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OTT and Rotavirus Vaccine

THE SHOT HEARD 'ROUND THE WORLD

by Fran Pollner

In the transformation of the rotavirus vaccine landscape from deserted to populous, Uri Reichman sees much to applaud.

"The more competition, the better," says the NIH Office of Technology Transfer infectious disease branch chief who has been the primary contact for the 10 companies thus far that have signed agreements with NIH or are nearing completion of negotiations to secure the right to pursue approval of rotavirus vaccines developed by NIH researchers.

Fran Pollner

Licensing branch chief Uri Reichman

"The more participants, the better for public health," Reichman said in an interview, "because there is plenty of need to go around. This vaccine is needed by infants in every little corner of the world."

And because the market is so large and potentially profitable—and previous doubts about the vaccine's safety have been answered (see main story, this page)—there may be more manufacturers seeking a license than is typical in a generally vaccine-wary climate.

Their interest, however, is not enough. Reichman's office has devised a detailed questionnaire to ascertain the resources, experience, and expertise of the companies seeking a rotavirus vaccine license. Each applicant must also submit a comprehensive development plan.

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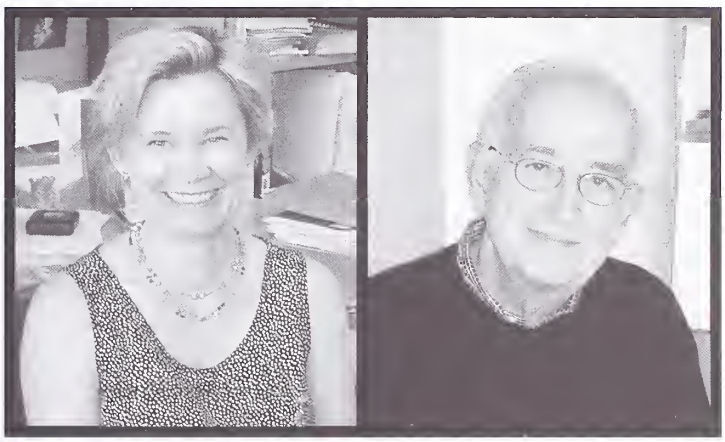
The Comeback Vaccine

FIRST- AND SECOND-GENERATION ROTAVIRUS VACCINES POISED TO PREVENT MAJOR CAUSE OF PEDIATRIC DEATHS

by Fran Pollner



Fran Pollner

Lone Simonsen (left), senior epidemiologist in the NIAID Office of Global Affairs, reanalyzed the CDC data that led to the withdrawal of the orginal rotavirus vaccine from the U.S. market. Her work counters the CDC intussusception projections and establishes a basis for a different rotavirus vaccine dosage schedule. "Her data are key," says Al Kapikian (right), to the confidence with which he and his team present their new rotavirus vaccine and schedule to the world. Companion articles' by Kapikian et al.[1] and Simonsen at al.[2] on the safety of rotaviral vaccines and prospects for eradicating severe rotaviral disease will be published in September in a supplement to the Journal of Infectious Diseases

After nearly six years in limbo, rotavirus vaccines developed in Al Kapikian's NIAID lab are back on track to worldwide distribution and the prevention of the severe rotavirus-associated diarrhea that kills 500,000 to 600,000 infants and young children annually.

Over the past few years, 10 companies in the United States and abroad have been negotiating licensing agreements with the NIH Office of Technology Transfer (OTT) for the right to manufacture and market one or the other of the NIH rotavirus vaccine inventions (see story, this page).

One company has secured the rights to RotaShield, which was the first and only FDA-approved rotavirus vaccine and had been on the market only nine months when it was withdrawn in 1999 on the heels of a CDC report showing a vaccine-asociated risk of intussusception (intestinal prolapse). Nine other companies have scrambled to pick up where testing left off for the second-generation version of the vaccine.

Chief among the factors contributing to this revived interest are:

■ A reanalysis of the intussusception data from the CDC study pointed to a compensatory decreased risk within the first year of life, suggesting the overall risk had been overestimated.

■ Further analysis uncovered an age-related vulnerability that pointed to an even safer alternative vaccine-delivery schedule than originally recommended.

Kapikian believes that this revised schedule has the potential to eliminate

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A Pitch for Intramural Support of Public Access

Michael Gottesman

Elsewhere in this issue (page 3), you will read a detailed account of a town meeting held by Dr. Zerhouni to present to the NIH staff important information about making NIH-sponsored research available to all scientists and to the general public. Earlier, I sent out a general notice to our scientific staff about this policy.

The general idea is that beginning May 2, 2005, NIH intramural authors (and extramural scientists reporting on NIH-funded research) may deposit their manuscripts that have been accepted for publication into the public NLM website called PubMed Central. The authors designate how soon after journal publication their papers will be released on PubMed Central—from immediately to up to 12 months after publication. Submission to PubMed Central is voluntary, and the process has been designed to be easy and quick. The details about how to do this are available at the website: <**http://www.nihms.nih.gov/**>.

If you would like help or perhaps a demonstration for your research group, contact the NIH Library at 301-496-2184 or <**http://nihlibrary.nih.gov**>.

Providing our published literature to our colleagues and the general public free of charge is responsive to the requests of Congress and most patient constituency groups and is clearly the right thing to do. So what's the fuss?

Providing our published literature to our colleagues and the general public free of charge is responsive to the requests of Congress and most patient constituency groups and is clearly the right thing to do. So what's the fuss?

The publishing industry and scientific professional societies have expressed concerns about the effect of this policy on their ability to market peer-reviewed journals, in part due to concerns about copyright. (As intramural scientists, we have no copyright in our work to assign to journals; simply informing the journal that we intend to provide the final manuscript to PubMed Central should satisfy concerns of this type.)

Scientists have worried about the potential appearance of two forms of their work in the public domain (the form submitted to PubMed Central, which is the original accepted version of the manuscript by the journal, and the copyedited journal version); they have also anticipated the possibility that journals will restrict publication by scientists who conform to the NIH policy on public access. With respect to the latter point, many journals have issued policies asking their authors to publicly release their articles within a stated period of time (six months for some, 12 months for others), whereas other journals have so far been silent on this issue.

There is currently no requirement for NIH intramural scientists to submit their articles to PubMed Central. But I am writing to urge you to make note of the public access policy, think hard about the importance of this policy for science and for the NIH, and spend a few minutes submitting your manuscripts to PubMed Central in as timely a way as possible.

Indeed, very early reports suggest that this request will be favorably received: PubMed Central began to receive manuscripts on NIH-supported research shortly after the new policy went into effect. As anticipated, submission time appears to range from six to eight minutes.

In addition to the obvious public benefits of PubMed Central submission, what are the advantages to scientists?

- In cases where public access is provided, we expect an immediate increase in citation rate because access to the publication is not limited to people who subscribe to the journal or can travel to a library.
- PubMed Central will format and index all articles so that they are fully text searchable—this amenity will make it easier for our colleagues and our own laboratories to find specific information embedded in our published work.
- Finally, it appears that many of the journals in which we publish our papers will actually benefit from the wider exposure afforded by PubMed Central. They will see an increase in their impact factors, which in turn will reflect positively on our work—a win-win situation.

So, do the right thing. Submit your articles that have been accepted for publication to PubMed Central and allow their release in as short a time period after publication as you deem feasible.

—Michael Gottesman
Deputy Director for Intramural Research

More of the World to Have Free Access To NIH-Supported Published Research

by Jacqueline Ruttimann

As of May 2, all NIH-funded researchers are being asked to comply with a new NIH policy aimed at providing the public with free and timely access to published findings arising from research funded in whole or in part by NIH.

Investigators are requested to submit copies of their accepted, peer-reviewed manuscripts to the NLM's PubMed Central (PMC) as quickly as possible—and in no case beyond one year—after publication in a scientific journal.

NIH-funded researchers encompass extramural and intramural scientists; the manuscript to be submitted to PMC is the final version accepted for journal publication, which includes all modifications generated during the publishing peer-review process but not any copyediting that may ensue before the article is actually published. That distinction will be made clear online.

Although NIH desires and expects that most researchers will follow these directions, compliance is voluntary, NIH Director Elias Zerhouni noted at a Town Hall meeting here in March to discuss the new policy. Relationships that an investigator may have with a certain publisher or professional society might not be compatible with submission of a manuscript to a free public website, he said.

Precedent Setting

About one-third of attendees at the meeting were intramural scientists—a cohort of NIH-funded researchers that Zerhouni called upon "to lead the way" in broadening public access to government-funded research findings. He noted that intramural scientists "have the right to publish online immediately."

Not only will online access via PMC transmit to the public the fruits of research carried out with taxpayer dollars, but it will also enable NIH to monitor and archive the output of funded research, as well as facilitate scientists' search for published data relevant to their own pursuits.

Moreover, Zerhouni said, "It's really creating a precedent . . . that a federal agency like the NIH has the right to create an archive of publicly funded research. . . . This is a pro-science policy."

