we received in response to questions posed or issues raised in the last two issues.*

### On Quality-of-Campus-Life Issues

The lack of parking and daycare impede efficiency for working parents who must juggle parenting and work-place responsibilities. NIH should definitely be making a larger investment in on-site daycare and a commitment to working parents.

*—Cathryn C. Lee, NCI*

*Good news. See the article on page 13 concerning parking. As for daycare, the Office of Research Services, with Dr. Varmus' blessing, has requested $3.5 million in the proposed FY 1998 Buildings and Facilities budget to build a new daycare center. The proposed site is near the Natcher Building, which is consistent with the NIH master plan. Of course, there are no guarantees that the money will be approved by Congress, but it looks hopeful. In the meantime, the Day Care Oversight Board will be discussing this with the ORS and making recommendations on a final plan for using this new resource. One plan on the table is that the current POPI (Parents of Preschoolers, Inc.) facility would move into the new building. The Building 35 facility, where POPI is now housed, would be renovated, and Childkind, Inc., would move into that space. In addition to addressing critical problems with the physical condition of the current facilities, this plan would significantly increase the number of infant and preschool daycare slots on campus, where care is most in demand.*

*—Michael Gottesman, Deputy Director for Intramural Research*

I have several thoughts concerning childcare at NIH. Although I have no small children now, childcare is an issue for many staff nurses and research nurses at the Clinical Center. I understand that the current [on-site] daycare is used to the maximum, with few openings. Also, this daycare is not an option for staff arriving for duty before 7 a.m.

Because of the daycare situation and the fact that private babysitters are very expensive and difficult to obtain, many staff choose to work only part-time or evenings, nights, or weekends. Flexiplace is feasible for some jobs, but the flexiplace program does not necessarily work for researchers who often need to be present to interact with patients.

Another problem is that many staff take sick days when their children are sick. They also get called at work when their children become ill and often must leave immediately to take them home. An idea worth considering is to use some of our resources to provide sick-child childcare for staff members' children.

*—Barbara Corey, CC*

I enjoyed the parenting issue and found especially pertinent the section on postdocs. I also share mixed feelings about the leave policy. It would be nice to have flexible-time and generous family-leave policies, but how about what your peers and your supervisor feel about it and, ultimately, what your c.v. is going to look like? Personally, while I felt I wanted to spend a long time at home with my babies, I also felt that as a scientist, I would lose ground compared with my colleagues who remained in the lab, as well as the esteem of my supervisor. Frankly, I am still wondering how feasible it is to be a good parent and to pursue an ambitious career.

I also think the $250,000 cost to upgrade NIH daycare facilities is worth it. It will create a better working environment, promote productivity in the long run, and, finally, fulfill a decisive and leading role in education.

As far as the preschool is concerned, how about taking advantage of the multicultural and multilingual environment of the NIH campus and of the preschool itself to turn it into an international preschool? In addition to American children, whose origins are already varied, the preschool hosts Indian, Chinese, Japanese, South African, French, Swiss, German, Polish, Italian, Argentinan, and Iranian children. Why not have teachers who know and could use another language? How about ethnic cooking; geography; new topics of conversation and circle time, such as the customs, music, dance, costumes, mythologies—the heritage—of other countries? A timid approach exists in the present preschool, but an officially international school would base its curriculum on the diversity of these kids—and use it as a source of knowledge as well. Food for thought.

*—Rosaura Valle, CBER, FDA*

NIH must commit *more* to daycare.... Whether you have kids or not, daycare is important to you because your co-worker can't do his/her work properly if childcare concerns interfere. We are all in this together.

*—anonymous*

Improve and expand NIH daycare now!

*—anonymous*

### On Parking Perplexities

As a recent recipient of a ticket for parking on the lawn in Lot 41 due to a total lack of any legal parking spaces, the current situation has caught my attention. I've been at NIH for close to seven years and understand the problems concerning parking here. The situation was brought into clear focus for me about a year after my arrival when I attended a retirement party for a technician with close to 30 years of service. She related a story about a "town meeting" with the new NIH director that occurred about 6 months after she started working at NIH.

The main complaints voiced at that meeting 30 years ago were the lack of parking and the down time of the elevators in Building 10. It was after hearing that story that I abandoned all hope. In light of that, I still have a couple of suggestions that may be helpful.

1. Allow postdocs to participate in the TRANSHARE program. While I understand that postdocs are not classified as federal employees, funding for this could come from other monies, including gifts, currently earmarked only for postdocs. I would estimate that close to 25% of the Bethesda campus population are postdocs. In addition, many live close to Metro lines and would use them if they could afford it. A directed focus on reducing the number of cars used by this population, as well as guest researchers, would help enormously.

2. Allow for "partial-TRANSHARE." In other words, some program for individuals who can use public transportation several days a week, but must still use their car on some days. One of the primary barriers to the Trans-share program is total surrender of your parking sticker. I could easily use public transportation at least two days a week, but the cost is prohibitive. It's cheaper for me to drive and take up a space. While I understand the difficulty in implementing such a plan, I think it's worth looking into.

3. Reevaluate the 0.5-spaces-for-each-employee law implemented with Mont-

gomery County. While Montgomery County enjoys the benefits of a substantial tax base, we suffer the idiocy of not having a place to park where we work. I think the harsh reality must be faced that this rule isn't working and will not work considering the long-range goals of moving more (not less) people onto the main campus. The addition of two or three underground or multilevel parking garages would solve many, if not all, of our current problems.

4. Reestablish parking for instrument and technical service engineers. During the "recent" parking crisis, we've had complaints from service reps who cannot find parking to come in and repair lab equipment. This is due primarily to the loss of some of the Building 10 parking spots due to construction. One possible solution is to allow service reps to park in the current bloodbank spots as well as visitor spots.

5. Finally, in light of ongoing construction and the reduction of the few spots we do have, I feel that any conferences scheduled for the main NIH campus should be canceled until these projects are completed and the parking spaces restored. I think it's grossly unfair to both conference participants and regular NIH employees to have to battle for a parking spot. Until NIH can solve the problems of finding spots for its own employees, I don't see how it can, in good conscience, invite 200–300 or more visitors onto campus for a meeting.

I hope that some of these suggestions will be helpful, and I hope that whoever came up with the 0.5 spots/employee rule pays the ticket I got last week. But as I said before, I've abandoned all hope.

*—Jack Simpson, NIMH*

### On the Telecommuting Solution

A large part of the research of some intramural scientists involves computing, writing papers, and reading papers—which could be done as well at home as at work. Some of us live very far from NIH because, for example, a spouse works in another city. With such a long commute, the amount of time saved by working at home and not sitting in traffic can be substantial. Needless to say, this extra time could be better spent—doing more research or spending more time with children. When one has a young child in daycare with both parents working far from home, the problem of long commutes makes it that much harder to juggle work and family responsibilities.

If our productivity is judged based on our research, what does it matter if we work at home or at NIH? Some private companies allow employees to work at home. In a memo dated July 11, 1994, President Clinton urged the heads of executive departments and agencies to expand family-friendly work arrangements. Other agencies have instituted pilot programs for working at home. I urge NIH to do the same.

*—Stuart G. Baker, NCI*

The article on "Parenting At NIH: It Takes a Campus" in *The NIH Catalyst* was highly informative with regard to various alternatives NIH parents have in utilizing available campus childcare facilities and community daycare centers. I have a suggestion that was not addressed in your article—the potential of telecommuting in balancing work and family responsibilities. For example, NIH scientists could utilize telecommuting technology as an alternative in facilitating greater flexibility in the area of work and family responsibilities. I'm sure you are well aware of telecommuting environmental benefits regarding lessening of air polluting and traffic congestion. We haven't addressed at NIH the social and organizational benefits of telecommuting, particularly in the areas of family leave, alternative work schedules, and scientific work productivity. I would like to suggest that an NIH committee composed of scientists and human resource professionals be convened to explore and, if feasible, promote greater use of telecommuting at NIH. . . . Let's have community-wide cost-benefit discussions with respect to NIH's crossing the bridge into 21st-century technology.

