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NIH Volunteers Sought VRC LAUNCHES FIRST IN A PROJECTED SERIES OF HIV VACCINE TRIALS

by Fran Pollner

Early this October, a scant year after its opening, NIH's Vaccine Research Center (VRC) put its first candidate AIDS vaccine to the human test.

Designed to maximize cytotoxic T-lymphocyte (CTL) activity against key core HIV proteins, the plasmid DNA vaccine encodes a modified gag-pol protein from a clade B virus. It was constructed by VRC director Gary Nabel and research fellows Yue Huang and Wing-Pui Kong. The trial's first volunteer was inoculated a little more than a year after the VRC materialized into the state-of-the-art vaccine research facility mandated by then-President Clinton (see "VRC Takes Its Place in Campus Skyline," *The NIH Catalyst*, September–October 2000, page 1).

Already in production are lots of the vaccine that will be tested in a second VRC trial, anticipated to begin next summer. The multiclade, multivalent vaccine contains a modified HIV envelope protein in addition to three internal proteins, according to Barney Graham, chief of the VRC Clinical Trials Core and the Viral Pathogenesis Laboratory.

Clinical testing of a cytokine-enhanced DNA vaccine is planned to begin around the same time, as are trials of VRC candidate vaccines in HIV-infected volunteers. Also on the agenda are protocols using the prime-boost strategy, with the boost packaged in either an adenoviral or a modified vaccinia vector, Graham said in an interview.

The goals of the first trial, which

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HUMAN EMBRYONIC STEM CELLS: OPPORTUNITY DELAYED BUT NOT DENIED

by Celia Hooper

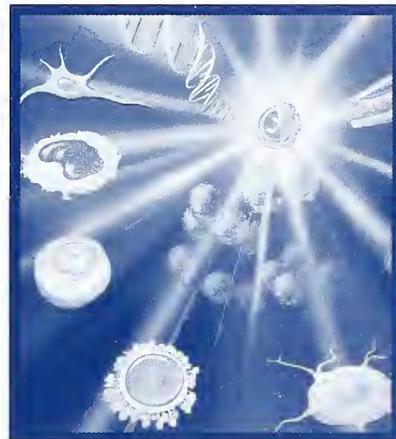
Among the many things on NIH appointment books for September 11 were some key meetings needed to embark upon a historic first—NIH-supported embryonic stem (ES) cell research. Although initially delayed by those tragic events, the registry of human ES cells is, indeed, now a reality.

Addressing the October 23 meeting of the NIH Director's Council of Public Representatives (COPR), Wendy Baldwin, deputy director for extramural research, said her office is responsible for implementing NIH's first ventures into supporting human ES cell research. Baldwin's office took over these duties after the Office of Science Policy (OSP) laid the groundwork. OSP produced the NIH stem cell report ("Stem Cells: Scientific Progress and Future Research Directions" <<http://www.nih.gov/news/stemcell/scireport.htm>>), testified before Congress, and drafted research guidelines based on President George W. Bush's August 9 television announcement on the availability of stem cells for research.

Bush's announcement cleared the way for NIH support of research on human ES cell lines already in existence at the time of the announcement that had been derived from embryos that no longer had the possibility of development as human beings.

These lines also met additional criteria of being derived from embryos that had been created for but were no longer needed for human reproduction. Also, donors of the embryos had given their informed consent, and there had been no financial inducements to donate the embryos.

The cells come from 11 different labs. These include labs in Australia, Sweden, India, and Israel, as well as WiCell, the University of Wisconsin (Madison)-based nonprofit group created to disburse their five original human ES cell



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lines from the pioneering research of Jamie Thomson's lab.

As the terrorist attacks blotted out lives and appointments, NIH was planning a web-based registry of approved cell lines that would be the first stop for researchers who want to do human ES cell research. Baldwin told the COPR members that NIH was working hard to catch up.

And just over two weeks after the COPR meeting, on November 7, the registry went live:

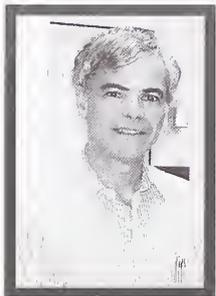
<<http://escr.nih.gov>>.

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EVALUATING THE INTRAMURAL HUMAN SUBJECTS PROTECTION PROGRAM: THE BEGINNING OF A NEW ACCREDITATION PROCESS



Michael Gottesman

Clinical research at NIH is conducted under the eye of a complex oversight system that was formulated in response to legal and regulatory requirements and international ethical standards. The system reflects the strong belief of our scientific staff that research with human participants is a special partnership.

Research involving humans has come under increasing scrutiny in the past several years. The HHS Office for Human Research Protections has suspended clinical protocols at such institutions as Duke University in Durham, N.C., and the Johns Hopkins University School of Medicine in Baltimore for deficiencies in their institutional review boards (IRBs) and procedures to protect human subjects.

These events have generated some rethinking about how best to protect participants in clinical trials. We have accelerated efforts to develop an accreditation process for programs dedicated to the protection of human research subjects.

Institutional oversight of NIH intramural clinical research is my responsibility as deputy director for intramural research. Key roles are also played by the director of the Clinical Center, John Gallin; the scientific directors and clinical directors of the NIH institutes; NIH's 14 IRBs; the Office of Human Subjects Research (OHSR) under the direction of Alan Sandler; and clinical investigators, research staff, and many others. The policies and procedures governing the human research program are found in the NIH Multiple Project Assurance and the Clinical Center's Medical Administrative Series; in various other documents, such as *Protomechanics*; and on the OHSR's and Clinical Center's websites (<<http://ohsr.od.nih.gov/>> and <<http://www.cc.nih.gov/>>).

Although various components of the NIH program engage in ongoing self-evaluation, the program as a whole has never been systematically evaluated by outside experts—and until recently there has not been an organization qualified to conduct such an evaluation.

Now, however, a new, nonprofit organization called the Association for the Accreditation of Human Research Protection Programs (AAHRPP) has been established. It will offer voluntary evaluation and accreditation of human research protection programs based on a set of written performance standards. These standards address five domains: (1) the organization, (2) IRBs, (3) research investigators and research staff, (4) research sponsors, and (5) research subjects and participants.

AAHRPP has not yet begun its formal accreditation activities, but will start pilot site visits in December 2001. The NIH Intramural Research Program will be the first of three pilot sites for evaluation. This pilot

visit, starting on December 10, will help NIH prepare for human subjects accreditation in the future and will also help AAHRPP test its draft performance standards and evaluation procedures.

The OHSR is preparing a pre-site visit application based on the AAHRPP's draft standards. Copies of the application will be available to the intramural community well before the visit and OHSR will also prepare briefing materials specifically for IRBs, clinical directors, and others to highlight the areas of concern to the review team. This is an excellent opportunity for all members of the intramural community to brush up on their knowledge of human subjects research through our computer-based training course at

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

with more specialized training for IRB members at

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

The AAHRPP site visitors will be interviewing the Clinical Center director, institute clinical directors, IRB chairs and members, principal investigators, and others, as well as me. They will visit various departments

in the Clinical Center, observe IRB meetings, and review protocols and other relevant documents. They will also visit NIDA in Baltimore and NIEHS in Research Triangle Park, N.C. Their interviews and visits will be scheduled in advance, and individuals involved will have ample time to prepare. Their observations and conclusions will be submitted in a confidential report to the deputy director for intramural research.

I strongly believe that the NIH IRP has an excellent human research protection program, with knowledgeable and responsible investigators conducting cutting edge research in keeping with federal regulations and the NIH Multiple Project Assurance. Our program will become even better as *Standards for Clinical Research*

within the NIH Intramural Program (<<http://www.cc.nih.gov/cc/clinicalresearch/index.html>>) are fully implemented in all institutes.

As with all programs, however, there is room for improvement, and this pilot site visit—which is not to be confused with an FDA or other regulatory “for-cause” audit or inspection—should be viewed as a constructive, collegial exercise that will benefit both the NIH and AAHRPP. We seek the cooperation of the NIH community in welcoming these site visitors to our campus so that we can demonstrate the strengths of our program, learn how to improve it, and prepare for a formal accreditation visit in the future.

If you have any questions or would like more information about AAHRPP standards or any of NIH's human protection policies, please call OHSR at 301-402-3444.

—Michael Gottesman
Deputy Director for Intramural Research

WE SEEK THE COOPERATION OF THE NIH COMMUNITY IN WELCOMING THESE SITE VISITORS TO OUR CAMPUS SO THAT WE CAN DEMONSTRATE THE STRENGTHS OF OUR PROGRAM, LEARN HOW TO IMPROVE IT, AND PREPARE FOR A FORMAL ACCREDITATION VISIT IN THE FUTURE

FIRST-RATE GRADUATE STUDENT RETREAT

by Nancy Bae

The NIH Graduate Partnerships Program (GPP) held its first annual graduate student retreat September 26th, 2001, at the Cloisters. NIH is home to more than 150 graduate students—from near and as far as England and Israel. The purpose of the retreat was to recapture a universitylike experience for the students and give them a time and place to discuss their research with one another and form bonds of community.