The policy was motivated in part by requests for access by members of Congress and patient advocacy groups, who started to inquire why all of NIH-sponsored publications were not available for their viewing, especially in light of the finding that most people with Internet access search that source for medical information before going to their doctor.

(The idea of PubMed Central itself was first proposed in 1999 by then–NIH Director Harold Varmus, who advocated free public access to the world's biomedical literature [see *The NIH Catalyst*, July-August 1999, page 1; <**http://www.nih.gov/catalyst/1999/99.07.01/page1.html**>]. PMC became operational in 2000.)

The proposal that all NIH-funded research be submitted to PMC appeared in the *Federal Register* in September 2004; it generated more than 6,200 comments, many in support, Zerhouni said. But there were also some objections based on fears of a dwindling subscription base that, in the case of some nonprofit scientific societies, would mean less money to support research and training programs. The proposed policy was finalized in February.

Speaking at the Town Hall meeting, Norka Ruiz Bravo, deputy director for extramural research, emphasized that that scientists will benefit from publication in PMC: It will fulfill grant-progress reporting requirements; the contents of the work will be cross-indexed to other federal databases, such as GenBank; and, she pointed out, investigators who have archived publications in PubMed Central get more hits on those articles.

David Lipman, director of the NLM's National Center for Biotechnology Information, noted that as of October 2004, 160 journals were participating in PMC (which increased to 178 by February 2005) and that more than 2 million people accessed it that month. By the end of 2005, he said, PMC will contain about 800,000 articles.

Stepping into PubMed Central

Lipman walked the NIH intramural community through the process of submitting a publication to PMC.

The first step for intramural scientists is to log on to the web site (<**http://www.nihms.nih.gov/**>), entering one's NIH ID and providing the information requested, such as the title and authors of the manuscript. Next, the scientist sends the Word version of the publication to PMC, where it is converted to a standard PDF format and then returned to the submitting scientist for approval (figures can be embedded in the document or submitted separately). At this time, the scientist is asked to indicate the date the manuscript may be released online to the public.

"The goal," Lipman said, "is for it to take less than 10 minutes from start to finish."

Extramural scientists will need an Electronic Research Administration (eRA) Commons account to transfer their work to PMC, continued Israel Lederhendler, director of the Office of Electronic Research and Reports Management. He noted that about two-thirds of extramural grantees already have such an account.

It's anticipated that by October 2005, submission to PMC itself will serve as a complementary means of completing the annual required progress report, he said. Beyond that, a working group will be established to devise ways to use PMC and the data within the archive to assist institutes with their extramural portfolio oversight activities.

During the question-and-answer period, copyright emerged as a thorny issue. A memo Zerhouni sent in February to intramural scientists states that "NIH strongly encourages authors and institutions to exercise their right to inform publishers, and if necessary specify in any copyright transfer agreement, that the author or institution retains the right to provide their manuscripts to PMC for public accessibility as soon as possible after journal publication." Some scientists expressed concern that a publisher might opt against printing an article the author intends to place in PMC.

Lipman commented that many of the "best pieces" published in biomedical journals come from NIH intramural and extramural researchers and that most journals will want to cooperate. He cited *Nature* as an example. Barbara McGarey, NIH general counsel, observed that the work of intramural scientists is inherently in the public domain—and that there is no copyright on government work.

Ruiz Bravo noted that the policy was purposely made flexible in case of recalcitrant publishers—but she foresaw a "culture change" that would minimize that situation. ■

Immunologists and Stem-Cell Transplant Team Join Forces In Innovative Lupus Trial

by Karen Ross

In a bold attempt to control or perhaps even cure their disease, two patients with intractable systemic lupus erythematosus underwent bone marrow stem-cell transplantation at the Clinical Center. They are participating in a clinical protocol organized by rheumatologists, immunologists, and stem-cell transplantation experts from NIAMS, NIDCR, NCI, NIDDK, NINDS, and the CC Department of Transfusion Medicine.

Since the transplants were done only a few months ago, it is too soon to say what the long-term benefits will be, but the initial results are encouraging, says NCI's Steven Pavletic, the principal investigator.

The patients tolerated the transplant procedure well, Pavletic says, and are being weaned off the medications they currently use to keep their symptoms in check. Ultimately, the team plans to do transplants on 14 patients and follow them for up to five years.

Karen Ross

A meeting of the minds: *(left to right) NCI's Steven Pavletic, NIDCR's Gabor Illei, NCI's Fran Hakim, and NIAMS' John Hardin bring their expertise to bear in a protocol using autologous stem-cell transplantation for patients with severe systemic lupus erythematosus*

Lupus at a Glance

Like multiple sclerosis and rheumatoid arthritis, lupus is an autoimmune disease—a disorder in which the immune system turns against its own host.

The immune system, says NIAMS rheumatologist John Hardin, is capable of generating millions of responses. Most of the time, these responses are protective, killing off viruses, bacteria, and even incipient cancer cells before they have a chance to cause harm. But in autoimmune disease, the system mounts an inappropriate response against some part of the patient's own body.

Lupus patients have an immune reaction to components of the cell nucleus, primarily DNA-protein complexes, which are released during the normal process of cell death. Antibodies bind to the nuclear material and form clumps that are deposited in organs throughout the body, causing kidney damage, arthritis, skin rashes, and numerous other symptoms.

Lupus, which often strikes in early adulthood and has no known cure, is a debilitating and sometimes fatal disease—approximately 10 percent of lupus patients die from their disease in an average five-year period, and the mortality rate is higher in those with major organ involvement.

Immunosuppressive drugs are the current standard treatment for severe lupus. Side effects arise because these drugs quash both helpful and disease-causing immune responses. Moreover, for many patients, the medication becomes less effective over time.

Stem-Cell Transplantation Rationale

Bone marrow stem-cell transplantation is a promising new avenue of treatment for lupus. Developed to treat cancers of the immune system like leukemia and lymphoma, hematopoietic stem-cell transplants involve destroying a patient's diseased immune system with radiation or chemicals and then injecting stem cells that will develop into a new, healthy immune system. Ideally, after transplant, lupus patients would be free of the self-reactive immune cells that caused their disease.

Transplants can be done with either donor stem cells (an allogeneic transplant) or the patient's own stem cells (an autologous transplant). Although allogeneic transplants using donor cells from individuals who are not genetically predisposed to lupus may reduce the chances of recurrence, the NIH team opted initially for autologous transplants.

Eliminating the risk of graft vs. host disease, a serious complication of allogeneic transplants, was one reason, says Pavletic. In addition, there is some evidence from animal models of autoimmune disease that autologous transplants are effective.

Finally, approximately 100 lupus patients have been treated with autologous transplants with some success in clinical trials at other institutions. They were not cured—many still required immunosuppressive medications or had lingering symptoms of their disease—but about half of the patients continued to benefit from their transplants after two to four years.

"The main message," says Pavletic, "is that patients who have failed all other treatments can experience durable remissions with transplantation."

The NIH Protocol

Several aspects of the NIH transplant protocol fuel the investigators' hope for improved outcomes:

- The regimen of drugs used to deplete the patient's original immune system is not only less drastic than that used in other protocols but also may have a better chance of eliminating all of the immune cells that contribute to lupus.
- The criteria used to enter patients into the trial and to measure their responses have been carefully defined to point more precisely to why the transplant does or does not work in specific patients.
- But the most significant new feature, the investigators agree, is the intensive collaboration among lupus experts and experts in both the clinical and laboratory aspects of stem-cell transplantation. "The level of collaboration is totally unprecedented," says Gabor Illei, chief of the Sjögrens Syndrome Clinic at NIDCR, who is involved with the protocol.

The work of the bench scientists not only guides the transplant team in the

clinic, but also contributes to the basic understanding of lupus.

Frances Hakim, of the NCI Experimental Transplantation and Immunology Branch, analyzes patients' T cells before, during, and after transplant. She examines the T cells that persist after the depletion procedure, focusing particularly on whether any of these are the "bad actors" that cause lupus symptoms, and she studies how T cell populations recover after transplant. Amrie Grammer, of the NIAMS Autoimmunity Branch, conducts similar studies on B cells.

This in-depth exploration of each patient's immune system, says Hakim, "should give some insight into the pathogenesis of lupus and the generation of the next level of immune therapy."

Projections

There are some possible downsides to treating lupus with autologous stem-cell transplantation. As with stem-cell transplants in general, the procedure itself is somewhat risky, and there is always the chance that some of the disease-causing cells will escape eradication and trigger a recurrence of the disease after transplant.

Lupus presents a particular problem, however, because it has a strong genetic component, says Hardin. Studies of identical twins have shown that if one twin has lupus, the other has a 40 percent chance of developing the disease. This genetic propensity may be retained in an autologus transplant.

On the positive side, lupus doesn't usually appear until after age 20, so there is some hope that the disease would take as long to develop the second time as it did the first time—decades. And if the disease did recur, Hardin noted, it would be like a "new" case of lupus for which conventional treatment could be offered.

Ideally, says Hardin, the meticulous study built into the protocol will suggest stem-cell transplantation strategies to eliminate the disease-causing immune cells and leave the rest of the immune system intact. ■

For more information about the trial, contact Steve Pavletic at 301-435-4000 or **<pavletis@mail.nih.gov>**.