*—Ron Sleyo, NIDDK*

### On Improving NIH Work Life

We need better space management, especially in Building 10. Some labs are so crowded OSHA would shut us down!

*—anonymous*

### On Clinical Research

Congress and the American public expect NIH to conduct research that would eventually benefit them. Without clinical research, NIH cannot live up to this expectation and will be irrelevant. Clinical research should be top priority—the H in NIH stands for public health.

*—anonymous*

### On Priorities for the NIH Director

Help foster closer ties with other local institutions, hospitals, and medical associations to help widen the patient base for clinical research.

*—anonymous*

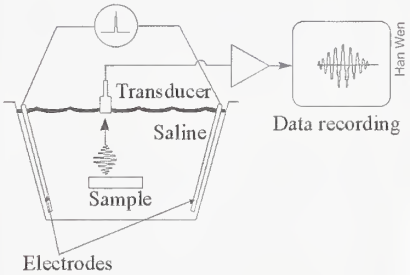
## *The Ombudsman Is In...*

In our last issue's Ethics Forum, we introduced Dave Robinson, newly appointed as ombudsman for scientific conduct issues, in a pilot project involving five ICDs: NIDA, NIAID, NIEHS, NHLBI, and OD. He now has an address and a phone number: Building 10, room 1C119, phone (301) 594-7231.

The ombudsman's e-mail address is <robinsod@od31em1.od.nih.gov>. (Be advised that no form of electronic mail is absolutely secure.) ■

## *Hall Effect Imaging: Look Again*

The schematic we ran last issue was not the reverse mode. The one below really is.




*Schematic of the experimental set-up for HEI in reverse mode. The sample is submerged in saline, and voltage pulses are applied across the electrodes. The combination of the electric field pulses and the presence of a large magnetic field (perpendicular to the page, not shown) causes ultrasound vibrations, which are detected by the transducer.*

**INVENTIONS**
*continued from page 1*

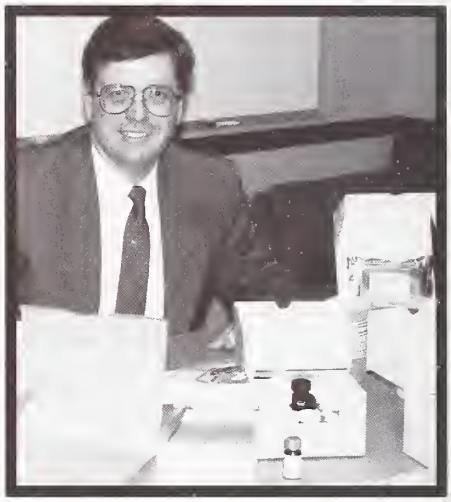
year-end meeting a few months ago. "You'd be surprised at how many people looked at the CHAPS bottle and said, 'CHAPS! I didn't know CHAPS was invented at NIH!'"

Some NIH inventors and inventions approach household-name status, like NCI's Robert Gallo and his standout moneymaker: a detection assay for HIV-1 antibodies. Gallo's kit brought in $5.5 million of the $27 million in royalties that NIH received last year and has accounted for $50.7 million of the $122 million total NIH royalties since 1987. But Gallo and his test are the exception. Most inventors—like CHAPS inventor Leonard Hjelmeland, a biochemist no longer at NIH—labor in relative obscurity.

Freire's concern at the moment is not winning fame for NIH inventors, but rather, making sure that nascent NIH inventors are not overlooking the "invention potential" of their research. Recently, the number of invention-disclosure reports has been going down, a worrisome trend, she says, since these reports constitute the pool from which OTT pursues patents and licensing agreements. They serve notice that the researcher and his or her ICD tech-development coordinator think they've got something new; the report is the first step in the tech-transfer process.

There were 196 reports in 1996, compared with 271 in 1995, with all institutes showing a decline except NICHD. "We need a bigger pool," Freire says. She notes that although OTT decided a few years ago to file fewer patents than in the past—selecting the patent route for about 60% of disclosure reports instead of 90%—that shift doesn't mean that discoveries are ignored, only that the transfer mechanism chosen is better tailored to the nature of the discovery.

"We were filing too many patents before; and each one costs about $24,000 to file. [Securing] worldwide protection can cost up to $150,000. But we can get things out to the public and make money for NIH and the inventor without patenting," she says, noting that the licensing process *sans* patenting costs NIH just $5,000 to $6,000. And licensing fees and royalties from sales can accrue with or without a patent.



Fran Pollner

*OTT's Steve Ferguson and some of the products he's negotiated.*

Freire points to the "neurotransmitter antibodies" entry on the "successful commercialized inventions" list as an example of a product that has paid off without patenting (see "Brainchild," page 7).

Products used as research tools are typically not the stuff of patents these days. Says Steve Ferguson, an OTT technology licensing specialist, "Generally, we seek patent protection for those inventions requiring a patent for commercialization—therapeutics, diagnostics, vaccines, instrumentation. We'd think long and hard now about spending that kind of money and resources to patent a research tool."

The OTT balance sheet has improved with the implementation of this approach. Overall, technology-transfer activities cost about $16 million a year. 1996 was the first year that a profit was actually generated—about $11 million, considering the $27 million received in royalties.

Freire observes that this income is very small relative to NIH's $12-plus-billion research budget, or even the $1.3-billion intramural research program portion, but that NIH's tech-transfer efforts are worth the trouble. "It's an inherently good thing to do."

Ferguson points out, "Not only does it bring inventions to the bedside, it rewards the scientists, and money is plowed back into the institutes. It incentivizes the system."

***PHS Inventions Amassing >$100,000 in Sales in 1995***

| | |
|---|---|
| **Research Materials** | |
| Non-denaturing Zwitterionic Detergents | NICHD |
| Reconstituted Basement Membrane Protein Complex | NIDR |
| Neurotransmitter Antibodies | NIDCD |
| G-Protein Antibodies | NIDDK |
| Human D-2 Dopamine Receptor | NINDS |
| Process of Site-Specific Mutagenesis without Phenotypic Selection | NIEHS |
| Silver Stains for Protein in Gels | NIMH |
| Method for the Sulfurization of Phosphorous Groups in Compounds ("Beaucage Agent") | FDA |
| Polyacrylamide Gels | NIMH |
| IL-4 Hybridoma Cell Line | NCI |
| **Diagnostics** | |
| Antibodies against Human Pneumocystis carinii | CC |
| Serological Detection of Antibodies to HIV-1 | NCI |
| Serological Detection of Antibodies to HTLV-1 | NCI |
| erb-2 Oncogene Receptor | NCI |
| Breast Cancer Monoclonal Antibodies | NCI |
| Soluble Interleukin-2 Receptor | NCI |
| Recombinant Cytochrome P-450 | NCI |
| Specific/Sensitive Diagnostic Test for Lyme Disease | NIAID |
| Cell Line Producing AIDS Antigens without Producing Viral Particles | NIAID |
| **Vaccines and Therapeutics** | |
| Cancer Chemotherapeutic Drug, 2-F-Ara-A | NCI |
| Antisense Phosphorothioate Nucleotides | NCI |
| Isolation of Hepatitis A Virus Strain HM-175 | NIAID |
| Treatment of HIV Infection with ddI | NCI |
| Treatment of HIV Infection with ddC | NCI |
| Trimetrexate as an Anti-Parasitic Agent | NCI |
| Adoptive Immunotherapy as a Treatment Modality in Humans | NCI |
| **Instrumentation and Devices** | |
| Flow-through blood centrifuge | NHLBI |
| Fecalator device (fecal parasite concentrator) | CC |

SOURCE: Office of Technology Transfer.

Could commercial incentive play too large a role in shaping NIH research, or could a company's forecast of commercial windfall influence a research project's direction?

Freire thinks not. "One thing you learn very early on," she says, "is that it's almost impossible to get a researcher to do what he or she does not want to do—researchwise. It's the researcher, not the company, who identifies the potential value of the research. And the value isn't in terms of money. Money doesn't matter."

But money does figure into NIH-industry collaborations. A licensing agreement may require a company to pay an initial fee for the license, a yearly fee on an active license, and benchmark payments when clinical-trial success or FDA approval has been achieved. "It's mix and match," depending on the nature of the product, says Ferguson, OTT's point person in such negotiations.

