

The NIH CATALYST

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ANTI-TAC TAKES OFF IN THREE DIRECTIONS

by Fran Pollner

Late last year, the Food and Drug Administration approved a new immunosuppressive agent to prevent graft rejection in kidney transplant patients. The agent was a "first" in several respects: It was the first humanized monoclonal antibody approved for use in transplantation; the first approved antibody directed against an interleukin receptor; and the first immunosuppressant to do the job without imposing drug-specific toxicity.

The drug sponsor, Hoffmann-LaRoche, named the agent Zenapax®. But to the people at NIH who have traveled the complete bench-to-bedside route with the antibody, it's always been known as "anti-Tac," short for its essential function—anti-T-cell-activation.

The anti-Tac work has been led by principal investigator Tom Waldmann, chief of the NCI metabolism branch, who moved anti-Tac from its production in the laboratory through to animal and clinical studies, modifying it along the way to make it more friendly to the human immune system and more deadly to its target. The anti-Tac antibody is a monoclonal antibody directed

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INTRAMURAL BUDGET HOPES HIGH, BUT NOT OUT OF SIGHT

by Celia Hooper

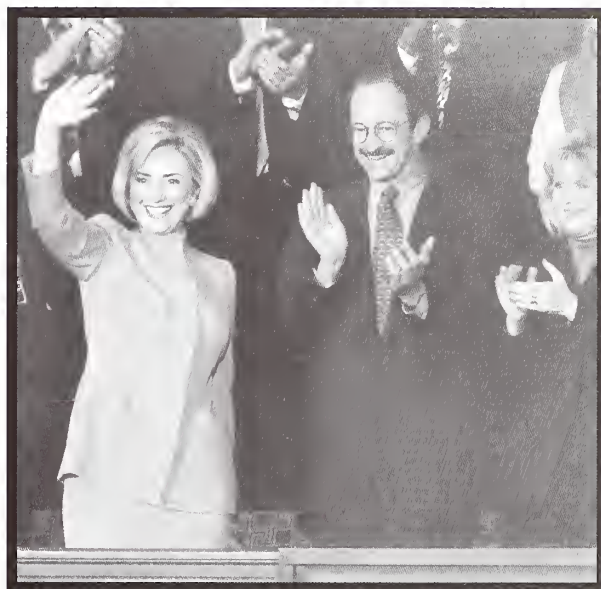
The budget news for NIH was so good that NIH Director Harold Varmus had the place of honor at the State of the Union Address—in the gallery beside First Lady Hillary Rodham Clinton.

The seating arrangement presaged not only a passage in the president's address extolling NIH research as a "gift to the millennium" but also the generous treatment NIH would receive in the president's forthcoming budget proposals.

Reaction from NIH quarters to the proposals was swift and delighted. "The President's budget for the National Institutes of Health calls for an unprecedented and dramatic increased investment in medical research of more than \$1 billion in FY 1999. No other Administration has asked the Nation to place such a high priority on medical research," proclaims the NIH budget press release. "Everyone is a winner in this budget," said NIH Director Harold Varmus at a news conference. In its February 6 issue, *Science* quotes HHS Secretary Donna Shalala as saying NIH institute directors are "ecstatic."

"I think the words 'pleased' and 'grateful' are better than 'ecstatic' to describe my feelings about the FY99 budget," says newly appointed NIDCD director James Battey. NIMH director Steve Hyman comes closer to being ecstatic: "I am extremely happy."

The proposal President Bill Clinton sent to Congress on February 2 recommends an NIH budget of nearly \$14.8 billion—an overall 8.4 percent increase over last year, with a 6.1 percent boost



The White House

Three Cheers: The State of the Union on January 27 looked good to Hillary Rodham Clinton, Harold Varmus, and Tipper Gore

for the Intramural Research Program. The president's plan envisions an increase of almost 50 percent in NIH's budget over the next five years, and the proposed increases for the extramural

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FROM CONSTRUCTION CONSTERNATION TO A CALMER CAMPUS



Michael Gottesman

With the groundbreaking last November for NIH's Mark O. Hatfield Clinical Research Center (CRC), a new era in clinical research at NIH was launched. Although most of us are entranced by a vision of 21st-century clinical research in a state-of-the-art facility, many NIHers, already dazed by the proliferation of building projects on campus, are wondering how long they must endure large construction projects on campus and whether parking will become even more vexing. Others are worried about the immediate effect on the research environment in Building 10 and about the process for assigning patient care and laboratory space in the new CRC. I would like to address each of these concerns.

Light at the End of the Tunnel

The source of most of the current disruption on campus is the construction of a grid of underground utility tunnels to ensure at least two life lines to each of our old and new laboratory buildings. This work takes a long time because of the need to reroute roads and sidewalks across campus as the tunneling proceeds, and also because it takes several months to cure the concrete that lines each of the tunnels. Construction for the tunnel project is scheduled to be completed by August of this year.

Building 50 construction has been another challenge to campus navigation. The building will start to rise out of its foundation in July, with the outside shell expected to be complete by June 1999 and the whole—including a new pedestrian mall on the Metro side of the building that should provide a visually exciting campus entrance and outdoor meeting area—completed and ready for use in July 2000. One underappreciated aspect of Building 50 construction was that all the excavation was done at night and on weekends to minimize dust and traffic congestion from the convoys of dump trucks hauling off the soil.

But even as the utility tunnel extension and Building 50 are completed, other projects will be starting up and coming to completion. Beginning in September 1998, a new HIV Vaccine Research Center will take shape on the west side of the campus between Buildings 37 and 49, with construction scheduled for completion in the spring of 2000. Also, construction of a new day-care facility will start around July 1999 and be finished by July 2000. The day-care center will be near the Natcher Building and will accommodate more than 100 children.

The ground clearing for the new CRC to the north of Building 10 has already begun with the demolition of Building 20 and the clearing of trees. The actual excavation and construction on the north entrance will not start until late fall. This work must await the completion of a new entrance to the south of the Clinical Center, expected by August. The first step will be to move Center Drive, which will circle the new CRC to the north to minimize disruption of traffic flow on campus. Unfortunately, CRC construction will again bring change in campus parking patterns, but this should be the last major shift, and plans are in the works to ease the transition to new parking and commuting arrangements. We should see the foundation of the new CRC by April 1999 and its outside construction and landscaping by fall 2001.

By the summer of the year 2000—just a little more than two years from now—most of the construction on campus will either be concluded or in a phase more conducive to the normal ebb and flow of pedestrian and automobile traffic on campus. Our beautiful campus will be returned to us.

Solving Rubik's Cube

The process for assigning patient and laboratory space in the new CRC is already well under way. The Clinical Center Advisory Council, consisting of representatives of several institutes and chaired by Steve Hyman (director, NIMH) and Ed Liu (scientific director, Division of Clinical Sciences, NCI), has created partnering groups to develop transinstitute patient-care units. All of the hospital portion of the new CRC has been assigned based on these deliberations, and, by all accounts, clinical researchers are pleased with the cooperative spirit informing these decisions.

We have initiated the process for assignment of laboratory space in the CRC. By mid-March, each institute will have nominated programs to be housed in the CRC. We are encouraging the institutes and centers to take a long view of the direction of translational and clinical research and to use the new facility to stimulate new research programs and recruitments. A committee of branch chiefs and clinical, scientific, and institute directors will assign space in the new CRC based on the following criteria: 1) need for a specific research program (not necessarily an entire lab or branch) to be close to patient-care units, 2) scientific excellence compared with competing programs, 3) need for proximity to other programs within or among ICDs in the area (programmatic clustering), 4) current location in E or F wings of Building 10, 5) equity among ICDs, and 6) minimization of total number of moves for a specific program during Building 10 renovations. There will be a chance to appeal decisions before final space allocations by Dr. Varmus in May or June.

Although the decision-making process has general acceptance, concern remains over the disruptiveness of CRC construction. Because the central core of Building 10 (between the B and D corridors) will be renovated after completion of the CRC, it is essential that all current occupants of the E and F wings (known to most of us as the North and South corridors of the central core of Building 10) be relocated either to the CRC or elsewhere. Since there is laboratory and office space in the new CRC lab buildings equivalent to the total of all such programs, this task should be doable, but everyone in E and F will have to move somewhere, and some labs in the periphery of the building will likely also be moved during this process and certainly will have to move later as the wings of Building 10 are renovated after the completion of the core renovation. Minimal renovation is envisioned for the ACRF in the next 10 years, but there will be some disruption as the new CRC and the ACRF are joined.

NIH leadership is committed to making this process as painless as possible. We have assurances from our planners and architects that scientific and programmatic concerns will be primary, and we will do our best to oversee the transition. I welcome your ideas as we inch our way across the bridge—over the mud puddles and trenches—into the 21st century. ■

LIKE FISH TO WATER, ZEBRAFISH TAKE TO NEW HOME

The new year began swimmingly for the NICHD Section on Developmental Biology, with the unveiling of a new zebrafish facility, a swankier version of the first zebrafish room that started earning its stripes at NIH three years ago.