Keynote speaker Francis Collins, NHGRI director, offered a brief history of the Human Genome Project and envisioned virtually unlimited research opportunities flowing from its completion—especially in the proteomics and drug development areas. More than their predecessors, he said, the current classes of graduate students have an amazing assortment of data and technology with which to approach their work.

Examples of that work were presented by 12 senior-level graduate students, whose current research spanned a broad array of topics from transcriptional regulation of an aging-related gene (Nancy Bae, University of Maryland) to the classification of placental mammals (Eduardo Eizirik, University of Maryland) and developing new Fourier transform infrared spectroscopic imaging techniques (Dan Fernandez, University of South Florida). NIH investigators moderated these discussions.

Students also had an opportunity to discuss their research on a one-on-one basis at a poster session, where the research presented was similarly diverse, including elaborations of protein structure threading (Natasha Sefcovic, the John Hopkins University) and the RNA polymerase of bacteriophage (Anne-Marie Hansen, Odense University, Denmark).

Michael Gottesman, deputy

director for intramural research, and Mary DeLong, GPP director, also addressed the gathering, praising both NIH for the vast scientific and human resources it offers students and the students for the quality of their work and their accomplishments. ■



Keynote Francis Collins



GPP director Mary DeLong (left) and office assistant Wade Nierenhausen



photos by Bill Branson

Poster Clusters: (foreground) Ron Skupsky explains "mathematical analysis of cyclic metabolic pathways for phosphoinositide synthesis" to Andre Phillips (holding glass) and Evan Thompson (holding helmet); (background, left to right) Anne Marie Hansen, Nancy Bae, and Walter Schlupf

NCRR FUNDS OPEN HOUSE FOR MUTANT MICE

The mutant mouse kingdom has a population of more than 3,000 strains, and it's growing daily. Some of its more famous citizens are the cystic fibrosis knock-out mouse and the Apo E3 transgenic mouse, but there's hardly a preclinical study of human health and disease these days that does not involve a mutant mouse model.

A national mutant mouse repository network that enables researchers to donate and acquire mutant mouse strains has been established with funding from NCRR.

Officially called the Mutant Mouse Regional Resource Centers (MMRRC), the network consists of four repository-distribution facilities that are electronically linked through an Informatics Coordinating Center (ICC) at the Jackson Laboratory in Bar Harbor, Maine.

The four centers are:

- The University of North Carolina at Chapel Hill
- The University of California at Davis
- Taconic Farms in Germantown, N.Y.
- Harlan-Sprague Dawley, Inc., Indianapolis, in collaboration with the University of Missouri.

Each facility is generally equipped to cryopreserve embryos or gametes, rederive strains, and characterize the genetic and phenotypic makeup of the mutants.

The ICC provides database and other informatics support to the MMRRCs and serves as a single point of entry to the network for the research community at the website

<http://www.mmrrc.org>.

Researchers may also contact each MMRRC through Section B of the NCRR Comparative Medicine Resource Directory posted on the NCRR website

<http://www.ncrr.nih.gov/ncrrprog/cmpdir/Sec%20B.htm>.

The network is now accepting genetic mouse strains for its collection and invites investigators who have created them to donate them.

For additional information, contact program head Franziska Grieder at 301-435-0744 or

griederf@ncrr.nih.gov.



HIV VACCINE TRIALS

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is recruiting 21 healthy, uninfected volunteers, are largely related to exploring a novel method for delivery of DNA constructs: determining the best dose range, scheduling, and timing of the analysis of immunological endpoints.

There is reason to believe that CTL responses induced by this particular vaccine will compare favorably with predecessors.

Rationale

Graham noted that the VRC website includes a detailed table of all candidate HIV-1 vaccines thus far tested in uninfected adults; more than 60 trials are listed. But although there have been other gag-pol constructs, he says, the HIV gene fragments that have been placed in the VRC vaccine have been codon-optimized to encode amino acids using the preferred mammalian translational machinery, which also eliminates some inhibitory sequences and improves nuclear export of message, resulting in higher levels of protein expression.

The site of injection—a muscle cell—becomes a factory, producing and processing the vaccine-encoded gene products; MHC molecules transport the processed epitopes from the cell cytoplasm to the surface to be seen by the T-cells. The activated T-cells expand and then eventually recede to a lower steady-state level, where they remain “for a very long time, maybe forever,” capable of recognizing those epitopes should they ever come calling, said Graham, charting the anticipated response to a successful vaccine.

Using flow cytometry and enzyme-labeled immunoassay, VRC research team members (Mario Roederer, Richard Koup, and Daniel Douek), will measure CD4+ and CD8+ T-cell response and intracellular cytokine expression (particularly interferon- γ , interleukin-2, and TNF- α). The protocol calls for an initial vaccine dose of 0.5 mg for the first cohort of volunteers, five of whom will receive vaccine and two of whom will receive placebo; the dose for the next group of seven will be 1.5 mg, and for the last, 4.0 mg. Each volunteer will receive a series of three vaccinations—one a month—at their given dose level. The aim, Graham said, is to maximize response, to reach a dose at which the CTL response plateaus. A plateau of 200–800/million HIV-specific CD8+ T-cells would be considered a good response.

The idea is that subsequent exposure to infection would be met by a kinetics different from that triggered by exposure in an unvaccinated individual. Presumably, antigen-specific CD8+ T-cells would speedily get to work clearing virus. The question, Graham observed, is “Can you get it done before the establishment of latency, high-level viremia, or sequestration in immunoprivileged sites, like in the brain?” That the virus will be cleared rapidly post-exposure is the rationale behind the potential efficacy of an AIDS vaccine like this one that is not likely to raise broadly neutralizing antibodies, Graham said. Should the vaccine clear large amounts of virus in that window of time between infection and latency and result in low viral load and reduced transmission efficiency, it would have a significant effect on the AIDS epidemic.

Support for such efficacy was gained in prior monkey studies conducted by Norman Letvin, director of the VRC Non-Human Primate Research Program (see “Videocast Viewing of VRC Seminars,” page 5, for access to a VRC seminar delivered by Letvin). Though not identical to the human DNA, the SIV gag-pol construct, delivered in a similar fashion, controlled infection in vaccinated macaques later exposed to S/HIV challenge.

Cytokine Enhancement

A cytokine that enhanced the efficacy of a DNA vaccine in monkeys will also be put to the test in humans. In another monkey study, a DNA vaccine enhanced by interleukin-2/Ig (a divalent IL-2 molecule made by fusion to the IgG2 Fc) not only increased CD8+ T-cell response but also prevented the loss of CD4+ T-cells, a phenomenon not achieved with DNA alone. Post-challenge viral loads were lowest in the cytokine-enhanced cohort, all of which remained clinically well 140 days out. Viral loads were intermediate in the DNA-alone group. Control animals fared very poorly.

Because IL-2/Ig tested so well in the monkey study, it will be used to augment a clade-B multivalent vaccine scheduled for clinical trials beginning in the summer of 2002. This DNA vaccine will include gag, pol, and nef internal proteins, as well as an envelope pro-



Barney Graham Fran Pollner

tein—gp145—modified from the native gp160 to increase its immunogenicity. The VRC will recruit about 30 volunteers for this trial, and other cohorts will be recruited by collaborating members of the extramural HIV Vaccine Trials Network.

IL-2 is not the only enhancing cytokine in line for testing. “There are theoretical reasons to believe that some others will be even more successful than IL-2,” Graham observed, but he hesitated to specify which might be selected for future studies since there are different opinions on this issue.

Clades and Boosters

The VRC is also aiming to launch another trial this summer—of a multiclade (A, B, and C), multivalent (gag, pol, nef, and modified gp160) candidate vaccine. “We’re heading there as fast as we can,” Graham said. This construct was generally accepted at a meeting at NIH earlier this year to discuss the design of a candidate vaccine that could have worldwide utility. The meeting was attended by high-level scientists from such countries as India, China, South Africa, Brazil, Zambia, Uganda, and Nigeria.

Like the gag-pol construct currently under clinical study, this DNA vaccine would be offered in escalating doses to three groups of patients, starting with 2 mg in the first group and proceeding to 4 mg and 8 mg in the next two groups. And, assuming regulatory and production activities go smoothly, the volunteers in this study would also receive an adenoviral boost six months later—at year’s end. Adenoviral vectors, Graham noted, serve as very efficient gene delivery vehicles and have been shown in preclinical mouse and monkey studies to be highly immunogenic. “While we face some production issues and attenuating effects of prior adenovirus immunity, this general approach is very promising,” he said.

Modified vaccinia Ankara (MVA) vector is also being looked at as a booster vehicle. There’s less convincing preclinical data on MVA, he said, but it is “very accommodating in terms of the amount of material that can be put in it,” a particularly useful attribute in vaccines that contain response-modulating cytokines.