If a marketed product actually emerges and generates sales upon which royalties can be assessed, the NIH cut varies depending on how much NIH contributed to its development.

Examples of a "high-rate" product, Ferguson says, are polyclonal antibodies or antisera sold as research reagents—which NIH typically makes and presents to companies as a finished product needing only to be tested, packaged, and distributed. In the case of a monoclonal antibody, in contrast, NIH provides the cell that secretes the antibody, but the company carries out purification and quality-control operations. The NIH cut would be lower in such cases.

But even "high rate" returns won't make NIH wealthy: 8% is pretty much the pinnacle of NIH reward. Royalties range from 1% to 5% for a diagnostic product and from 3% to 8% for a therapeutic product, Ferguson says. (Royalties are dispersed by a formula to NIH and the individual inventors their ICDs; see "Divided Royalties," page 8.) NIH royalties, Freire says, "are never crippling to the cost of the product," an outcome that would run counter to NIH's main concern—and NIH's Technology Transfer Act mandate—that taxpayer-supported biomedical discoveries find their way to the public bedside. ■

# Brainchild Without Patent Yields Anybody's Antibodies

Bob Wenthold's Laboratory of Neurochemistry at NIDCD was one of the first three labs, in 1989, to clone a member of the brain's ubiquitous glutamate receptor family. In 1990, Wenthold made the first antibodies to these receptors—a feat that coupled his name with "neurotransmitter antibodies" on the exclusive list of commercialized NIH inventions that attracted more than $100,000 in annual sales in 1995 (see "NIH Inventions chart," page 6). Unlike many NIH inventions, however, this one became a commercial success without benefit of patent.

Instead, the NIH Office of Technology Transfer negotiated a nonexclusive license with a private partner, and Wenthold's antibodies went on the market at a relatively modest price.

Fran Pollner

*Bob Wenthold*

Wherein, then, lies the product's commercial cachet? "Essentially every neuron in the brain expresses at least one of these receptors, and most express many. So anybody studying any aspect of the brain is going to be interested in glutamate receptors," says Wenthold. Not only is glutamate the major excitatory neurotransmitter, he points out, but it's also neurotoxic in excess, figures in current models of learning and memory, and has relevance to the auditory system, which is why his lab was studying it in the first place. "And you cannot study the protein directly if you just have the structure of the gene; you can only project," he says. What's needed to study the way the protein works are antibodies to specific parts of the glutamate receptors, which is what is his lab made.

"And we got lucky," he adds. "It's not always the case that the antibodies work, but we obtained a number that have worked very well for us—and for many other people. An antibody is an extremely useful reagent, and they're often hard to come by. You write people, begging for antibodies, and if you're lucky, you get them. We published a first little paper in 1990, and a major one in 1992, and I started getting hundreds of requests because it's much better to get a proven antibody from somebody else than to try to make it yourself. We sent out some, but we just couldn't keep up."

Licensing the product to a private partner through the Office of Technology Transfer was the obvious way to go, and although ensuring the quality of the new product was more time-consuming and painstaking than he'd anticipated, eventually "things smoothed out, the product became widely available, and it's helped the field a lot."

It also helped his lab, he says, searching his computer screen for a record of items bought with the royalties the laboratory received. "Most of the NIH portion of the royalties comes back to the lab here. I think that varies from institute to institute, at the scientific director's discretion . . . but in our case, it comes back here, and that's been very useful. Just last year, we got some equipment for anatomical studies we couldn't have gotten before—to localize receptors by freeze substitution using colloidal gold. It looks like over $30,000 went to that."

But Wenthold considers 1995 an "unusual" year—the first year the product was "really out there and with no competition." He predicts that royalties will diminish now that about a dozen companies are filling the market with rival products. Since the license is nonexclusive, however, collaborative arrangements with other companies could also be in the offing for his lab, which, Wenthold notes, would spread not only the wealth but the science, "which should be the way science is done, especially at NIH."

As for his personal portion of that wealth, "it hasn't been that much. I didn't trade in my Honda for a Mercedes, or anything like that," he says. His own research on the distribution of glutamate receptors and the regulation of their expression continues, uninfluenced by the lure of further commercial potential. ■

*—Fran Pollner*

# Two NIH Inventors And Their Just Desserts

*by Fran Pollner*

The "fecalator" and "laser-capture microdissection" may be worlds apart in complexity and cost, but both sprang from a scientist's need to target and capture the invisible mechanisms of disease so they can be deciphered and disarmed. And both earned patents for the NIH scientists who invented them.

The 17-year patent on the fecalator expired in March 1995, but it still kept its place on the PHS top moneymaking inventions list (see "Inventions" chart, page 6) that year, despite the fact that each fecalator costs less than a dollar. Millions of these devices are used the world over to recover parasites from stool specimens.

The patent application for laser-capture microdissection was filed in November 1996 and was scheduled to be issued three months later, as this issue of *The NIH Catalyst* went to press. According to its inventors and the NCI technology development officer who handled the filing, laser-capture microdissection will revolutionize diagnosis and treatment and will become a critical component of every clinical pathology lab in the world. The first-generation, no-frills prototype machine costs about $50,000 and is used to extract, precisely, just the relevant cells from a tissue sample being probed for disease.

### *Prospecting for Parasites*

Two decades ago, Willadene Zierdt built a better parasite trap; a patent was issued in her name March 28, 1978. She's still getting royalty checks, twice a year, and her latest was the "biggest payment ever"—about $3,000.

Zierdt, who retired in 1993, ran the Clinical Center parasitology lab for 25 of her 35 years there. Her invention, which she dubbed the "fecalator," yielded a hundredfold increase in parasite recovery from stool samples compared with direct examination methods and afforded better protection from these parasites for laboratory personnel.

Fran Pollner

*Willadene Zierdt displays the invention used the world over that earned her a U.S. patent (certificate shown) and decades of royalties.*

The impetus for developing the new apparatus, Zierdt recalls, was a disconnect between specimen yield and the severity of illness in the patient.

"These were sick people, and I knew that we were not recovering all the parasites we should have been recovering," she says. The problem was the use of a nearly century-old method of straining specimens through a gauze-and-funnel apparatus in an attempt to concentrate parasites. "I started sifting through the debris that remained on the gauze and I made dozens of little smears and, sure enough, kept discovering more and more parasites that had been missed." The gauze, Zierdt realized, would have to go.

She puzzled over what sort of nonadherent material she could use to replace the gauze and hit upon stainless steel. She cut out and tested about 20 different stainless steel mesh screens before settling on pore dimensions that let the parasites through while holding back fecal debris. She put the screen between two plastic test tubes that coupled together, then added a small plastic pipe to the top tube where the fecal samples are placed in the device. (The pipe aerates the formalin-washed specimen, enabling the parasites to drip through the mesh screen and concentrate at the bottom of the second plastic tube.) Zierdt taped the pieces of her prototype apparatus together and named it a "fecalator" because it reminded her somewhat of a percolator. Staff in the NIH machine shop glued the pieces of her invention together and made a few more of them. All in all, the fecalator was close to two years in the making.

"I was just trying to help myself do my job. I never dreamed this would become what it became," Zierdt says, recalling that it was the clinical pathology chief who advised her to visit the NIH patent office. After she'd secured her patent, the Department of Commerce requested that she entertain offers from businesses to commercialize the apparatus, and before long, a license was negotiated and the Fecal Parasite Concentrator™ was born. Although the patent was issued for the "fecalator, an apparatus and method for concentration of parasite eggs and larvae," the manufacturer did not like her quaint term and renamed the

### *Divided Royalties*

According to a law passed last spring, the first $2,000 in royalties is shared among the inventors; beyond that, and up to $150,000, at least 15% must go to the inventors and the rest to their institutes. NIH has modified this formula to be a bit more generous to the individual inventors. To wit:

- The first $2,000 is shared among the inventors.
- Beyond $2,000 and up to $50,000, 15% goes to the inventors.
- Beyond $50,000, 25% goes to the inventors.
- Once an inventor receives $150,000, he or she gets no more royalties—for that year.