The zebrafish darted gracefully through the waters of their new home in Building 6B as about 75 people who attended the ribbon-cutting ceremony and tour gazed in wonder at their striped sleekness and contemplated the wealth of developmental data there for the investigating.

Zebrafish (*Danio rerio*) have become a popular model for studies of developmental genetics in recent years, thanks to some unique advantages over other experimental animals.

For example, unlike *Drosophila*, the zebrafish are vertebrates and follow typical vertebrate development. Unlike higher organisms, however, zebrafish have transparent eggs and embryos, providing a clear, unobstructed view of many developmental processes.

Moreover, zebrafish are comparatively easy and inexpensive to keep and easy to spawn, and they produce large numbers of offspring.

By studying mutations in the zebrafish embryos, researchers can identify the earliest expression of those genes associated with cardiovascular, gastrointestinal, neurological, and other structural defects—and search for counterparts in human developmental disorders.

NICHD researchers are currently investigating three areas of development. One focus is on a zebrafish mutation known as "gridlock," in which the two aorti fail to merge properly during development. This defect mimics the human birth defect known as coarctation of the aorta, which affects one to two in 1,000 births.

Another NICHD research team is investigating a mutation in the so-called "notch" receptor, crucial for getting cells to differentiate. Abnormalities of the notch receptor have been implicated in many human cancers.



Ernie Bransom

First Cut: (front row, left to right) Doreen Bartlett, animal administrator; Art Levine, NICHD scientific director; Igor Dawid, chief, laboratory of molecular genetics; (back row) Anthony Clifford, director, engineering services; Rosemary Riggs, animal program administrator; John Bartholomew, chief, research animal management branch.



Bill Bransom

Adult zebrafish



Bill Bransom

Juvenile zebrafish and fry

A third team is studying a transcription factor that plays a key role in early development of the nervous system.

After the open house, the zebrafish facility assumed typical laboratory and animal facility security precautions, but potential collaborators interested in visiting may contact facility staff.

—Bob Bock
NICHD

CATALYTIC REACTIONS

On Student Training

As a former Office of Education staff member who was around for the launching of the Pre-IRTA program, I can't tell you how pleased I was to read in the January-February issue about the impact the Pre-IRTA program is having on its participants and NIH. During my three years at NIH (1991–1994), I became convinced that NIH had an immense capacity to mentor future scientists, and I was impressed by the number of scientists who willingly gave their time to mentor high school and college students.

Now, as director of admissions for 11 Ph.D. programs, I can tell you how important good mentoring is to development of a successful Ph.D. or M.D./Ph.D. applicant. It's obvious in reading letters of recommendation from NIH scientists that the program is achieving its goals—many participants are obtaining the type of experience that the program was meant to provide. That's saying quite a bit for a government program!

During my visits to 40 campuses each year, I strongly recommend the Pre-IRTA program in conversations with students. Those of us in the extramural community appreciate the experience NIH is providing to our future students.

Jeffrey J. Sich, Ph.D.
Director of Admissions
Division of Biology & Biomedical
Sciences
Washington University
Saint Louis, Missouri

On Clinical Research Protocols

I recently learned that NEI has launched a new comprehensive clinical trials database for NEI-funded studies. It is located at

<<http://www.nei.nih.gov/neitrials/index.htm>>.

—Dennis Rodrigues
Office of Communications

We would like to give the correct CRISP Web address as

<<http://www.nih.gov/grants/award/gophercrisp.htm>>

instead of the one given in the January-February 1998 *NIH Catalyst*. CRISP is the transinstitute database of funded extramural and intramural NIH projects and includes both clinical and nonclinical studies.

—Miriam Gershfeld
Office of Extramural Research

JUST ASK!

Dear Just Ask:

Do IRTAs have to pay self-employment tax? Can IRTAs contribute to an IRA?

What tax forms do visiting fellows file?

—*composite questions from confused NIH-based taxpayers*

Dear Taxpayers:

Ah, taxes. Bad enough when you know exactly what you need to file, but so much worse when you are not sure of the tax laws for your particular situation. Here is some useful information, but be warned that interpretation and implementation of tax laws are the domain of the IRS and the courts, and the IRS is the final arbiter on all tax issues.

IRTA fellows are paid in the form of a taxable grant, which NIH reports to the IRS. Early each year, IRTAs should receive a green 1099G (for U.S. citizens) or a 1042-S (for green-card holders), which states what was paid them the preceding year. This form replaces the standard W-2—or any other form you may be used to. If the 1099G has not arrived by January 31 or the 1042-S by March 15, call the Office of Financial Management at 496-5635 to get the form sent.

Federal and state taxes are not withheld from IRTA awards; therefore, estimated taxes must be filed quarterly on form 1040-ES for federal taxes and the equivalent form for state taxes. Due dates for estimated taxes are the 15th of April, June, September, and January. At tax time, IRTAs should file the 1040 tax form, not the 1040A or 1040EZ.

IRTA fellows need to file federal and state taxes; forms are available at public libraries, post offices, and on the Web at http://www.irs.ustreas.gov/prod/forms_pubs/index.html.

State forms can be downloaded from <http://www.dccfo.com/taxpmain.htm> (District of Columbia) <http://www.comp.state.md.us/main.htm> (Maryland) <http://www.state.va.us/tax/tax.html> (Virginia) <http://www.dor.state.nc.us/DOR/>



Celia Hooper

Susan Chacko

(North Carolina)
<<http://www.mt.gov/revenue/rev.htm>>

(Montana)

<<http://www.revenue.state.az.us/index.html>> (Arizona).

Because IRTAs are paid from a taxable grant, not salaried for services rendered, the NIH Legal Counsel advises they are not subject to Social Security and Medicare withholdings. They are also not self-employed and so should not file Schedule C or pay self-employment tax. Also, the medical coverage cost paid by NIH for IRTAs is *not* income and should not be added to

the 1099G income.

The amount from the 1099G or 1042-S should be reported on Line 21 (taxable grant), not Line 7 (taxable income), of the 1040 tax form. If it's reported on the wrong line, the IRS may question why you have not paid Social Security or Medicare. If that happens, you should respond with a letter stating that your income is from a taxable grant and *should* have been reported in Line 21. You can also include copies of the description of the award program:

<<http://www.training.nih.gov/handbook/appoint.html>>,

and the information on taxes for fellows:

<<http://www.training.nih.gov/handbook/taxes.html>>

and

<<ftp://helix.nih.gov/felcom/www/tax98.html>>.

IRTA fellows cannot contribute to an IRA, because their stipends are not considered compensation and are not subject to Social Security. If they get additional income from other sources and pay Social Security taxes on that income, then they may be able to contribute to an IRA. If you have questions, you can contact Ed Everitt (Division of Financial Management, NIH) by e-mail at THEPUMP@MSN.COM

(include your phone number, so he can discuss the situation with you) or ask your local IRS office.

Senior staff fellows are employees of

NIH and therefore have the same benefits as other government employees. Taxes are withheld from their salaries, including Social Security and Medicare. They get W-2 forms and must file taxes like any other government employee.

No general tax information can be provided for visiting fellows, because the tax laws that affect them arise from their country of origin. Each has its own tax treaty with the United States, so some visiting fellows have to pay U.S. taxes and others do not. The Fogarty Center publishes a tax handbook each year, available from the receptionist in Building 16A. The Center also holds monthly tax meetings and workshops around tax time for its visiting foreign scientists.

—Susan Chacko

Where To Get Tax Help

IRS publications that cover fellows' tax issues are:

- * Publication 17: Your Federal Income Tax
- * Publication 520: Scholarships and Fellowships
- * Publication 590: Individual Retirement Arrangements (IRAs)

The local IRS Office: For Bethesda employees, the closest IRS office is at 11510 Georgia Ave., Wheaton, Maryland 20902.

IRTA tax questions for U.S. citizens: Contact Ed Everitt by e-mail at THEPUMP@MSN.COM.

Visiting scientist tax issues: Call your Fogarty immigration specialist at 496-6166 to attend the next tax seminar, or contact Fogarty's tax contractor, Peter Canonico, Valley Tax Financial Service, by e-mail at taxman@aol.com.

The Fellows Committee website has tax information at

<<ftp://helix.nih.gov/felcom/>>.

Tax issues are sometimes discussed on the fellows' mailing list, and you can also ask a tax question there. Subscribe to this list by sending e-mail to listserv@list.nih.gov, with the body of the message reading 'subscribe fellow-I'.

The Fellows Handbook is given out in hardcopy form to all new fellows and can also be accessed on the Web at

<<http://www.training.nih.gov/handbook/index.html>>.

'Hey, Buddy, Can You Spare a Cell Line?'

FELLOW-L OPENS 800 CUPBOARDS

by Lee Mack

You are in the middle of a key experiment and suddenly realize you've run out of a critical reagent. A mad search through the lab's shelves and even your secret stashes turns up nothing. You ask next door and down the hall. Nothing. Frantic, you call the suppliers. Your reagent is on back order and could be shipped in a month. Unfortunately, your experiment has to be done in a week if you are going to present this fabulous new information at the national meetings. What to do, what to do. . .