A description of the trial can be found at

<http://clinicaltrials.gov/ct/show/NCT00076752?order=1>.

Graduate Students at NIH: "The Faces of Tomorrow's Science"

by Aarthi Ashok

Three hundred twenty students in graduate programs the world over are currently enrolled in the NIH Graduate Partnerships Program (GPP). About 85 percent are U.S. students enrolled in Ph.D. programs and the rest hail from a variety of international universities. Forty-five new students will join the partnership programs next fall. Expanding their research projects in labs at 21 of the NIH institutes, GPP students have access here to specialized resources that enable them to ask—and perhaps answer—more complex questions than otherwise possible in their universities, says Richard McGee, director of GPP Student Affairs, who opened the Second Annual Graduate Student Research Symposium, held April 22.

In oral and poster presentations, the research of 66 graduate students was showcased. Below are two examples of the presented thesis work done at NIH. The coveted Outstanding Mentor Award, selected from among nominations by the graduate students, went to NIDA's Toni Shippenberg, integrative neuroscience chief, who was named by student Raf Schepers.

Proteomic analysis of mouse melanoma tumor progression: a study to identify proteins associated with tumor immune evasion

W. David Culp, Jr., Protein Biochemistry Section, NEI, and Cancer Centrum Karolinska, Karolinska Institute, Sweden

David Culp wanted to understand how tumor cells evade the immune system and decided to examine changes in protein expression in solid tumors during the growth of the tumor in vivo.

Aarthi Ashok

David Culp

He was intrigued by a previous finding that showed that when a mouse was challenged with a melanoma and given a vaccine three days later to kill the tumor, the mouse successfully eliminated the tumor cells and was able to survive. However, if the vaccine was delayed to seven days after the initial challenge, then the mouse was not able to eliminate the cancer cells and succumbed to the tumor. He therefore decided to look for protein expression differences between a day-3 and a day-7 tumor.

Aarthi Ashok

Ana da Veiga, and mentor Ivo Francischetti

Culp and his colleagues used 2-D–gel electrophoresis and subsequent mass spectrometric analysis to identify any proteins that were altered in expression between the day-3 and day-7 tumors in the B16-F10 mouse model of highly metastatic melanoma. They identified 29 proteins (P <0.01) with a 1.6 to 5.6-fold change in expression and 92 proteins (P <0.05) with 1.6 to 19.3-fold change in expression. The highest number of changes occurred between day 5 and day 7 of tumor progression. Translationally controlled tumor protein, which is known to be associated with cell growth, is dramatically upregulated in their system, and such proteins will now be their focus. Culp sees using RNAi to knock down expression of such proteins as a potential antitumor treatment strategy.

A Catalog for the transcripts from the venomous structures of the caterpillar* Lonomia obliqua: *Identification of the proteins potentially involved in the coagulation disorder and hemorrhagic syndrome

Ana da Veiga, Laboratory of Malaria and Vector Research, NIAID, and Universidade Federal do Rio Grande do Sol, Porto Alegre, Brazil

The caterpillar *Lonomia obliqua* is covered with spiny bristles that deliver venom to anybody who might happen to brush against it in Southern Brazil. The venom-induced hemorrhagic syndrome and coagulation disorder are severe and in extreme cases can cause kidney failure and death.

Ana Veiga sought to explore the molecular mechanisms by which this venom induces these severe symptoms. She and her colleagues used SDS-PAGE to separate out the proteins present in the venomous structures of the caterpillar and Edman degradation to obtain the sequence of these proteins. They also constructed cDNA libraries to generate a transcriptome—a catalog of *L. obliqua* cDNAs that encode proteins involved in venom induction.

Analysis of the protein families found in the transcriptome showed that several proteins with toxic functions, such as serine proteases, serpins, and lectins, were all present in the bristles of *L. obliqua*. Veiga has also been able to characterize cDNAs that encode for a prothrombin activator–like protein and for a fibrinogenase. The group's current hypothesis, she said, is that the prothrombin activator–like protein and the fibrinolytic protein are two venom constituents responsible for severe hemorrhagic syndrome and that many other molecules identified in the study may also play a role in venom production and release. ■

Ed. note: This sample of the work done by two GPP students is a prelude to future articles that will feature innovative research by graduate students at NIH.

Rotavirus Vaccine Back on Track To Worldwide Distribution

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the risk of intussusception following vaccination—and he is jubilant that the vaccines are on the threshold of delivery to high-mortality areas.

Global Distribution

"It will be a great thing to be able to say that this vaccine is finally where it is most needed—in the developing countries where so many children have died from this preventable disease," Kapikian said in an interview in April, shortly after his return from Brazil, where he was honored at a ceremony to celebrate the signing of a licensing agreement between OTT and the Butantan Institute of São Paulo.

"And what is really wonderful," he said of the situation in Brazil, "is that the vaccine will be free for every child. The Butantan Institute is state funded and produces 81 percent of all the vaccines in the country—that's 188 million doses."

The vaccine licensed to the Butantan Institute is the second-generation bovine rotavirus–human rotavirus reassortant vaccine, which was developed alongside the rhesus-human reassortant vaccine that was licensed and marketed as RotaShield (see "The Ups and Downs," this page).

For use in Brazil, the basic quadrivalent vaccine will be augmented with the serotype 9 strain. Serotype 9, says Kapikian, has emerged as an important strain in Latin America and the most important serotype in parts of Brazil. Serotype 8, he notes, is prevalent in certain African countries—"and we will put that strain in our vaccine for Africa. And when we do the vaccine for India, we will undoubtedly put in serotype 9."

In a paper[1] that will be published in September in a supplement to the *Journal of Infectious Diseases*, Kapikian and his colleagues recommend a hexavalent design (strains 1, 2, 3, 4, 8, and 9) for many of the developing countries. "The first four of these reassortants were made by Dr. Karen Midthun and others in our lab, and serotypes 8 and 9 were made later by Dr. [Yasutaka] Hoshino—next door—and they are available to be added to the vaccine," Kapikian notes. As licenses with OTT are concluded, the team will be sending relevant strains to each licensee.

He expects his work for the next few years will be focused on assisting the licensees in adapting the vaccine to the realities in their areas. His lab will provide technical assistance and, as space permits, will serve as a training site for those seeking to update relevant lab skills. Such a request has already come from China, where licenses are pending with three different entities.

Kapikian is pleased to point out that the advice he gives—regarding vaccine design, dosage schedule, and clinical trial protocol—to the many manufacturers who would bring the vaccine to their countries is part and parcel of his responsibilities as an NIH scientist with a public health mission.

The Ups and Downs of Rotavirus Vaccine

Al Kapikian's rotavirus research—first on the nature of rotavirus infection and then on a vaccine to undercut the otherwise potentially fatal severity of the first episode—began in 1974 and involved clinical collaboration with Children's Hospital National Medical Center, Washington, D.C., and clinical trial collaboration with centers in the United States and overseas, as well as a CRADA with Wyeth and contracts with DynCorp.

That work culminated in July 1998 with FDA approval of the Kapikian team's quadrivalent, live-virus oral vaccine. Wyeth received a product license from the FDA and took the vaccine—called RotaShield—to market with the recommended schedule of three doses delivered at 2, 4, and 6 months of age. The CDC Advisory Committee on Immunization Practices (ACIP) endorsed the routine use of the vaccine at the recommended schedule.

A rhesus rotavirus–human rotavirus reassortant, the vaccine was designed to raise antibodies to rotavirus strains prevalent in the United States—G1, G2, G3, and G4—and to be augmented with additional strains as needed in other areas of the world.

Alongside the rhesus-human vaccine construct, the team had also developed and was testing a bovine-human reassortant vaccine, which—in clinical trials in Finland—was proving to be as effective as the rhesus-based product and also to be free of the self-limited but bothersome fever experienced by about a third of those given RotaShield.

In July 1999, however, the CDC published findings of increased intussusception risk within two weeks of RotaShield vaccination, especially after the first dose. Based on initial studies and Adverse Events Reporting, the CDC initially estimated the risk to be about one excess intussusception in 2,500 to 5,000 vaccinated infants.

The ACIP withdrew its recommendation in October 1999, and Wyeth withdrew RotaShield from the market, suspending the introduction elsewhere of the rhesus-human vaccine, the evaluation of the bovine-human vaccine, and what was to have been a long-awaited worldwide campaign against severe rotavirus disease. (See *The NIH Catalyst*, March-April 1999 and March-April 2000, for previous coverage of the vaccine's approval and subsequent withdrawal from the U.S. market.)

Since that time, NIAID investigators have reanalyzed the CDC data and proposed that a two-dose schedule, the first dose at 0 to 4 weeks and the second at 4 to 8 weeks, may virtually eliminate intussusception risk associated with rotavirus vaccine.

Their published reports[1–4] and presentations at international meetings have generated a worldwide interest in these NIAID vaccines that has translated into licensing agreements between the NIH Office of Technology Transfer and companies around the world.