Notes Maria Freire, director of the NIH Office of Technology Transfer, "some people argue that if those inventors were working in a different setting, they could be making millions. But these are federal scientists," she observes, "and their mission, their mandate, their interests are not driven by money." ■

product. The commercial device, manufactured with a screen made of no-stick plastic instead of stainless steel, is disposable. Sales, Zierdt says, have increased each year the product has been on the market. "It's quite a popular item, and hasn't been surpassed by anything else. It's sold around the world and is especially useful in developing countries—it's inexpensive and doesn't require electricity," she says.

The fact that it's disposable not only guarantees presumably perpetual sales but also contributes to enhanced safety over the previous apparatus, as does the placement of the screen within the device.

Zierdt's royalties, which she saves for her children, keep coming in, despite the patent expiration—and she still visits the Clinical Center Microbiology Service frequently, often supplying the desserts for celebratory occasions.

### *Capturing the Disease Process*

The driving force behind the invention of laser-capture microdissection was an urgent research need in NCI's Laboratory of Pathology.

"Imagine having the ability to look under a microscope at a disease process, to sample different cellular elements within that disease process, and then place the RNA or DNA from the samples onto a microhybridization system so that thousands of genes can be tracked. . . . We usually diagnose and treat cancer when it's too late. The real opportunity, in the understanding of the genetic basis and somatic progression of cancer, is in looking at premalignant lesions, at the progression from normal epithelium to in situ cancer. We would like to be able to sample each stage of this progression . . . and look at all the genes that are associated with the transition from one step to another. . . . We need a method to microdissect out these cellular elements of interest."

And that method, said Lance Liotta, chief of the NCI Laboratory of Pathology, to a rapt audience on Clinical Research Day, February 10, was on display, right outside the auditorium in one of the hallways filled with posters showcasing clinical research at NIH: laser-capture microdissection.

During his lecture, Liotta showed examples of laser-captured cells: neurofibrillary tangles from the brain tissue of Alzheimer's patients and premalignant lesions of breast carcinoma in situ. "Now," he said, "these individual cellular groupings can be analyzed for RNA, DNA, and protein." He noted, particularly, the utility of microdissection to analyze loss of heterozygosity in premalignant breast lesions and singled out the extraction of RNA—and with it the ability to develop cDNA libraries and to discover "previously unknown expressed genes that might be associated with that . . . [as] probably the most important advance that can be supported by microdissection." This approach, he said, is being used by Michael Emmert-Buck and David Krizman at NCI to study prostate cancer.

Fran Pollner

*Lance Liotta*

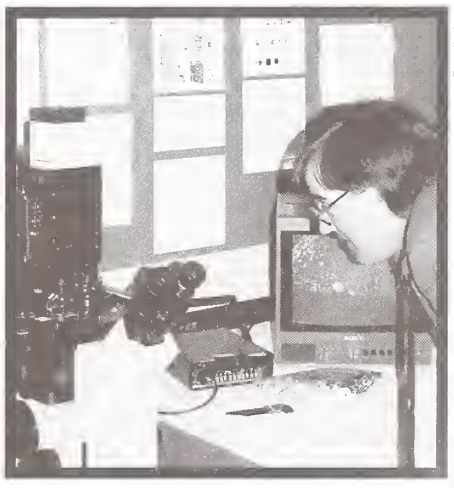
In laser-capture microdissection, described by Emmert-Buck et al. in the Nov. 8, 1996, issue of *Science*, a thin, transparent, laser-activated film is placed on top of the tissue being studied. Watching via direct microscopy, the researcher procures individual cells by spotlighting them with a laser, inducing the film to stick to just the selected cells. The film with its quarry is removed from the tissue and transferred immediately to appropriate buffers for analysis.

In a booth outside the auditorium, crowds of curious scientists got a chance to see for themselves. Similar excitement was sparked by a demonstration of laser-capture microdissection at the February meeting of the National Cancer Advisory Board when NCRR's Robert Bonner demonstrated the technique there. Bonner heads the instrument-development team for the technique and has produced four generations of laser-capture microdissection prototypes.

"This is probably going to be huge," predicts Gary Colby, senior technology development and patent specialist at the NCI Office of Technology Development. Colby, who is handling tech transfer for laser-capture microdissection, notes that the imminent patent is but one of several anticipated in connection with this invention. Other patents will cover particular aspects of the process and machinery and wide-ranging aspects of its use. The number of inventors on these patents ranges from six to more than a dozen people, including staff in the NCI lab and in NCRR's Biomedical Engineering and Instrumentation Program, Colby says. For Liotta, the laser-capture microdissection patents are but the latest in a succession of more than 60 patents, dating back to 1973 and including toys, cell lines, genes, proteins, and diagnostic methods.

The first of an anticipated series of laser-capture microdissection CRADA collaborations with commercial developers has already begun. A demonstration project is being launched at Johns Hopkins, after which the instrumentation will be tested at multiple sites around the country. Patent applications are pending in countries around the world. Prototypes should be available for use at NIH by late summer.

"Every lab is going to need this," Colby says. ■



Fran Pollner

*Laser-capture microdissection: a main attraction on Clinical Research Day.*

# THE CAPSAICIN STORY: SOME LIKE IT HOT

For Peter Blumberg, coming up with a better birdseed while investigating a compound that acts on neurogenic inflammatory pathways is not serendipity.

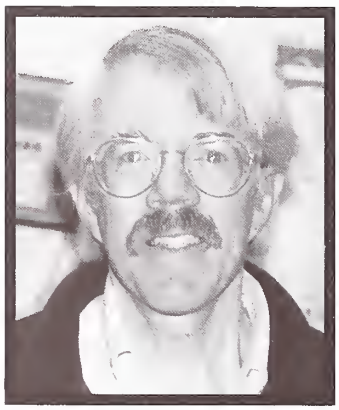
"Serendipidity suggests that one stumbles on something by chance, but in discovery research, which is the core mission of NIH, one does not simply start with a problem and try to come up with a solution," says Blumberg, an NCI section chief whose group explores the molecular mechanisms of tumor promotion. An integral part of discovery, he says, is recognizing when one's findings represent a solution to a problem that is not on one's list of problems to be solved. A second key element is appreciating that this solution might well be translated into a product—and alerting the Office of Technology Transfer to that possibility.

Blumberg has had frequent interactions with the OTT in the course of his long-term studies of phorbol esters—tumor-promoters derived from medicinal plants in the poinsettia family (Euphorbiaceae) first described in 40 BC by Euphorbus, court physician to King Juba II of Mauritania. One structurally related compound, called resiniferatoxin, which proved highly potent in a screening assay (the ability to turn rodent ears red) for this class of tumor promoters, also proved to have a different mechanism of action from others of its class. "Because of its extraordinary potency and our sense that it could not fail to tell us something important about inflammation, we tried to identify its target, and we found that it acted the same way as capsaicin, the hot ingredient in red peppers," Blumberg recalls.


*Peppery, squirrel-repellent birdseed adorns the garden-supply shelves at a Hechinger's store in Maryland.*

That was the first step in the creation of one of NIH's more unlikely inventions: squirrel-proof birdseed.

The second step emerged during a species-specific hunt for receptors to the capsaicin-like compound: it turned out that mammals had the receptors; birds did not. Voilà!



Fran Pollner

*Peter Blumberg*

"As the owner of a horse farm," Blumberg says, "I know the kinds of problems animal people have, and squirrels eating birdseed is one of them." And as a laboratory scientist, he reasoned that birds would eat capsaicin-coated birdseed, blissfully unaware of its fiery qualities, while rapacious squirrels would back off.

Aside from its squirrel-deterring qualities, capsaicin is therapeutically interesting, first activating and then desensitizing C-fiber sensory neurons involved in pain perception and neurogenic inflammation. Resiniferatoxin, Blumberg says, acts like capsaicin but preferentially causes desensitization, giving it a "much more attractive spectrum of activity for therapeutic applications," a discovery made early in the course of his group's research.