The construction of recombinant poxviruses was pioneered by another NIAID investigator, Bernie Moss, and much of the pivotal work in nonhuman primates with these types of vectors has been done by Vanessa Hirsch (NIAID) and Genoveffa Franchini (NCI).

Neutralizing Antibodies?

The general strategy of eliciting strong CD8+ T-cell response has proved to be effective in controlling viremia in animals and appears to be achievable in humans. But the traditional *modus operandi* of successful preventive vaccines—inducing broadly neutralizing antibodies to prevent infection—has yet to be achieved in candidate HIV vaccines.

"It's hard to elicit the right kind of neutralizing antibodies—antibodies that are broadly cross-reactive and can neutralize common transmitted forms of the virus," Graham said. Researchers have had some success neutralizing the "X4 viruses," the ones that utilize the CXCR4 co-receptor to gain entry into the host cell, but these are more commonly represented among lab strains and are not commonly transmitted among people. The latter are the strains that utilize CCR5 as a co-receptor—the R5 viruses—and raising antibodies against them remains elusive.

The modified gp160 envelope protein that will be used in the multiclade test vaccine has been designed to be more immunogenic than native envelope, but "it still may not be the full answer to inducing broadly cross-reactive neutralizing antibodies," Graham said.

He is confident, however, that the VRC team is on the threshold of the "new discoveries in antigen structure and immunogen design" that are needed to

crack the neutralizing antibody code. The basis for this confidence rests squarely on the shoulders of Peter Kwong and Richard Wyatt, who solved the crystal structure of gp120 and are working daily on developing novel structure-based approaches to this aspect of HIV vaccine design. They will be working closely with John Mascola, VRC deputy director and director of the BSL3 Core Virology Laboratory.

Therapeutic Vaccine Trials

In tandem with the preventive vaccine trials in healthy, HIV-negative volunteers, the VRC will also conduct trials designed to test the therapeutic efficacy of these vaccine constructs in HIV-positive patients. As with the uninfected cohorts, the first trials will be aimed at dose-ranging and other logistics. There probably will not be a therapeutic vaccine trial counterpart to the gag-pol study just underway—essentially because production resources are now concentrated on the multivalent constructs scheduled for testing this summer.

Participants in the therapeutic vaccine trials will continue whatever therapy they are currently taking—presumably highly active anti-retroviral therapy (HAART)—and they could also come from among that group of infected persons for whom HAART is inappropriate or is not working. Prevacination status will be compared with postvaccination status with respect to viral load and degree and breadth of immune response.

"We haven't decided yet how many people are needed for the therapeutic trials. We're arguing over that," Graham said. "There are a lot of strong personalities here, and these are healthy arguments, the kind that lead to better con-

cepts and better trial designs."

On Terror

HIV is not the only subject of imminent VRC vaccine trials. Spurred by the urgency of "new perceived threats of bioterror," Graham hopes to conduct a trial in the spring of 2002 that he's actually wanted to do for years: find out whether MVA vector by itself will protect against vaccinia. Now, however, there would be implications for protection against smallpox.

Initially, the idea arose from a desire to see whether MVA would protect against recombinant vaccinia in lab workers. His idea was to give MVA to lab staff who would later be undergoing routine vaccinia immunization to protect against lab exposure. If the lesion that typifies reaction to vaccinia vaccine failed to materialize, then it could be posited that MVA had conferred the desired protection. That would be known within 7 to 10 days of the vaccinia inoculation.

Further study of immune responses—CD4+ and CD8+ T-cells and antibody responses to vaccinia—would be carried out to evaluate the likelihood of protection against smallpox.

Graham anticipates enrolling 60 individuals under 30 years old (previously unvaccinated) who are about to work with recombinant vaccinia in their labs and therefore slated for vaccinia immunization anyway.

Although the potential public health benefits of a successful vaccinia trial would be gratifying, Graham observed that for the world at large the "terror of HIV is more profound than anything we've been facing since September 11. The terror of 7,000 dead each day from AIDS is still with us." ■

Calling NIHers for HIV Vax Trials

"We want NIH volunteers." Barney Graham, chief of the VRC's Clinical Trials Core couldn't be more blunt about the desirability of NIH natives as healthy volunteers for preventive AIDS vaccine trials. "They're familiar with the science, and they're right here on campus"—and therefore less likely to be unduly worried about risks or unduly burdened by monthly visits to the Clinical Center for the year's duration of most of the projected trials.

Twenty-one healthy, uninfected volunteers between the ages of 18 and 60 are needed for the first trial. An estimated 200 individuals will be needed annually.

To learn about the trial under way, visit <<http://www.vrc.nih.gov>>; to volunteer, call 1-866-833-LIFE (5433) or e-mail <VRCforlife@mail.nih.gov>. ■

Videocast Viewing of VRC Seminars

Starting on January 23, 2001, and continuing weekly on Tuesdays (with a summer break), the VRC has held late-afternoon seminars on its own and others' cutting-edge research related to AIDS vaccine development.

The first talk, given by VRC director Gary Nabel, includes details of the steps taken to develop the DNA vaccine construct now being tested in the VRC's first clinical vaccine trial. Nabel also describes efforts to construct HIV-1 envelope mutants and to optimize delivery of candidate vaccines, as well as parallels between AIDS and Ebola virus—and the DNA prime-adenoviral vector boost strategy to protect animals against Ebola in studies conducted by VRC fellow Nancy Sullivan. This year's 28 VRC seminars may be accessed from <<http://vrc.nih.gov/cgi-shl/vrc/seminars2001.cfm>>.



STEM CELLS: DELAYED BUT NOT DENIED

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Paperwork

Investigators can click on each of the 11 cell line listings to get the information known about each line, as well as contact information for the labs offering the cells. Each line will have a unique NIH identifier that the researcher must include in his or her research plans. Extramural investigators will then need to go through the usual grant application procedures. Intramural investigators will need to secure the approval of their institute director and scientific director to obtain the cells. Also required will be detailed tracking of each cell line's identifier, a check on whether the cells are subject to provisions of human subjects research rules, a material transfer agreement, and shipping permits for cells imported from abroad.

Researchers who have initiated negotiations with providers and started the paperwork to obtain the cells may finalize their acquisitions and begin receiving cells in federally supported labs as early as December 7.

Starting Out

Baldwin anticipates that acquisitions and start-up might be hard. "The first six months may be a little rocky as things get going," she said. Scientists say there is a fine art to handling even the best-known cells. With little information on some of the cell lines, more than handling expertise may be needed.

In late summer, the Office of Technology Transfer (OTT) helped smooth the path to acquiring the cells. OTT negotiated an agreement with WiCell that would permit NIH-supported scientists access to the cells, free of onerous restrictions on reporting results or patenting new discoveries from the cells. An OSP staffer who has followed the stem cell issue credits OTT's Mark Rohrbaugh and Steve Ferguson with playing key roles in facilitating licensing agreements among the sources of cells that will encourage sharing of these research re-

sources. OTT is continuing to work on more agreements like the one with WiCell, which was expected to charge \$5,000 to transfer a culture of its cells. Other derivivers were expected to offer various arrangements and packages for acquiring their cells. And in November, a stem cell lab at Technion University in Haifa, Israel, led by Joseph Itskovitz, expressed interest in finding NIH collaborators.

Core Values

To help labs deal with some of the initial bumps, NIDDK scientific director Marvin Gershengorn is leading an exploratory committee to formulate plans for a core facility that would acquire and disburse information and cultures of human embryonic stem cells to intramural scientists. Gershengorn says the core lab

"will try to get our hands on every [ES] cell line we can."

"The most important thing will be recruiting a core lab director with experience working with ES cells," Gershengorn says. He envisions additional core staff of two technologists, with further growth depending on demand. The existence of a core lab "will not preclude any scientist from

getting their own cells," he says. It is uncertain how many labs will want to work through a core or face the learning curve on their own.

Gershengorn sees other advantages in the core. "I am very much a proponent of cores—they foster interactions and collaborations, and that would be a real benefit," with respect to stem cells. The core might also sponsor a seminar series or other activities to pull scientists out of the woodwork who have been working on ES cell-related issues on their own. Gershengorn says that especially as work moves toward clinical applications, it will be critical for ES cell



Celia Hooper

Marvin Gershengorn

researchers to have broad collaborations.

"I am very excited about stem cells," Gershengorn concludes. His own NIDDK lab and others will be pursuing new human ES cell work in close conjunction with ongoing transplantation research, in efforts to perfect pancreatic islet transplants to treat diabetes.

Labs across the NIH waterfront will be looking at the potential of ES cells in neurodegenerative diseases, heart disease, aging, and development—from

basic cell biology to specific therapeutic applications. Basic studies of the ES cells may point the way to methods for reprogramming less controversial adult cells to make them more useful in therapies.

Stem Cell Interest Group

Anticipating the stem cell developments, a new scientific interest group was launched this summer—see

<http://tango01.cit.nih.gov/sig/home.taf?_function=main&SIG_Info_SIGID=115>.