—Fran Pollner

The Road to Establishing Safety

From the time the rug was pulled out from under RotaShield, NIAID scientists set to work to understand the unexpected turn of events. Lone Simonsen, now senior epidemiologist in the NIAID Office of Global Affairs, recalls that NIAID was "caught unaware" when the CDC reported on the intussusception association in the *MMWR* of May 16, 1999. "They had never seen the data." Simonsen was called in to take a look at the evidence.

She cites three major findings in a series of reports from 2001 to the present. (see the two papers cited below[3, 4].)

First, during the nine-month period the vaccine was used, there was no increase in intussusception in states using the vaccine, contradicting the impression that the increased relative risk in the immediate postvaccination week would mean the vaccine had caused a substantial number of intussusception events.

"The important point was that, no, this was not a public health disaster," Simon-

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sen said in an interview. "To explain the unchanging intussusception rates during the nine-month use period, we hypothesized that the vaccine was harvesting events that would have happened anyway—and then, working further with the CDC case-control database, we found the phenomenon of compensatory decrease over time. This observation strongly supported our harvesting hypothesis."

Still concerned about the intussusception risk in the immediate postvaccination weeks, Simonsen and her colleagues set out to study carefully the role of age as a risk factor, analyzing data from the CDC, the National Center for Health Statistics National Immunization Survey, and hospital discharge data from the Agency for Healthcare Research and Quality.

During the nine-month introductory period for RotaShield use, many infants received the first dose beyond 2 months of age—so they could "catch-up" to the recommended schedule. More than 35 percent of first doses were given to "catch-up" infants between 3 and 7 months of age, and more than 80 percent of all implicated intussusception cases were amongst these older infants, Simonsen said.

"Were immunization to be completed before 3 months of age, we project that the intussusception risk would be far lower than previously thought—and comparable to severe adverse events linked to other approved vaccines currently in use," she said. In this scenario, RotaShield could be reconsidered for use—even in the United States, where the rotavirus burden of disease (though real, with 50,000 hospitalizations and 20 deaths a year) pales before the global toll.

Kapikian notes that in the natural history of intussusception, the first two months of life is a relatively refractory period, while peak incidence is between 3 to 4 months and 9 months. The cause of intussusception is not known, but, he says, it makes sense to give the vaccine before the peak period of susceptibility.■

Lone Simonsen and Al Kapikian wish to acknowledge the late John La Montagne, NIAID deputy director who died in November 2004, for being a source of strength, support, and encouragement in this unfolding rotavirus vaccine saga.

It was BIOVIRx, of Shorefield, Minn., that started the march back to the live-virus oral vaccine first marketed as RotaShield.

"BIOVIRx had followed the literature [challenging the reports of increased intussusception risk] and approached us with their intention to revive the vaccine and launch it in developing countries," Reichman said. He noted that his office had attempted in 2003 to convince Wyeth, the original RotaShield licensee, to act on the new data and bring RotaShield to market again.

"It was still an approved vaccine; the FDA had never reversed its approval or revoked Wyeth's license to market the vaccine. But Wyeth would not involve itself further," Reichman recalled.

Termination of the OTT license agreement with Wyeth cleared the way for other interested parties to seek intellectual property rights and with them the go-ahead to produce and test the vaccine to gain approval from the FDA or regulatory agencies in other countries.

Wyeth shipped back to NIH all materials related to the RotaShield license and its CRADA involving research on both the rhesus-human and the bovine-human rotavirus reassortant vaccines developed by Al Kapikian and his NIAID team. These included 183 boxes of documents and other materials such as viral strains; all have been safely stored and will be shipped to new licensees as warranted.

After BIOVIRx, nine more companies have entered the field, all seeking to market the second-generation bovine-human rotavirus vaccine.

The first applicant, also a U.S. company, sought to secure exclusive worldwide rights. As is standard procedure, OTT put a notice in the *Federal Register* that a qualified company had requested and, absent objections, would be granted an exclusive license for that particular vaccine.

In a sense, the *Federal Register* serves as a marketing tool for OTT, Reichman commented. A notice there alerts interested companies to the fact that an NIH invention is now available for licensing, and it invites qualified parties to apply.

Fran Pollner

Technology licensing specialists Susan Ano (left) and Chekesha Clingman (right) round out the core team headed by Uri Reichman, chief of the OTT Infectious Disease Branch, that has devised the questionnaire and conducted negotiations with prospective rotavirus vaccine manufacturers

In the case of the bovine-human rotavirus vaccine, eight more companies applied and qualified for licenses—four based in India, three in China, and one in Brazil.

The Brazilian license, with the Butantan Institute of São Paulo, was concluded in February 2005 (see main story) at an on-site ceremony in which Luis Salicrup, OTT senior advisor for global licensing, participated. Negotiations with the others were near conclusion at *NIH Catalyst* press time. Reichman expects all will be signed by September.

In addition to the NIH vaccines, Reichman said, there are two other rotavirus vaccine products in clinical trials and "close to launch." One, by Merck, is a pentavalent bovine-human reassortant vaccine similar to the NIH bovine-human design; the other, by GlaxoSmithKline, is a monovalent human attenuated strain vaccine.

The immensity of the market, Reichman said, ensures each manufacturer a healthy return on its investment—as well as royalties for NIH.

More important, he said, the more manufacturers there are, the larger the hedge against inadequate supplies in the event of spoiled vaccine lots, which is occasionally bound to happen but will not be calamitous if there is more than one lone supplier. ■

*The companion papers to appear in a September supplement to the *Journal of Infectious Diseases* are:

1. A. Kapikian, L. Simonsen, T. Vesikari, Y. Hoshino, D. Morens, R. Chanock, J. La Montagne, and B. Murphy, "A hexavalent human-bovine reassortant vaccine designed for use in developing countries and delivered in a schedule with the potential to eliminate the risk of intussusception," *J.Infect Dis.* (in press, 2005).

2. L. Simonsen, C. Viboud, A. Elixhauser, R. Taylor, and A. Kapikian,"More on RotaShield and intussusception: the role of age at vaccination," *J.Infect Dis.* (in press, 2005).

3. L. Simonsen, D. Morens, A. Elixhauser, M. Gerber, M. Van Raden, and W. C. Blackwelder, "Effect of rotavirus vaccination programme on trends in admission of infants to hospital for intussusception," *Lancet* **358**.1224 (2001).

4. B. Murphy, D. Morens, L. Simonsen, R. Chanock, J. La Montagne, and A. Kapikian, "Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions," *J.Infect.Dis.***187**: 1301(2003).

From Bench to Tech Transfer and Back to the NIH Scientist

by Fran Pollner

There is a firewall between NIH scientists and the financial end of NIH tech transfer, says the director of the NIH Office of Technology Transfer.

In all matters scientific, however, OTT Director Mark Rohrbaugh emphasizes, NIH researchers are the heart of tech transfer—from the point of discovery through the successful introduction of a new therapy into clinical practice.

There's a growing awareness among NIH researchers of the mission of OTT, which is to disseminate to the world at large the discoveries made in NIH labs. These include research tools for the greater research community and vaccines, drugs, devices, and techniques with clinical application for the bedside, wherever they are needed.

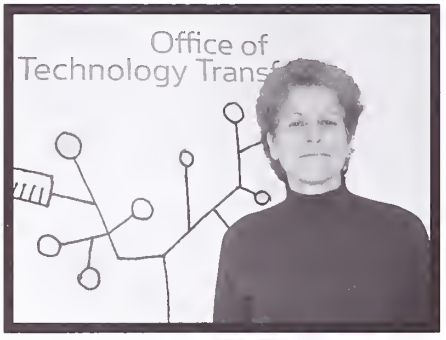
The tools of tech transfer in NIH's repertoire include CRADAs (cooperative research and development agreements) and material transfer agreements, managed at the institute/center level, and—managed by OTT—patenting of NIH inventions and licensing them to commercial entities that can bring them to market in the United States and/or abroad.

Not all new "art" needs or warrants patenting, observes OTT Deputy Director Bonny Harbinger, but a patent secures intellectual property rights for NIH, may generate royalties, and becomes a tool for securing favorable terms in licensing negotiations—terms typically aimed at maximizing access to an invention that meets a public health need.

Fran Pollner

Mark Rohrbaugh

"The conflict-of-interest issue certainly should not decrease the number of formal collaborations between NIH scientists and industry. The new policy in no way limits such activities as part of one's official duties. Scientists are encouraged to establish such links, select CRADA partners based on their knowledge and working relationships with them. . . . Licensing is another story. The scientists are not involved. They can't make requests on behalf of a company. We keep a wall between them and the financial terms of a license related to what they're doing in the lab."



Fran Pollner

Bonny Harbinger

"We have one of the largest tech transfer programs, and we are inundated with requests for training. We now have visitors from Ireland and China—for six months of training, and two groups are coming from India and Hungary. This [interaction] provides us with contacts in these countries to help us place licenses and gives us the opportunity to teach others the way we think tech transfer should be conducted to provide the greatest public health benefit—which is critical to us."