In fact, birdseed is the subject of but one of the 12 patent applications Blumberg's research has generated, five of which have already been licensed to private industry. Three of these five are related to the clinical development of resiniferatoxin and its homologues and have been licensed to a company that is now testing them for clinical use against diabetic neuropathy, postherpetic neuralgia, vasomotor rhinitis (and possibly allergic rhinitis), and urge incontinence. The compounds act as an analgesic against neurogenic pain and desensitize hypersensitive nerve pathways that disrupt bladder function.

Potential clinical applications in the care of cancer patients are numerous, including reducing the discomfort of cancer-drug–induced mucositis, cystitis, and emesis; and relieving postmastectomy and other surgically induced neuropathic pain.

Blumberg feels technology transfer of his inventions has worked very well, reaping royalties for NIH and the inventor from the time of issuance of a license, even before any products are commercialized. (In the case of the birdseed, which is already on store shelves, the patent is still pending.) He also feels product development is better left to the private sector. His birdseed was licensed to a former postdoc who founded a company "specifically to license and exploit this government invention." Similarly, the company that licensed the other patents was formed by "scientists with entrepreneurial interests, one of whose principals had been at NIH years earlier, was an authority on capsaicin, read our first publication describing the spectrum of resiniferatoxin activity, and recognized, as we had, the exciting therapeutic possibilities. Both of these are examples of the spinoffs of government research leading to initiatives in the private sector."

Commercialization of his discoveries has not altered Blumberg's own career and research choices. "I came here because I thought the opportunities for doing research at NIH were even more exciting than the obviously very good opportunities I had had at Harvard Medical School. NCI is the foremost institution in the world for cancer research, and, so far, I've been able to afford to remain here."

Nor have royalties altered his standard of living, "it's really not very significant," he said. "I've earned $24,000 in royalties over the total number of years I've been here, since 1981. So this is not going to buy me too many horses.

"On the other hand," he added, "a lot of these patents are still in the early stages of development." ■

*—Fran Pollner*

# CyberSites For Biomedical Research

*by Dale Graham, Ph.D., DCRT*

The WorldWideWeb Interest Group (WIG), in response to a request from *The NIH Catalyst*, has put together a list of sites of various kinds relating to NIH's mission. The last article on this topic focused on clinical medicine sites. This one focuses on biomedical research sites.*

This article didn't start out pointing predominantly to NIH resources to help you harness the web to work for your research goals, but it ended up that way, based on the effectiveness of these NIH sites for campus researchers. NIH itself, naturally, has a powerhouse of sites useful to researchers, and some of the resources are accessible only from an NIH computer or a Parachute (NIH remote internet access) account. Such sites are referred to as "NIH access only," which means that you will not be able to access them from an Erol's, AOL, or any other non-NIH account. The biomedical sites list at the end of this article at

**<http://mantis.dcrt.nih.gov/Sites/Sites.html>**,

however, includes uniform resource locators (URLs) pointing to sites around the world.

Need to find literature information online? A terrific tool, Medline, can be searched on the web. The URL for "Internet Grateful Med" is

**<http://igm.nlm.nih.gov/>**.

This site can be accessed from any location, provided you have an account and password.

The NIH Library has a whole series of journals (full text!!) for NIH-only access, including clinical journals, as well as those oriented to basic research, such as the *Journal of Biological Chemistry*. From there, navigate to Online Resources. This raft of goodies can be reached at

**<http://libwww.ncrr.nih.gov/>**,

with a point-and-click at Online Resources. If you want the most up-to-date references, Current Contents can be found online (again, this is NIH-only access) from the NIH site at

**<http://www.nih.gov/science/library.html>**.

The web represents a vast repository of information, especially databases of sequence information and the like. Don't be shy about using a search engine to find specific kinds of information, in addition to visiting some of the recommended sites. Two good choices would be either AltaVista at

**<http://altavista.digital.com/>**

or Excite at

**<http://www.excite.com>**.

Don't neglect, either, to use the search engine on the NIH Home Page—

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

—if you are interested in information or resources that might be found closer to home.

Much research data, however, is kept stored in databases (and thus is invisible to search engines) and can only be accessed at the site housing the database. In that case, you can try to visit the most appropriate site. For example, the best site for up-to-the-minute GenBank data is the one for the National Center for Biotechnology Information, where GenBank databases are maintained. That home page also has links to numerous other useful tools created or maintained by NCBI, such as Entrez, Blast, and the like. The URL for this site is

**<http://ncbi.nlm.nih.gov/>**.

What makes the web especially rich for researchers, though, is the incredible array of analytical tools available—either at work or at home (assuming there's internet connectivity at both places)—at no cost whatsoever. Some tools are NIH-access only. One such site is GCG Lite, developed by DCRT's Peter FitzGerald. It offers much of the power of GCG with none of the pain! Try it, you'll love it. Its URL is

**<http://molbio.info.nih.gov/molbio/gcglite/>**.

Another such site is the recently developed MMIGnet (molecular modeling resources for the campus) at **<http://cmm.info.nih.gov/MMIGnet/>.** This site was developed by Bob Pearlstein as an NIH-only adjunct to his immensely popular Molecular Modeling site, which has worldwide access at **<http://cmm.info.nih.gov/modeling/>**.

If you need to reformat sequences for use with GCG Lite, visit another DCRT site, maintained by the BioInformatics and Molecular Analysis Section, which not only has the reformatting tool online (READSEQ), but also has specialized tools for sequence analysis, such as searching for transcription factors, HLA binding sites, etc. That address is **<http://bimas.dcrt.nih.gov/molbio/>**.

Lists of more research resources available on the web can be found on the following two pages:

**<http://molbio.info.nih.gov/molbio/>**

and

**<http://mantis.dcrt.nih.gov/Publications/Internet_Talk/Tools/Tools.html>**.

The main list (as provided by WIG members) contains more than 60 research sites and more than 60 sites pointing to online publications. The clinical list is also available at this cyberscience web site:

**<http://mantis.dcrt.nih.gov/Sites/Sites.html>**. ■

*Special thanks for their many suggestions go to DCRT's Roger Fajman and Tim Oliver.

## *At Your Service*

***Custom Programming***

Customized programming services are now available from Science Applications International Corporation (SAIC) and Systems Research and Applications Corporation (SRAC), under two new multiyear DCRT contracts. Expertise in scientific computing is available in the following disciplines: molecular modeling, sequence analysis, structure analysis, time-series analysis, neural-network modeling, combinatorics, probability theory, simulation, image processing, computational chemistry, and statistics. For more information, send an e-mail message to <ITSS@exchange.nih.gov>.

***Scientific CyberShopping At the NIH Intramall***

Coming soon to a computer near you. . . The NIH Intramall hopes to open its web site this spring, bringing you the ability to order your scientific supplies over the web. Multiple-vendor catalogues, item descriptions and pricing, a built-in item-search feature (just click for competitive pricing information), and electronic ordering, order tracking, automated reconciliation, and generation of procurement and budgetary trend reports are among the system's features.

Although anyone at NIH will be able to assemble an Intramall order basket, only actual IMPAC/VISA purchase card holders will be able to place orders through the mall. If a credit card is not available to the orderer, the purchase request can be sent electronically to his or her local purchasing agent for processing by traditional purchasing procedures. If a particular order cannot be secured by credit card or requires additional approval or clearance, it will automatically be forwarded to the designated approving official for action. For more information, contact Jeffrey Weiner at 496-7058. ■

# Just Ask!

**Dear Just Ask:**
Does anyone know of any programs that could use donations of used scientific journals?

*—Suzanne Miyamoto, NHLBI*

**Dear Dr. Miyamoto:**
We've all seen piles of journals being thrown out of offices and labs as people clean up or move, and many of us have wondered whether some worthy recipient can't be found for them. As it turns out, there are several organizations, some right here at NIH, that collect old books and journals and ship them to needy institutions in this country and abroad. But before you start packing them up, here are some caveats. . . .

If you have a large pile of 10-year-old issues of the *Journal of Somethingerother*, *don't* ship them off to any of the addresses listed below. Almost all the organizations require preapproval before they accept shipments. The best approach is to contact the organization, give them a list of your journals, and get their consent before sending them anything. Since these organizations generally work on shoestring budgets and have very little space, flooding them with unwanted boxes of journals is probably not a good idea!

