The NIH CATION FOR NIH INTRAMIRAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH 🗰 OFFICE OF THE DIRECTOR 🗰 VOLUME 12, ISSUE 4 🗰 JULY-AUGUST 2004

Nonmyeloablative Conditioning OUTPATIENT STEM-CELL TRANSPLANTATION A FIRST AT NIH

by Fran Pollner



Breaking new ground: Ricbard Childs (left) and Ramaprasad Srinivasan, medically responsible investigator and principal investigator, respectively, of the first NIH study that involves transplantation on an outpatient basis

o borrow an old merchandising slogan, it's not your grandfather's allogeneic stem-cell transplantation.

It's a formula for transplantation so different from the characteristically toxic standard myeloablative procedures, it can be done on an outpatient basis.

All that's missing are the patients. So far, one of a projected 58 patients has been enrolled in the "phase I/II study of HLA-matched mobilized peripheral blood hematopoietic stem cell transplantation for advanced mycosis fungoides [MF]/Sezary syndrome using nonmyeloablative conditioning with Campath-1H."

But the PIS—NCI's Ramaprasad Srinivasan and NHLBI's Richard Childs—are optimistic. The study is estimated to last for three to five years, and they expect that accrual will speed up once the anticipated favorable responses with the first few patients become known. *continued on page 6*

Worksbop Explores Adult Stem-Cell Research NIH CORE FACILITY SUPPORT SOUGHT FOR 'TRANSITIONAL' STEM-CELL RESEARCH

by Celia Hooper

R adical new therapies using today's government-approved embryo stem-cell lines may still be five or more years from trials in patients. In the meantime, NIH scientists developing therapies based on adult cells are making interesting strides in basic and clinical studies.

At an NIH workshop in late May, these investigators said they hope their realworld experience turning scientific concepts about stem cells into human celltherapy trials will also ultimately facilitate embryo stem-cell treatments.

Speaking at the May 24 workshop, "Clinical Applications of Stem Cells at the NIH," John Barrett of NHLBI acknowledged that he had "a slightly crusading purpose" behind his talk—not just to show promising clinical trial results, but also to highlight the challenges of his 10-year effort to take a promising idea from theory to clinical trial.

Effecting Smooth Transitions

From this experience, Barrett sees a need for a core facility to assist what he prefers to call "transitional" research the work needed to go from "proof of principle" experiments with human cells to the manufacture of an FDA-approved clinical-grade cell product.

A transitional research laboratory would facilitate interactions with industry partners to study and perfect the systems for cell separation, selection, culture, and preservation so that the techniques for making new cell products could be brought within reach of cellprocessing laboratories and blood banks nationwide.

The Cell Processing Section in the CC's Transfusion Medicine Department, which operates under rigorous GMP (good manufacturing practice) conditions, would be an essential partner in that effort, he emphasized.



Fran Poliner

Cell Isolation: E. J. Read (left), chief of the CC Cell Processing Section, watches as medical technologists Quyen Chau and Tamara Felton run the CliniMACS, a closed, sterile system that uses magnetically labeled antibody to separate enriched hematopoietic progenitor cells from a donor's mobilized peripheral white blood cells. A typical donor sample, containing 40 billion white blood cells, provides about 400 million progenitor cells for one allogeneic transplant.

Creating a transitional research facility *continued on page 4*

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FROM THE DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH

Renewing Trust in NIH



Michael Gottesman

The editorial in *The Washington Post* on Monday, July 5, entitled "Double Dipping at NIH" is a reflection of continuing public and congressional concern about the nature and extent of outside activities by NIH scientists.

Beginning last fall and continuing through this summer, we have been faced with allegations and revelations about lucrative consulting arrangements between NIH scientists and industry, some approved by NIH ethics officials and some not. These revelations have led to the perception that the integrity of NIH science and scientists may be compromised.

It is worth noting that the credibility of intramural scientists is of paramount importance to Congress and the public, who rely on us for unimpeachable information about basic research and crucial public health issues. It is therefore essential that NIH do

whatever is necessary to restore public confidence in the work that is done here and the scientists who do it.

NIH Director Elias Zerhouni has appeared twice before the Oversight and Investigations Subcommittee of the House Committee on Energy and Commerce—the "Greenwood committee" (chaired by Rep. James C. Greenwood [R-Pa.])—to offer solutions to the current quandary.

In the first hearing, on May 18, he outlined steps that NIH had already taken, including creation of a central committee of scientists and ethics officials (the NIH Ethics Advisory Committee, or NEAC) chaired by Raynard Kington, NIH deputy director and deputy ethics counselor. This com-

mittee, which I co-chair, has brought uniformity and rigor to the review of requests for many different kinds of outside activities.

Dr. Zerhouni also reviewed the recommendations of a Blue Ribbon Panel on Ethics at NIH. But Greenwood committee members faulted some of the panel's specific recommendations as being inadequate to prevent some abuses of concern to them. Subsequently, on June 22, Dr. Zerhouni outlined several significant changes in the ethics program at NIH that were received more enthusiastically by the Greenwood committee.

The principles behind these changes include:

Removing any ambiguity about which activities are acceptable and which are not to restore public trust and clarify policies for NIH staff

■ Increasing transparency in reporting outside activities

Allowing researchers at NIH to engage in certain types of consulting agreements with industry to expand the intellectual horizons of our scientists and their ability to contribute to the public health but barring such activities for others, including NIH leadership, scientific directors, and clinical directors. Creating a system that allows effective and efficient monitoring and oversight

The full testimony can be found at

<http://www.nih.gov/about/director/ 062204zerhouni_COI.pdf>,

which is part of the NIH website pertaining to ethics issues:

<http://www.nih.gov/about/ethics_COI.htm>.

Highlights of Dr. Zerhouni's specific plans to eliminate perception of conflict of interest at NIH and enhance public trust include:

Eliminating or reducing stock holdings in biotech and pharmaceutical companies

Verification of authenticity of research honors and awards

Limitations on the amount and nature of compensation for consulting activities (including disallowing stock or stock options)

Prohibitions on membership on corporate boards

Prohibitions on consulting with grantee institutions

Expanded public reporting of outside activities, including an increase in the number of NIH staff who file financial reports

Many of these changes in current policy require regulatory authority from the Office of Government Ethics, a process that takes many months. And specific details about how to implement these plans without causing undue hardship in individual cases are being worked out.

In the near future, NIH will be providing guidance about what activities

may be possible while the new program is being developed.

The experience from NEAC suggests that many of the outside activities requested by NIH scientists are clinical care or academic—editing, writing, and teaching in a course—and most of these should continue to be approvable under the new rules.

Other outside activities, such as consulting with grantee organizations (for example, giving a scientific talk at a university or serving on an external advisory board to an NIH grantee), will not be allowed as outside activities, but can be conducted as official duty activities with approval from a supervisor and/or appropriate extramural staff, with or without sponsored travel, as appropriate.

The intent is to encourage intellectual exchanges with academia and industry as part of official duties, but to limit or prohibit compensation for such activities.

Much more information will be forthcoming as the new ethics program develops, and every effort will be made to inform the NIH community as new policies are formulated and implemented.

> *—Michael Gottesman* Deputy Director for Intramural Research

THE INTENT IS TO ENCOURAGE INTEL-LECTUAL EX-CHANGES WITH ACADEMIA AND INDUSTRY AS PART OF OFFICIAL DU-TIES, BUT TO LIMIT OR PROHIBIT COM-PENSATION FOR SUCH ACTIVITIES

THE RESPONSIBLE CONDUCT OF RESEARCH: A New Online Course

In keeping with a new policy issued by the PHS Office of Research Integrity that requires training in the responsible conduct of research (RCR) for all researchers supported by PHS funds, we have launched a computerbased course on Research Ethics. You will find it at:

<http://researchethics.od.nih.gov/>.

In keeping with the NIH tradition of crafting useful and stimulating online ethics exercises, this RCR course makes for very interesting reading, is crisp and quite informative, and offers provocative problems to solve and questions to answer.

Who Must Take the Course, And When

Under this policy, all research staff in the NIH IRP who have "direct and substantive involvement in proposing, performing, reviewing, or reporting research, or who receive research training," will participate in RCR instruction.

We define those staff as senior investigators, tenure-track investigators, senior scientists, and clinicians, staff scientists and clinicians, research and clinical fellows, pre- and postdoctoral trainees, technicians, research nurses, and special volunteers or guest researchers involved in these activities.

All current staff must complete the course by October 31 of this year, and all new staff will take it as part of the web-based orientation package they are required to complete.

Baseline Nuts and Bolts

The NIH Committee on Scientific Conduct and Ethics (CSCE) spent the better part of a year developing this web-based Research Ethics course.

The course puts forth standards of research integrity for the performance, presentation, and review of scientific results that are well known to NIH researchers.

These standards cover a variety of issues, from determining authorship to data management, handling collaborations, management of conflicts of interest, peer review, and the ethical issues related to the use of humans and animals in research. Mentoring is also a key component.

The course is designed to ensure that all intramural scientific staff have a baseline understanding of these standards. And it sets the stage for the research ethics case discussions that have been integrated into the conduct of research at NIH (see below).