It Takes a Scientist

The road to a patent, Harbinger emphasizes, begins with an NIH researcher's recognizing that he or she has come up with something unique and useful—and, consequently, filing an "employee invention report," or EIR, with the institute's technology development coordinator. If a researcher doesn't know whether an EIR is warranted, the coordinator or OTT is always on hand to offer advice.

There were more than 400 EIRs submitted to OTT in 2004, compared with 268 in 1997; OTT sought patents for 199 of these. It's helpful, Harbinger notes, if researchers file their invention reports several months before they anticipate public disclosure of the research—to allow time for OTT and the ICs to review the invention report and OTT's contract law firms to apply for a patent should that be desirable.

Many NIH inventions, says Steve Ferguson, director of the OTT Division of Technology Development and Transfer, emerge from career scientists looking at basic mechanisms—"when suddenly there's a breakthrough observation—often when something has gone terribly wrong."

That "darkest before the dawn" insight has been described by NIH inventors who have participated in the Research Festival "Eureka!" minisymposium, organized by Ferguson as a way to recognize the genius of NIH scientist-inventors.

The Eureka! session, says Brian Stanton, the new director of the OTT Division of Policy, also highlights the "fundamental value of scientists in the lab just playing around, so to speak." This freedom is unique to NIH, Stanton says, and—something Congress may not realize—it's essential to the success of the NIH tech transfer program.

In interviews with *The NIH Catalyst*, Rohrbaugh, Harbinger, Ferguson, and Stanton discussed what they characterized as the very healthy state of NIH tech transfer. The OTT has undergone reorganization and expansion, has become a training ground for scientists interested in tech transfer, hosts visiting scientists from around the world, and is involved in international groups that formulate global tech transfer policies.

The office set a record last year in the licensing arena, concluding 276 licenses—one for each business day, Ferguson noted—including 32 new and amended licenses with foreign countries.

The International Arena

Part of the OTT emphasis on licensing, says Rohrbaugh, is to facilitate access in developing countries to NIH technologies that meet public health needs. "One person now works full time in that area, developing ties and identifying institutions—companies, government entities—interested in and capable of bringing needed products to market," he said, referring to the new position of senior advisor for international tech transfer, filled by Luis Salicrup.

Licensing and discussions in developing countries were particularly successful last year, he said, and aimed at facilitating the production at lower cost of needed drugs and vaccines, especially for infectious and tropical diseases—rotavirus, dengue, malaria, tuberculosis, HIV, and meningitis—as well as cancer and diabetes.

Once OTT negotiates a license with a company that will move an NIH invention out of the lab, the NIH inventors can be involved in the continuing development of the product and are encouraged to discuss scientific questions about the technology as part of their official duties. They can advise a prospective licensee on such matters as how best to grow cells, interpret data, or design a clinical trial. They cannot advise on such

matters as royalties or other financial terms of the licensing agreement—or advocate on behalf of a particular company.

Balancing Acts

Many interests must be balanced in the process of licensing, Ferguson noted. "Being a catalyst for research is an NIH mission, and we have to be careful that licensing doesn't get in the way of that," he said. Some of the language in negotiated agreements stipulates that NIH and others will retain the rights to do research related to the license.

If a company balks, that can become a point of negotiation, he said, with NIH perhaps compromising with terms more favorable to the company in exchange for broader dissemination of the technology. In such a case, the financial goal takes a back seat to the goal of advancing research.

Deciding to place as much as possible of the Human Genome Project into the public domain is an example of putting public interest first, Stanton said. "This was a conscious choice not to patent and to license nonexclusively."

Fran Pollner

Steve Ferguson

"At NIH, very often competing treatments for the same disease are being funded or researched. It's a mutual fund philosophy: You may not know which approach will work, but you know that something will. And whatever works, the public benefits. Here's an example: NIH was involved in the development of a drug for AIDS-related cytomegalovirus; it was the first of its class—an antisense drug for CMV. And we were also involved in the development of anti-HIV cocktails that have preempted CMV eye infections. So we have a novel wonder drug that makes no money for the company or for NIH. Overall, it's a success story because we are a public health agency, but that may not be so for the company that did the clinical trials—they got proof of principle, but not return on investment."

But OTT also has an obligation to NIH scientists and institutes, Stanton noted.

"There is an expectation that we will receive a reasonable return for technologies we license," he said. "We want to give something back to our inventors—and to the institutes so they can do additional research."

Some Stats for FY 2004
(covering NIH and FDA)

Invention disclosure reports	403
New U..S. Patent Applications Filed	199
Issued Patents	122
Executed licenses	276
Royalties (in millions)	$56.3
Executed CRADAs (NIH only)	87
Standard	43
Material	44

Returns of the Days and Decades

There is no question that NIH inventions generate income. The payments to NIH negotiated in exchange for licensing rights have been increasing year by year as the portfolio swells with new inventions and continuing returns on old ones.

At a meeting of the Scientific Directors in February, Rohrbaugh reported that there were about 2,300 issued or pending patents and 1,650 active licenses that in 2004 generated over $56 million in royalties, $9 million of which went to the inventors.

At NIH, the royalties are apportioned such that the first $2,000 in royalties is shared among the inventors; above that up to $50,000, 15 percent goes to the inventors and the rest to their institutes; above $50,000, 25 percent goes to the inventors and 75 percent to the institutes. An inventor can receive up to $150,000 a year, every year. "And wherever the inventor may be, we send out the royalties—and beyond that, the royalties will go to his or her estate," Harbinger noted. Last year, Rohrbaugh added, about 400 former and current NIH researchers were paid royalties.

Fran Pollner

Brian Stanton

"How does NIH define a return on investment, a tech transfer success? Is it in dollars? In the number of licenses negotiated? Or is it in benefit to the public health? OTT has many customers: there's the public at large, our scientists, the institutes, and the companies that are our partners. There are ways to preserve commercialization of a product with an exclusive license—and still break down the component parts of the technology to be licensed. We can negotiate separate agreements with the company so that researchers still have easy access to the antibodies, the reagents, the pieces of DNA, while the company has exclusive rights to market the downstream product."

Many of the inventions that generated the most in royalties in 2004 have been around for more than a decade (see list on page 10).

Rohrbaugh noted that nowadays, among inventions likely to interest prospective corporate partners are those that combine technologies, such as the cardiovascular stent that releases a known anticancer drug that interferes with cell proliferation, thereby reducing the incidence of restenosis after coronary angioplasty. This invention was one of three new OTT-licensed technologies that gained FDA approval in 2004 and was also one of the 20 that generated the most royalty income for NIH in 2004 (see lists on page 10).

"Personalized medicine, such as cancer therapies and diagnostic techniques—tailored to the susceptibility of your cancer—is another growing area of interest," Harbinger added. "Instead of throwing spaghetti on the wall and seeing what sticks, you determine in advance what *will* stick," she said.

Since April 2005, OTT has listed as available for licensing more than 40 new technologies. ■

Tech Transfer

continued from page 9

OTT-Licensed Products Approved by FDA in FY 2004

Between 1991 and 2004, FDA approved 23 products based on technologies developed in the NIH Intramural Research Program. The three 2004 newcomers were:

- Paclitaxel-eluting coronary stent system to inhibit restenosis after coronary angioplasty (James Kinsella et al., NIA)
- Generic form of didanosine (ddI) delayed-release capsules in the treatment of HIV infection (Hiroaki Mitsuya et al., NCI)
- Recombinant human keratinocyte growth factor protein, the first and only therapy for the severe mouth sores accompanying myelotoxic therapy for hematologic cancer (Jeffrey Rubin et al., NCI)

Top 20 Inventions in Royalties, 2004

(year refers to FDA approval or date of introduction)

Vaccines and Therapeutics

- Monoclonal antibody to treat respiratory syncytial virus—the first MoAB licensed by the FDA to treat any infectious disease (1998, Brian Murphy et al., NIAID)
- Didanosine (ddI), reverse transcriptase inhibitor that interferes with HIV replication (1991, Hiroaki Mitsuya et al., NCI)
- Paclitaxel as a cancer treatment (1992, Wyndham Wilson et al., NCI)
- Proteosome inhibitor to treat multiple myeloma—the first of its class approved by FDA (2003, Shanker Gupta, NCI)
- Synthetic thyrotropin as adjuvant in thyroid cancer (1998, Fredric Wondisford et al., NIDDK)
- Nutritional supplement to treat macular degeneration (2003, Rick Ferris et al., NEI)
- Hepatitis A vaccine (strain HM-175) (1995, Richard Daemer et al. and Ann Funkhouser et al., NIAID)
- Radioinmunotherapy for non-Hodgkins lymphoma—the first such product approved by the FDA (2002, Otto Gansow, NCI)
- Dideoxycytidine (ddC), reverse transcriptase inhibitor that interferes with HIV replication (1992, Hiroaki Mitsuya et al., NCI)

Diagnostics

- Serological detection of antibodies to HIV-1 (1985, Robert Gallo et al., NCI; Luc Montagnier et al., Pasteur Institute)
- DNA probe for breast cancer diagnosis (2001, Charles Richter King et al., NCI)
- Genotyping of HIV protease gene (1996, Stephen Oroszlan et al., NCI)
- Serological detection of antibodies to HTLV-1 (1985, Takis Papas et al., NCI)

Instrumentation and Devices

- Paclitaxel-eluting coronary stent system to inhibit restenosis after coronary angioplasty (2004, James Kinsella et al., NIA)
- Enhanced magnetic resonance imaging through magnetization transfer (1998, Robert Balaban et al., NHLBI)
- Laser capture microdissection (1997, Lance Liotta et al., NCI)

Research Materials

- Reconstituted basement membrane (1993, Hynda Kleinman et al., NIDCR)
- Recombinant cytochrome P-450 (1993, Harry Gelboin et al., NCI)
- Transforming growth factor-β (2002, Michael Sporn et al., NCI)
- Anthrax protective antigen (2002, Stephen Leppla, NIDCR)

The Past is Prologue

Instruments of the '60s and Beyond

The NIH Stetten Museum and the Office of NIH History announce the display of two 1960s-era scientific instruments and the cutting-edge research for which they were used. The exhibit is sponsored by the OD Office of Communications and Public Liaison.