If the journals are your own (i.e., you paid for them), the procedure is relatively simple. After the organization agrees to your shipment, pack up some boxes and send them off. In most cases, you are responsible for the postage/shipping, but some of the organizations listed are in this area and will accept dropoffs by car. NIH funds can't be used to ship personal donations.

If the journals were bought with NIH money, they may still be donated under some conditions, but you need to get permission from the Personal Property Branch, Division of Logistics, Office of Acquisitions. Here's some information about the procedures involved:

**— For donations within NIH (for example, to an NIH library).** A Transfer Form 649 is required, and such donations are treated like any other property transfer between ICDs.

**— For donations to domestic institutions.** The bad news is that NIH does not have the authority to make gifts or donations to domestic institutions. Only GSA can authorize this. For such donations, a memo describing the journals and their value, and including the name and address of the contact person (the donor), should be sent to Dave Talley, Section Chief, Utilization, PPB. PPB will process this through GSA. After permission for the donation has been obtained, the recipient organization is responsible for the postage/shipping costs.

**— For donations to foreign countries.** According to a PHS act, such donations can be made when the participating organization, institute, or individual in a foreign country is connected (through a collaboration, for example) in some way with NIH research. In this case, the donation is considered to be beneficial to the U.S. government and will be permitted. Form 2489-1, Record of Loan/Donation of Personal Property to Foreign Countries, must be completed and sent to Building 13, Room 2E65. Paperwork processing is expected to take about two weeks. The recipient organization is then responsible for the postage/shipping costs.

If this sounds like a lot of paperwork, the good news is that the current rules for such donations should be simplified soon, so if you are considering donating NIH-owned journals or books, check the latest regulations with Dave Talley (496-5712) for domestic donations and Dan Reggia (496-4248) for foreign donations.

If you donate your own journals, you may be able to deduct the cost as a charitable contribution if it is made to a qualified organization.* The organization can tell you if it is qualified and if donations to it are deductible. You need to file Form 1040 and itemize the deductions on Schedule A. You need to fill out Section A or Form 8283, if your total deduction for all noncash contributions is more than $500. If the journal subscription is part of membership to a professional society, you cannot write off the journal donation if you are already deducting your professional dues as a business expense. If you plan to take a tax deduction for your charitable contribution, you need a dated and signed receipt as a record of the donation. For more information, see the IRS web page at
**<http://www.irs.ustreas.gov/plain/tax_edu/teletax/tc506.html>** and
**<http://www.irs.ustreas.gov/plain/tax_edu/faq/faq9.html>.**

In researching this "Just Ask" question, we sent a query out to the subscribers to NIH's famous Fellow's Listserv list (Fellow-L). We thank the numerous people—including scientists who had earned degrees or done fieldwork abroad—who suggested particular institutions that need book or journal donations. Unfortunately, we don't have space here to include these responses, but that information can be obtained from me (see my address at the end of this article). Potential donors who would like to send their own personal journals to a particular institution but can't afford to pay the shipping

Celia Hooper

*Susan Chacko*

costs should contact the recipient institution to find what they need and what (if anything) they can afford to pay for the shipping costs. If you don't have the funds, consider contacting one of the organizations listed here and getting the institution added to its recipient list. Another possibility is contacting the country's embassy (a list of embassy locations, phone numbers, and home pages is at <http://www.embassy.org/embassies/eep-1100.html>) to ask if they already have a donation program or if they can help with the cost of shipping and postage. Rotary Clubs sometimes have book-donation programs; contact the local Rotary for more information.

The African Studies Association provides some funds for groups of individuals to ship reading materials to African libraries and schools. It can be reached at (404) 329-6410 for more information.

Professional organizations such as the American Chemical Society and the American Physical Society may also have donation programs; contact them to find out more.

The American Council for Learned Societies has a manual, available online at <http://www.indiana.edu/~oah/acdsman.html>, for international book and journal donations. Some of the information there may help you in setting up your own journal-donation program, if none of the organizations listed below meets your needs.

**Organizations that Accept Donations**

- Gloria Rasband is starting the EPS library at NCI in Rockville. She is particularly interested in books and journals related to cancer, epidemiology, statistics, and biostatistics. The journal list is available online at <http://www.dcpc.nci.nih.gov/EPS_Library/journals.html>. Potential donors should contact her by phone at 496-8646 or e-mail at <gloria@helix.nih.gov>.
- The NIH Library may be interested in specific journals to fill holes in their collection, as well as in recent books. Contact Jean

Wyse (496-3541) or Susan Whitmore (496-1156).

• The Minority College Program at NIH, now in its 18th successful year, accepts all scientific journals (paperbacks less than 5 years old, hardbacks less than 10 years old) and ships them to high schools and colleges in the United States and Puerto Rico. Journals are accepted by appointment only, and the EEO office pays for postage and shipping to the colleges. Call Sandra Thomas at 496-6266.

• The World Bank Book Project ships used books (less than 10 years old) and journals (less than 5 years old) to many underdeveloped countries. They are particularly interested in reference books, such as encyclopedias and dictionaries. A phone call—(202) 473-8960—to discuss your donation before dropping it off is highly recommended.

Donations of 10 or fewer boxes may be dropped off at their loading dock at 1775 G Street, N.W., Washington, D.C., between 10 a.m. and 2 p.m., Monday, Tuesday, and Wednesday. Larger donations may be sent to their Maryland warehouse. Call (301) 390-4317 and ask for Dave.

• Bridge to Asia takes common scientific journals, such as *Science* and *Scientific American*, for shipment to China and Indochina. Journal runs should be continuous, reach the 1990s, and span 20 years or more. Donors pay for the postage to Chicago. See their web page at <http://www.bridge.org/ Books.html>.

• The Brother's Brother coordinates distribution of scientific textbooks and journals to the Philippines, East/Central Europe, Africa, and the Americas. They work with other agencies to distribute materials in countries where they do not have a program. The donor pays for shipment to Pittsburgh. Call them at (412) 431-1600.

• The Sabre Foundation, a tax-exempt, charitable organization, provides books and journals to Eastern Europe and the former Soviet Union. It is in the process of establishing programs in Ghana, Grenada, South Africa, the West Bank, and Gaza. Scientific, medical, or technical materials should have publication dates within the last five years, and journals should be consecutive runs. You'll need to fill out their donation form and fax it to them. Donors pay for shipping to a U.S. warehouse. For more information, see <http://www.sabre.org/SAP/book.journal.html>.

• Donations to Argentina are coordinated by Lucio Castilla with the Argentine Embassy. Contact him by phone at 435-2252 (Building 49, Room 3C28) or e-mail at <lucioc@nchgr.nih.gov>.

• The Nigerian Universities Office, at the Nigerian Embassy, coordinates donations to Nigerian universities. All university-level books and journals, less than five years old, are acceptable. Donors can request specific institutions in Nigeria. Donations can be dropped off at the embassy. Send inventory to Barbara Bundy, NIO, Embassy of Nigeria, 2010 Massachusetts Ave., N.W., Suite 400, Washington, DC 20036; phone: (202) 659-8113; fax: (202) 659-8116.

• The Sudan-American Foundation for Education ships to Sudanese universities. Most books in all disciplines and consecutive runs of journals not more than 5–10 years old are acceptable. Donors are responsible for delivery to Arlington, Va. Contact Lee Burchinal at (703) 525-9045.

• The American Psychological Association Office of International Affairs coordinates donations of books and journals to 143 institutions around the world. Make a list of the journals you want to donate. E-mail it to Marian Wood at <mzw.apa@email.apa.org> or fax to (202) 336-5919. Lists are forwarded several times a year to their prospective recipients, who contact the donors directly. Donors send the journals directly to the recipients, and postage/shipping is ordinarily paid for by the recipient institutions unless the donor agrees to pay.

• 1,000 Books for México, a program set up by a group of Mexican students, accepts textbooks for undergraduate and graduate education. English or Spanish texts are welcome. Journals are not desired because of limited space. Donors pay the cost of shipping to Mexico. For more information, see the web page at >http://www.udg.mx/udg/academico/donacion.html>. If the cost of shipping is a problem, contact Arti Patel, NIEHS at (919) 541-3241 or <patel1@niehs.nih.gov>, who may be able to help.