PHS Objectives

The long-term goals of RCR training, as defined by the PHS, are:

To increase researchers' knowledge of, and sensitiv-

ity to, issues surrounding the responsible conduct of research

To improve the ability of our scientific staff to make ethical and legal choices in the face of conflicts involving scientific research

To develop an appreciation for the range of accepted scientific practices for conducting research

To provide information about the regulations, policies, statutes, and guidelines that govern the conduct of PHSfunded research

To develop positive attitudes toward lifelong learning in matters involving the responsible conduct of research

The PHS policy requires a combination of one-time training in a set of core areas (including data acquisition, management, sharing, and ownership; mentor and trainee responsibilities; publication practices and responsible authorship; peer review; collaborative science; research misconduct; and conflict of interest and commitment; and research involving human subjects and animals) and yearly follow-ups.

Ethics Case Discussions

The yearly follow-ups have been ongoing here at NIH for several years through the use of research ethics case discussions, led by trained facilitators and given to groups of 20–30 people at a time.

Each year the CSCE chooses a theme for the next year, generally based on the issues that have risen to the top of our attention, or been recommended by intramural scientists, during the previous year. We review a collection of possible cases and select those we feel will be most stimulating and informative for discussion.

A website within the Intramural Research Sourcebook

--<http://www1.od.nih.gov/oir/ sourcebook/ResEthicsCases/casestoc.htm>---

contains the set of cases to be used for each topic, along with supplementary information.

Staff have been trained in each IC to serve as facilitators, whose primary tasks are to ensure that everyone takes part in the discussion, that the key points are



Joan P. Schwartz

This year (2004)—given the interest stimulated by Dr.

lively.

covered, and, most impor-

tantly, that the discussion is

Zerhouni's Roadmap initiatives—the theme is collaborative science.

The ICs have some flexibility in how they choose to carry out the yearly training, but are expected to adopt the theme chosen for a given year. That allows us to update staff on new policies in a relatively rapid and all-inclusive way. Any scientist interested in serving as a facilitator should contact his or her scientific director or CSCE member. For a list of IC representatives, see

<http://www1.od.nih.gov/oir/ sourcebook/comm-adv/sciconduct.htm>.

Most of you have participated in these research ethics case discussions, so you already know that they are not only intellectually stimulating but also fun.

The case discussions have been supplemented over the years with Ethics Forum columns such as this one, published in *The NIH Catalyst*, that address new or difficult issues that come to our attention.

But no part of the training has ensured that everyone has the same baseline understanding of RCR that is outlined in the NIH Guidelines for the Conduct of Research (<http://www.nih.gov/campus/ irnews/guidelines.htm>)—hence the computer course.

In Your Court

As you go through the course, you will find at the end of each module a quiz or mini-case to test your understanding of what you have just learned, and we hope that you will find these interesting and fun also.

Equally important, we designed the course to serve as a research ethics resource, with a Resources section and a Glossary, and we recommend that you bookmark the course for future reference.

Also built in is the ability to print out "Key Points to Remember from the NIH Ethics Course on the Responsible Conduct of Research," along with a certificate demonstrating that you have completed the course.

We invite you to share your ideas on topics for case discussions and on how to improve the training experience. Comments can be sent to

<researchethics@od.nih.gov>.

—Joan P. Schwartz Assistant Director, OIR

Adult Stem-Cell Research

continued from page 1

might be expensive, he said, but the ultimate savings from transplants using sophisticated cell products that could emanate from such a facility would be enormous.

Barrett cited comparative costs within his own area of hematopoietic stem-cell transplantation for malignant diseases: The creation of complication-free transplants-purified stem cells free of cells that cause graft-vs-host (GVH) disease and enriched for immune cells that specifically react against troublesome viruses and the patient's cancer-could cost as much as \$20,000 per patient. But that expense pales in comparison to the possible \$250,000 price tag for the prolonged hospitalization that often attends allogeneic stem cell transplantation and the cost of treating recurring disease if the transplant fails.

Cancer

And Graft-vs-Host Disease

Barrett, along with NCI's Michael Bishop, described research that uses hematopoietic stem cells in treating cancer patients.

Barrett uses allogeneic transplants of peripherally harvested bone marrow cells to treat leukemia. The HLA-matched donor stem cells repopulate the leukemia patient's blood-producing system after their own cancerous blood cells are killed with anticancer chemotherapy.

But beyond that, Barrett's team is trying to improve their patients' odds by delicate application of one edge of a dangerous two-edged sword.

Investigators have seen that immune reactions by grafted donor immune cells can have a powerful antileukemic effect. But even in apparently perfectly matched donor-recipient pairs, some immune cells attack the patient's normal tissues, causing potentially fatal GVH disease.

Because older leukemia patients are especially vulnerable—about half may die of GVH disease—the team targets this older cohort (whose average age is 64) for clinical trials of measures aimed at minimizing GVH reactions, while maximizing the allogeneic attack on leukemia cells that may have withstood chemotherapy.

In 14 patients thus far, the investigators have seen 100 percent transplant engraftment, with significant reduction in GVH disease and no deaths to date attributable to that cause.

The key to this GVH reduction in Barrett's work, as well as in Bishop's, has



elia Hoope

Wrap-Up: (left to right) Cynthia Dunbar, senior clinical investigator, NHLBI, E. J. Read, chief of the Cell Processing Section, Department of Transfusion Medicine, CC; Betsy Nabel, director of clinical research programs, NHLBI; and Ron McKay, senior investigator, Laboratory of Molecular Biology, NINDS, lead a general discussion at the end of the daylong workshop on "Clinical Applications of Stem Cells at the NIH"

been to temper immune reactions by selectively eliminating the cells responsible for them—GVH-specific T cells. Studies with mice showed that low doses of fludarabine and cyclophosphamide effect a slow depletion of T cells in a transplant recipient, permitting engraftment of even HLA-mismatched cells without having to completely destroy the recipient's immune system.

Working with patients with metastatic breast cancer, Bishop is employing chemotherapy regimens that gently, slowly deplete T cells as they kill breast cancer cells. Patients are left with disease-attacking natural killer (NK) and other immune cells, but free of the T cells' destructive reactions.

Bishop says a key may be promoting Type 2 cytokine interactions that suppress GVH reactions, while squelching Type 1 reactions that promote them.

He emphasizes that hematopoietic stem cell therapy (HSCT) goals differ among patients. In some patients, the target of therapy may not be cancer but, rather, anemia and other nonmalignant blood diseases in which there is no benefit in retaining potential for graft-vs-tumor reactions.

Among cancer patients, the blood cells themselves may be cancerous or blood may harbor cancer cells. Similarly, T-cell numbers and reactivity may be naturally high or low.

"We don't believe one regimen fits all," Bishop said He envisions blood stemcell therapy will be pretty much "designer therapy."

Array of Applications

Roland Martin of NINDS is examining the use of HSCT for a completely different purpose—stopping the decline of patients with multiple sclerosis (MS). Martin's group shows that HSCT halts the progress of the autoimmune disease by eliminating MS patients' immune cells that are programmed to attack their own myelin, causing inflammation and subsequent brain-cell loss. The patients' immune systems are rescued with naive cells from transplanted hematopoietic stem cells.

In the seven patients treated thus far, this approach has reset the immunological clock, leaving patients free of the inflammatory component of MS.

Stopping the clock, however, doesn't reverse neurodegeneration that has already occurred. For this, Martin says, one has to look at a second transplant of some other stem cells—oligodendrocyte precursor cells alone or with local delivery of growth factors. Transplantation of these precursors in mouse models of MS has restored myelinated cells and appropriate brain architecture, left no scarring, and, as a result, improved motor function.

Other research presentations in the center ring of the workshop featured a diverse array of results, ranging from NIDCR's Pam Robey's elaboration of stem cells in the dental pulp of children's baby teeth to NIAID's Harry Malech's description of progress toward effective gene therapy for chronic granulomatous disease. For example, Rocky Tuan of NIAMS described continuing refinements in a bag of innovative tricks designed to charm mesenchymal stem cells into making replacements for tissues damaged by arthritis and other ravages of age and degenerative joint disease.

Tuan has been inching ever closer to producing lab-grown tissues that closely mimic human bone and cartilage in texture, strength, ability to support appropriate growth and differentiation of cells, and even transmission of critical signals for cell-cell interactions.

Tuan noted that understanding these signals—and learning how to control them—may someday obviate the need for transplants of stem cells or lab-grown tissues.

The ideal course would be to reprogram cells or call in residual mesenchymal stem cells already within the body to repair damaged joints. Look at the salamander's ability to regrow complete limbs, Tuan urges. "It does all these things without any government intervention or support!"

Do Reparative Cells Come from Near or Far?

One key question for scientists working with some adult stem cells is where the cells actually come from. Do repairing cells already reside in tissues and multiply when needed to repair adjacent damage? Or are the cells summoned from a stem-cell source elsewhere in the body?

NIDDK'S David Harlan and Nadya Lumelsky say that their studies aimed at diabetes suggest that insulin-producing β -cells may not arise, at least not to date with clinically relevant efficiency, from circulating stem cells or other pancreatic cells. Harlan presented work that did not support the existence of bone-marrow resident stem cells capable of differentiating into insulin-producing cells.

In other work with human pancreatic cells, Lumelsky had variable success in cultivating new insulin-producing cells in comparatively short-term cultures. The success of the culture varied greatly depending on the specific human islet isolation.

That said, her laboratory takes cellular clusters from the disaggregated human pancreas and grows cells from the mixture on fibronectin in defined culture medium (with a cocktail of growth factors), promoting cellular re-aggregation.