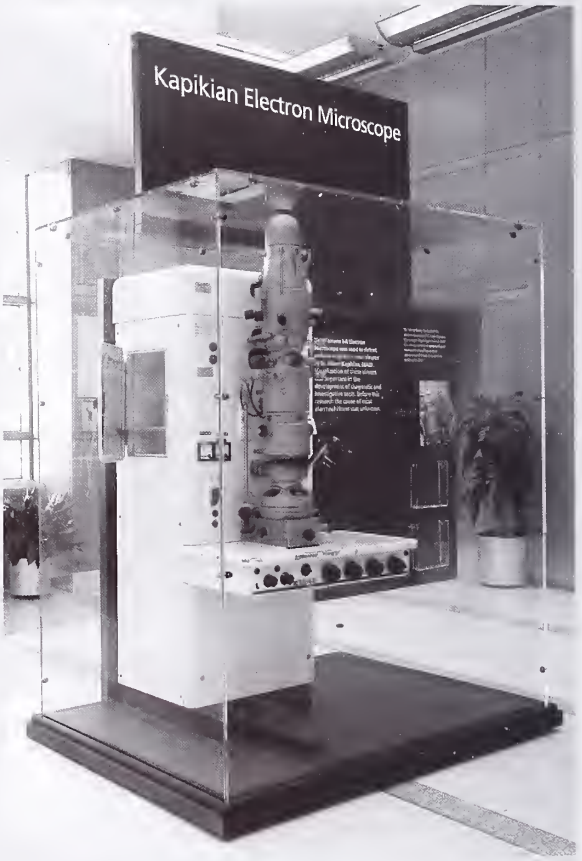
The Siemens 1-A Electron Microscope now on display in the lobby of Building 50 remained in use at NIH for over four decades. Albert Kapikian, NIAID, utilized immune electron microscopy to detect viruses. Specifically, he discovered and visualized Norwalk virus particles—known for striking cruise ships. This was the first time a virus was linked to diarrheal illness. NIH researchers also used this microscope to detect and characterize hepatitis A and hepatitis C, as well as to visualize human rotavirus.

Kapikian will describe his research on **Tuesday, June 28,** 1:00 p.m., in the Bldg. 50 lobby conference room.

The Varian A-60 NMR (nuclear magnetic resonance) spectrophotometer on display in the Natcher lobby is an example of the first low-cost, user-friendly instrument of its kind. It used powerful magnetic fields to line up the nuclei of atoms in the same direction and then flip them over. By tracing the energy the nuclei released when they flipped, the machine could record the unique spectra associated with each type of atom. The NMR led to the development of magnetic resonance imaging and the visualization of large molecules such as proteins. The display showcases the brain development research of Jay Giedd, NIMH, and the study in Adrian Bax's NIDDK laboratory of how large proteins move and function, with emphasis on immunodeficiency viruses.

NIDDK scientist emeritus Edwin Becker will speak on the history of NMR at the NIH on **Tuesday, May 24**, 1:00 p.m., in the Natcher Balcony A conference room.

—Michele Lyons
Curator
NIH Stetten Museum



Siemens 1-A Electron Microscope

Varian A-60 NMR

The Past is Prologue

Approaching the Mind in the '50s and Beyond

The Office of NIH History, NIMH, and NINDS announce the publication of Mind, Brain, Body, and Behavior: Foundations of Neuroscience and Behavioral Research at the National Institutes of Health *(Ingrid G. Farreras, Caroline Hannaway, and Victoria A. Harden, eds. Amsterdam: IOS Press, 2004).*

This book emanated from a symposium, "NIMH and NINDB Intramural Research in the 1950s," held at NIH April 11, 2003, to recapture the historic work of both institutes' intramural programs during their first decade of research at the NIH—a time when they shared a joint intramural basic research program.

Symposium participants donated historical photographs, correspondence, unpublished documents, laboratory notebooks, and other items from this time period to the Office of NIH History archives.

Author Ingrid Farreras, a Stetten Memorial fellow, supplemented the early history of the two institutes and detailed analysis of their joint program with extensive photographs and appendices that serve as references to who was in which laboratory when. Because NIH did not keep these records, she had to reconstruct the labs painstakingly via phone books, unpublished annual reports, and other sources.

Senior intramural scientists wrote firsthand accounts of their memories of the various labs and branches of the joint intramural program, and current NINDS director Story Landis traced the evolution of the research over the decades.

A major aim of this volume, say its editors, is to spur NIH scientists and administrators to collect, preserve, and donate archival materials to the Office of NIH History and the NLM. ■

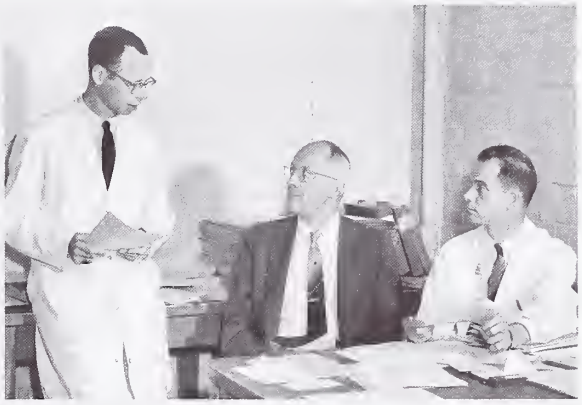


Photo courtesy of the Office of NIH History

In 1959, NIMH and NINDB intramural scientists were leaders in the NIH Assembly of Scientists. Left to right: Sanford L. Palay, Secretary, from the Laboratory of Neuroanatomical Sciences, NINDB; Karl Frank, Vice President, from the Laboratory of Neurophysiology, NINDB, and Haldor E. Rosvold, President, from the Laboratory of Psychology, NIMH. .

The Catalyst Bids Adieu to Our Very Own Catalyst

It's our bittersweet pleasure to bid farewell this month to Lance Liotta, *The NIH Catalyst's* founding father.

Lance Liotta

Liotta, chief of NCI's Laboratory of Pathology since 1982, is moving across the Potomac to become Professor of Life Sciences and Co-Director of the Center for Applied Proteomics and Molecular Medicine at George Mason University.

Lance was named NIH's Deputy Director for Intramural Research in July 1992. In this capacity, he launched *The NIH Catalyst*—with a welcoming message that highlighted our goal: to "Extend the spirit of the NIH Research Festival throughout the year." Liotta directed our "Hot Methods" series and has served as *Catalyst* editor through this issue.

Upbeat and encouraging, Liotta is a hands-on mentor. He directed one of NCI's largest, most active laboratories, training hundreds of the world's cancer pathologists and launching dozens of research careers as he urged young scientists into intriguing veins of investigation.

Liotta's restless creativity and energy fueled the development of new technologies that are answering some of the most difficult questions in cancer research. In the March-April 1997 issue, we noted that Liotta's laser-capture microdissection invention, which he co-patented, was one "of more than 60 patents, dating to 1973."

Kudos, thanks, and good luck, Lance!

What Is the Fellows Editorial Board?

The Fellows Editorial Board (FEB) was created in the spring of 2002 to meet the scientific editorial demands of postdoctoral and clinical fellows in the NCI Center for Cancer Research. FEB has recently expanded to include fellows from the entire NIH.

The objectives of FEB are twofold: to provide scientific editing services for NIH fellows and training and editorial experience to board members. Editorial board members edit submitted manuscripts, grant proposals, abstracts, and other scientific documents for grammar, structure, and style, but do not comment on scientific merit. All activity is confidential.

Who can join FEB?

FEB is an all-volunteer organization of postdoctoral and clinical fellows, professional science writers and editors, and scientists trained in editing. FEB now accepts members from all NIH institutions. Editorial experience is not required—FEB will train.

What is the editorial process?