Many NIH fellows and other seekers in such dire straits are turning to an electronic mailing list created by postdoc Kevin Becker for the NIH Fellows Committee (FELCOM) four years ago. Facilitating the exchange of scientific information, reagents, and cell lines has proven to be one of the main functions of the list, but was not what the fellows had in mind at the outset.

The FELCOM list was launched when Becker found himself stuffing envelopes for the newly created FELCOM in 1994 and figured there had to be a more efficient way to reach the highly scattered postdoc and clinical fellows populations on campus. He and fellow Fellow Steve Scherer approached DCRT about setting up a list to operate under LISTSERV software technology (see box). The list was officially approved as a method of "promoting fellowship between postdoctoral staff and to provide a forum for educational, scientific and employment issues," according to the FELCOM Website. Becker sent out notices to the lists serving various interest groups on campus, and within six months the FELCOM list boasted more than 800 subscribers. Today it serves roughly that number—close to 40 percent of the intramural fellows.

The LISTSERV software (L-Soft, Landover, Md.) serves as a hyperefficient secretary, postal carrier, and librarian rolled into one. It addresses and distributes electronic messages to subscribers' e-mail boxes, automatically maintains the list of current subscribers, and archives the messages that have gone out over the list. The FELCOM list, known as Fellow-L is one of the largest electronic mailing lists at NIH; its reach, speed, and utility has helped shape a group identity among the subpopulation of researchers it serves.

Becker says he had envisioned the list as a primarily nonscientific forum to address "the quality of life for postdocs on campus and how to improve it."

The list is moderated by two volunteers from the postdoc population who evaluate messages under the guidelines etched out by FELCOM and screen out messages that are personal and not research related—like personal housing requests or solicitations for employment, according to current moderator John Newitt, a fourth-year NIDDK postdoc. After a second of thought, he adds, "No spamming, either!" ("Spamming" is flooding e-mailing lists with commercial requests.) Most people, he says, use common sense and stick to the science; it's infrequent that he finds himself censoring messages.

A couple of instances in the past few years have proved the list's potency in clarifying issues of general interest to subscribers not only in Bethesda but also at NIH's Montana and North Carolina campuses. One such issue was taxes. A long, confused e-mail debate over the tax status of fellows and the relationship of their IRAs to the IRS resulted in clarification from a tax specialist and the posting of tax information on the Fellow's Website at

<ftp://helix.nih.gov/felcom>

(also, see "Just Ask!" page 4). Another issue was health insurance.

Although Fellow-L has not solved all the fellows' problems, most people asking for reagents, advice, or collaborations get positive responses, sometimes the same day. Sunita Agarwal, NIDDK postdoc, put out a request for NIH3T3 cells for an RNA isolation and the same day received several offers that allowed her to complete her experiment—and the interchange, she says, put her in contact with other NIH researchers and postdocs beyond her own institute.

Becker says he would like to see the list used more along the lines of his original conception, including to ferment discussion of touchy issues, such as NIH mentoring policy—to "thaw the block of ice," he says. Such discussions are not restricted by the FELCOM guidelines, but, historically, the institutionalized nature of the list has hindered such openness, according to Becker. Becker and others, however, have used the list to "seed" discussions of delicate topics that are then mediated by the Fellow-L

List-en Up

Currently, NIH is home base for more than 600 DCRT-supported LISTSERV software-managed lists that serve subpopulations ranging in number from three (Listmaster list) to more than 26,000 (NIH-Staff list) on and off campus. The lists link up subscribers through what amounts to an electronic postman to deliver mail to a set of e-mail addresses in minutes—a system tailor-made to NIH, where people are researching related questions in buildings flung across campus and whose paths may never cross.

Electronic lists are ideal for grassroots attempts to unite people across space. Anyone on the NIHnet can set up a list by simply filling out a short electronic application (on the Web at **<http://list.nih.gov>**), outlining the purpose and some characteristics of the list and establishing a list owner willing to be responsible for the list. The application goes to LISTSERV software administrators, and Bronna Cohen, DCRT's primary LISTSERV software user liaison at NIH, says the request is processed within two working days.

I decided to test the system and set up my own list. Within a half-hour of submitting my idea, I found myself the proud owner of Fantasticideas-L, a brand new list touting itself as a vehicle for the spread of new science ideas.

To subscribe to Fantasticideas-L, or any LISTSERV software-managed list, address an e-mail message to **<listserv@list.nih.gov>**. To subscribe, the body of your message should say: **<subscribe fantasticideas-L Your Name>** (Replace "fantasticideas" with Fellow-L or whatever list you want to subscribe to, and "Your Name" with your own name). For a compilation of all lists on campus, e-mail **<listserv@list.nih.gov>** and just write **<lists>** for your message.

A description of how to access a list's archives is at this Web address:

<http://list.nih.gov/LISTSERV_WEB/listserv_archives.htm>.

An exhaustive discussion of LISTSERV software operations and technology is posted on the Web at

<http://list.nih.gov/LISTSERV_WEB/ownrsgde.htm#What_is_LISTSERV>.

moderators and concomitantly archived at

<ftp://helix.nih.gov/felcom/www/fellow-l-archive/maillist.html>.

Tyra Wolfsberg, current FELCOM co-chair, acknowledges that the list is more effective for some objectives than others, but concludes, "In the end, it's far better to have it than not have it." ■

DIPLOMACY WINS CREDIT WHEN CREDIT IS DUE

One of the postdoctoral training goals enumerated by NIH Deputy Director for Intramural Research Michael Gottesman in a recent *Catalyst* column (November-December 1997, p. 2) was the cultivation of negotiating skills.

He suggested that mentors should teach their postdocs "how to work through bureaucratic channels, how to convince others of the importance of their needs, and how to avoid antagonizing the very people who are pivotal in helping secure the desired items." Although the column refers to negotiation for a postdoc's research resources, these same negotiating skills are essential throughout a research career in nearly all aspects of one's functions as a scientist.

One of the most critical areas calling for excellent negotiating skills is also one of the major areas of dispute among colleagues—getting credit for contributions, be it authorship on a paper or an acknowledgment when a collaborator presents a talk or seminar. These are important issues, and everyone needs to learn how to discuss them frankly but diplomatically when they arise. I would like to explore this topic through four fictitious, but close-to-real-life, examples, presenting alternative diplomatic approaches that are more likely to have a positive outcome than an undiplomatic response.

In **Scenario One**, Dr. Jones, a postdoctoral fellow, sees a manuscript written by his lab chief that contains a table of Jones' data, but does not have him listed as a coauthor. Jones is furious—after all, one of the major goals of being a fellow is to demonstrate scientific proficiency, and publications are probably the most important evidence of this.

Jones marches into his lab chief's office and in an accusing voice says, "You did not list me as a coauthor on this paper even though you used my data." His lab chief is immediately put on the defensive and attempts to justify his actions, but is also angry at being put on the spot. The situation has already become combustible and is heading toward intractability.

But what if, instead, Dr. Jones uses his best diplomatic skills and makes an appointment to see his lab chief after, one hopes, he has had time to cool down. At the meeting, Jones starts out

by saying, "I saw this manuscript and thought that I might deserve authorship, since some of my data appear to be an important part of the paper. I am starting to look for jobs, so every publication helps. Could we discuss how authorship is decided upon and whether my name could be added as a coauthor?"

With this approach, Jones has presented several strong arguments for his inclusion as an author and has done so in an open atmosphere that allows his lab chief to discuss his rationale for deciding authorship. It gives the lab chief a way to agree gracefully to make Jones a coauthor. Both of them are satisfied with the result, and the discussion has clarified the rules of authorship in that laboratory.

The same approach applies in **Scenario Two**, in which another fellow, Dr. Wong, hears a talk by her branch chief at a national meeting. The branch chief presents some of Wong's data, but does not acknowledge Wong's contribution either during the talk or with an acknowledgment or collaborators slide at the end. If Wong storms up to her branch chief after the talk, demanding that she acknowledge her in her next talk, Wong will create a public spectacle and undoubtedly antagonize her branch chief.

The better negotiating strategy would be sitting down with the branch chief on their return from the meeting. Wong would point out how important it is to be acknowledged for her contributions, especially in a public talk at which a future employer or a former mentor (who could be writing a letter of recommendation) might be part of the audience. This approach makes the same point in a much more diplomatic way that is far more likely to achieve the desired result.

Another positive suggestion Wong could make to her lab chief would be to include the names of collaborators and fellows on data slides, and in discussion of the research as it is presented,

in addition to slides at the beginning as well as the end of a talk. This approach avoids omission of the contributors on a final acknowledgment slide should the speaker inadvertently run out of time.

Scenario Three is more difficult and involves tenure-track investigators at NIH. For the most part, these early-career scientists are recruited into specific laboratories or branches where they interact with more senior scientists, but, if they are to achieve tenure, must establish themselves as independent investigators. What should Dr. Stone do if her lab chief presents collaborative results,

thereby stealing her thunder before she herself has had a chance to discuss the data publicly or publish them?