With this system, Lumelsky finds that a minority of such preparations make more C-peptide (a marker for insulin production) than what she started with, while most make less.

Evidence of remote sources of stem cells came from NEI's Karl Csaky, who presented data on bone marrow as one key source of cells involved in neovascularization in the eye.

Csaky's mouse studies on ocular overexpression of VEG-F or laser-induced ocular damage showed that 70 percent of macrophages, 58 percent of endothelial cells, and 60 percent of smooth muscle cells involved in neovascularization and repair came from the bone marrow.

In contrast, none of the retinal cells in the repaired tissue came from the bone marrow. Csaky is interested in identifying factors responsible for summoning and triggering appropriate differentiation of stem cells at sites of damage in the eye.

The Heart of the Matter

Focusing on heart repair, Richard Cannon of NHLBI recalled studies from 1997 that detected endothelial progenitor cells in peripheral blood and evidence from animal models of hind-limb ischemia that injection of these cells can stimulate growth of new blood vessels and improve blood flow to the affected extremity.

Attempts to use such cells to revascularize human hearts suggest benefit to myocardial blood flow and function, but the nonrandomized clinical trials reported to date have involved small numbers of patients who often underwent coronary revascularization at the time of treatment.

Studies performed in the NHLBI Cardiovascular Branch suggest that there may be variation in the ability of people's stem cells to accomplish the feat of repairing heart damage.

The researchers isolated mononuclear cells from blood samples of middle-aged men with varying levels of risk for heart disease and examined the ability of progenitor cells to produce endothelial-like cells needed to form new vessels in damaged hearts.

Cells from subjects with the fewest risk factors produced the most colonies of reparative cells, and those with the greatest number of risk factors had the lowest numbers of functional colonies.

Further, endothelial function, as tested by nitric oxide–mediated vasodilation, correlated strongly with subjects' endothelial colony-forming capacity. The researchers speculate that loss of the cells' ability to repair endothelial damage in the heart may be yet another independent contributing factor in cardiovascular disease.

Cannon and his colleagues studied whether just mobilizing stem cells from bone marrow with the cytokine granulocyte–colony-stimulating factor (G-CSF) might be sufficient to help repair hearts damaged by severe cardiovascular disease. Although they were successful in augmenting endothelial progenitor cells in the circulation after G-CSF administration, the numbers of cells were small, the duration of mobilization short, and the benefits to patient health undetectable on cardiac MRI and treadmill stress tests.

Cannon will soon be trying direct myocardial administration of stem cells to patients' damaged hearts.

In a collaborative study with Suburban Hospital's (Bethesda, Md.) Cardiopulmonary Rehabilitation Unit, Cannon is exploring interrelationships of exercise, endothelial function, endothelial progenitor cell mobilization, and nitric oxide bioactivity in hopes of giving heart patients a vascular repair profile more like that of healthy individuals.

More Tools for the Trade

Still other NIH investigators are developing tools and facilities to aid stem-cell research. New tools include in vivo imaging and clinical-grade reagents that permit investigators to "see" stem cells at work inside the human body.

Robert Lederman of NHLBI described sophisticated MRI techniques that could be used to watch precise delivery of bone marrow stromal cells to the margins of an infarct, for example, or to calculate peripheral vascular function by measuring reperfusion of blood into tissue when a restraint on circulation is abruptly removed.

"These images are incredibly sensitive tools," Lederman finds. But frustrations in working with industry partners to develop the techniques have led Lederman to agree with Barrett that NIH needs a "transitional" core. If there were one, "I'd be discussing results rather than experimental design," Lederman said.

Lederman says one key to his work is a technique for magnetically labeling cells developed by the CC's Laboratory of Diagnostic Radiology Research. Joe Frank, who leads LDRR, described ongoing development of the superparamagnetic iron oxides that are taken up by cultured stem cells, for example.

As few as 50,000 labeled cells can be injected into a living animal and then observed via 1.5 Tesla MRI—a field strength that could also be used in human studies.

Frank says nondividing cells, such as T cells, retain label for 40 to 60 days, and there is no change in apoptosis or reactive oxygen species in labeled cells. As paperwork wends its way through the FDA to get the magnetic label approved for clinical use, Frank has been collaborating on studies that put the vital stain to work to study angiogenesis, stroke, MS, and cardiovascular disease.

The Challenges Of Product Development

If NIH wanted to take up Barrett's call for a transitional research core, perhaps the best advice on such a facility would come from E. J. Read, chief of the Cell Processing Section of the CC Department of Transfusion Medicine.

"Product development," Read says categorically, "is different from basic science." Product development studies aim to design cellular products that meet the needs of the clinical trial as well as FDA's regulatory requirements. The new products must ultimately be prepared in a GMP environment to ensure that they are safe and effective for patients who receive them.

Translation of cell therapies requires working collaboratively with investigators, starting in the preclinical phase, to define and characterize specific details of each product.

Challenges abound. The most striking, Read says, is the variability of cells—starting material from different patients. This variability means contingency planning is critical because things will go wrong. Scale-up and movement from lab to clinic may not be straightforward. Closed, automated systems are more desirable, she said, because they reduce human error and the risk of contamination from microbes in the environment when cells are processed.

Collaboration with industry brings in lots of additional challenges. Read says her best allies in coping with FDA oversight have been the facility's masterfile of operational and quality procedures, written in responses to FDA's formal queries and published guidelines, and copious documentation during the preparation of each clinical product. "This has really helped a lot," Read says.

NINDS' Ron McKay gave the workshop a view on another core facility with an update on the NIH Human Embryonic Stem Cell Unit (see *The NIH Catalyst*, March-April, page 1).

That facility is growing and characterizing human embryo stem cells, "currently the most useful" stem cell of all, by virtue of its capacity "for infinite expansion to lots of cell types," McKay said. "Somatic stem cells are not designed for infinite expansion."

McKay says studies of embryo stem cells in rats show that they can be differentiated into dopamine-secreting neural precursor cells and implanted into the ventral midbrain, where they engraft beautifully and are electrophysiologically and behaviorally functional.

"In five years," McKay predicted, "human embryo stem cells will routinely be put to many clinically relevant uses."

Regulatory Hurdles

Whether the prediction is borne out depends in part on reasonably swift approval of stem-cell procedures by the FDA. FDA's Steve Bauer acknowledged that stem-cell-based therapy is a relatively new regulatory area for the agency, but he noted that development of specifications for stem-cell-based products is evolving rapidly as scientific information increases.

The agency will be looking not only at the end products but also at initial starting materials, culture, and other processing of cells. Bauer said key issues might include:

Potency of cells

■ Freedom of starting materials from infectious disease

- Derivation of the cells
- Stability of the cells
- Propagation conditions
- Characterization of the cells

■ Where implanted cells go and how long they live

Tumorigenicity of implanted cells

Ectopic development of tissue from implanted cells

In a panel discussion concluding the workshop, Barrett said the NIH intramural program has a unique opportunity in stem cell research. "We have all the pieces in one place and lots of expertise to see the research through to clinical trials." NHLBI Clinical Director Betsy Nabel concurred, citing the workshop's display of "incredible breadth and depth, from basic to applied research."

OUTPATIENT STEM-Cell TRANSPLANTATION

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Richard Childs (left) and Ramaprasad Srinivasan

Already, this first patient is a standout: Not only the lead-off patient on the protocol, he's the first patient on any NIH transplant protocol to have undergone the procedure as an outpatient. Considering only NHLBI and NCI, Childs estimated that between 600 and 700 patients have undergone transplantation on intramural NIH protocol over the last decade or so—all inpatient.

"This is a big step in the right direction," Childs observed.

"We're doing something different," Srinivasan said. "In the old days, people going through allogeneic transplantation had to undergo intensive chemotherapy and/or radiotherapy that required hospitalization. They got very sick, couldn't eat, threw up, got all kinds of infections, and were basically bedridden for the early part of the transplantation, anywhere between four and six weeks."

"About one in three patients died from the transplant itself," Childs added. Consequently, it was only when patients faced death from the disease the usual fate within one to five years of the onset of advanced MF—that transplantation was considered.

The nonmyeloablative regimen of the current protocol is designed to eliminate the toxicity from an otherwise therapeutic, potentially curative approach. Not only does the pretransplant regimen prepare the host to accept the donor cells, it also has some inherent antitumor activity. The fourweek preparative regimen includes escalating doses of Campath-1H, an anti-CD52 monoclonal antibody, on days 28 to 15 pretransplant, and fludarabine, an anticancer agent, for the last five days before transplant.

The investigators will conduct lab

studies to document the effect of the preparatory regimen on the host immune system and the effect of donor immune cells on host tumor cells. They will look specifically at the following:

The roles of Campath-1H and fludarabine in the development of donor chimerism and the extent to which Campath-1H potentiates the depletion of donor T cells

The cell types and rate of donor cell repopulation post-transplant

The ability of cells of donor origin to battle the tumor, as demonstrated in a laboratory-based confrontation between isolated and expanded donor CD4 and CD8 cells and tumor cells

The ability of donor cells to recognize and presumably fight the patient's tumor, as suggested by the presence (or absence) of cells of donor origin in skin-lesion biopsies

"If we don't see a substantial number of patients engrafting, we would add another agent—cyclophosphamide—to the preparatory regimen in the next set of patients," Srinivasan said.