It got rolling with its first speaker on November 1—John Gearhart, the Johns Hopkins (Baltimore) investigator who first grew human embryonic germ cells, which are derived from fetal tissue and share some of the special properties of human ES cells.

Interest group leader Kevin Becker, from NIA's Baltimore campus, says interest in ES cells is high. "People are chomping at the bit," he said while waiting for the stem cell registry to finally make its appearance on the web. "It's a tidal wave about to happen." NIA scientists, he said, are planning experiments in anticipation of the cells' eventual arrival. Becker plans to use microarrays to follow the activation of genes during development, as he has been doing with mouse stem cells thus far.

Becker says the interest group is off to a good start, with standing room only at an organizational meeting. But he's hoping to get still more scientists—especially from the Bethesda campus—to join and help lead the enthusiastic group in the exploration of this newly opened research territory. ■



Celia Hooper

Wendy Baldwin

INTRAMURAL STEM CELL RESEARCH POLICY: FROM THE DDIR TO ALL INSTITUTE DIRECTORS AND SDs—AND TO ALL PIs

November 8, 2001

Dear Colleagues:

On November 7, 2001, NIH posted the embryonic stem (ES) cell registry (<<http://escr.nih.gov>>) on its website. This registry lists the cell lines that may be used in NIH-supported research. Providers of these cells have assured the government that they meet the President's eligibility criteria for ES cells that we may use. These providers are prepared to establish collaborations and material transfer agreements with NIH scientists to convey the cells to us.

I am hoping to help support a central core facility to maximize our efficiency and speed in acquiring the cells and learning about them. In the meantime, intramural scientists who are prepared to begin work more quickly may proceed to make individual lab arrangements with cell providers.

For each cell line, the Registry lists a unique NIH identifying code, as well as information on the providers of the cell lines. Scientists who want to work with these cells should discuss their plans with their Lab Chiefs and Scientific Directors and then contact the providers of the cells. On December 7, 30 days after the posting of the Registry, and withdrawal of the old ES cell guidance (*NIH Guidelines for Research Using Pluripotent Stem Cells as Applied to Human ES Cells*), scientists may transfer government funds to obtain the cells, bring them into NIH labs, and begin research on them.

NIH is accountable for all uses of ES cells. To this end, **you must track the unique identifier of all ES cell lines that you use throughout your work.** Specifically:

1. You must obtain written permission from your Institute Director, through your Scientific Director and Lab Chief, for each acquisition of an ES cell line. Your memo of acquisition must include

■ The unique identifier for each line you will be getting

■ The names of intramural staff who will be using the cells

■ The status of the cells with respect to human subjects research requirements (see below)

■ A copy of the Material Transfer Agreement with the cell provider (NIH has negotiated a model MTA with the Wisconsin group only (WA-series cells))

■ For all cells that come from foreign sources (ES-, SA-, KA- NC-, RL- or TE-series cells), you should indicate that you have completed and filed three import forms and paid the associated fees:

— Permits to Import or Transport Controlled Material or Organisms or Vectors Forms **16-3** and **16-7** from the USDA. (See <<http://www.aphis.usda.gov/ncie/>> to obtain information and the forms.)

— CDC's Application for Permit for Import or Transport of Agents or Vectors of Human Disease (Document #101000—may be obtained from <<http://www.cdc.gov/od/ohs/biosfty/impptper.htm>>) should be filed with the Quarantine Permit Service Office at NIH (301-496-2960). They will provide a courtesy letter to help with customs clearance. *Do not send the application to CDC.*

2. Scientific Directors must report all ES cell acquisitions to the Office of Intramural Research by forwarding a copy of the approved memos of acquisition to the DDIR (<mgottesman@od.nih.gov>; Bldg. 1, Rm.114, NIH, 20892-0001)

3. Each lab should be able to link its data and re-plated cells back to an original acquisition and cell line identifier.

4. Every report of research on the cells, including your ZO1 annual report and all publications, must include the unique identifier for the cells used.

Even with the approved cell lines, certain uses of ES cells are not allowed: Human pluripotent stem cells **may not** be used to create or contribute to a human embryo. The cells **may not** be used for research in which human pluripotent stem cells are combined with an animal embryo; and **may not** be used in combination with somatic cell nuclear transfer for the purposes of reproductive cloning of a human. Derivation and study of embryo germ (EG) cells—because they come from fetal tissue—fall under existing regulations regarding the use of fetal tissue in NIH-supported studies (additional guidance is expected; for now see

<http://grants.nih.gov/grants/policy/nihgps_2001/part_ii_2.htm#_Toc504811801a>).

The Office for Human Research Protec-

tions, DHHS, gives the following guidance on research involving human embryonic stem cells or human embryonic germ cells derived from fetal tissue:

In vitro research using cell lines that are already derived and established, and for which the identity of the donors cannot be determined, does not require IRB review and approval.

Research using cell lines that are identifiable with a donor, including cells that retain links to coded information that would allow identification of donors, is generally considered human subjects research. For cases in which the investigator obtains a written agreement from the holder of the identifiable private information (e.g., the deriver of the cell line) that such information will not be released to the investigator under any circumstances, IRB review and approval is not required. (See: <<http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm>>.)

For intramural scientists, this means you should determine with the provider whether the cells you seek can be linked to the donors. If so, you should contact the NIH Office of Human Subjects Research (301 402-3444) to determine what steps you need to follow.

At this time, an NIH committee is considering the establishment of an NIH ES Cell Core Facility which will be dedicated to acquiring, culturing, and distributing approved stem cell lines to intramural investigators. The Core may also establish and maintain a shared storehouse of knowledge on the cells, receiving and posting data as they and other NIH scientists collect it.

Additional information on stem cells, including the answers to frequently asked questions, is available on the web (<<http://escr.nih.gov>>). More background is posted at <<http://www.nih.gov/news/stemcell/index.htm>>. If you have further questions, you should send them to <DDER@nih.gov>.

—Michael Gottesman, M.D.
Deputy Director for Intramural Research

CLINICAL CENTER SETS NEW POLICY ON USE OF HERBAL AND OTHER ALTERNATIVE SUPPLEMENTS BY CC PATIENTS

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The escalating use of dietary supplements in the United States over the past few years, with herbal products representing the most rapidly growing segment, has generated new concerns related to patient safety.

These supplements are consumed by 30–40 percent of Americans, and an estimated 15 million adults are taking herbal products concurrently with prescription medication.¹ As a result, there has been a dramatic increase in published reports on adverse consequences of herb-drug interactions, including loss of drug efficacy, physiologic disturbances, skewed laboratory results, and compromised perioperative care.

These concerns for patient safety are reflected in specific questions posed by the Joint Commission on Accreditation of Healthcare Organizations to hospitals seeking accreditation. They ask how patients who bring herbal products from home are handled, whether herbs are on the hospital formulary, and whether physicians are required to assess the use of herbals during the hospital stay.²

Impact on Research

The effect of herbal and alternative supplement use by people participating in biomedical research protocols has been a concern of NIH's.³

Recently, NIH investigators reported a significant reduction in the bioactivity of the protease inhibitor indinavir—up to a 75 percent decrease—in HIV-infected patients who were prescribed indinavir and were also taking St. John's wort.^{4,5} The studies also showed that low plasma concentrations of protease inhibitors are a cause of antiretroviral resistance, treatment failure, and cross-resistance among members of this class of compounds. Such findings demonstrate that in some contexts, herbal supplements may not be the harmless agents some health-care workers take them to be.

How prevalent is the use of these natu-

ral products by patients enrolled in NIH clinical trials? In surveys conducted at the Clinical Center (CC), 25–42 percent of patients reported taking herbal and other supplements.^{6,7,8,9,10}

Encouraging Patient Disclosure

A major theme in complementary and alternative medicine literature is the communication barrier between physicians and their patients.¹¹ Though slowly changing, health professionals still do not routinely question their patients about use of herbals and other kinds of alternative supplements.

Understanding why patients seek out and use these products can help physicians and investigators detect such practices and discuss them more openly. Patients may have accepted anecdotal evidence or slick marketing as sufficient information for use and they may be unaware of the potential effect of supplements on research results, not to mention potential complications or adverse effects on their own health.

Furthermore, patients eager to be selected for a clinical trial may be hesitant, even if asked, to disclose anything that may threaten their acceptance into a protocol. They may be less reluctant once a clinical trial is under way.

Assessment of herbals and other alternative supplements may be omitted in a biomedical research setting, where significant focus is on the clinical trial. For an investigator to venture into these uncharted areas is to have to consider many issues not addressed in protocol development nor routinely raised during the institutional review board (IRB) process. However, there is a trend beginning to include questions about patient use of these natural products in protocols.

It is incumbent upon health-care providers at the CC to provide a safe environment for disclosure and to understand the strong beliefs many patients have in the value of alternative approaches.

Questions must be direct, open, and specific to avoid underreporting.¹² Fur-

thermore, to maintain a trusting credible relationship with their patients, physicians need to become educated about herbal and dietary supplements.¹³ Only through a combination of patient disclosure and availability of reliable information can there be informed decisions.