Dr. Stone needs public recognition of her results if she is to make tenure, but she also needs her chief's support to reach that milestone. She needs to demonstrate independence, yet collaborations are a way to enhance her scientific productivity. The senior investigators within her lab are Stone's most obvious potential collaborators, given that they selected her to join their lab based, at least in part, on how Stone's scientific

interests fit with the lab's mission. This is clearly another delicate situation in need of thoughtful discussion and negotiation.

In Stone's case, advice or mediation by a third party, such as mentors from outside the lab or the institute, might be helpful. Anyone who mediates probably needs to be a neutral and relatively senior person. NIAID recently made arrangements for tenure-track investigators to select mentors from a pool of senior investigators in that institute. This seems like a useful approach. Interinstitute interest groups could also serve as a contact point for finding an outside perspective.

Consider **Scenario Four**, not quite as common as the others, but frequent enough to require discussion. A fellow, Dr. Braun, has completed what he considers a significant piece of work, written a manuscript, and handed it over to

ONE OF THE MOST
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CONTRIBUTIONS, BE IT
AUTHORSHIP OR AN
ACKNOWLEDGMENT WHEN
A COLLABORATOR
PRESENTS A TALK . . .

by Joan Schwartz, Ph.D.
NINDS

his section chief, Dr. Metski, who will be the last author on the paper. Metski adds a figure containing data generated by a previous fellow in the lab whom she feels was instrumental in starting the project. She inserts the fellow's name as middle author, and submits the paper to *The Journal of Biological Chemistry*.

The paper comes bouncing back, not accepted, with suggestions by both reviewers for additional control experiments and a question about the figure added by Metski. Meanwhile Dr. Braun is busy looking for jobs. He doesn't have time to do the suggested controls, which he feels are not necessary, and urgently needs to have the paper on his CV as something more than "In Prep." Furthermore, Braun believes that the data in the extra figure not only are irrelevant, but actually distract from the significance of the paper—hence the reviewers' questions. Braun insists that the other fellow's contributions do not merit authorship.

What then? Consider this unacceptable approach: Braun tells his section chief that he wants to go ahead and submit the manuscript to *The Journal of Chemical Biology*. He proceeds to do so without further discussion and after removing the figure and the other fellow's name. The paper is accepted and published, thereby justifying Braun's actions in his mind. However, Braun has not told section chief Metski what he did, and she only learns about it when a colleague mentions seeing the paper in the library.

This approach leaves the section chief furious, for several reasons. First, the senior author is responsible for the quality of the research—quality that has been diminished by not including controls deemed essential by the first set of independent reviewers. Second, guidelines at NIH require that all authors approve each submitted version of a manuscript and that the senior author sign off on papers before they are submitted. Third, the senior author has the ultimate responsibility for determining authorship, although *The NIH Guidelines for the Conduct of Research* state that all authors should come to agreement on authorship.

All of these issues are discussed in *The Guidelines*, a copy of which every scientist at NIH should possess, read, and understand.

I hope no one reading this column will feel that what Dr. Braun did was the correct way to proceed. But what should a fellow do who feels that his or her work is being delayed because the supervisor "just doesn't have time to work on the manuscript," or wants the fellow to do more experiments than the fellow feels are necessary, or wants to add another scientist's name and data to the paper?

Again, this is a situation that calls for negotiating skills. The fellow should sit down with the supervisor and talk. He or she should discuss why the experiments are not needed or propose another way of getting them done—perhaps by a new fellow in the lab who may be continuing the project or might benefit by learning the techniques involved.

The fellow and mentor should discuss the relevance of data added to a paper, and whether the addition warrants authorship.

An important key to effective negotiation is being ready to compromise, as long as the scientific excellence and the integrity of the work will not be affected.

In the end, it will be more beneficial to the fellow to have another publication, even if it does contain some extra data and an additional author. It also helps a fellow to remain in the good graces of his or her supervisor.

In sum, good negotiating skills are essential for preserving relationships that will be important for career development. Supervisors and colleagues will



Fran Pollner

Joan Schwartz

*"Soon enough the roles will be reversed:
The colleague being evaluated will
become the evaluator . . ."*

continue to provide recommendations and evaluations, whether written or oral, throughout a scientist's career. These may or may not be requested by the scientist being evaluated. If a scientist has cultivated good will through diplomacy and good negotiating skills, his or her colleagues will be to be able to say, "Dr. Jones (or Wong or Braun) is a superb scientist, intelligent, insightful, AND a pleasure to work with—willing to go an extra mile when that will promote the science."

Soon enough, the roles will be reversed: The colleague being evaluated will become the evaluator. The newly tenured scientist will be welcoming a new tenure-track collaborator. And former postdocs will be applying their hard-earned negotiating skills in dealing with their own postdoctoral fellows. ■

Alternative Dispute Resolution Forum, April 30

Did you know that there is an NIH Center for Cooperative Resolution and that it is founded on principles of alternative dispute resolution?

You can learn about both on April 30th—all day—at a conference sponsored by the Department of Health and Human Services (HHS). Called the "Alternative Dispute Resolution Forum: Achieving Desired Results," the meeting will be held on campus at the Natcher Building.

The general sessions will introduce the concepts of alternative dispute resolution (ADR) and their utilization to improve work relationships in HHS agencies. Morning and afternoon breakout sessions will allow participants to select smaller, focused programs for the ADR-naïve and -experienced. The breakout sessions will include presentations on: the basic concepts of ADR, the role of agency ombudsmen, the application of ADR in resolving workplace disputes, how ADR may be utilized to improve labor relations, the role of attorneys in ADR, and the practice of negotiated rulemaking in HHS.

There's no charge, but pre-registration is recommended. Call 443-6790/TDD 443-6990 for a registration form. ■

ANTI-TAC TAKES OFF

continued from page 1

against the alpha subunit of the interleukin-2 receptor (IL-2R α).

"For the last 14 years, there has been an array of protocols directed toward the IL-2 receptor," Waldman recounted in an interview. "The scientific basis for these trials is that IL-2R (Tac) is expressed by a whole series of leukemia and lymphoma cells—but not normal resting cells; it's expressed also on the surface of T-cells involved in a retroviral-associated neurological disorder and a host of autoimmune diseases, such as uveitis, arthritis, systemic lupus erythematosus, inflammatory bowel disease, and the like," as well as the rejection of organ grafts.

In sum, any condition marked by deranged T-cell activation—significantly, autoimmune diseases and certain cancers—may be a candidate for anti-Tac maneuvers, Waldmann said.

A series of NIH clinical protocols dating to 1983 has brought the anti-Tac approach to the threshold of recognition as a treatment in these other conditions, as well as in organ transplantation. The cDNAs encoding IL-2R α were cloned and sequenced in Waldmann's lab, where, in 1981, Waldmann and Takashi Uchiyama created the anti-Tac antibody. There are about a dozen clinical protocols now going on, most with fewer than 20 patients and none targeted to recruit more than 45. Waldmann envisions more trials in the not-too-distant future.

One of Waldmann's central projects is the development of anti-Tac as a vehicle for directed internal irradiation of T-cell malignancies. It is that use, he says, that is serving as a prototype for a strategy in cancer therapeutics that he

calls systemic radioimmunotherapy. He sees the application of this basic strategy not only in leukemias and lymphomas but also in the more common and more difficult-to-reach solid tumors, like breast, ovarian, and gastric cancer, if appropriate tumor-specific receptors, comparable to Tac, can be found.

From Bench to Bedside in ATL

From the outset it was clear that anti-Tac had exciting potential for improving treatment of one of the most intractable types of leukemia. Waldman recalls, "Using hybridoma technology, we first produced our antibody—a mouse monoclonal antibody—to Tac in 1981 and relatively quickly showed that virtually all the leukemic cells and none of the normal cells in patients with adult T-cell leukemia (ATL) expressed the Tac antigen." The next step was defining the antigen as one of three chains in IL-2R, which itself was undefined at the time. Waldmann's lab is currently conducting therapeutic trials of antibodies to the beta chain as well as the alpha chain.

Initial clinical trials focused on diseases caused by human T-cell lymphotropic virus-1 (HTLV-1), predominantly ATL, an extremely aggressive leukemia. Regardless of which chemotherapy ATL patients receive, their median survival duration is just nine months postdiagnosis. ATL was clearly a malignancy in need of a new therapeutic approach.

Waldmann's laboratory studies indicated that anti-Tac might be just the ticket. He had demonstrated differences in receptor expression between normal and malignant cells in ATL patients, with the normal cells nonreactive to anti-Tac. By contrast, the malignant cells each displayed 10,000 to 35,000 reactive IL-2R α chains of the receptor on their surfaces. The leukemia cells were also locked into an autocrine feedback loop in their early stages of malignant proliferation as the virally induced IL-2 production drove heightened IL-2R α expression.

Using the murine anti-Tac monoclonal, Waldmann and his team set out to saturate the receptors and block IL-2 bind-

ing, essentially starving the leukemic cells of the cytokine that was central to their proliferation. Thus far, in their first ATL protocol, 19 patients have been treated. Six patients have had remissions—two of them complete. "I saw one of these two yesterday, as a matter of fact," Waldmann noted during an interview in February. "Eight years out, and he is still in complete remission," he said, smiling.