At more than 100 days post-transplant (at *Catalyst* press time), the patient, a 58-year-old African American man with a five-year history of progressive disease, was showing progressive donor engraftment and no signs of graftvs-host disease. The first evidence of donor cells was spotted 15 days posttransplant, Srinivasan noted.

The investigators also saw evidence of antitumor activity but concluded that at that early stage the observed effects could be attributed entirely to the preparatory regimen. While transient, this effect is beneficial because it provides sufficient time for manipulation of the newly engrafted immune system to generate a durable immune response against the cancer. They plan to document laboratory correlates that indicate that donor immune cells are staving off disease over the long haul, as opposed to the short-term slaughter effected by the chemotherapy.

MF and its leukemic variant Sezary syndrome are the most prevalent forms of primary cutaneous T-cell lymphomas. The protocol is designed to see not only whether MF is successfully treated with this approach but also whether use of this relatively nontoxic agent—Campath-1H—is compatible with donor engraftment.

"If we can actually get a graft in this context, this approach could be applicable in a wide variety of conditions normally amenable to transplantation and the nonmyeloablative regimen, such as non-Hodgkins lymphoma," another condition in which the immunosuppressive regimen also has antitumor activity, Srinivasan said.

In general, patients with fast-growing, "out-of-control" disease do worse on nonmyeloablative regimens," Childs remarked.

In contrast, patients with slower growing disease or disease in remission before the procedure are more likely to benefit from the anticancer effects generated through engrafting donor T lymphocytes.

Moreover, Childs said, patients "with an immune system that is already beaten up" from prior chemotherapy before undergoing nonmyeloablative transplantation are more likely to achieve the rapid, sustained donor engraftment that is a prerequisite for the potentially curative donor-immune– mediated antimalignancy effects that occur after these types of transplants.

AUTUMNAL RITES: THE NIH RESEARCH FESTIVAL

Late September to early October is a great time for changing leaves, end-of-summer visits to the beach . . . and the NIH Research Festival.

The 2004 Festival runs from **Tuesday, September 28, through Friday October 1**, at the Natcher Conference Center. It kicks off Tuesday at 9:00 a.m. with a keynote address by DDIR Michael Gottesman on new and emerging prospects in the NIH Intramural Research Program.

Minisymposia Tuesday and Wednesday focus on:

- Emerging Infectious Diseases
- Epigenetics and Cell Cycle Control: From DNA Replication to Cancer Therapy
- Proteomics in Disease
- Gene-based Analysis of Parkinsonism
- The Challenge and Promise of Stem Cells for Regenerative Medicine
- Mast Cell Function: Biological and Clinical Implications
- Signaling Mechanisms during Development
- NIH Pharmacology and Therapeutics—The Road to Identification of Molecular Targets and Their Structures
- Technological Advances in Structural Biology and Biophysics
- New Frontiers in Mammalian Genomics
- Molecular Imaging: A Tool for Studying Systems Biology in Vivo
- Worms, Flies and Fish as Models of Human Disease
- Computer-aided Detection in Diagnostic Radiology
- Chromatin Remodeling and Gene Regulation
- C-AMP-dependent Protein Kinase Signaling and Human Disease
- Complex Genetics and Common Brain Disorders

Festival food and music burst forth midday Tuesday and Wednesday; Thursday offers the ever-popular Job Fair for NIH postdocs and research and clinical fellows; and the Technical Sales Association Exhibit Tent show runs Thursday and Friday.

For more details, see <http://festival04.nih.gov>.

INTERINSTITUTE INTEREST GROUP DIRECTORY

Web Access

Although not all the sites are up to date, nearly all the Interest Groups have web sites that can be accessed through <http:// www.nih.gov/sigs/sigs.html>).

MAJOR INTEREST GROUPS

Cell Biology Interest Group

Meeting time: Not specified Meeting place: Building 32, Library Contact: Jennifer Lippincott-Schwartz Phone: 402-1010; 402-1009 E-mail: <jlippin@helix.nih.gov> ListServ: subscribe to CELBIO-L

Clinical Research Interest Group

Meeting time and place: sponsors ĈC Grand Rounds once every other month Contact: Cliff Lane Phone: 496-7196 E-mail: <clane@nih.gov>

Genetics Interest Group **

Meeting time and place: Two all-day symposia a year to be announced Contact: Dan Kastner Phone: 496-8364 E-mail: <tf60y@nih.gov> ListServ: subscribe to <GIG-L@list.nih.gov>

Immunology Interest Group

Meeting time: Each Wednesday (except summer), 4:15 pm Meeting place: Building 10, Lipsett Auditorium Contact 1: Jennifer Cannons Phone: 435-1907 E-mail: <jcannons@mail.nih.gov> Contact 2: Margaret Mentink Kane Phone: 594-2345 E-mail: <mmentink@niaid.nih.gov> ListServ: subscribe to IMMUNI-L by joining the interest group at its web site

Molecular Biology/Biochemistry Interest Group

Meeting time: Yearly to consider WALS speaker nominations Meeting place: By e-mail Contact: Carl Baker Phone: 496-2078 E-mail: <ccb@nih.gov>

Neuroscience Interest Group

Meeting time and place: Check website Contact 1: Chip Gerfen Phone: 496-4341 E-mail: <gerfenc@intra.nimh.nih.gov> Contact 2: Bruce Cumming Phone: 42-8097 E-mail: <bcg@lsr.nimh.nih.gov>

Structural Biology Interest Group

Meeting time and place (2004-05): Usually 3rd Thursday, 4:00 pm, Building 50; notices by e-mail and on the SBIG website Contact 1: Susan Buchanan Phone: 594-9222 E-mail: <skbuchan@helix.nih.gov> Contact 2: Sanford Markey Phone: 496-4022 E-mail: <s.markey@nih.gov> To register for e-mail announcements, join SBIG at <www.nih.gov/sigs/sbig>

Other Interest Groups

14-3-3 Proteins Interest Group

Meeting time: Usually the third Wednesday, 4:00–5:00 pm Meeting place: Building 40, First-floor Conference Room Contact 1: Surajit Ganguly Phone: 496-8423 E-mail: <surajit@codon.nih.gov> Contact 2: David C. Klein Phone: 496-6915 E-mail: <klein@helix.nih.gov>

Advanced Technologies Interest Group

Meeting time and place: Check the website Contact: Steven Hausman Phone: 402-1691 E-mail: <hausmans@mail.nih.gov>

AIDS Interest Group

Meeting time and place: Varies Contact: Fulvia Veronese Phone: 496-3677 E-mail: <veronesf@od.nih.gov> ListServ: subscribe to AIDSINTG-L

Apoptosis Interest Group

Meeting time: 1st Monday, 4:00 pm Meeting place: Building 49, Room 1 50/59 AB Contact 1: Richard Youle Phone: 496-6628 E-mail: youle@helix.nih.gov Contact 2: Yves Pommier Phone: 496-5944 E-mail: <yp4x@nih.gov>

Behavioral and Social Sciences Interest Group

Meeting time: Varies; mainly sponsors lecture series Meeting place: See NIH Calendar of Events Contact: Ronald Abeles Phone: 496-7859 E-mail: <abeles@nih.gov>

Bioethics Interest Group

Meeting time: 1st Monday (except 2nd Monday following holidays; usually does not meet during summer), 3:00 pm Meeting place: Natcher, Room D, or Building 31, conference room; check yellow sheet or web site Contact: Miriam Kelty Phone: 496-9322 E-mail: <mk46u@nih.gov> Sign up at <http:// BIOETHICSinterestgroup@list.nih.gov/>

Biomedical Computing Interest Group

Meeting time: Third Thursday, 3:00 pm Meeting place: Building 10, Room 2C116 (Medical Board Room) Contact 1: Jim DeLeo Phone: 496-3848 E-mail: <jdeleo@nih.gov> Contact 2: Susan Harris Phone: 435-8721 E-mail: <sharris@mail.cc.nih.gov> ListServe: subscribe to BCIG-L

Biophysics Interest Group

Meeting time and place: Varies (often Building 10, Bunim Room) Contact: Peter Basser Phone: 435-1949 E-mail: <pjbasser@helix.nih.gov>

Biosciences Business Interest Group

Meeting time: Monthly, 12:00–1:00 pm Meeting place: Building 37, 4th Floor Conference Room (4041/4107) Contact 1: Val Bliskovsky Phone: 435-7249 E-mail:
bliskovv@pop.nci.nih.gov> Contact 2: Gil Ben-Menachem E-mail: <gilben@mail.nih.gov

Birth Defects and Teratology Interest Group

Meeting time: Quarterly seminars Meeting place: Videoconference between Bethesda and Research Triangle Park, N.C. Contact: Megan Adamson Phone: 443-4354 E-mail: <madamson@mail.nih.gov>

Calcium Interest Group

Meeting time and place: Not regularly scheduled at this time Contact 1: Arthur Sherman Phone: 496-4325 E-mail: <asherman@nih.gov> Contact 2: Indu Ambudkar Phone: 496-1478 ListServ: Subscribe to CALCIUM-L

Cancer CAM Research Interest Group

Meeting time and place: Varies Contact: Jeffrey White Phone: 435-7980 E-mail: <jeffreyw@mail.nih.gov>

Chemistry Interest Group

Meeting time: Periodic seminars Meeting place: Varies Contact 1: John Schwab Phone: 594-5560 E-mail: <schwabj@nigms.nih.gov> Contact 2: Kenneth Kirk Phone: 496-2619