Clinical Center Policy

Understanding the complexity of the issue and recognizing the need for guidelines, the CC moved forward in early 2000 with an initiative to construct a policy to guide hospital staff in the management of patient use of herbal and alternative supplements.

An interdisciplinary task force was formed by the CC Quality Committee to assess physician, nurse practitioner, and physician assistant understanding of this issue. Further goals were to examine and

benchmark practice and policy in other hospitals, draft a policy based on findings, engage focus groups throughout the CC to assist in shaping the final form of the policy, and gather input on how to achieve successful implementation.

On May 15, 2001, the CC's Medical Executive Committee approved a policy on the "Use of patient's own dietary supplements and alternative consumable products brought into the Clinical Center." The policy took effect June 28, 2001.

The underlying basis of the policy was that "Patients shall use their own dietary supplements and alternative consumable products only upon authorizing orders by their CC physician." This would be accomplished by the following procedures:

■ Through the established admission assessment process, within 8 hours of admission the nurse will screen all in-



Herb Research Foundation

Two of the more popular
herbal products, St. John's wort
(above) and echinacea

patients for current use of dietary supplements and alternative consumable products.

■ Products currently being used by a patient will be promptly reported to the physician in order to determine whether inpatient use is allowed. If inpatient use is allowed, the physician will generate MIS orders to authorize use of each product by name. If the physician does not specifically authorize usage, the patient will not be allowed to take the product.

■ Patients will be responsible for the initial and ongoing supply of these products during the course of the hospital stay.

In the focus groups held prior to policy approval, medical staff strongly voiced their need for resources to support decision-making in clinical practice—the tools to learn about these products and easy access to existing scientific evidence on risk. In response, the CC secured a site license for an online database of herbal monographs. The selection of the *Natural Medicines Comprehensive Database*

<[http://](http://www.naturaldatabase.com/)

www.naturaldatabase.com/>

was based on its scientific integrity, completeness, ease of navigation, timely updating of existing data, and ongoing addition of new products as they become popular.¹⁴ The database became available on desktops throughout the CC on August 1, 2001.

Policy Implementation

The standards of practice for nurses were changed to incorporate use of herbal and alternative supplements as a mandatory area of inquiry during the admission assessment process, and computerized nursing documentation screens were modified accordingly. A new set of physician order screens was also constructed to document approval of continued use by a patient of his or her own supply of such a supplement during hospitalization.

It was also decided that the same process would be applied in the outpatient setting: Outpatient nurses would use the same standard of practice and documentation pathway, ascertaining whether patients on protocol were using herbal or other supplemental products and then alerting the physician to the findings. The physician would then determine whether the patient should con-

tinue use—and, ideally, engage in open dialogue with the patient about the issues that informed that decision.

Around the Corner

The implementation of the Herbal and Alternative Supplement Policy will inevitably lead to other necessary steps within the CC to help raise awareness and to ensure compliance. IRBs might contemplate including a section on patient use of herbal and alternative supplement products in all protocols; expectations that patients will disclose and discuss such use with their physician might be included in the written informed consent.

The challenge to clinical investigators and biomedical research facilities is to create policies and follow practices that respect the choices of individuals participating in clinical trials while ensuring patient safety and preserving the scientific integrity of the study. ■

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Targeting Lupus

Targets for New Therapeutics," a conference on systemic lupus erythematosus (SLE), will be held **January 10-12, 2002**, at the Hyatt Regency, Bethesda.

Sponsored by NIAMS, NIAID, NIDDK, ORWH, the S.L.E. Foundation, and the Lupus Research Institute, the conference will explore extrinsic and intrinsic triggers of autoimmunity, SLE genetics, immunoregulatory mechanisms, mediators of tissue injury, and novel therapies.

Posters and workshops will cover basic mechanisms, clinical features and epidemiology, and outcome measures. A plenary will address SLE clinical trials. Registrants are invited to submit abstracts for poster and/or oral presentations related to these topics. The abstract deadline is **November 27, 2001**. For info on the meeting and abstract submission, call (202) 973-8680 or e-mail

<niams@courtesyassoc.com>.

A registration brochure is at <<http://www.niams.nih.gov/ne/mcw/index.htm>>.

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Leslie Biesecker received his M.D. from the University of Illinois in 1983 and did postgraduate work at the University of Wisconsin, Madison (pediatrics), and the University of Michigan, Ann Arbor (medical and molecular genetics), before joining the Genetic Diseases Research Branch of NHGRI in 1993. He is now a senior investigator in that branch.

My research focuses on the clinical and molecular delineation of human malformation syndromes. Currently we are working on two classes of disorders, those that involve classic multiple congenital anomaly syndromes and disorders with progressive postnatal overgrowth.

The multiple congenital anomaly syndromes include Pallister-Hall syndrome, Greig cephalopolysyndactyly syndrome, McKusick-Kaufman syndrome, Bardet-Biedl syndrome, and the Lenz microphthalmia syndrome. These disorders include varying combinations of polydactyly and central nervous system and visceral malformations, and some also have functional complications such as mental retardation, seizures, and visual loss.

Our research is both clinical and molecular. The clinical component includes phenotypic characterization and natural history studies to delineate the range and consequences of the disorders. For many of these disorders, the range of severity and the long-term prognosis are unknown.

Several of the disorders under study are frequent in closed Anabaptist sects such as the Old Order Amish and Mennonites of Lancaster County, Pa., and certain regions of Ohio and Kentucky. These disorders are approached via field studies to evaluate patients, computerized genealogical analysis, and clinical testing and treatment.

In the laboratory, we perform classical positional cloning studies to find the genes that cause these syndromes, perform genotype-phenotype correlations, and delineate the pathogenesis of these disorders using animal models and cell biological approaches.

The first disorder we studied was the Pallister-Hall syndrome, which we showed is caused by mutations in the *GLI3* zinc finger transcription factor. This discovery demonstrated that Pallister-Hall syndrome was allelic to Greig cephalopolysyndactyly syndrome, a distinct mal-

formation syndrome. We have developed a model to explain the genesis of two distinct syndromes from mutations in a single gene and are carrying out ongoing studies to support that model.

The other disorders we study were selected because they have physical features that overlap with the Pallister-Hall and Greig cephalopolysyndactyly syndromes. We hypothesize that disorders that share manifestations will also share pathogenic mechanistic features in development.

We are also studying a disorder of postnatal overgrowth, the Proteus syndrome. This disorder includes severe disproportionate overgrowth of many tissues, occasional malformations of the

limbs and central nervous system, cutaneous nevi, and other manifestations. It appears to be associated with two serious complications—massive pulmonary embolism and tumor predisposition. The disorder is hypothesized to be caused by somatic mosaicism for a mutation that is lethal in the nonmosaic state. This model explains the sporadic nature of the disorder, the patchy distribution of overgrowth, and its discordance in monozygotic twins.

We are testing this model by screening for alterations in gene structure or expression and comparing affected and unaffected tissues of patients with this condition.

This project also has significant clinical and laboratory components. Clinically, we are conducting a longitudinal natural history study to determine the range of manifestations, severity, and natural history of the condition. In the laboratory, we are using modern molecular techniques—including microarray expression analysis, representational difference analysis, and two-dimensional Southern analysis—to characterize gene alterations.

Understanding the cause of Proteus syndrome will be important both for developing specific therapies and for understanding the mechanisms of control of human postnatal growth.

Kevin Brown received his medical degrees from Cambridge University in England in 1982. He did internships in internal medicine and infectious diseases

in London before specializing in virology. He joined the Clinical Hematology Branch in NHLBI as a visiting associate in 1992 and became an investigator in the Hematology Branch in 1996. He is now a senior investigator in the Hematology Branch, NHLBI.

The main focus of my research is the study of the interaction of viruses with hematopoiesis. My work can be broadly divided into two main areas: studying the interaction of known viruses—such as the small DNA viruses—with blood cells and their precursors; and looking for novel viruses that may be associated with bone marrow failure. These studies involve a wide range of different experimental approaches, including molecular biology, tissue culture, and animal-based technologies.

Small DNA viruses and hematopoiesis. Parvoviruses are small DNA viruses that cause disease in both humans and animals. However, the only parvovirus known to cause disease in humans is parvovirus B19. Approximately 60 percent of adults show evidence of previous infection.

Acute B19 infection can cause fifth disease in children, polyarthropathy syndrome in adults, transient aplastic crisis in patients with underlying chronic hemolytic anemia, chronic anemia due to persistent infection in immunocompromised patients, and fetal loss in pregnant women.

B19 virus cannot be readily grown in cell culture and, when I started my studies, there was no animal model for B19 infection. However, studies with human bone marrow cultures from volunteers had shown that the virus could replicate in human red cell precursors.

My initial focus on joining the Clinical Hematology Branch was to characterize the cellular receptor for B19. Using a modification of the hemagglutination assay, I was able to identify the receptor as globoside, or blood group P antigen, a glycosphingolipid found on the cell membranes of red cells and their precursors.