"In a true complete remission, you are eliminating all malignant cells. We have no evidence—on any level—of residual tumor in this 72-year-old patient, whom we evaluate every year," he elaborated. "There is no evidence of monoclonal rearrangement in T-cells; the level of soluble IL-2 receptor, a surrogate marker of leukemia, is even lower than normal; there are no malignant cells in the peripheral blood; his serum calcium levels are fine; there's no evidence of the retrovirus. He's lived well enough to have had a successful hip replacement procedure."

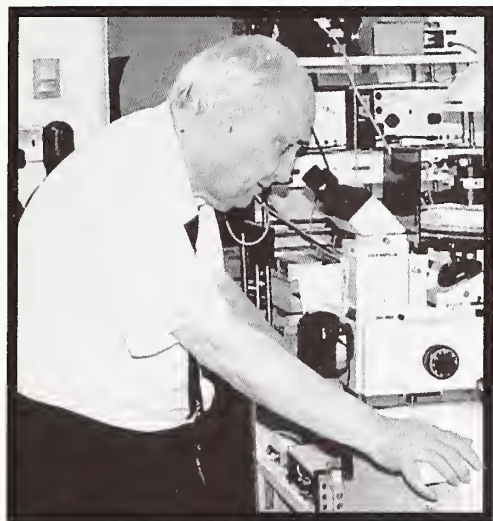
Waldmann says the stage of a patient's disease when he or she enters the trial is a factor in the success or failure of the approach. Patients with chronic ATL, a subset with a more favorable median survival duration of 24.1 months, tended to respond better to anti-Tac. In these patients, ATL is still in a self-stimulatory mode—with leukemic cells produced by the IL-2-IL-2R α autocrine

interaction. Oddly enough, the eight-year survivor did not fit this pattern. "Overall, our success in chronic ATL is seven of nine patients; in acute ATL, it's nine of 26; and in acute ATL with a history of repetitive chemotherapy failures, it's zero of nine," Waldmann said.

But, he quickly added, these first studies used unmodified murine anti-Tac. "There are major limitations to this treatment: The mouse monoclonal survives only 40 hours in humans; it's recognized as foreign by the human immune system, which means repeat courses often must be abandoned; and, finally, it is not a very effective killing agent. It can prevent the cell from seeing its growth factor, but it cannot carry out antibody

"THE SCIENTIFIC BASIS FOR THESE TRIALS IS THAT IL-2R (TAC) IS EXPRESSED BY A WHOLE SERIES OF LEUKEMIA AND LYMPHOMA CELLS—BUT NOT NORMAL RESTING CELLS."

—Tom Waldmann



Fran Pollner

Tom Waldmann

"We continue in an iterative or developmental way to recognize limitations, modify our protocol accordingly, and move to hopefully better therapeutic approaches to the IL-2 receptor."

dependent cellular cytotoxicity (ADCC) against human cells."

Those limitations pointed the way to improvements and subsequent trials. "We continue in an iterative or developmental way to recognize limitations, modify our protocol accordingly, and move to hopefully better therapeutic approaches to the IL-2 receptor," Waldmann said. The original ATL protocol remains open to patients who would be ineligible for a new Phase I trial of a later-generation anti-Tac.

Anti-Tac with a Human Face Overcomes Transplant Rejection

One of the first modifications was to humanize the anti-Tac antibody, a project undertaken with Cary Queen, then of the NCI biochemistry branch and soon after of Protein Design Labs, a company he established. The antigen-combining region from the mouse was retained and the remaining 90 percent of the antibody was converted to a human IgG1. The modified antibody still bound tightly to the Tac leukemic cells; it had drastically reduced immunogenicity; its half-life in the human body was now a whopping 20 days; and to top it off, it had ADCC function against human cells.

Clinical trials with humanized anti-Tac initially focused on graft rejection and autoimmune conditions rather than can-

cer, and it was this fact that led to graft rejection's becoming the first approved application for anti-Tac, rather than leukemia, in which it first showed promise. With NHLBI collaborators, Waldmann's group had demonstrated the utility of murine anti-Tac in preventing cardiac graft rejection in cynomolgus monkeys. Collaborators at Harvard Medical School in Boston, led by Robert Kirkman, then evaluated anti-Tac in a Phase I/II clinical trial in kidney transplant patients. The results of these trials encouraged Hoffmann-LaRoche to step in and sponsor multicenter Phase III randomized, placebo-controlled clinical trials involving 535 kidney transplant patients.

"Phase III trials are almost always best done by industry," Waldmann observed, "and in this case, it was imperative, since NIH does not do organ transplants at the Clinical Center." In two sets of clinical trials—one in Europe involving two standard immunosuppressive agents plus humanized anti-Tac or placebo and the other in the United States that followed the same protocol but involved three standard immunosuppressants plus or minus anti-Tac—anti-Tac achieved a 40 percent re-

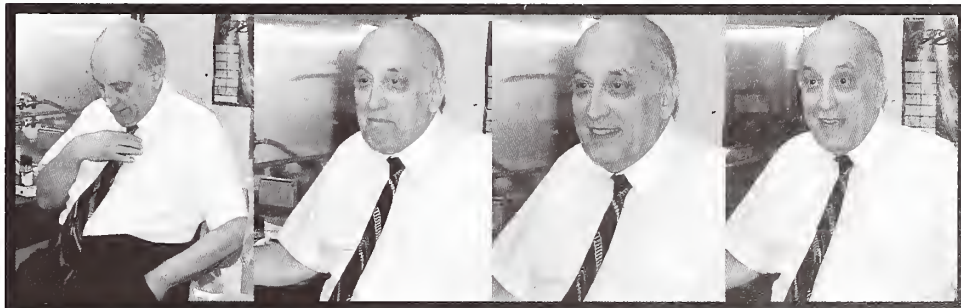
FDA approval for marketing to prevent kidney transplant rejection.

The company stated its intention to test the product in other organ transplantation procedures, an undertaking Waldmann projects will prove successful for any vascularized solid organ transplants. Only in bone-marrow transplants, where the graft-vs.-host disease does not involve IL-2, would anti-Tac not be effective, he said.

An Autoimmune Tack

Other anti-Tac studies at the Clinical Center have targeted autoimmune diseases: uveitis, a T-cell-mediated blinding disease of the eye, and tropical spastic paraparesis (TSP), an HTLV-1-induced demyelinating neurological disease with effects akin to multiple sclerosis. Both are being conducted in collaboration with other institutes. NEI's scientific director, Robert Nussenblatt, serves as principal investigator in the uveitis studies. The TSP work is a joint endeavor with NINDS co-PIs Henry McFarland and Steve Jacobson.

Blocking the self-stimulatory cycle of IL-2 and its receptor is proving its value in both conditions. Most uveitis patients treated with humanized anti-Tac either



Fran Pollner

"Eight years out, and he is still in complete remission," Waldmann exulted at the status of a 72-year-old ATL patient, who has received no treatment beyond his original NIH protocol. "In a true complete remission, you are eliminating all malignant cells. We have no evidence—on any level—of residual tumor (in him)," the researcher said

duction in organ rejection episodes; prolonged graft and patient survival were also documented. Moreover, Waldmann noted, typical immunosuppressant-associated toxicity was not associated with anti-Tac administration. "It appears that by reducing the rejection episodes and the need for salvage with high-dose corticosteroids or OKT3, both of which are associated with increased infection," anti-Tac overcame that particular drawback, he said. The results were impressive enough to win anti-Tac (Zenapax®)

retained their visual acuity or improved, even though they were withdrawn from the potent immunosuppressive agents (steroids and cyclosporine) that they had previously depended upon for their sight.

Among TSP patients treated with humanized anti-Tac, viral load diminished by 30 to 70 percent, and abnormal T-cell proliferation abated. Progression of neurologic disease was halted in all patients, and many actually showed improvement.

CLINICAL TRIALS

Waldmann and his colleagues believe that another cytokine is involved along with IL-2 in TSP. In the chain of events initiated by HTLV-1 infection—T-cell activation through a transactivating protein called *tax*, triggering T-cell division and autocrine production of IL-2 and IL-2 receptors—it appears that “these cells are also making a cytokine we codiscovered during our adult T-cell leukemia trials—IL-15,” Waldmann said. He believes that an antibody to the beta chain of the IL-2 receptor, which is shared by IL-2 and IL-15, would stop the IL-15-driven division and, in select circumstances, also block IL-2 effects.

In fact, Waldmann serves as study chairman of a protocol headed by NCI’s Jeffrey White, who is testing an antibody to the beta subunit of IL-2R in patients with T-cell large granular lymphocytic leukemia. The antibody—Mik- β -1—is directed against IL-2R β , which is expressed by the leukemic T-cells but not by normal resting cells. Mik- β -1 appears to block the actions of both IL-2 and IL-15 on the receptor beta chain. In Phase I clinical safety trials, Mik- β -1 has been tested in six leukemia patients in late stages of disease—stages that are probably “beyond the time when IL-2 and IL-15 are the driving forces,” Waldmann noted, which would explain the absence thus far of hints of clinical improvement. Nevertheless, the study is “showing that this is a safe approach to blocking IL-15 function—and one that might more easily be effective in autoimmune conditions.”