Chromatin and Chromosomes Interest Group

Meeting time: One Tuesday a month, 4:00 pm Meeting place: Building 41, Conf. Room Contact: David Clark Phone: 496-6966 E-mail: <clarkda@mail.nih.gov>

Chronobiology Interest Group

Meeting time: 1st Wednesday, monthly, 4:00–5:00 pm Meeting Place: Building 36, Room 1B13, or USUHS Rm A2054 Contact: Steven Coon Phone: 496-8293 E-mail: <coons@mail.nih.gov>

Clinical Applications of Stem Cells Interest Group

Meeting time and place: To be announced; contact <cmoyers@nhlbi.nih.gov>to be added to the Listserv Contact: Cynthia Dunbar Phone: 496-1434 E-mail: <dunbarc@nhlbi.nih.gov>

Clinical Immunology Interest Group

Meeting time: Monthly, last Wednesday, noon Meeting place: Building 10, Room 98235 Contact: Oral Alpan Phone: 402-3447 E-mail: <oalpan@nih.gov>

Clinical Pharmacology Interest Group

Meeting time: 2-3 times a year in conjunction with special lectures in the NIH Principles of Clinical Pharmacology course, 6:30– approx. 7:45 pm Meeting place: Building 10, Lipsett Contact: Donna Shields Phone: 435-6618 E-mail: <dshields@mail.cc.nih.gov>

Cognitive Neuroscience Consortium

Meeting time: Every two months, last Wednesday, 4:15 pm Meeting place: NSC Building, Conference Room A (starts September 2003; Extramural Program Directors' forum: last Friday every 3rd month, 3:00 pm, NSC Building, Conf. Room 2120, starts October 2003) Contact: Emmeline Edwards Phone: 496-9964 E-mail: <ee48r@nih.gov>

Cultural and Qualitative Research Interest Group **

Meeting time: 2nd Tuesday of February, April, June, September, November, 9:30 am Meeting place: As announced Contact 1: Sabra Woolley Phone: 435-4589 E-mail: <woolleys@mail.nih.gov> Contact 2: Suzanne Heurtin-Roberts Phone: 594-6655 E-mail: <sheurtin@mail.nih.gov>

Cytokine Interest Group

Meeting time: three to four symposia/year Meeting place: Varies; one symposium/ year at NCI-Frederick Contact 1: Calman Prussin Phone: 496-1306 E-mail: <cprussin@niaid.nih.gov> Contact 2: Robert Seder E-mail: <rseder@mail.nih.gov>

Dendritic Cell Interest Group

Meeting time and place: TBA Contact: Uri Lopatin Phone: 496-7473 E-mail: <uri@nih.gov> Contact 2: Brian Kelsall E-mail: <bkelsall@mail.nih.gov>

Diabetes Interest Group

Meeting time: Once a month, days and times to be announced Meeting place: Building 10, Lipsett Auditorium Contact: Renee Rabben Phone: 496-6289 E-mail: <ReneeR@intra.niddk.nih.gov> Contact 2: Derek LeRoith E-mail: <derek@helix.nih.gov>

DNA Repair Interest Group

Meeting time: 3rd Tuesday, 12:30 pm Meeting/Videoconference: Natcher, Room J; GRC (Baltimore), Room 1E03; FCRDC, Building 549, Conf. Rm. A; NIEHS (Research Triangle Park, NC) Building 101, Room B200; SUNY, Stony Brook; Univ. of Texas, M.D. Anderson Cancer Center, Smithville, TX; Univ. of Texas, Galveston; Lawrence Livermore National Laboratory, Livermore, CA; Brookhaven National Laboratory, Upton, NY; Univ. of Michigan, Ann Arbor; Univ. of Kentucky, Lexington; Univ. of Pittsburgh, Pittsburgh, PA Contact 1: Kenneth Kraemer Phone: 496-9033 E-mail: <kraemerk@nih.gov> Contact 2: Vilhelm Bohr E-mail: <vbohr@nih.gov>

Domestic Violence Research Interest Group

Meeting time and place: To be announced Contact: John Umhau Phone: 496-7515 E-mail: <umhau@nih.gov>

Drosophila Interest Group

Meeting time: 3rd Tuesday, 1:15 pm Meeting place: Building 6B, Room 4B429 Contact 1: Sue Haynes Phone: 301-295-9791 E-mail: <shaynes@usuhs.mil> Contact 2: Jim Kennison E-mail: <James_Kennison.nih.gov>

Drosophila Neurobiology Interest Group

Meeting time: Every other Friday, 12:00 noon (starting September 10) Meeting place: Porter Neuroscience Research Center (Building 35), Room BB-1000 Contact: Benjamin White Phone:435-5472 E-mail: <WhiteB@intra.nimh.nih.gov>

Drug Discovery Interest Group **

Meeting time: Usually one Thursday a month, 3:00 pm Meeting place: Building 37, 6th-floor conference room Contact: John N. Weinstein Phone: 496-9571 E-mail: <weinstein@dtpax2.ncifcrf.gov>

Economics Interest Group

Meeting time and place: Varies Contact 1: James A. Schuttinga Phone: 496-2229 E-mail: <js41z@nih.gov> Contact 2: Agnes Rupp E-mail: <ar24f@nih.gov>

Endocrinology Interest Group **

Meeting time and place: Varies Contact 1: George Chrousos Phone: 496-5800 E-mail: <George_Chrousos@nih.gov> Contact 2: Phil Gold Phone: 496-1945

End of Life Research Interest Group

Meeting time: Typically Thursdays, 3:00 pm, on an as-needed basis Meeting place: Natcher, room as available Contact: Alexis Bakos Phone: 594-2542 E-mail:
bakosa@mail.nih.gov>

Epidemiology and Clinical Trials Interest Group

Meeting time and place: Varies (subscribe to ListServ for notices) Contact: Martina Vogel-Taylor Phone: 496-6614 E-mail: <martinav@nih.gov> ListServ: subscribe to Epidem-L at <listserv@list.nih.gov>

Epilepsy Interest Group

Meeting time and place: Seminars and annual Data Blitz session announced by email and on website Contact: Mike Rogawski Phone: 496-8013 E-mail: <epilepsySIG@nih.gov>

Fluorescence Interest Group

Meeting time: Usually even Fridays, 4:00 pm; see website; join to receive upcoming events e-mail Meeting place: Building 10, usually Room 5N264 Contact: Jay Knutson Phone: 496-2557 E-mail: <jaysan@helix.nih.gov> Contact 2: Dan Sackett E-mail: <sackettd@mail.nih.gov>

Gene Therapy Interest Group

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

INTERINSTITUTE INTEREST GROUP DIRECTORY

Genomics and Bioinformatics Interest Group

Meeting time: Usually one Thursday a month, 3:00 pm Meeting place: Building 37, 6th-floor conference room Contact: John N. Weinstein Phone: 496-9571 E-mail: <weinstein@dtpax2.ncifcrf.gov>

Glycobiology Interest Group

Meeting time and place: Varies Contact: Diana Blithe Phone: 435-6990. E-mail: <blithed@nih.gov> ListServ: Subscribe to GLYCO-L@LIST.NIH.GOV

GTP Binding Proteins Interest Group

Meeting time: Irregular Meeting place: FAES Social & Academic Ctr. Contact: R. Victor Rebois Phone: 496-2007 E-mail: <reboisv@nidcd.nih.gov>

Handheld Users Group (HUG) **

Meeting time: Every third Monday, 3:00 pm Meeting place: Building 10, NIH Library training room Contact: Ben Hope Phone: 594-6473 E-mail: <tallguy@nih.gov>

Hard Tissue Disorders Interest Group

Meeting time: Day varies, 9:30 am Meeting place: Building 30, Room 117 Contact: Pamela Robey Phone: 496-4563 E-mail: <probey@dir.nidcr.nih.gov> Contact 2: Michael Collins Phone: 496-4913

Head and Neck Cancer Interest Group **

Meeting time: To be announced Meeting place: Building 30, Room 117 Contact 1: Adrian Senderowicz Phone: 594-5270 E-mail: <adrian.senderowicz@nih.gov> Contact 2: Wendy Weinberg E-mail: <weinberg@cber.fda.gov>

Health Services Research Interest Group

Meeting time: Quarterly (day, time, and place to be announced); the group will have its second meeting in early September (time and place TBA) Contact 1: Emily DeVoto Phone: 496-6615 E-mail: <DeVotoE@od.nih.gov> Contact 2: Jack Stein Phone: 443-4060 E-mail: <js413y@nih.gov>

HIF (Hypoxia Inducible Factor) Interest Group

Meeting time: Last Thursday, 11:30 am– 1:00 pm Meeting place: Building 10, room varies Contact : Tawnya McKee Phone: 301-846-1943 E-mail: <mckee@ncifcrf.gov>

History of Biomedical Research Interest Group

Meeting time: Second Tuesday, 1:00 pm Meeting place: Varies; check web site Contact 1: Office of NIH History Phone: 496-6610 Contact 2: Victoria Harden E-mail: <hardenv@od.nih.gov>

Image Processing Interest Group

Meeting time and place: Distributed by email and on <image.nih.gov> Contact 1: Benes Trus Phone: 496-2250 E-mail: <Benes_Trus@nih.gov> Contact 2: Matt McAuliffe Phone: 594-2432