• The Association of Scientists of Indian Origin in America, with the Indian Embassy, organizes donations to India. They currently ship to nine medical institutions in India. Make a list of the journals and books (all journals welcome, but books from the last 10 or 20 years only) and fill out their donation form. Donors pay for postage and shipping to New York. Contact me, Susan Chacko at <susanc@helix.nih.gov>, 435-2982, or Building 12B, Room 2017, to get a copy of the donation form or for more information.

*—Susan Chacko*

*All tax information presented here is meant only as guidelines; for a definitive answer to tax questions, contact the IRS or a tax consultant. ■

## *A Parking Message*

As everyone is aware, parking on campus has recently become tighter. NIH's success in securing the necessary funds for a series of projects to improve building and campus infrastructure and to expand our research and clinical facilities has resulted in many of the difficulties you are experiencing in getting around and parking on the campus. Since federal parking policies limit the amount of parking we can provide on the campus, the Office of Research Services, in concert with other NIH offices and employee groups, is working on creative short- and long-term measures to minimize the impact of ongoing and future construction projects.

These include increased leasing of off-campus parking spaces with enhanced shuttle bus service to the campus, increasing TRANSHARE and carpool participation (for example, NIH is requesting legislation in FY 1998 to make IRTAs and visiting fellows eligible for the subsidy), and expanding the privatization of parking management, similar to that occurring in the ACRF garage. The latter would include a fee for parking for visitors and service contractors to cover the cost of a contract-operated system and to fund more effective shuttle service. Under this proposal, visitor parking would be consolidated in a few attendant-controlled locations. Attendant-assisted parking could be expanded to employee lots to increase the capacity of the existing parking facilities.

The problem of parking and transportation, however, cannot be addressed by NIH management alone. It will require all NIH employees working together toward the common goal of building a better NIH. Your ideas and input are welcome. The NIH Parking and Transportation Working Group (P&TWG) is soliciting additional members to work on these issues. Please e-mail Acting Chairman Tim Wheeles (<tw36t@nih.gov>) with your ideas.

The Office of Research Services will be starting a new web page in the next few weeks that will provide detailed information about campus construction activities, their impact on circulation and parking, and parking mitigation measures as they are introduced. In the meantime, the P&TWG web page discusses off-campus parking, shuttle service, TRANSHARE subsidies, ride sharing, etc., at <http://www.nih.gov/od/ors/parking/parking.htm>. Alternatively, you can call the Employee Transportation Services Office at 402-RIDE for more information. ■

*—Steve Ficca, Office of Research Services*

# "Cool" Methods Clinic*: Molecular Interaction Analysis Using Surface Plasmon Resonance

A new category of biotechnology—molecular-interaction analysis using surface- plasmon resonance—is increasingly picking up steam and has been drawing mounting interest worldwide since its introduction in 1990. This class of techniques exploits changes in the behavior of light at boundaries of different refractive indices to detect the concentration and mass movement of biomolecules. Analytical instruments designed around the optical phenomenon detect surface-plasmon resonance (SPR) and yield sensitive, radioactive-label-free measurements of biospecific interactions in real time.

SPR signals in these instruments are generated by changes in the refractive index of a solution close to the surface of a specially coated sensor chip. The changing refraction of the boundary layer solution is directly related to the concentration of solute and molecular interactions taking place on the surface of the chip, where one of the system interactants is bound.

The new methodology is useful for studying a tempting variety of molecules, including proteins, peptides, nucleic acids, carbohydrates, lipids, and low-molecular-weight molecules, such as signaling ribonucleotides and therapeutic drugs. The specificity of the selected probe coated on the sensor permits direct analysis of biomolecules in complex mixtures, such as serum, tissue-culture supernatant, and membrane extracts, even without purification.

In the pharmaceutical and biotechnology industries, SPR is replacing earlier techniques for interaction analysis and beginning to provide some new kinds of information. For example, Schuster and co-workers have used SPR to demonstrate the functional formation on the sensor-chip surface of a tetrameric complex involving four components of the chemotactic signaling system in *E. coli*.[1] Other examples include identification of B61 as a ligand for the ECK[2], a member of a large orphan receptor protein–tyrosine kinase family headed by EPH, and measurement of T-cell-receptor affinity and thymocyte-positive selection[3].

The first step in SPR analysis is immobilization of one of the interactants in a dextran matrix on a sensor chip, which forms one wall of a micro-flow cell. Immobilization can be achieved using a range of chemical techniques, such as direct amine coupling or ligand capturing. The machine then injects samples containing the other potential interactant(s) over the surface of the chip in either a controlled flow or stirred-cell–type system. Any changes in surface concentration resulting from the interaction between the immobilized interactant and a component of the bulk solvent sample generate an SPR signal, which is expressed in arbitrary units, called resonance units (RU). One RU is proportional to 1 pg of mass per square millimeter of surface area. The continuous display of RU as a function of time, referred to as a sensorgram, tracks the progress of interactants' association and dissociation. When analysis of one interaction cycle is completed, the sensor-chip surface can be regenerated by treatments that remove any bound analyte but don't affect the activity of the immobilized ligand.

Major advantages of SPR over other techniques for detecting and measuring interaction include label-free detection and real-time monitoring. Label-free detection means that practically any interactant can be studied, often without having to purify it in advance. Real-time measurement allows investigators to monitor the association and dissociation processes extremely closely—down to a time resolution of 0.1 s—thus providing a kinetic description of the interaction that is seldom possible with other existing techniques such as colormetric, fluorometric, or Scatchard plot analyses.

Several companies have been active in developing SPR-based technology†. Biacore, Inc., (formerly Pharmacia Biosensor) first introduced a commercial instrument exploiting this technology in 1990 and currently has two instruments on the market—the BIAcore 1000 and BIAcore 2000. These systems use a carboxymethylated dextran surface for the standard chip, to which ligand is then coupled, usually by amine coupling. This chip then forms one surface of a flow cell, and solute containing the second ligand(s) is allowed to flow across the chip. These systems offer an alternative to direct coupling, known as ligand capture, in which the surface is first coated with an immobilized capturing molecule (such as a specific antibody or streptavidin) that selectively binds the first ligand of interest. Recent adaptations of this approach include use of nickel ions to capture His-tagged recombinant proteins.

Amersham International, PLC, has been developing SPR-based immunotechnology that uses antibodies labeled with latex particles (beads). The beads amplify changes in refractive-index properties of the sensor surface-solution interface that occur when the antibodies bind to the immobilized antigen layer. This technology is promising, provided that nonspecific interaction between latex-labeled antibodies and the sensor surface is minimal.

Serono Diagnostics is now developing a fluorescence-based evanescent-wave immunosensor that incorporates a novel capillary-fill design. The system consists of two glass plates separated by a narrow capillary gap of ≈100 nm. The lower plate acts as an optical waveguide and is coated with an immobilized layer of antibodies. Some fundamental drawbacks of this technology include low capillary flow for viscous samples, such as blood; the necessity of an incubation time of several minutes; and system-changeover costs. Unfortunately, each analyte to be tested requires a dedicated sensor—and this entails labeling and immobilization of antibodies on the plate prior to physical reassembly of the instrument.

The NCI Extracellular Matrix Pathology Laboratory has successfully incorporated SPR technology into several studies. For example, one area where SPR technology has been helpful is in understanding the interactions between gelatinases and their endogenous tissue inhibitors of metalloproteinases (TIMPs). Gelatinases A and B are two members of the matrix metalloproteinase (MMP) family. The MMPs are collectively responsible for the degradation of most components of the extracellular matrix. Gelatinases A and B degrade elastin, fibronectin, gelatin, and collagen types IV, V, and VII, and they have been closely associated with the invasive phenotype of many human tumors. Gelatinases are synthesized and secreted from cells as inactive precursors (progelatinases), and they have been shown to bind to TIMPs through the C-terminal domains of these two molecules. Because the activity and activation of gelatinases A and B are tightly regulated by TIMP-1 and TIMP-2, respectively, the exact mode of binding of TIMPs to gelatinases is of tremendous interest, as is their exact mechanism for inhibition of MMP activity.