The senior editor solicits three FEB members to serve as primary editors for each submission. All board members review the submission, and during the weekly meeting (videoconferenced to Frederick and Research Triangle Park), three primary editors lead the discussion of that manuscript. The editors' comments are compiled into an electronic report and a hard copy, which are returned to the author within 10 business days.

Who can submit documents to FEB?

All NIH fellows can submit their scientific documents to FEB.

What has FEB accomplished so far?

FEB has edited more than 125 documents for fellows. FEB-edited manuscripts have been published in high-impact, peer-reviewed journals including *Molecular and Cellular Biology, Cancer Research, Oncogene, The Journal of Biological Chemistry, Molecular Cell*, and *Neuroscience Research*. FEB has also organized three workshops in its "Become Your Own Best Editor" series to help fellows improve their scientific writing. FEB is planning two workshops, English as a Second Language and Scientific Editing as a Career.

For more info, check out <**http://ccr.cancer.gov/careers/feb/**> for submission instructions and membership applications or send e-mail to <**ncieditors@mail.nih.gov**>.

Recently Tenured

Mark Connors *received his M.D. from Temple University in Philadelphia in 1985 and completed his pediatrics residency and chief residency at Tufts-New England Medical Center in Boston. He then joined NIAID in 1989 as a fellow in the Laboratory of Infectious Diseases. In 1993, he began a year of infectious diseases training at the Clinical Center and Childrens Hospital of Philadelphia. He returned to NIAID to the Laboratory of Immunoregulation in 1994 and is currently a senior investigator in the Clinical and Molecular Retrovirology Section.*

Fran Pollner

Mark Connors

Despite prolonged investigation, the fundamental mechanisms by which the immune response might control HIV are poorly understood. This area remains one of the most important in HIV research. A better understanding of the breadth and magnitude of effective HIV-specific immune responses, the HIV protein targets of these responses, and the mechanisms by which protection or control occur may provide insights critical for the development of effective immunotherapies and prophylactic or therapeutic vaccines.

To provide a better understanding of the basis of immunologic control, we have recruited a cohort of very rare patients that represent the best example available of a successful immune response to HIV and studied these patients' responses in extreme detail.

The patients, referred to as long-term nonprogressors (LTNP), maintain immunologic restriction of HIV replication despite prolonged infection. It is likely their study holds important clues to the components of an effective immune response to HIV. Conversely, they also hold important clues regarding how control of HIV replication is lost in most infected individuals.

Prior definitions of LTNP have varied, were based on peripheral blood $CD4^+$ T cell counts alone, and tended to delineate highly heterogeneous cohorts. Use of HIV replication circumscribes a much smaller, more homogeneous group of patients. This subgroup of LTNP patients—without the use of antiretroviral therapy—manages to maintain normal $CD4^+$ T cell counts and plasma viral RNA below the level of detection of current widely used assays (<50 copies/mL plasma). Many of these patients have been infected for up to 20 years with no $CD4^+$ T cell decline. It is 17 of these patients that we have now assembled as a unique cohort with nonprogressive disease. Our studies compare cells from these patients with those from MHC-matched and -mismatched control patients whose disease is progressing. Through these comparisons, we are systematically dissecting the mechanisms of immune-mediated restriction of HIV replication.

Many mechanisms have been proposed to explain the inability of cell-mediated immunity to control HIV replication in the majority of infected patients. These include viral factors and quantitative and qualitative factors within the HIV-specific $CD8^+$ T cell pool. We have examined many of these parameters and our work has provided some surprising and counterintuitive answers.

For example, we have found that approximately 95 percent of the LTNP in our cohort carry the same MHC allele—HLA B*5701. The HIV-specific $CD8^+$ T cell responses of these individuals is completely focused on peptides presented by the B5701 molecule, providing a functional link to this genetic association. But the HLA B*5701 allele alone is not sufficient to confer restriction of HIV replication. Progressors with this allele occur at expected frequency and have very high viral loads.

We also rule out the possibility that immunologic control in LTNP is based on the epitopes targeted, viral mutations, or higher numbers of HIV-specific cells. Most patients, LTNP and progressors, maintain very high percentages of $CD8^+$ T cells in peripheral blood that are HIV-specific (10–40 percent). The persistence of such high frequencies of HIV-specific T cells—with or without immunologic control—indicates that the ability of LTNP to control HIV is based on qualitative rather than quantitative aspects of the immune response. These data also suggest that we are missing some fundamental parameters that govern this control.

Thus far we have found one qualitative parameter that distinguishes HIV-specific $CD8^+$ T cells of LTNP from those of progressors. This is their ability to proliferate in response to HIV-infected cells in vitro. Whereas the $CD8^+$ T cells of progressors divide poorly in response to HIV-infected cells, those of LTNP expand rapidly and synchronously. This expansion is paralleled by, or is coupled to, production of perforin, a molecule critical for cell-mediated killing of infected cells.

A deeper understanding of the basis of immunologic control in LTNP and the loss of immunologic control in progressors is likely to provide information that is critical to harness cellular immune response for immunotherapies or prophylactic vaccination. It will be very important to understand how qualitative changes in the HIV-specific response occur, whether they can be avoided in vaccinees that become infected, and whether they are reversible. In addition, we are looking for genes in LTNP that may have modified the HIV-specific response to permit such potent immunologic control over such a long period of time.

Traci Hall *received her Ph.D. in 1992 from the Department of Pharmacology and Molecular Sciences at the Johns Hopkins School of Medicine in Baltimore. After studies with Mette Strand on the parasitic disease schistosomiasis, she was an American Association for the Advancement of Science diplomacy fellow at the U.S. Agency for International Development. In 1994, she began a postdoctoral fellowship with Daniel Leahy in the Department of Biophysics and Biophysical Chemistry at the Johns Hopkins School of Medicine. In 1998, she joined NIH as a tenure-track investigator at NIEHS and is currently leader of the Macromolecular Structure Group in the Laboratory of Structural Biology.*

Stephen McCaw

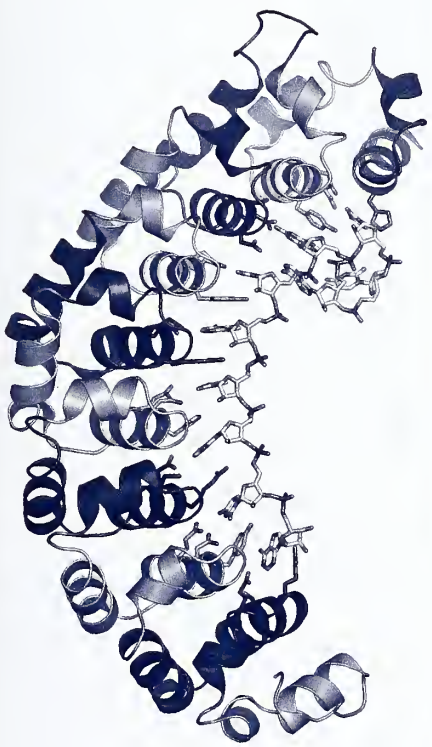
Traci Hall

My laboratory studies the mechanisms of post-transcriptional gene regulation, using structural and biochemical techniques to understand how gene expression is controlled after a messenger RNA (mRNA) is produced.

I was drawn to this area of research because of the importance of post-transcriptional gene regulation during embryonic development. In addition, post-transcriptional gene regulation is important for normal cellular processes. For

example, regulation by microRNAs—which are small noncoding RNAs—falls into this category of gene regulation, and recent predictions suggest that about 30 percent of vertebrate genes may be regulated by microRNAs. My lab is particularly interested in understanding how protein-RNA interactions affect the function of proteins that control gene expression.

Two examples from our work illustrate the diverse ways in which proteins can recognize RNA. In collaboration with Phillip Zamore's laboratory at the University of Massachusetts Medical School



Ribbon drawing of human Pumilio1 protein bound to Nanos Response Element RNA (stick model).

in Worcester, we examined the structure and RNA-binding characteristics of a Pumilio protein. Pumilio proteins are important for stem-cell maintenance and differentiation in many organisms. They work by binding specifically to sequences in target mRNAs, downregulating expression of the protein.

We determined the crystal structure of the human Pumilio1 protein, both alone and bound to a high-affinity RNA ligand. Pumilio proteins comprise eight sequence repeats. Our structures showed that these repeats bind to the RNA, one base per repeat. We were amazed when we examined the details of the protein-RNA interaction and found that there appeared to be a "code" for sequence-specific recognition. Three protein side chains interacted with each RNA base, and particular sets of protein side chains seemed to recognize specific bases. For example, glutamine, asparagine, and tyrosine recognized uracil, or glutamine, cysteine, and arginine recognized adenine.

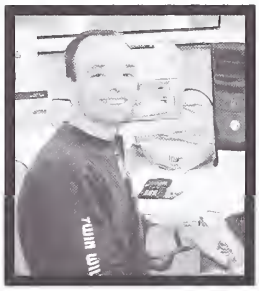
This result suggested that we could make point mutations in the protein and predictably alter the RNA-binding specificity. We tried this and it worked! We created a mutant protein that preferred the new RNA sequence over the original sequence. Our work suggests that Pumilio may be the first RNA-binding protein to use a true code to read RNA sequence. We are continuing to design additional mutant proteins to target particular RNA sequences.