Imaging Ligand Development Consortium

Meeting time and place: To be announced (every 3 months; steering committee meetings will be held every 2 months in the Neuroscience Center) Contact: Jamie Driscoll Phone: 443-5288 E-mail: <jdrisco1@mail.nih.gov>

Integrative Neural-Immune Interest Group

Meeting time and place: To be announced Contact: Socorro Vigil-Scott Phone: 496-9255 E-mail: <vigilscs@intra.nimh.nih.gov>

Integrative Neuroscience Interest Group

Meeting time: Alternate Thursdays, 4:00 pm Meeting Place: Building 49, Room 1A51 Contact: Bruce Cumming E-mail:

c@lsr.nei.nih.gov>

In Vivo NMR Interest Group

Meeting time: Varies Meeting place: Building 10, Room B1N256 Contact: Jeff Duyn Phone: 594-7305 E-mail: <jhd@helix.nih.gov>

Knowledge Management Interest Group

Meeting time and place: Quarterly; other details to come; check the website (which is in the process of being updated) Contact 1: Geoffrey Marsh Phone: 301-594-9683 E-mail: <geoff@mail.nih.gov> Contact 2: Paul Beatty E-mail: cpbeatty@mail.nih.gov>

Lab Managers Interest Group

Meeting time: Monthly, noon Meeting place: Varies Contact: Dawn A. Walker Phone: 402-7149 E-mail: <walkerd@exchange.nih.gov>

Lambda Lunch (Bacterial and Phage Genetics)

Meeting time: Each Thursday, 11:00 am Meeting place: Building 37, Room 6107/ 6041 Contact: Susan Gottesman Phone: 496-3524 E-mail: <susang@helix.nih.gov> Contact 2: Robert Weisberg E-mail: <rweisberg@nih.gov Anonymous FTP site:FTP.CU.NIH.-GOV directory "LAMBDA_LUNCH"

Light Microscopy Interest Group

Meeting time: Monthly, Tuesday, noon Meeting place: Building 10, Room 4B51 Contact: James McNally Phone: 402-0209 E-mail: <mcnallyj@mail.nih.gov> Contact 2: Christian Combs Phone: 496-0014

Mass Spectrometry Interest Group

Meeting time: 1st & 3rd Thursday, 10:30 am Meeting place: Building 10, Room 7C101 Contact: Jeff Kowalak Phone: 496-4242 E-mail: <jkowalak@intra.nimh.nih.gov>

Membrane Microdomains Interest Group

Meeting time: 1st Tuesday, 1:00 pm Meeting place: Building 10, Room 9C209 Contact: Paul Roche Phone: 594-2595 E-mail: <rochep@pop.nci.nih.gov>

Membrane Protein Interest Group

Meeting time: Usually one Wednesday a month, 1:00 pm; check website: <http:// www.nih.gov/sigs/mpig> Meeting place: Building 5, Room 127 Contact: Reinhard Grisshammer E-mail: <rkgriss@helix.nih.gov>

Microarray Users Group

Meeting time and place: Usually first Wednesday; Journal Club meets weekly or bimonthly, as the group decides Meeting place: Varies Contact: Katherine Peterson Phone: 402-5678 E-mail: <petersonk@nei.nih.gov>

Mitochondria Interest Group

Meeting time: 1st Monday, 3:00 pm Meeting/Videoconference: Natcher, Room H; NIEHS, Research Triangle Park, NC; GRC, Baltimore; NIST, Admin. Bldg, Room B113, Gaithersburg, MD; VA Hospital, Cleveland; Podell Auditorium, Beth Israel Medical Center, NYC; Baylor Univ.,Texas; Louisiana State University Health Science Center

Contact: Steve Zullo Phone: 435-2810 E-mail: <zulło@helix.nih.gov> Contact 2: Salvatore Alesci E-mail: <alescis@mail.nih.gov>

Molecular Modeling Interest Group

Meeting time: See <http://mmignet.nih.gov> Meeting place: Building 12A, conf. rooms Contact: Peter Steinbach Phone: 496-1100 E-mail: <steinbac@helix.nih.gov>

Motility Interest Group

Meeting time and place: Varies Contact: Jim Sellers Phone: 496-6887 E-mail: <sellersj@nhlbi.nih.gov>

Mouse Club

Meeting time: 1st Tuesday, 4:00 pm Meeting place: Building 6A, Room 4A05 Contact: Heiner Westphal Phone: 402-0545 E-mail: <hw@helix.nih.gov>

Muscle Interest Group

Meeting time: Alternate Thursdays, noon Meeting place: Building 40, Room 1203 or 1205 Contact: Andres Buonanno Phone: 496-0170 E-mail:
buonanno@helix.nih.gov>

Neurobiology Interest Group

Meeting time and place: TBA Contact: Chip Gerfen Phone: 496-4341 E-mail: <gerfenc@intra.nimh.nih.gov> ListServ: <http://intra.ninds.nih.gov/nig/>

Neuroinformatics Interest Group

Meeting time and place: To be announced Contact 1: Stephen Koslow Phone: 443-1815 E-mail: <koz@helix.nih.gov> Contact 2: Barry Davis Phone: 402-3464 E-mail:

barry_davis@nih.gov>

Pain Interest Group

Meeting time: Tuesday, 3:00 Meeting place: Building 30, Room 117 Contact 1: Raymond Dionne Phone: 496-0294 E-mail: <rdionne@dir.nidcr.nih.gov> Contact 2: Michael Iadarola E-mail: <miadarola@dir.nidcr.nih.gov>

PET Interest Group

Meeting time: Friday, 2:00 pm; see website for seminar listing Meeting place: Building 10, Room 1C520 Contact: Peter Herscovitch Phone: 451-4248 E-mail: <hrscovitch@nih.gov>

Phage-Tech Interest Group **

Meeting time and place: Varies Contact 1: Dean Scholl E-mail: <dscholl@helix.nih.gov> Contact 2: Carl Merril Phone: 435-3583

Pigment Cell Research Interest Group **

Meeting time: One Tuesday every other month, lunch meeting 12:00–1:30 pm; once a year a daylong meeting Meeting place: Building 40, Room 1201-1203 Contact 1: Bill Pavan Phone: 496-7584 E-mail:

 E-mail:

 Aufan Huizing Phone: 402-2797

E-mail: <mhuizing@mail.nih.gov

Polyunsaturated Lipid Function Interest Group

Meeting time: Usually 1st Wednesday of each month, as announced (journal club; resuming in September), 1:00 pm Meeting place: Flow Bldg. Conference Room, Rockville, 12501 Washington Ave. Contact: Norman Salem Phone: 443-2393 E-mail: <nsalem@niaaa.nih.gov>

Prostate Cancer Interest Group

Meeting time: Monthly, Tuesday, 4:00 pm Meeting place: Building 10, Room 2S235 Contact: Sildiz Ali Phone: 496-6353 E-mail: <alis@mail.nih.gov>

Protein Trafficking Interest Group

Meeting time: 2nd Tuesday, 3:30 pm Meeting place: Building 50, Room 2328 Contact 1: Harris Bernstein Phone: 402-4770 E-mail: <harris_bernstein@nih.gov> Contact 2: Peng Loh Phone: 496-3239

Proteomics Interest Group

Meeting time: Monthly 1st Friday seminars Meeting place: Building 50; check website: <http://proteome.nih.gov> Contact: Donita Garland Phone: 496-6999 E-mail: <dgarland@helix.nih.gov>

Reactive Oxygen Species Interest Group *

Meeting time and place: Monthly seminars with Oxygen Club of the Greater Washington Area (info via NIH Calendar, members' e-mail, and <Jayasree.Nath@NA.AMEDD.ARMY.MIL>) Contact 1: Mike Chiueh Phone: 496-3421 E-mail: <chiueh@helix.nih.gov> Contact 2: Mike Espey Phone: 496-7511

RNA Club

Meeting time: 1st Tuesday (except August), 4:00 pm Meeting place: Building 41, Room C509 Contact 1: Carl Baker Phone: 496-2078 E-mail: <ccb@nih.gov> Contact 2: Susan Haynes E-mail: <shaynes@usuhs.mil>

Signal Transduction Interest Group

Meeting time: Alternate Wednesdays, 5:00 pm Meeting place: 5 Research Court, Conference Room Contact 1: John Northup Phone: 496-9167 E-mail: <drjohn@codon.nih.gov> Contact 2: James Battey Phone: 402-0900

Stem Cell Interest Group

Meeting time and place: Monthly seminars to rotate through Baltimore, Bethesda, and Frederick campuses; check website Contact 1: Minoru Ko Phone: 1-410-558-8359 E-mail: <kom@grc.nia.nih.gov> Contact 2: Nadya Lumelsky Phone: 301-451-9834 E-mail: <nadyal@intra.niddk.nih.gov> Contact 3: Colin Stewart Phone: 301-846-1755 E-mail: <stewartc@ncifcrf.gov>

Stroke Branch Interest Group/Seminar

Clinical Stroke Rounds (year-round) Meeting time: Wednesdays, 8:30 am Meeting place: Suburban Hospital Stroke Branch Seminars (September through May Meeting time: Thursdays 3:30 pm Meeting place: Building 36, Conf. Room 1B13 Contact 1: John Kylan Lynch Phone: 496-1187/1714 E-mail: <LynchJ@ninds.nih.gov> Contact 2: Zurab Nadareishvili Phone: 496-6231