Waldmann sees multiple sclerosis, psoriasis, sarcoid, and systemic lupus erythematosus among autoimmune diseases that would be candidates for IL-2R α therapy with humanized anti-Tac. Mik- β -1 therapy, however, may be more suitable in rheumatoid arthritis and inflammatory bowel disease, in which IL-15 seems to have the dominant role, he said. He will test this strategy as soon as the humanized form of Mik- β -1 becomes available, probably later this year.

Anti-Tac Armed Against Malignancy

In the clinical testing of anti-Tac against malignancy, the antibody has not only been humanized but also souped up to deliver a killing agent to the surface of the tumor cell. “When one turns to malignancy,” Waldmann explained, “one wishes to arm the antibody with a toxin* or a radionuclide. My focus is on systemic radioimmunotherapy, which replaces the large external radiation-delivering machine with a radionuclide with a relatively short distance of action and the ability to kill the cells in its environment.”

Beginning in 1990, first with murine and then with the humanized version, anti-Tac has been coupled with a beta-emitting radionuclide, yttrium-90 (^{90}Y) in protocols involving patients with ATL and other Tac-expressing leukemias and lymphomas. NCI radiation oncologists Otto Gansow and Martin Brechbiel made this attacker-antibody, Waldmann noted.

Radiolabeling murine anti-Tac improved its clinical powers, bringing remissions in nine of 16 patients enrolled in its trial. Two of the remissions were complete and long lasting, and the partial remissions were sustained for longer periods than had been achieved in earlier trials with simple murine anti-Tac. As with those earlier trials, repeat courses were often precluded by the mobilization of the patients’ immune defenses against the mouse antibody.

The most active protocols today are those testing ^{90}Y -radiolabeled humanized anti-Tac, not only in ATL but in other leukemias and lymphomas that display IL-2R α . The most recent ATL trial, started by Waldmann in late 1996, includes the addition of a chelating agent—calcium-DTPA—to accelerate urinary excretion of ^{90}Y , thereby increasing the maximum



Fran Pollner

“The challenge is on those of us in the field to develop radiolabeled antibodies to common tumors. . . . I think an anti-Her2-neu antibody labeled with astatine could be tested three years from now (in a solid tumor adjuvant setting). . . .”

tolerated dose 1.5- to twofold. “Not enormous,” Waldmann commented, “but in a range where increase may alter efficacy.” A companion protocol, begun last year and headed by Jeffrey White, includes patients with other hematologic malignancies that express Tac, such as non-Hodgkin’s lymphoma, Hodgkin’s, cutaneous T-cell lymphoma, and peripheral T-cell lymphoma.

Future Paths

“Not too far down the road,” Waldmann said, “we will move from the beta-emitting radionuclides, like ^{90}Y , to the alpha-emitting radionuclides, which have a much shorter distance of action. Beta-emitters have approximately a half-centimeter of effective action, which means they can be toxic to bone marrow. Alpha-emitters have only one or two cell diameters of action—and are very effective in killing the cell on which they sit.” Among the alpha-emitting radionuclides that are being studied in his lab, astatine 211 (AT-211) is a prime candidate for future studies, he said. Agents linking it to anti-Tac antibody are under investigation, and he anticipates using the alpha-emitting astatine-labeled anti-Tac monoclonal antibody in the treatment of leukemia and lymphoma within a year or two.

Moreover, following the same strategy, he continued, astatine radionuclide

‘FOR SLOW-GROWING, SOLID TUMORS, ONE WANTS NEW APPROACHES. WHETHER THEY BE CANCER VACCINES OR GENE THERAPY, WE NEED TO GIVE OTHER APPROACHES A CHANCE, AND I SENSE THAT SYSTEMIC RADIOIMMUNOTHERAPY IS ONE OF THEM.’

—Tom Waldmann

*Another protocol based on the same strategy hitches a toxin fusion protein, instead of a radionuclide, to anti-Tac antibody. Opened in 1996, this study represents a collaboration with Robert Kreitman, who is the PI, and Ira Pastan, of NCI’s Laboratory of Molecular Biology, and uses *Pseudomonas* exotoxin (see box, page 11, and *The NIH Catalyst*, July-August 1997, page 4).

could be coupled to a monoclonal antibody directed against antigens other than Tac, such as those expressed in solid tumors. "We have done in vitro studies with *Her2-neu* as the target. *Her2-neu* is overexpressed by the tumors of 30 percent of patients with breast, ovarian, and gastric cancers, including many with the worst prognosis," Waldmann said. "So the *Her2-neu* receptor would be our target for these malignancies. Each malignancy would define its own receptor." He noted that microarray techniques comparing tumor tissue with normal tissue will aid in defining surface receptors as targets for therapy. "The basic approach," he said, "requires that the tumor cell display a receptor that is not expressed by a cell you must retain for good life."

He sees its use first in the adjuvant setting, to eliminate residual tumor cells after primary radiation or surgical therapy. "I think an anti-*Her2-neu* antibody labeled with astatine could be tested three years from now," provided current studies yield means to ensure its rapid relay to the tumor cells, he said. Trials with bulky tumors and metastatic disease are still some time away.

Closer at hand, Waldmann expects, are modest Phase III trials to establish systemic radioimmunotherapy as a valuable approach to cancer therapy. Acceptance of systemic radioimmunotherapy is stalled by the lack of such trials, he said. He proposes that the Clinical Center serve as a site for the controlled comparison of anti-Tac alone vs. ⁹⁰Y-radiolabeled anti-Tac. "Basically, I would share the view that the Clinical Center is not the place for a Phase III trial, but we feel that with a total accrual of only 25 patients in each arm," efficacy might be demonstrated and a "precedent would be set," he said. This, in turn, could open the doors to large studies conducted by regional cancer trials groups to see whether systemic radioimmunotherapy might become a standard weapon against cancer.

"The challenge is on those of us in the field to develop radiolabeled antibodies to common tumors," Waldmann said. "For slow-growing, solid tumors, one wants new approaches. Whether they be cancer vaccines or gene therapy, we need to give other approaches a chance, and I sense that systemic radioimmunotherapy is one of them." ■

Phase I/II Study of Tac-Expressing Adult T-Cell Leukemia with Yttrium-90 (⁹⁰Y)-Radiolabeled Humanized Anti-Tac and Calcium-DTPA

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Treatment of T-Cell Large Granular Lymphocytic Leukemia Using the Mik-β-1 Monoclonal Antibody Directed toward the IL-2Rβ Subunit

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Phase I Study of Anti-Tac (Fv)-PE38 (LMB-2), a Recombinant, Single-Chain Immunotoxin for Treatment of Tac-Expressing Malignancies

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PEOPLE

RECENTLY TENURED

Mel DePamphilis received his Ph.D. from the University of Wisconsin at Madison in 1970 and then did postdoctoral work there and at Stanford University Medical School in Palo Alto, Calif., before joining the faculty at Harvard Medical School in Boston. He was a laboratory head at the Roche Institute of Molecular Biology in Nutley, N.J., and an adjunct professor at Columbia University before coming to NIH in 1996 as a member of the Senior Biomedical Research Service and head of the section on eukaryotic DNA regulation in the NICHD Laboratory of Molecular Growth Regulation.

Most of the work in our lab has focused on DNA replication in eukaryotic cells and on the activation of zygotic gene expression at the beginning of mammalian development.

In the course of our work in developing subcellular systems that support simian virus 40 (SV40) DNA replication and unraveling the sequence of events at replication forks, we identified and characterized RNA-primed DNA synthesis and the enzyme responsible, DNA primase-DNA polymerase- α . We elucidated the assembly and arrangement of nucleosomes in and around the actual sites of DNA synthesis, identified replication pause sites, and elucidated the mechanism of replicon termination.

We have identified a role for transcription elements in viral replication origins and developed methods to map—at nucleotide resolution—the transition from discontinuous to continuous DNA synthesis that defines the site where bidirectional replication begins.

This research led to the first identification of specific initiation sites in mammalian chromosomes and to the discovery that prereplication complexes at these initiation sites can be activated by incubating nuclei from mammalian cells in a *Xenopus* egg extract. Subsequent work has shown that specific replication origins are established during each G1-phase in proliferating cells.

Current research focuses on identifying the proteins involved in site-specific initiation and on the role of nuclear structure, DNA sequences, and sequence modifications in establishing replication origins at specific genomic sites.

To investigate the requirements for

DNA replication and transcription at the beginning of mammalian development, members of my lab have used microinjection and nuclear transplantation techniques.

These techniques revealed that oocytes and preimplantation embryos have the capacity to use specific *cis*-acting sequences and *trans*-acting factors to express genes or replicate DNA.