Rare individuals do not have globoside on their red cells, and I was able to show that these individuals did not have evidence of previous infection with B19, and in vitro their bone marrow could not be infected with B19 virus, even at



Leslie Biesecker



Fran Pollner

Kevin Brown

high viral concentrations.

Globoside is also found on fetal myocardial cells and endothelial cells and in placental tissue, and this identification of the receptor has prompted other studies to determine the full complement of diseases caused by this virus. Further studies are also in progress to identify other factors, including a possible second receptor, that are important in the narrow tropism of this virus. Globoside is also found on the cell surface of nonhuman primates' erythrocytes, and although we can show that B19 will replicate in the bone marrow of cynomolgus monkeys *in vitro*, inoculation studies of primates have been unsuccessful.

While these animal studies were underway, I was asked to study a fatal outbreak of anemia in cynomolgus monkeys at Wake Forest University in Winston-Salem, N.C. There we identified a simian parvovirus (SPV), distinctly different from but related to B19. With colleagues now at the University of Minnesota, we have cloned and sequenced the virus. Infection studies indicate that cynomolgus infection with SPV mimics human B19 infection, and we are currently using it as an animal model to study parvovirus-induced fetal infection. Similar studies of outbreaks of anemia in other primate species have allowed me to identify two other primate parvoviruses, with the possibility that they may also be exploited as animal models.

Novel viruses and hepatitis-associated aplastic anemia. Hepatitis-associated aplastic anemia (HAA) syndrome is a bone marrow failure occurring usually within two to three months of an episode of non-A, non-B, non-C hepatitis. Classically it affects young people, especially boys and men (mean age 20 years). If untreated, it is usually fatal. The etiology is unknown, but scientists think it is triggered by a viral infection.

In collaboration with Neal Young in the Hematology Branch, I have been collecting epidemiological and clinical data on HAA and samples from these patients and control subjects. We have shown that the patients have evidence of activated cytotoxic lymphocytes in their peripheral blood and that many of these patients can be successfully treated with immunosuppression. In addition, we have observed some HLA associations, supporting the hypothesis that the bone marrow failure is mediated through immunopathological mechanisms.

Recently, a number of putative hepatis

tis viruses have been described, including hepatitis G (or GBV-C), TT virus, SENV, and a novel picornavirus A2 that we described. My studies indicate that none of these appear to be associated with HAA. We have also inoculated patient material into primates, rodents, and tissue culture, but so far all the studies are negative for viruses, as are screens of a number of libraries made from patient material. We are currently looking at the immunological profile, especially at the levels of different cytokines and other antigens, in patient and control tissue to identify better markers and to determine which samples to use for gene subtraction and DNA chip analysis.

Robert Innis received his M.D. degree from the Johns Hopkins University in Baltimore in 1978 and a Ph.D. in neuropharmacology from Johns Hopkins in 1981 under the mentorship of Solomon Snyder. He completed a residency in psychiatry at Yale University in New Haven, Conn., in 1984 and then joined the Yale faculty in the departments of psychiatry and pharmacology. In October 2001, he came to NIH as chief of a newly formed Molecular Imaging Branch at NIMH.

The overall goal of this new branch is to elucidate pathophysiological mechanisms associated with neuropsychiatric disorders. We expect that such knowledge will ultimately decrease the burden of these illnesses by suggesting better therapies.

Several investigators in this new branch are directly linked to NIMH's new Mood and Anxiety Disorders Program, directed by Dennis Charney. Patients with these psychiatric disorders will receive the focused, although not sole, attention of this branch.

The primary methodologies used by investigators in the Molecular Imaging Branch are PET (positron emission tomography) and NMR (nuclear magnetic resonance).

New PET radiotracers are synthesized for use as *in vivo* ligands to measure many different molecular targets, including membrane-bound receptors, proteins associated with intracellular signal transduction, and other expressed genes. Several NMR methods are also studied to measure molecular targets: magnetic resonance spectroscopy, local neuronal activity (functional MRI), and structure of

the brain (structural MRI).

My own area of research focuses on the use of PET to localize and quantify molecular targets in the brain. The overall goals of my laboratory are to develop new radiotracers that image molecular targets in the brain, to evaluate these tracers in animals and healthy human subjects, and then to extend their use to patients with several neuropsychiatric disorders.

The PET research proposed in my lab critically depends on sophisticated radiochemistry, and NIMH is fortunate to have recruited Victor Pike earlier this year to direct the section on PET radiochemistry. Pike is internationally renowned as a radiochemist and was formerly head of the Chemistry-Engineering Group at the Hammersmith PET Center in London, England [see *The NIH Catalyst*, May-June 2001, page 13].

Because PET was not available at Yale in the 1980s, I used SPECT (single photon emission computed tomography) for studies of receptors in the brain. My work on benzodiazepine receptor imaging clearly confirmed that SPECT was capable of quantitative measurements, with

validation comparable to that in PET.

My SPECT work expanded to include other neurotransmitter systems, including dopamine, serotonin, GABA, and acetylcholine.

In these earlier studies, I helped to develop several new radiotracers, including probes for the dopamine transporter. In fact, the dopamine transporter is a biological marker for Parkinson's disease—and SPECT imaging of the dopamine transporter was approved last year in several European countries to aid in the early diagnosis of Parkinson's disease. To my knowledge, this SPECT tracer is the first biological test for Parkinson's disease and also the first neuroreceptor imaging agent approved for clinical use.

As mentioned above, while at Yale, I performed neuroimaging primarily with SPECT. SPECT cameras are widely available in community hospitals and use radionuclides with relatively long half-lives: 6 to 12 hours for SPECT vs. one-half to two hours for PET.

The longer half-life allows SPECT radiopharmaceuticals to be distributed over wide distances. However, SPECT has significantly lower sensitivity than PET



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(~100-fold) and lower anatomic resolution (9–12 mm vs. 3–5 mm). I performed a relatively small amount of PET research at Yale, due to the university's limited resources for this methodology.

In contrast, the NIH Clinical Center has substantial PET resources under the direction of William Eckelman: three cyclotrons, three whole-body PET cameras, and a sizeable radiochemistry lab and staff. In addition, Mike Green (Nuclear Medicine) has continued years of PET camera development and has constructed a new high-resolution device for imaging in rats and mice.

Realizing the critical role of radiochemistry, NIMH committed significant funds to expand in this area and enhance the existing facilities. A new radiochemistry lab is currently under construction in the basement of Building 10, and additional "cold" (or nonradioactive) chemistry labs are planned for adjacent areas in the new Clinical Center building.

In addition, NIMH spearheaded efforts of several institutes to purchase a new state-of-the-art high-resolution, high-sensitivity PET camera that can image both the human head and rodents. This new device should be constructed and delivered in about one and a half years.

I am truly enthusiastic about these and other neuroimaging opportunities that are emerging at NIH. New tracers that are currently available or under development include probes for the serotonin transporter, amyloid, cortical dopamine receptors, the substance P receptor, norepinephrine transporter, nicotinic acetylcholine receptor, metabotropic glutamate receptor, a PET reporter probe system, and more promising measures of intracellular signal transduction. From my perspective, a major attribute of NIH is the ability to collaborate with other researchers, both in the development of new radiotracers and in their use in both animals and humans. I look forward to hearing from intramural collaborators with these interests.

Xinhua Ji received his Ph.D. in chemistry from the University of Oklahoma in Norman in 1990. He was a postdoctoral fellow and then a research assistant professor at the Center for Advanced Research in Biotechnology of the University of Maryland Biotechnology Institute in Rockville, Md., and the National Institute of Standards and Technology before joining the NCI-Frederick in 1995. He is now a senior investigator and chief of the

Biomolecular Structure Section, Macromolecular Crystallography Laboratory, NCI.

As a structural biologist and a chemist with medical experience, I am interested in the structure and function of biomolecules with anticancer and antimicrobial significance and in structure-based drug design. To pursue these subjects, I have established collaborations within NIH as well as with extramural investigators.

The systems I am working on are at three different points on the basic-to-applied spectrum of research studies: Pro-drug design research with minimal basic emphasis for glutathione S-transferase (GST); basic structure and activity studies of 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase (HPPK) with some initial efforts in drug design; and basic studies of the structure and function of two potential anticancer targets—G protein ERA and ribonuclease III (RNase III), which play essential roles in RNA processing control.

GST represents a superfamily of detoxification enzymes. Many tumors become drug resistant by overexpressing π -class GST (GSTP), one of the major GST isoenzymes in humans. We have been attempting to design agents that will overcome the drug resistance of cancer cells that overexpress GSTP. The comparison of the active site architectures and transition-state analogs of GST isozymes revealed a strategy: generating nitric oxide (NO) selectively in the active site of isoenzyme. Application of this strategy yielded a GSTP-selective NO donor that improves the potency of arsenite, a clinically useful anticancer agent, in cancer cells overexpressing GSTP.