Synaptic and Developmental Plasticity Interest Group

Meeting time: Wednesday, once a month, 12:00 noon Meeting place: Building 49, Room 1A50 Contact: Bai Lu Phone: 435-2970 E-mail: <bailu@mail.nih.gov>

Systems Biology Interest Group **

Meeting time: Every second Thursday, 3:00–4:30 pm (starting September 11, 2003) Meeting place: Natcher, Room 2AS10 Contact 1: Victor Pollara Phone: 402-1620 E-mail: <pollarav@mail.nih.gov> Contact 2: Martin Meier-Schellersheim Phone: 496-5046 E-mail: <mms@niaid.nih.gov>

Technology Transfer Interest Group

Meeting time: First Tuesday each month, 3:00 pm Meeting place: 6011 Executive Blvd., suite 325 Contact 1: J.P. Kim Phone: 435-5377 E-mail: <kimj@od6100m1.od.nih.gov> Contact 2: Robert Baughman Phone: 496-1779 E-mail: <baughmar@ninds.nih.gov>

INTERINSTITUTE INTEREST GROUP DIRECTORY

Therapeutic Oligonucleotides Interest Group

Meeting time: Last Thursday, 4:00 pm Meeting place: Building 10, Room 2C116 Contact: Yoon Cho-Chung Phone: 496-4020 E-mail: <chochung@helix.nih.gov>

Tobacco and Nicotine Research Interest Group **

Meeting time: Bimonthly (date and time vary) Meeting place: Executive Plaza North Contact: Matthew Fritts Phone: 594-6637 E-mail: <frittsm@mail.nih.gov>

Transcription Factor Interest Group

Meeting time: 1st Thursday (except July-Sept.), 2:00 pm Meeting place: Building 50, ground-floor Conference Room (Room 1227) Contact 1: Stoney Simons Phone: 496-6796 E-mail: <steroids@helix.nih.gov> Contact 2: Uli Siebenlist Phone 496-8917 ListServ: subscribe to TFACTORS

Tumor Angiogenesis & Invasion Working Group

Meeting time and place: Posted at web site Contact 1: William Figg Phone: 402-3622 E-mail: <wdfigg@helix.nih.gov> Contact 2: Steven Libutti Phone: 496-5049

IGs on the Horizon

R Users Group

Contact: Terry Cox Phone: 496-6583 E-mail: <TAC@NEI.NIH.GOV>

According to Terry Cox, who is organizing a mailing list and meetings, R is a free, open source system for statistical analysis and graphics (see <http://www.rproject.org/>).

Among the packages that have been written for R is Bioconductor, an open source set of software for bioinformatics.

Biomedical Enabling Sciences and Technologies (BEST) Cluster Contact: Mohammad Al-Ubaydli Phone: 451-6716

E-mail: <alubaydl@ncbi.nlm.nih.gov> Not an official IG umbrella, BEST is a coordinated cluster of IGs that thus far includes the Biomedical Computing IG, the Advanced Technologies SIG, the Knowledge Management IG, the Handheld Users Group, and the Microarray Users Group.

Viral Hepatitis Interest Group

Meeting time: 1st or 2nd Monday, 4:15 pm Meeting place: Building 10, Room 1C726 (DTM conference room) Contact: Marian Major Phone: 301-827-1881 E-mail: <major@cber.fda.gov>

Virology Interest Group

Meeting time: 4th Tuesday, 12:15 p.m.; minisymposium in November Meeting place: Building 29B, Room A/B Contact 1: Alison McBride Phone: 496-1370 E-mail: <amcbride@niaid.nih.gov> Contact 2: Carolyn Wilson E-mail: <wilsonC@cber.fda.gov> ListServ: Contact <CBuckler@nih.gov>

Washington Area NMR Interest Group

Meeting time: Three times a year, generally in December, February, and May Meeting place: Building 5, Room 127, or the Cloister (Building 60) Lecture Hall Contact: Robert Tycko Phone: 402-8272 E-mail: <robertt@niddk.nih.gov>

Washington Area Yeast Club

Meeting time: 2nd Wednesday, 4:30 pm Meeting place: Building 6A, Room 4A05 Contact 1: Reed Wickner Phone: 496-3452 E-mail: <wickner@helix.nih.gov> Contact 2: Alan Hinnebusch Phone: 496-4480 E-mail: <ahinnebusch@nih.gov>

Scientific Integrative Medicine Interest Group

Meeting time and place: To be announced Contact 1: David Goldstein Phone: 496-2103 E-mail: <goldsteind@ninds.nih.gov> Contact 2: Eleanor Hanna E-mail: <hannae@mail.nih.gov>

The general goal of this new group is to foster patient-oriented clinical research that leads to the prevention or presymptomatic treatment of multisystem disorders. The group will sponsor seminars led by members and invited speakers, grand rounds within institutes and the NIH Clinical Center, and lectures for the broader NIH community.

Considering starting a new Interest Group? Contact Celia Hooper: <hooperc@od.nib.gov> or fax: 301-402-4303.

Need to correct yonr group's listing? Contact CIT's web publisbing gronp: <pnblisb@cit.nih.gov>.

Women's Health Special Interest Group

Meeting time and place: Usually one Friday a month, 11:30 am–12:30 pm Meeting place: Varies; see website for upcoming lectures Contact: Vicki Malick Phone: 301-496-7989 E-mail: <malickv@od.nih.gov>

WorldWideWeb Interest Group

This group is still seeking someone to take on the administrative activities to keep the group going smoothly. Interested? Contact: Dale Graham E-mail: <degraham@helix.nih.gov>

X-ray Crystallography Interest Group

Meeting time and place: See biweekly newsletter: http://mcl1.ncifcrf.gov/ nihxray/ Contact: Fred Dyda Phone: 402-4496 E-mail: <dyda@ulti.niddk.nih.gov>

Zebrafish/Xenopus Interest Group

Meeting time and place: Monthly, rotating through participating labs; space is limited Contact: Tom Sargent Phone: 496-0369 E-mail: <sargentt@mail.nih.gov>

** Last year's listing—not verified or updated.

INTRO COURSE TO CLINICAL RESEARCH

Registration for "Introduction to the Principles and Practice of Clinical Research" begins **August 18** and closes **October 4**.

The course runs from October 18, 2004, through February 15, 2005, Monday and Tuesday evenings from 5:00 p.m. to about 6:30 p.m. There is no tuition fee, but students must buy the required textbook. There are a final exam and a certificate for successful completion of the course.

Nearly 700 students registered for the 2003-2004 program, which was also broadcast to nine other universities and medical centers in the United States; San Juan, Puerto Rico; and Lima, Peru.

For more information or to register, visit

<http://www.cc.nih.gov/researchers/training/ippcr.shtml>

or call the NIH Office of Clinical Research, Training, and Medical Education at 301-496-9425. For reasonable accommodations, call 301-496-9425 between 8:30 a.m. and 5:00 p.m. at least seven business days before the event.

COMMENTARY

GUIDE TO THE FIRST YEAR OF MOTHERHOOD AT NIH

by Fatima Husain, NIDCD



(1) How to get your baby to fall asleep? Read bim/ber your mentor's latest review article. Guaranteed to work when all else fails.



(2) Register your baby in NIH day-care before you conceive of conceiving.



(3) You will be transported back to elementary school—small benches, tight spaces, and easy friendships.



(5) You may be tempted by the –80 degrees refrigerator, but it is really NOT a good place for breast milk. Tip o' Pen to Jacquie Shukaliak



(4) Get ready to become a bag lady baby bag, lactation bag, office bag, hinch bag, and baby!

Thanks to Kimberly Griffin for our "bag lady" discussion.



Naser Pablo at 11 months—none the worse for NIH wear and on the waiting list for NIH daycare

MORE POSTBAC POSTERS: THE MEMORIES OF MAY LINGER ON

by Myrna Zelaya-Quesada. NIAID

Verónica Chávez, Georgetown University, Washington, D.C., and Kathleen Sullivan, State University of New York, College at Genesco: "Spontaneous" Disclosnre in Forensic Interviews

Preceptor: Margaret-Ellen Pipe, Laboratory of Comparative Ethology, NICHD

Spontaneous disclosure of sexual abuse by a victim, particularly a child, is unusual in the context of forensic interviews. Chávez and Sullivan set out to identify factors that might contribute to a child's willingness to discuss such an experience.

They examined variables related to the children, their family circumstance, the nature of the abuse, the suspect, and the context of the disclosure within the interview.

They found that "spontaneous" disclosure most often occurred among younger children who had been prompted to tell the truth, children who had experienced a prior abuse investigation, and those who had suffered severe abuse—such as penetration.

The victim-suspect relationship and the

events that triggered the investigation were not contributing factors. The researchers now plan to explore interviewer variables.

Michelle Geiss, Bates College, Lewiston, Maine: Sex Differences in Familial Transmission of Migraine Preceptor: Kathleen Merikangas, Mood

and Anxiety Disorders Research Program, NIMH Geiss' group sought to examine whether

familial transmission could explain the sex differences in lifetime prevalence of migraine headache—about twice as high in women.

Assuming that women's threshold of risk for migraine is lower than men's, the investigators reasoned that familial transmission would emerge as an important factor in sex differences if the relatives of men with migraine were found to be at greater risk than the relatives of women with migraine.