We have identified specific regulatory sequences and transcription factors that are used at the very beginning of mammalian development, and we have uncovered several novel features of zygotic gene activation (ZGA), including:

1) A biological clock delays both initiation of transcription and translation of nascent transcripts until it is time for ZGA. 2) A general, chromatin-mediated repression of

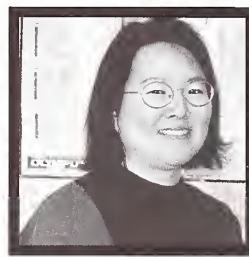
promoter activities appears concurrent with formation of a two-cell embryo and ZGA. 3) The ability to use enhancers to alleviate this repression depends on the appearance of a coactivator at the beginning of ZGA. In addition, TEAD-2, a transcription factor that can activate enhancers in preimplantation embryos, is first expressed at ZGA. 4) The mechanism by which enhancers communicate with promoters changes during development. In differentiated cells, a TATA box is required for enhancer-mediated stimulation of promoters, but in undifferentiated cells (for example, mouse cleavage-stage embryos), a TATA box is dispensable and enhancer stimulation is mediated via an Sp1 site. During development, this arrangement allows early enhancer-mediated stimulation of essential promoters that lack a TATA box—such as those governing housekeeping genes—while reducing stimulation later on.

Together, these events impose a directionality at the beginning of animal development that is evident from the inability of fertilized mouse eggs to reprogram gene expression in nuclei taken from cells at developmentally advanced stages. We now aim to identify the roles of specific transcription factors and chromosomal changes in activating key genes at the start of mammalian development.



Fran Pollner

Mel DePamphilis



Fran Pollner

Peggy Hsieh

Peggy Hsieh received her Ph.D. in biochemistry from the Massachusetts Institute of Technology in Cambridge in 1983 and joined NIDDK's Genetics and Biochemistry Branch as a postdoctoral fellow in the laboratory of R. Daniel Camerini-Otero. In 1990, she became a principal investigator in the Genetics and Biochemistry Branch.

My group's work focuses on mechanistic studies of homologous recombination and DNA mismatch repair. Recombination gives rise to genetic diversity by creating new combinations of genes and ensures the proper segregation of homologues during meiosis, thereby preventing chromosome nondisjunction.

We've been studying a central molecular intermediate in recombination known as the Holliday junction. This remarkably dynamic DNA structure constitutes the exchange point between two DNA molecules and consists of four DNA duplex arms emanating from a crossover point. When flanked by sequence homology, the junction can migrate spontaneously by the stepwise breakage and reformation of Watson-Crick hydrogen bonds as one DNA strand is exchanged for another.

Igor Panyutin, a visiting associate, devised an ingenious experimental system for monitoring movement of the Holliday junction under a variety of conditions. These experiments revealed that branch migration is extremely slow and is blocked by sequence heterologies as small as a single base pair. Panyutin and Indranil Biswas, a visiting fellow, showed that the rate of branch migration is determined by the structure of the DNA at the crossover point.

More recently, Biswas and Akira Yamamoto, a special volunteer, calculated the thermodynamic barrier to branch migration posed by mismatches. These studies highlight the ways in which recombination proteins remove both structural and mechanistic barriers to branch migration. Perhaps our biggest contribution has been to underscore the importance of understanding DNA structures in recombination reactions.

Recombination and repair, like transcription and replication, require that proteins have access to the DNA helix.

A long-term goal is to understand how branch migration is propagated through chromatin in the eukaryotic nucleus.

Mikhail Grigoriev, a visiting fellow, has shown that, unassisted, the Holliday junction cannot migrate through DNA organized in a nucleosome; however, he recently demonstrated that the *Escherichia coli* RuvAB protein complex can direct rapid branch migration through a nucleosome in the presence of ATP.

We have now embarked on a search for the eukaryotic DNA "motor" proteins analogous to RuvAB that may propagate branch migration through chromatin.

My interest in DNA mismatch repair (MMR) stems from our work on recombination and mismatched bases. MMR plays a critical role in reducing mutations in almost all organisms, correcting mispaired or unpaired bases that arise through replication errors, physical damage to bases, and homologous recombination.

Recognition of mispaired bases is mediated by the family of MutS proteins that are conserved in species ranging from bacteria to humans. The importance of MMR in reducing mutations is highlighted in its role in cancer biology: Defects in MMR are implicated in hereditary nonpolyposis colon cancer as well as some sporadic tumors.

How does MutS protein recognize mispaired but otherwise normal bases that are constituents of DNA? Biswas isolated a thermostable MutS homologue from *Thermus aquaticus* and deduced by chemical footprinting studies of a MutS-DNA complex that the protein interacts with both the major and minor grooves of DNA in the immediate vicinity of an unpaired base.

Photo-crosslinking of the MutS-DNA complex has allowed us, in collaboration with Vlad Malkov in Dan Camerini-Otero's lab, to achieve the first identification of a DNA binding region in an MMR protein.

Our studies of recombination and MMR have come full circle, with our work now directed toward the identification of molecular interactions involved in the regulation of homologous recombination by MMR.

Understanding recombination and repair in molecular terms may help us to understand how organisms simultaneously balance the need to ensure diversity and to avoid the accumulation of deleterious mutations.

David Schlessinger received his Ph.D. in biochemistry from Harvard University in Cambridge, Mass., in 1960 and did his postdoctoral work at the Pasteur Institute in Paris. He was professor of molecular microbiology, genetics, and microbiology in medicine at Washington University in St. Louis before coming to NIH in September 1997 as a member of the Senior Biomedical Research Service and chief of the newly established NIA Laboratory of Genetics.

Our research program is designed to study events critical for the aging of specialized mammalian cells and concomitant aging-related phenomena.

We are using developmental genomic approaches to analyze inherited genetic conditions and relevant embryonic processes. Throughout the studies we have

planned, our work interweaves genomic approaches to aid in developmental analyses, with the further aim of studying physiology in aging populations.

Our current investigations focus on two broad areas. The first is studies of gene regulation in chromatin. Projects are designed to understand tissue- and developmentally restricted expression of the genes which, when mutated, cause Simpson-Golabi-Behmel syndrome and X-linked anhidrotic ectodermal dysplasia (EDA) (see below). The regulatory processes in these cases involve features of chromatin, which we will attempt to study in artificial chromosomes recovered in chromatin form.

The second broad area of our work is the analysis of cohorts of genes involved in selected processes, using a genome approach to developmental phenomena. This approach starts with human inherited conditions and relevant embryological studies in mouse models, in which sets of genes from embryonic stages can be easily mapped in the genome, localized in sections, and studied with knock-out technologies. Examples include:

■ **Premature ovarian failure.** Menopause is certainly a feature of aging, but premature ovarian failure (POF), affecting 1–3 percent of all women, results from high attrition of follicles in embryonic and fetal life. To study the embryology of this condition, we are starting from a subset of translocation breakpoints associated with POF, all fall-

ing in a critical region of the X chromosome. We are analyzing the breakpoints to look for genes or structural features in the chromosomal DNA that can limit ovarian function. In correlated developmental work, we're beginning systematic studies of gene cohorts specifically expressed during the development of the kidney and urogenital tract, including ovary and testis.

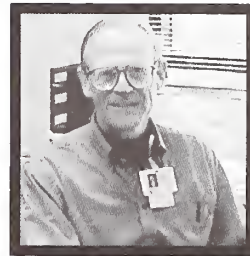
■ **X-linked hypophosphatemic (HYP) rickets.** The gene responsible for this disease has been sequenced and is involved in the regulation of bone turnover. It encodes a putative endopeptidase (with an as-yet-unknown substrate) and is expressed along the kidney-urogenital developmental axis and in bone precursors. We will investigate the gene and its protein developmentally and biochemically; the HYP mouse has been shown

to be an experimental model for the human disease.

■ **Simpson-Golabi-Behmel syndrome.** This and similar syndromes, affecting about one in 20,000 individuals, are characterized by gigantism and overgrowth, particularly of mesoderm-derived tissues and organs, such as muscle, heart, and kidney, and result from mutational lesions in a matrix glycoprotein, glypican 3.

In this case, the key biological questions are how the set-point for organ size is determined and how overgrowth is related to pathophysiology. Our speculative model for the etiology of the syndrome is based on concentrations of insulin-like growth factor II and features of growth hormone action. We plan to test and extend this hypothesis through developmental studies and mouse models.

■ **X-linked anhidrotic EDA** is one of the most common of a group of conditions affecting skin appendages and the only one linked to the X chromosome. The EDA gene provides an entree to an embryonic branch point that leads to teeth, hair follicles, and sweat glands, which are all rudimentary or lacking in affected individuals. The Tabby mouse serves as an experimental model for the human condition, and interacting genes can be found both by genomic approaches and by genetic studies of some of the other 150 inherited ectodermal dysplasias. ■



Jerri Muller

David Schlessinger

BUDGET HOPES

continued from page 1

budget next year should generate 8,267 new Research Project Grants, bringing the total number of grants to more than 30,000—an all-time high. Also included in the president's budget is a recommendation to raise stipends for scholars in the National Research Service Awards program by 25 percent.

Hyman says what pleases him most about the new budget is its emphasis on sustained support of NIH—a concept that has also found favor among members of Congress. The concept is one that HHS Secretary Shalala has been pushing hard, in part as the result of ongoing conversations with NIH Director Varmus on the importance of attracting and keeping promising new investigators in biomedical research. The administration is recommending doubling the size of the NIH budget over the next decade; some members of Congress would like to see a five-year doubling time.