Folate cofactors are essential for life. Mammals derive folates from diet; most microorganisms must synthesize folates de novo. HPPK is the first enzyme in the folate biosynthetic pathway. It is not the target for any existing antibiotics—and is therefore an ideal target for developing novel antimicrobial agents to fight the worldwide crisis of antibiotic resistance.

HPPK contains 158 amino acids and is thermostable, which also makes it an excellent model system for the mechanistic study of pyrophosphoryl transfer.

Having elucidated high-resolution (up to 0.89 Å) structures of well-chosen complexes, we have mapped out the trajectory of pyrophosphoryl transfer. This work also reveals unusual conformational changes of HPPK in its catalytic cycle.

The structural information is now the basis of inhibitor design effort. We have synthesized a bisubstrate-mimicking inhibitor and a one-substrate analog and determined the crystal structures of HPPK in complex with these inhibitors.

ERA and RNase III play key roles in the control of gene expression. ERA is an essential GTPase found in every bacterium sequenced to date. In these bacteria, ERA has a regulatory role in cell cycle control by coupling cell growth rate with cytokinesis.

A highly conserved ERA homolog is also found in humans and is a candidate for a tumor suppressor. Our crystal structure of ERA reveals a novel protein architecture that consists of a Ras-like NH₂-terminal domain and a K homology-module-containing COOH-terminal domain. Together with other observations, the structure indicates that ERA interacts with ribosomal RNA 16S.

In the crystal lattice, ERA molecules form loosely associated dimers. Previously, however, no dimer had ever been detected in solution. Guided by our hypothesis of a monomer-dimer conversion mechanism, we demonstrated that dimerization is indeed essential for RNA binding in vivo.

RNase III family members are among the few nucleases that show specificity toward double-stranded RNA (dsRNA). Evolutionarily, RNase III is conserved in bacteria, worms, flies, plants, fungi, and mammals. RNase III from bacteria is the simplest, containing an endonuclease domain and a dsRNA-binding domain.

Our structure of the catalytic domain of *Aquifex aeolicus* RNase III reveals another new protein fold and suggests a mechanism for dsRNA cleavage. Every member of the RNase III family contains one or two copies of such endonuclease domain(s).

Therefore, the information derived from our structure also sheds light on the structure and function of other RNase III enzymes, such as Dicer. Dicer plays an essential role in RNA interference, a broad class of RNA silencing phenomena found in fungi, plants, and animals.



Xinhua Ji

Allan D. Kirk received his M.D. from Duke University, Durham, N.C., in 1987 and completed his general surgery residency at Duke in 1995. He also did several years of basic work with Olivera Finu and earned his Ph.D. in immunology from Duke in 1992. He completed a multiorgan transplantation fellowship at the University of Wisconsin, Madison, in 1997 and over the past four years has been a principal investigator at the Naval Medical Research Center in Bethesda. In 1999, a formal collaboration was forged between the U.S. Navy and NIDDK to allow for a combined basic and clinical research effort to establish a means of inducing transplantation tolerance. He has served as the section chief of transplantation surgery for the Transplantation and Autoimmunity Branch of NIDDK since that time. He now joins the NIH as a senior investigator.



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Allan Kirk

of transplantation to test therapies for initial clinical use. Therapies that show promise in these models are investigated in humans at the Clinical Center under approved renal transplant protocols.

My lab is investigating several methods for tolerance induction. One critical regulatory pathway involved in T-cell immunity involves the co-stimulation receptor-ligand pair CD40:CD154. We have been successful in targeting CD154 with monoclonal antibodies to prevent allograft rejection in nonhuman primates without chronic immunosuppression. We are now evaluating multiple sources of anti-CD154 preclinically and evaluating other agents that work synergistically in this system in hopes of moving this approach into the clinic.

Of particular interest is the expression of CD154 on activated platelets and the implications this has for immune activation caused simply by surgical trauma. We are particularly focused on platelet-monocyte interactions. We hypothesize that trauma-induced platelet activation contributes to initial antigen presenting cell activation and maturation. We are also investigating other co-stimulatory molecules, including the B7 molecules, CD80, and CD86.

Another favored hypothesis is that transient immune depletion prevents trauma-induced alloimmune activation and may thus skew an alloimmune response towards tolerance rather than rejection. This hypothesis is the basis for two clinical trials.

Using the monoclonal antibody Campath-1H or, alternatively, the polyclonal antibody preparation thymoglobulin to temporarily deplete T-cells prior to allograft reperfusion, we have been able to substantially reduce the need for postoperative immunosuppression in humans. This is presumably due to the avoidance of antigen presentation to T-cells at the peak of immune activation—the surgical procedure itself.

We are now modeling several variations of this approach in nonhuman

primates to understand how a reconstituting immune system interacts with a transplanted organ. Again, monocyte activation plays a key role in this response, and we are evaluating human allograft-derived monocyte populations to gain clues into their regulation at the time of a traumatic insult. CD40 ligation clearly plays a role in this approach as well, though responses to reperfusion-associated cytokines and responses to graft-derived cellular debris or apoptosis appear to be important immune modulators.

King Li received his M.D. in 1981 from the University of Toronto, where he then completed a residency in diagnostic radiology. After completing a fellowship in magnetic resonance imaging at the University of Michigan, Ann Arbor, he was an associate professor of radiology at Stanford (Calif.) University Medical Center. He came to NIH earlier this year as associate director of the CC Radiology and Imaging Sciences Department and director of diagnostic radiology.

Although my clinical interest is in abdominal imaging with an emphasis on magnetic resonance imaging (MRI), my research focus is on molecular and functional imaging and exploiting the synergy between imaging and molecular tissue-analysis techniques.

From the time of the first X-ray, medical imaging has served a vital function for

medical research and diagnosis by permitting researchers and clinicians to assess, in real time and a spatially resolved manner, what is happening in vivo. The recent explosion of information in the fields of genomics and proteomics has provided a rich ground for the discovery of molecular targets for therapeutic and/or diagnostic agents. The major goal of my research is to combine these endeavors and use imaging tests as in vivo surrogates for tissue analysis such as functional genomics and proteomics.

Tissue analysis data should provide new targets for target-specific imaging and image-guided therapeutic agents. The resulting agents can then be used to provide individualized in vivo assessments of the temporal and spatial distribution of the important molecular tar-



Fran Pollner

King Li

When patients undergo an organ transplant, they are required to take immunosuppressive medications for life to prevent immune rejection of the transplanted organ. These drugs are relatively nonspecific and exact a significant cost in terms of infectious, malignant, and physiological side effects. Thus, transplant patients trade a disease for a condition. Conventional wisdom has held that since the immune system causes rejection, it must be suppressed to prevent graft loss. My lab, and others, are showing otherwise.

The immune system is not an offensive system devoid of regulation. Rather, it is an elegant defensive network that is tightly regulated to provide protective immunity through measured responses to specific threats to homeostasis. As such, it must downregulate responses as well as augment them, and it is as capable of preventing rejection as it is of causing it.

My research aims to understand the regulatory aspects of immunity and exploit them to achieve transplant tolerance—a state in which the immune response favors acceptance of an organ rather than rejection. Our primary goal now is to take promising therapies from the laboratory into proof-of-concept clinical trials. My group thus uses both rodent and nonhuman primate models

RECENTLY TENURED

gets. With this approach, therapeutic regimens can be individualized and tailored according to the imaging data obtained at different times over the course of treatment. As a result, we can ensure that the therapeutic regimen is always the most appropriate, given the pattern of gene and protein expression at different times and in different spatial distributions throughout the course of the disease.

My specific research projects can be broadly grouped into four areas that fit in very well with major research initiatives of the NIH.

In vivo monitoring of physiology and pathology using MRI. We have validated MR blood flow measurement techniques and in vivo MR oximetry in animal models and applied these techniques to different animal models of mesenteric ischemia. We have also shown that these techniques are potentially useful in diagnosing and monitoring acute and chronic mesenteric ischemia in patients. In the future, I would like to extend this research to other areas, including the renal vascular bed and coronary circulation.

Development of novel target-specific contrast and therapeutic agents. At Stanford, I recruited a multidisciplinary team including chemists, molecular biologists, and radiologists in developing novel target-specific contrast and therapeutic agents. Seven years of work led to a patented development of polymerized liposomes for target-specific delivery of contrast and therapeutic agents to endothelial receptor target sites.

The advantage of using polymerized liposomes include long recirculation time, multivalency, high payload, low toxicity, and ease of chelating ligands or antibodies and drugs on the surface. Preclinical trials of these particles for targeting vessels in tumor angiogenesis are very promising.

Image-guided drug delivery. In the past four years, I have been working on image-guided, focused ultrasound energy to disrupt endothelial and interstitial barriers to facilitate drug delivery to specific target sites in the body. This research has already led to a patent and several publications. We have shown that using this approach, the delivery of liposome-encapsulated doxorubicin (Doxil) to mouse tumors can be increased as much as 200 percent.