They interviewed male and female probands and their first-dregree relatives, as well as control subjects and their relatives (a total of 1,501 people). Supporting previous findings in the field, they found a 2.4 times higher incidence of migraine among women and a three times higher incidence among relatives of people with migraine.

But the relatives of male probands were not at greater risk than the relatives of female probands, refuting the notion that familial transmission might explain the sex difference in prevalence. "In fact," Geiss said, "the relatives of female probands were at greater risk—just the opposite of what we thought might be the case."

The researchers will be exploring other explanations, such as maternal transmission and psychosocial factors.

Lindsay Zemba, Millersville University, Millersville, Pa.: Sex Differences in Play Bebavior among Captive Common Marmosets (Callithrix jacchus) Preceptor: Lucille Roberts, Laboratory of Comparative Ethology, NICHD

Researchers believe that play in young animals may be one form of preparation for social interactions as adults. Zemba and her of Chekol and her colleagues.

Using a human cancer profiling array that included 13 tumor types, the team documented sparse or absent TLP in 20 to 45 percent of the solid cancer tissue samples they examined, including kidney, colon, stomach, uterus, and breast.

Chekol thinks this downregulation may demonstrate the involvement of the *TLP* gene in signaling pathways critical in the development of cancer.

To explore this possibility, Chekol cloned the target gene in antisense orientation into a tetracyclin-inducible retroviral vector system with which she infected human breast cancer cells. She intends to inject those tumor cells with reduced TLP levels into nude mice and monitor tumor growth rate.



PostBacs in the Spotlight: (left to right) Verónica Chávez and Kathleen Sullivan, Michelle Geiss, Ludsay Zemba, Seble Chekol, and Janet Benjamin

colleagues observed social groups of common marmosets at the NIH Animal Center in Poolesville to determine how play behavior relates to their social organization.

Common marmosets are monogamous primates that exhibit minimal sexual division of labor as adults. The researchers hypothesized that if social play is "affiliative," it would occur more frequently between the sexes; if "simulative," there would be little sex difference in quantity or quality of play.

Results demonstrated that "play is a form of affiliative behavior," with females receiving and males initiating more social play, especially rough and tumble play, Zemba said. Because the social organization of common marmoset families is similar to that of humans, the findings may be relevant to understanding the role of social play in children, including the potential negative effects of play deprivation in childhood, she added.

Seble Chekol, North Carolina State University, Raleigh: *The Role of TLP (Traplike Protein) in Varions Cancers* Preceptor: Angelina Felici, Laboratory of Cell Regulation and Carcinogenesis, NCI-CCR

Trap-like protein (TLP), which is structurally similar to TGF- β receptor-associated protein, is downregulated or absent in a variety of human cancers, according to the findings

Janet Benjamin, University of Maryland, Baltimore County: *Identification of Natural Killer Cells Marker in Rbesus and Pig-tailed Monkeys* Preceptor: Domenico Mavilio, Laboratory of Immunoregulation, NIAID

Natural killer (NK) cells play an important role in simian and human immune systems as the body's first line of defense against virus and tumor cells. They lyse infected cells by signaling both activating and inhibitory receptors on their surfaces. Benjamin and her colleagues sought to gain a better understanding of the immunophenotype and function of NK cells in monkeys—a pursuit that could aid in HIV vaccine development.

In this study, the researchers turned to the receptors to tease out NK cell function in monkeys. They used flow cytometry analysis to determine the expression of NKp46, NKp30, and NKG2D activating receptors, as well as NKp80 (an activating co-receptor) and NKG2A (an inhibitory receptor) in rhesus and pig-tailed monkeys.

"These new flow cytofluorometric analyses of NKG2A and NKp80, together or alone, combined with CD16 (a marker of human NK cells that is nonspecific in the monkeys), will allow us to identify the entire NK cells subset and to better understand the different roles of NK cells in the pathogenesis of different diseases," Benjamin said.

CELEBRATING INSTITUTIONAL MEMORY: NIH HISTORY DAY, SEPTEMBER 21

by Victoria Harden Director, Office of NIH History and Stetten Museum

Tuesday, September 21, 2004, marks the second annual NIH History Day. This year's theme—"Scientific Biography"—spot lights how advances in biomedical research depend on individual curiosity, perseverance, and creativity, augmented occasionally by serendipity.

Featured speaker Thomas Söderqvist, professor of the bistory of medicine and director of the Medical Museion at the University of Copenhagen, will lecture on "The Seven Virtues of Biography, or: What's the Use of Biographies of Life Scientists?" at 3:00 p.m., September 21, in Lipsett Auditorium, NIH Clinical Center (Building 10). Söderqvist's most recent book is Science as Autobiography: The Troubled Life of Niels Jerne, a personal and scientific portrait of the 1984 Nobel laureate in physiology or medicine. The Office of NIH History encourages senior NIH scientists to send in digital or paper copies of their CVs along with photos, both

candid and posed, to be added to its biographical reference files. On NIH History Day, collection stations will be staffed in the lobbies of Buildings 10, 50, and 37 for the convenience of scientists who want to donate in person.

For more information or special accommodations, contact Sarah Leavitt: <leavitts@od.nih.gov> or 301-496-8856 or consult <http://history.nih.gov>

Following are two biographical sketches that illustrate the theme. Charles Armstrong was the first intramural scientist elected to the National Academy of Sciences, and Margaret Pittman was the first woman to be named chief of an NIH laboratory.

CHARLES ARMSTRONG: ESTABLISHED A MOUSE MODEL FOR POLIO

harles Armstrong (1886-→ 1967), best known for his work on polio, studied many contagious diseases in his years with NIH. Armstrong received his PHS commission in 1916 and made a name for himself conducting studies of disease outbreaks.

His first triumph came in 1920 when he correctly traced the cause of an outbreak of botulism among party-goers in Ohio to tainted olives. This discovery led to a half-milliondollar upheaval of the olive canning industry in California. Assigned to the Hygienic



Courtesy of the National Library of Medicine Charles Armstrong

Laboratory (the predecessor of NIH) in 1921, Armstrong traveled to several locations-among them Haiti and a Navajo reservation-to study epidemics. Attuned to the practical side of public health practice, Armstrong was able to solve several health mysteries.

One important example is the case of usually fatal postvaccination tetanus in children who had been given smallpox vaccinations. The culprit turned out to be the dressings, often celluloid shields, which harbored the tetanus spores.

His work in the new field of virology led to discoveries of new diseases and strains of diseases-and also led him to contract at least six of the diseases he studied, including psittacosis, encephalitis, and Q fever.

Armstrong's work in polio research earned him a place in the Hall of Fame of the National Foundation for Infantile Paralysis. He had spent years doing experiments with nose sprays that would temporarily prevent the spread of polio, and, perhaps more importantly, had been able to induce the disease for the first time in mice, thereby providing an affordable animal model that would eventually lead to the development of a vaccine.

Armstrong served as chief of the Division of Infectious Diseases from 1940 to 1950 and-in 1944-became the first NIH staff member elected to membership in the National Academy of Sciences.

MARGARET PITTMAN: VACCINE STANDARDS PIONEER

argaret Pittman (1901-M 1995) is best known for her pioneering work in the production, testing, and standardization of vaccines to prevent typhoid, cholera, and pertussis.

In a career that included 35 years with the Division of Biologics Standards (later renamed and transferred to FDA), Pittman traveled to the far reaches of the world in her quest to develop and encourage the use of safe vaccines.



Pittman began her research career in the 1930s at the

Margaret Pittman Rockefeller Institute In New York (now the Rockefeller University), where she studied the microbiology and immunol-

ogy of infections caused by Haemophilus influenzae. Her discovery-that there were six varieties of the organism, of which only one type caused serious disease in childreneventually led to the development of the flu vaccine for preschoolers in 1985.

After coming to NIH in 1936, Pittman turned to research on pertussis. This work led her to develop a usable mouse model for the disease in 1944. She then used the information gleaned from the mouse studies to develop a vaccine potency standard. These studies led to the international potency requirement issued by the World Health Organization (WHO) in the 1950s. Pittman was also involved in finding and standardizing vaccines for other diseases and was at the forefront of research in eliminating toxins from vaccines.

She took on administrative duties when she was named NIH's first female laboratory chief (of the Laboratory of Bacterial Products) in 1958, but continued to work in the field.

In the 1960s, Pittman was selected to join the Southeast Asia Treaty Organization's cholera project and traveled to what was then East Pakistan to help develop standards for a cholera vaccine. As a WHO consultant in the 1960s and 1970s, Pittman traveled to Egypt, Iran, and Spain to work out vaccine standards and conduct field trials.

CATALYTIC **REACTIONS?**

Also, we welcome "letters to the editor" for publication and your reactions to anything on the Catalyst pages.

In Future Issues... NIH Presence At International

> AIDS Conference Entry Point!:

Bench to Bedside:

No Bars Held

Targeting AIDS

Tf you have a photo or Lother graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not send it to us via email: catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2E26.

Mackall's Lab Scooters: Doing Their Part for NIH Parking



The three Vespa/Piaggio scooters belong to Pediatric Oncology Branch members (Crystal Mackall, head, Îmmunology Section, Kevin Chua, senior biologist; Melinda Merchant, clinical fellow). Their motto: The lab that scoots together spends less time walking from the multilevel.

[School's out for summer! Kids' Catalyst returns in September.]

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

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