"The key to my happiness," says Hyman, "is not just the specific number that is in the president's budget, but the promise of stability. The NIH budget roller coaster of the past has made strategic planning all but impossible and, more importantly, has served to discourage bright young people from entering careers in science. I am enormously gratified that Secretary Shalala has focused on the need for stable



Steve Hyman

part of a high-visibility collection of science and health initiatives collectively referred to as the "Research Fund for the 21st Century" in the State of the Union Address (see box).

Diane Wax, NIH associate director for legislative policy and analysis, says the source of money for the Research Fund—and thus NIH's budget increase—is the tobacco legislation. Wax says many experts on Capitol Hill doubt that Congress will manage to resolve, in this very short election-year session, the extremely complex swarm of tobacco issues, bills, and even legal entanglements completely outside the legislative purview.

It's uncertain where that would leave NIH's budget increase. With no tobacco

growth as a critical factor in the health of American science."

One of several unknowns in the budget equation at the moment is to what extent the money derived from pending tobacco legislation will fuel increases in the NIH budget. The totality of NIH's budget increase for next year is currently assembled as



Jim Battey



Fran Pollner

Diane Wax

funds, Wax points out, the House and Senate committees that consider the HHS budget are back to their bottom line—a limited pot of money that must be distributed among numerous departments and programs.

Even if NIH remains the top priority it has been for the committee chairmen, Rep. John Porter (R-Ill.) and Sen. Arlen Specter (R-Pa.), without the tobacco money, budget increases for NIH could be smaller or at least more politically painful and could entail making difficult trade-offs with other programs. "I'm not sure we can know at this point," says Wax, "but they just don't have enough money to work with, and there's a limit to the possible increases to give, even with the president's recommended 8.4 percent."

But Hyman says support for the president's budget increase should remain solid, and NIH must start planning now, even if Congress isn't able to come to closure on the tobacco issues. "Secretary Shalala has said publicly that the NIH budget increase is not dependent on tobacco legislation. Although we understand that there is a serious political process ahead in consideration of the budget proposal, we clearly must plan for the opportunities created by potential budget increases."

NIMH, like other institutes, is getting busy. "For NIMH the planning process has involved our national advisory council, working groups that have reported publicly to council, our various constituency groups, and NIMH staff, and it has also involved collaborative interactions with other ICDs that fund neuroscience research," says Hyman. Some of the scientific opportunities NIMH is eyeing include the genetics of mental disorders, neuroimaging, clinical trials focused on the needs of children and adults with serious mental disorders, studies of gene expression in the brain (the Brain Molecular Anatomy Project), studies of brain development and brain plasticity, the neurobiology of emotion, and investigation of risk factors that lead to mental disorders in children, with a view to developing preventive interventions.

A 'Gift to the Millennium'

Tonight, as part of our gift to the millennium, I propose a 21st Century Research Fund for path-breaking scientific inquiry—the largest funding increase in history for the National Institutes of Health, the National Science Foundation, the National Cancer Institute.

We have already discovered genes for breast cancer and diabetes. I ask you to support this initiative so ours will be the generation that finally wins the war against cancer, and begins a revolution in our fight against all deadly diseases.

As important as all this scientific progress is, we must continue to see that science serves humanity, not the other way around. We must prevent the misuse of genetic tests to discriminate against any American. And we must ratify the ethical consensus of the scientific and religious communities and ban the cloning of human beings.

—Bill Clinton, "State of the Union," January 27, 1998

Batthey says NIDCD also has some priorities in mind. "We hope to put a number of initiatives on line in response to FY99 increases. These include: 1) new approaches to the prevention, diagnosis, management, and treatment of otitis media; 2) molecular mechanisms of sensory neuronal regeneration; 3) diagnosis and intervention strategies for neonates with hearing impairment; 4) functional real-time neuroimaging to identify brain activity patterns associated with normal and disordered communication; 5) identifying genetic bases for human communication disorders; 6) research into pathogenesis and intervention strategies to ameliorate specific language impairment; 7) research on the related subjects of noise-induced and age-related hearing impairment; and 8) increased support for clinical investigators and first-time RO1 grant applicants."

NIDCD intramural research plans emphasize the genetics of human communication disorders; identifying and developing mouse models of hereditary and environmentally induced hearing impairment; expanding a collaborative effort between NIDCD, NCI, and NIDR to study the pathogenesis and treatment of head and neck cancer; developing a vaccine against otitis media; and the use of functional neuroimaging in studying the pathogenesis of human communication disorders.

Another budget unknown is how much earmarking will carve up the NIH increase. In the president's budget, specific areas of emphasis are cited, including cancer and diabetes research, but the Research Fund—at least in its original conception—is intended to serve the broad range of laboratory and clinical research, cutting across disease- and institute-specific lines. In the past, often to the quiet dismay of NIH directors, the NIH budget has lost versatility after being heavily earmarked for special interests and particular disease research areas championed by members of Congress.

How the money designated for the NIH intramural research as a whole is portioned out among its components is another unknown. Although the Clinton budget calls for a 6.1 percent increase overall, this doesn't necessarily mean that each intramural program will see exactly that increase—or any increase, conceivably. Each institute and center will decide on its specific intramural budget. Batthey, who continues as act-

ing scientific director of his institute, says, "Our IRP is about 7 percent of the NIDCD budget at present. I would hope to be able to support growth at a rate equal to or slightly exceeding the annual increase received by the NIDCD in total."

Arthur Levine, scientific director of NICHD, expects FY99 budget increases to have a more significant effect on extramural than intramural activities—bringing more new investigators into the grants pool and sustaining a larger number who are continuing in that pool. "The effect



Fran Pollner

Art Levine

plaud this level of support for the totality of biomedical research, looking beyond our own walls." ■

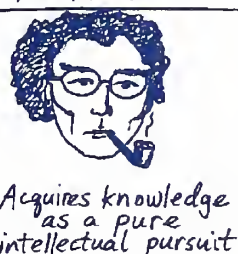
The National Institutes Guide to Why People Become Scientists

The Humanitarian



Acquires knowledge to help mankind

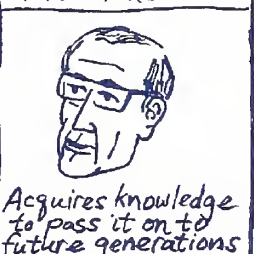
The Academic



Acquires knowledge as a pure intellectual pursuit

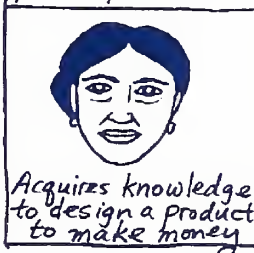
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The Mentor



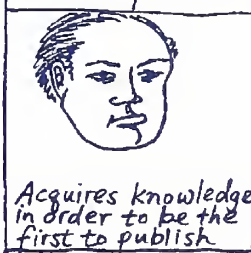
Acquires knowledge to pass it on to future generations

The Capitalist



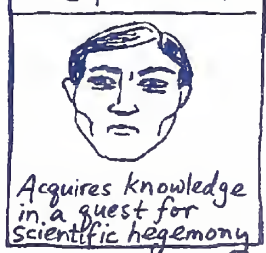
Acquires knowledge to design a product to make money

The Competitor



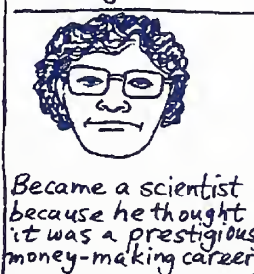
Acquires knowledge in order to be the first to publish

The Empire Builder



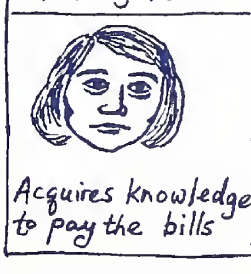
Acquires knowledge in a quest for scientific hegemony

The Regretter



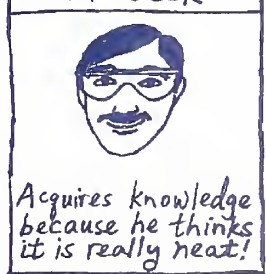
Became a scientist because he thought it was a prestigious money-making career

The Pragmatist



Acquires knowledge to pay the bills

The Geek



Acquires knowledge because he thinks it is really neat!

CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: campus construction, the NIH budget, the fellows' e-mail list, and the development of diplomatic skills in science.

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 209.

In Future Issues...

- Meet the Press
- More IRP Reviews: NIAMS, NIAAA
- Hot Methods: Presentation Is All

1) Any suggestions on how to minimize consternation over campus construction projects? What factors should decide who moves into the new Clinical Research Center?

2) Assuming NIH receives steady budget increases over the next five years, how do you think intramural increases should be spent?

3) What has been your experience using the Fellow-L e-mail list? How could the service be improved?

4) What is your reaction to this issue's "Ethic's Forum" on the cultivation of diplomatic skills and sharing credit? Is this a serious problem area for mentoring at NIH? How can negotiation skills best be learned?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 209, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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