In addition, we have shown that this technique can be used to facilitate delivery of plasmid DNA to rabbit muscles. This technology can potentially aid the delivery of many different biologically active agents to any tissues accessible by ultrasound with high spatial accuracy and minimal or no permanent damage to the tissue.

In vivo cellular and molecular imaging. Another multidisciplinary project at Stanford was the application of a large variety of imaging techniques—including MRI, optical imaging, SPECT, and PET—to study various diseases in animals and humans. We also used the information obtained from a combination of imaging tests to guide tissue biopsies and process these tissues using immunohistochemistry, functional genomics, proteomics, and other tissue analysis techniques.

This led to several interesting molecular targets for solid tumors. We are now validating the new targets and developing imaging probes for monitoring them in vivo. We are planning to extend this approach to study other disease processes.

Michael Seidman received his Ph.D. in biochemistry from the University of California, Berkeley, in 1975. He held postdoctoral fellowships in virology at NIAID and Princeton (N.J.) University. In 1980 he joined NCI, where he and his colleagues developed the *supF* reporter system, which has received extensive application in the field of mammalian mutagenesis. He then directed molecular and cell biology programs in the biotechnology industry for a number of years before joining NIA in 1998. He is currently a senior investigator and chief of the Section on Gene Targeting in the Laboratory of Molecular Gerontology, NIA.

I have been interested in problems associated with genome stability for much of my career. In the past five years, I have turned from studying mechanisms of mutagenesis in mammalian cells to developing an approach that would permit facile gene targeting and genome manipulation, that is, directed mutagenesis in mammalian cells.

The strategy is based on a discovery made at NIH more than 40 years ago (G. Felsenfeld, D. Davies, and A. Rich (*J. Am. Chem. Soc.* 79:2023, 1957)). Only a few years after the elucidation of the structure of the DNA double helix, these scientists showed that certain DNA se-

quences could form a sequence-specific triple helical structure. They established a field of study that continues to this day, motivated, in part, by the tantalizing possibility that triple helix-forming oligonucleotides could be used as gene-targeting reagents in living cells.

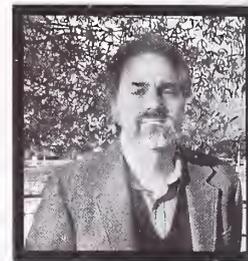
Unfortunately, conventional DNA oligonucleotides do not form stable triplexes under physiological conditions. Furthermore, the protein-DNA complexes that constitute eukaryotic chromatin have been shown to block triplex formation. For years, these have seemed to be insurmountable obstacles.

To circumvent these problems, we exploited recent advances in oligonucleotide chemistry to construct reagents that can form stable triplexes in vitro under conditions that approximate the intracellular environment. We linked a DNA-reactive mutagen to these novel oligonucleotides that were designed to form a triplex with a specific sequence in the mammalian genome. We then showed that these could be used to knock out a gene in cultured cells.

These experiments were the first demonstration of chromosomal targeting in living mammalian cells by triplex-forming oligonucleotides. Since then we have synthesized oligonucleotides with a variety of modifications and have greatly increased the bioactivity of these reagents.

An intriguing implication of these studies is that some fraction of the target sequences must be in a chromatin structure that permits access to the oligonucleotide and triplex formation. It seems likely that these reagents will be used as probes of chromatin structure as well as for genome manipulation.

Our current work focuses on identifying the properties of these oligonucleotides that support bioactivity; expanding the range of chromosomal targets; determining the influence of transcription, replication, and chromatin structure on target accessibility; and understanding how cells respond to targeted DNA damage. Practical applications of this work would include gene knockout for target validation, construction of novel cell lines and transgenic animals, and, perhaps in the future, some form of gene therapy. ■



Fran Pollner

Michael Seidman

Clinical Research Courses

Principles and Practice

The deadline for registering for the 2002 "Introduction to the Principles and Practice of Clinical Research" is **January 4, 2002**. The course will run from January 15, 2002, to April 23, 2002. Classes will be held on the NIH campus on Tuesday and Wednesday evenings from 5:30 p.m. to approximately 7:00 p.m. There is no charge for the course, but students must buy a textbook. Students will receive a certificate upon successful completion of the course and final exam. For additional information regarding coursework or to register, please visit the course website:

<<http://www.cc.nih.gov/od/core>>.

NIH-Duke Masters Program

Applications for the 2002-2003 NIH-Duke Training Program in Clinical Research are available in Building 10, Room B1L403.

Designed primarily for clinical fellows and other health professionals who are training for careers in clinical research, the program offers formal courses in research design, statistical and decision analysis, research ethics, and research management.

Courses for this program are offered at the Clinical Center by means of videoconferencing from Duke or on-site by adjunct faculty. Academic credit earned by participating in this program may be applied toward satisfying the degree requirement for a Master of

Health Sciences in Clinical Research from Duke University School of Medicine in Durham, N.C.

Enrollment in this program is limited. The deadline for receipt of applications is **March 1, 2002**. Applicants who have been accepted into the program will be notified by July 1, 2002. Applications from both intramural and extramural divisions are encouraged.

For additional information regarding course work and tuition costs, please refer to the course website at

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

E-mail queries regarding the program may be addressed to William E. Wilkinson, program director, at

<tpcr@mc.duke.edu>.

NCI Recognizes Outstanding Mentors



Center Stage. (left to right) Donna Vogel, director of the NCI Fellowship Office, Lalage Wakefield, Frank Gonzalez, Elaine Jaffe, and Alan Rabson, NCI deputy director

The first NCI Outstanding Mentor Award was presented to three investigators at the annual NCI awards ceremony: Elaine Jaffe, deputy chief of the Laboratory of Pathology; Frank Gonzalez, chief of the Laboratory of Metabolism; and Lalage Wakefield, senior investigator.

Eight NCI investigators were recognized as Mentors of Merit: Frank Balis, Frank Cuttitta, Scott Durum, Genoveffa Franchini, Ira Pastan, Mark Schiffman, Thomas Walsh, and Grace Yeh. ■

Seminar Series for Women in Science

The Bethesda chapter of AWIS (Association of Women in Science), with support from ORWH, OD, and the Office of Community Liaison, announces the following seminar series:

■ Thursday, **December 6, 2001: How Networking Really Works**, Hrisi Samartzidou, microarray systems, Molecular Dynamics/Amersham Pharmacia Biotech

■ Thursday, **January 31, 2002: Scientists Shaping Policy**, Robert Cook-Deegan, Robert Wood Johnson Foundation investigator and director, Robert Wood Johnson Health Policy Program, Institute of Medicine; Josette Lewis, biotechnology advisor, Center for Economic Growth and Agricultural Development, USAID

■ Thursday, **March 21, 2002: Breaking the Glass Ceiling: A Networking Success Story**, Jozetta Todd, vice president of information technology, Abbott Laboratories

■ Thursday, **April 25, 2002: Networking Opportunities Workshop**, a celebration of the **AWIS 30th Anniversary** with NIH intramural researchers and extramural administrators and people from other government agencies and industry

Seminars are held in the chapel at the Cloisters (Building 60) on the NIH campus from 4:30-6:00 p.m. Speaker presentations start at 5, with networking and light refreshments before and after. For information, contact Mini Varughese (301-523-6322) <gthomas@gateway.net> or Meredith Temple (301-496-1447) <templem@ninds.nih.gov> or visit the AWIS website:

<www.awisbethesda.org>.

CSR Training Program

The Center for Scientific Review (CSR) is seeking recruits for its Review Internship Program, which offers training in scientific research administration. NIH intramural scientists interested in gaining first-hand experience with the peer review process are encouraged to apply by **February 1, 2002**, for positions that will start **August 1, 2002**. Additional information and application forms can be found at <<http://csrweb.nih.gov/Internship/Internship2002.htm>>.

A forum to discuss and answer questions about the program will be held on **January 14** from 1:00-3:30 p.m. in Building 31C, 6th-floor Conference Rooms 6 and 10. General inquiries can be directed to Mary Elizabeth Mason at 301-435-1114. ■



"Gene" Expression

CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in five areas: embryonic stem cell research, vaccine research, NIH graduate partnerships, CC patient use of alternative products, and human research protections.

Send your responses on these topics or comments on other intramural research concerns to us via e-mail:

**<catalyst@nih.gov>;
fax:402-4303; or mail:
Building 2, Room 2W23.**

In Future Issues...

- Bench-to-Bedside:
Griff Rodgers
- Animal-Imaging
Facility
- Cancer Vaccines

1) How will availability of human embryonic stem cells influence your scientific work? What exciting science do you think will emerge from the study of human embryonic stem cells?

2) Should the Vaccine Research Center continue its focus on HIV vaccines or, given recent events, accelerate the timetable for broadening its approach?

3) The NIH Graduate Partnerships Program is growing. What effect do you think this will have on NIH?

4) Do you feel comfortable with the Clinical Center's new strategy to handle the use of herbs and other alternative agents by patients on protocol?

5) What is your opinion of the NIH human research protection program? What do you think of the idea of formal accreditation of such programs?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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