We use the biosensor system to study systematically the kinetics of gelatinase-TIMP interactions. The interaction of surface-bound TIMPs with the progelatinases and gelatinases in solution is monitored in real time. Progelatinase A binds tightly to immobilized TIMP-2 with a rapid $k_{on}$ rate and a very slow $k_{off}$ rate. The $k_{on}$ rate for the active enzyme is approximately the same as that for the proenzyme, whereas the $k_{off}$ rates are different. The estimated association equilibrium constant for activated gelatinase A is $6 \times 10^9$ $M^{-1}$. As expected, TIMP-2 binds to activated gelatinase B with lower affinity and does not bind to progelatinase B. Unexpectedly, the association of progelatinase A with immobilized TIMP-2 was biphasic, and saturation binding is influenced by the free $Ca^{++}$ concentration. The kinetics of the binding of progelatinase A to TIMP-2 suggest that the enzyme possesses a single binding site with two binding states. This kinetic data from the SPR analysis suggest that the initial interactions between TIMP-2 and both progelatinase A and gelatinase A are identical, probably occurring by initial binding between the C-terminal domains of this inhibitor and enzyme pair. However, activation provides a binding site for the N-terminus of TIMP-2, resulting in tighter binding and a slower $k_{off}$ rate (A. E.

*by Anita E. Yu, Ph.D., NCI.*
*Robert Fisher, Ph.D., NCI,*
*and William G. Stetler-Stevenson, M.D., Ph.D., NCI*

Yu, R. J. Fisher, D. E. Kleiner, U. M. Wallon, C. M. Overall, and W. G. Stetler-Stevenson, unpublished observations).

Robert Fisher at the NCI-Frederick Cancer Research and Development Center and members of his lab have pioneered the design, interpretation, mathematical modeling, and global data-fitting of SPR data and have used this technology to study and model several systems, including the interaction of transcription factors with duplex DNA[4]. They find that by using SPR technology, appropriately designed experiments will yield information about stoichiometry of the components, association rate constants, and dissociation rate constants—even for very complex molecular interaction systems.

A serious drawback of the SPR technology-based instruments is the cost. For example, the approximate base price for BIA 1000 and 2000 are $155,000 and $235,000, respectively. (More information is available from the company's home page at <www.biacore.com>). Affinity Sensors (a division of the Thermo BioAnalysis Corp.) manufactures biosensor instruments and has a home page at <www.affinity-sensors.com>. Due to the popularity of SPR technology, almost all biosensor instruments on the NIH campus are heavily used. Interested individuals are encouraged to talk to one of the contact people below to find out more about instrument availability and the process for obtaining service or scientific applications.

Despite the cost, SPR technology offers many benefits and potentially has a wide range of applications, providing researchers with an avenue to data not otherwise easily approachable. Scientists who turn to SPR as a way to reduce their reliance on radioactive tracers may ultimately find that the technology gives them more than they bargained for and opens some new doors. ■

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*In response to the recommendations of the NIH Committee on Alternatives to the Use of Radioactive Techniques, *The NIH Catalyst* will now use its "Hot Methods Clinic" as a forum also for methods that do not rely on radionuclides. This is the first in what we hope will be a series of articles.

†Disclaimer: Mention of a specific product in this article does not constitute a commercial endorsement of that product, nor does it constitute a rejection of other techniques and products that may be equally effective but unknown to the author and editors of this article.

## *Joint Maneuvers At Frederick Research Festival*

This year, April showers bring May research festivals—the Ft. Detrick–NCI–Frederick Cancer Research and Development Center Spring Research Festival, to be specific.

This marks the first time the U.S. Army Medical Research and Materiel Command has teamed up with its civilian housemate to showcase the vast array of biomedical research in progress at the Frederick-based facilities. The event will take place on the "blue-gray field," just inside the Ft. Detrick gates in front of the main Army building, May 21 and 22, from 8:30 a.m. to 6:30 p.m., followed by public lectures geared to a lay audience each evening at 7:00 in Strough Auditorium.

Friday, April 4, is the deadline for poster submission by NCI-FCRDC scientific staff, (posters are being solicited from Frederick-based personnel only). Electronic poster registration is available at <http://www.ncifcrf.gov/FCRDC/conf/springfest>.

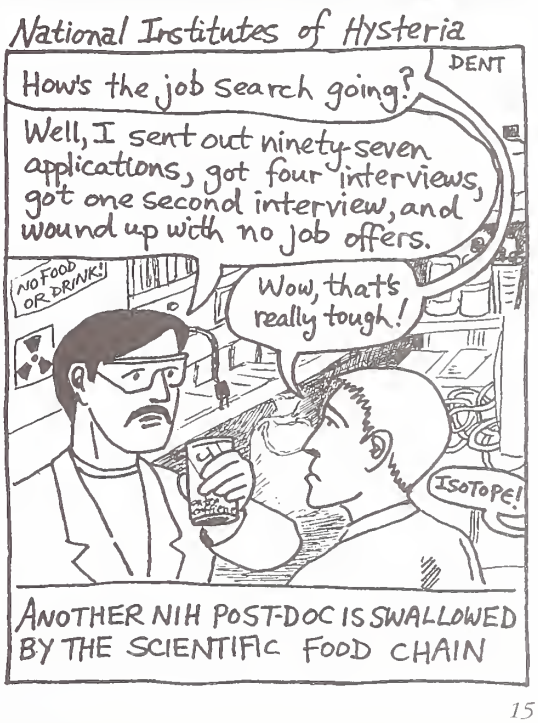
Events planned include

- *Scientific presentations.* Research posters will be on exhibit throughout the festival, with selected submissions scheduled as 10-minute talks during scientific sessions both days from 8:30 to 10:30 a.m. Four Young Investigator Awards ($100 each) will be given for the best posters presented by FCRDC students, technical support staff, and postdocs.
- *Student presentations.* Frederick County Middle School and High School Science Fair participants, as well as Werner Kirsten student interns at FCRDC, will be participating in the poster exhibit. An award will be given to the best poster by a Werner Kirsten student intern.
- *Other special exhibits.* Exhibits designed to demonstrate to both the scientific staff and local community the large number of different biomedical efforts under way at the Frederick facility will be sponsored by the Army, NCI, NIAID, the USDA, and SAIC.
- *Health fair.* The Safety and Environmental Protection Program, the Office of Occupational Health, and the NCI Office of Cancer Communications will offer health tips, advice, and information on cancer and AIDS.

For more information about poster registration or fair events, contact Howard Young: phone, 1-301-846-5700; e-mail, <youngh@ ncifcrf.gov>. ■

## *IL-12 Next Cytokine of Interest*

The NIH Cytokine Interest Group will hold its second 1997 minisymposium on May 13 at NCI-FCRDC (Frederick) in the Building 549 auditorium. The topic will be IL-12. Contact Howard Young at <youngh @ncifcrf.gov> for times and the FCRDC home page at <http://www.ncifcrf.gov> for directions. ■



# CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: the ramifications of the ongoing review of NIH intramural research programs, the proper role of patenting and commercialization in a government research facility, the impact of bans on research related to human embryos and cloning, and the ever-popular "Hot Methods Clinic." **Send your responses on these topics or your comments on other intramural research concerns to us via e-mail: <catalyst@nih.gov>; fax: 402-4303; or mail: Building 1, Room 334.**

***In Future Issues...***

- Stem Cells, Sequencing Find Campus Homes
- Bioethics and Bans
- Clinical Research: The Way Up

1) Do you think implementing the NIMH recommendations will restore a proper balance? Why or why not? Could other institutes benefit from some of these changes?

2) How prominently does the urge to "invent" figure in your own research priorities? Are NIH inventors rewarded appropriately—in recognition or payments? Are you satisfied with the mechanisms available to move NIH research from the lab to the market?

3) How do recent bans on the use of federal funds for research on human cloning and on certain types of human-embryo research affect NIH's research agenda? Do they affect your own research?

4) What's been your experience with the "cool" BIA method presented in this issue? Any suggestion—hot or cool—for a future "Hot Methods Clinic"?

The *NIH Catalyst* is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 334, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail:<catalyst@nih.gov>

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