In a second example, we examined the structure and binding specificity of a plant viral protein known as p19 that suppresses RNA silencing by binding to small interfering RNAs (siRNAs). This was in collaboration with József Burgyán's laboratory at the Agricultural Biotechnology Center in Gödollö, Hungary. Our crystal structure of p19 protein in complex with a 21-nucleotide (nt) siRNA revealed that the protein forms a dimer to interact with the RNA and uses two sets of tryptophan side chains to clamp the ends of the double-stranded middle of the siRNA. It suggested immediately that p19 recognizes the siRNA by measuring the length of the duplex RNA.

We tested this by measuring the binding of the protein to siRNAs of different lengths. We found that p19 binds poorly to siRNAs of only 19 nt, tightly to siRNAs of 20–22 nt, and progressively weaker to siRNAs as the length increases from 23–26 nt. Thus, p19 is specific for a particular size of RNA. In plants this is important because siRNAs come in two sizes, ~21 nt and ~24 nt. Thus, p19 inhibits processes directed by the smaller class such as mRNA degradation, but does not appear to affect processes directed by the longer class such as DNA methylation.

It has been fascinating to study Pumilio, which recognizes RNA based on sequence, and p19, which recognizes RNA based on size. We will continue to use structural and biochemical approaches to study RNA silencing and other mechanisms of post-transcriptional gene regulation and hope that future projects will yield results as fun and illuminating as these.

Matthew Kelley *received his Ph.D. from the University of Virginia, Charlottesville, in 1993. After a postdoctoral fellowship at the University of Washington, Seattle, he became an assistant professor at Georgetown University in Washington, D.C., in 1996. In 2000, he joined the Laboratory of Cellular Biology at NIDCD. He is now a senior investigator and head of the Section on Developmental Neuroscience.*



Matthew Kelley

One of the most intriguing events in developmental biology is the generation of cellular diversity. All complex organisms include groups of cells with distinct functions and phenotypes. In most cases, these specialized cells arise from undifferentiated progenitor cells that can assume different phenotypes in response to both intrinsic and extrinsic cues.

A better understanding of the factors that influence cells to develop as one cell type versus another will lead to a better understanding of the bases for different congenital disorders and provide valuable insights into the signaling pathways that must be activated for therapies based on stem cells.

In my laboratory, we investigate the development of different cell types within the highly invariant cellular mosaic of the sensory epithelium of the mammalian inner ear. Several factors led to the selection of this structure for my studies. First, the inner ear sensory epithelium comprises six different cell types that are generated in specific ratios to one another and are then arranged into a specific cellular pattern.

Because the number of cells and their pattern are so regular, defects in the pattern, even very subtle ones, are easily identified. In addition, progressive loss of cells within the sensory epithelium leads to deficits in hearing. Although interventions such as hearing aids and cochlear implants are available, it would obviously be preferable to restore normal function.

The cells within the sensory epithe-

Recently Tenured

lium of the inner ear can be grossly divided into mechanosensory hair cells, which transduce sound waves into nervous impulses, and nonsensory supporting cells, which surround the hair cells and fill crucial anatomical and physiological roles within the epithelium.

Research from my laboratory demonstrated that virtually all of the cells within the developing epithelium initially attempt to develop as hair cells through the activation of a specific transcription factor called Math1. However, as development continues, individual cells compete with one another to maintain expression of Math1. Ultimately, some cells win this competition, increase expression of Math1, and go on to develop as hair cells. Subsequent experiments in the laboratory demonstrated that the number and position of cells that ultimately maintain expression of Math1, and therefore develop as hair cells, is dictated through the downregulation of a group of genes, called Ids, which function to dampen the activity of Math1.

As developing hair cells increase their expression of Math1, they generate extrinsic signals that act to shut down expression of Math1 in neighboring cells. At the same time, hair cells generate a second signal that induces these same neighbors to develop as supporting cells. We have not identified this second signal yet, but hope to in the near future.

A second research emphasis in the laboratory is determining the molecular factors that lead to the uniform orientation of cell types within the ear. All hair cells are only sensitive to vibrations in a single plane, so the correct orientation of each cell is crucial for normal auditory function. There are other examples of uniform orientation among groups of cells, but the molecular pathways involved have not been determined.

We recently identified the first genes that are required for uniform orientation in vertebrates, and we are now using these genes as probes to further understand the signaling pathways that coordinate these events.

Our results are beginning to point to signaling pathways and cellular interactions that are required to generate the precise cellular pattern within the mammalian inner ear. We hope to generate a more complete model of how this structure, and other complex structures, are assembled from pools of undifferentiated progenitor cells.

Sue Priola *received her Ph.D. in microbiology and immunology in 1990 from the University of California, Los Angeles, for studies on the molecular mechanisms of herpesvirus latency. In 1991, she joined NIAID at the Rocky Mountain Laboratories (RML) campus, where she completed her postdoctoral work on the transmissible spongiform encephalopathies. She was converted to a tenure track position in 1998 and is currently a senior investigator at RML.*

Celia Hooper

Sue Priola

I study transmissible spongiform encephalopathy (TSE, or prion) diseases. These are infectious, rare, and fatal neurodegenerative diseases of mammals. One of the most intriguing aspects of TSE diseases is that they have no known viral or bacterial component. Rather, conversion of the normally protease-sensitive mammalian prion protein (PrP-sen) into an abnormal protease-resistant form (PrP-res) appears to be at the center of events that occur during TSE infection, and PrP-res has been proposed as the TSE infectious agent. The fact that a cattle TSE—bovine spongiform encephalopathy (BSE)—has infected humans and concerns that chronic wasting disease of deer and elk in the United States may do the same underscore the importance of understanding how these diseases work.

Susceptibility to TSE infection can be influenced by amino acid homology between PrP-sen and PrP-res. Because the amino acid sequence of PrP-sen differs between mammalian species, I reasoned that these differences could be the basis for species-specific barriers to TSE infection. My laboratory used cell-associated and cell-free assays to study the role of the PrP amino acid sequence in PrP-res formation for three different mammalian species. We found that a single amino acid mismatch between PrP-sen and PrP-res, as well as post-translational modifications to PrP-sen, influenced species-specific PrP-res formation, suggesting a molecular mechanism for TSE species barriers that involves PrP-sen/PrP-res homology.

There are no in vitro systems to monitor early events that occur during TSE infection, and very little is known about how they infect cells. To address this issue, my laboratory recently developed a novel tissue culture system that enables us to monitor PrP-res formation immediately after exposure of cells to TSE. Using this system, we found that TSE infection is at least a two-stage process: 1) an initial stage of PrP-res formation that is independent of cell type and TSE strain and 2) a second cell-type– and TSE strain–dependent stage leading to persistent PrP-res formation and infection. Our results provide a basis for why TSE infection in vivo is restricted to certain cell types and suggest that cell-specific factors are involved that may provide new targets for TSE treatment. Currently, we are working to identify these factors.

One surprising result of these experiments was the finding that NIH3T3 mouse fibroblasts, long assumed to be resistant to TSE infection, could be persistently infected with mouse TSE agents. These results have rekindled concerns in the vaccine industry that even non-neuronal vaccine-producing cell lines exposed to substrates contaminated with the BSE agent could potentially become infected.

Our new tissue culture system also allowed us to address an unresolved question in TSE biology: How can an infectious agent with no known nucleic acid component have biologically distinct strains? We found that certain strain characteristics are the result of a complex interaction between PrP-sen, PrP-res, and the host cell. Currently, our hypothesis is that the cellular microenvironment where PrP-res formation occurs influences TSE strain characteristics, and we are working to identify these cellular microenvironments. For me, the most exciting aspect of this work is that it may help to explain some of the unique in vivo pathological phenotypes associated with different TSE strains.

In addition to understanding the molecular basis of TSE pathogenesis, my laboratory is also actively pursuing effective TSE therapeutics. We found that cyclic tetrapyrroles, a vast group of compounds that had never been tested in vivo against any infectious disease, are potent TSE inhibitors when given prophylactically (*Science* **287**:1503–1506, 2000). These results are particularly exciting given the possibility that, because of their properties, cyclic tetrapyrroles

may be useful against other diseases of protein folding such as Alzheimer's or Huntington's disease.

Barbara Rehermann *earned her M.D. from Medizinische Hochschule in Hannover, Germany, in 1991. Her research interests started with a doctoral thesis in T cell receptor signaling at the same university from 1987 to 1988 and a research year on lymphocyte biology at Memorial Sloan-Kettering Cancer Center in New York from 1988 to 1989. After internship and residency at the Universities of Essen and Medizinische Hochschule from 1991 to 1993, she completed a postdoctoral fellowship in viral immunology at The Scripps Research Institute, La Jolla, Calif., from 1993 to 1995. She then returned to Hannover, set up her own research laboratory, and received the Venia Legendi (an academic title in the German system) for Immunology at the same university. In 1998, she joined the NIDDK intramural program as a tenure-track investigator and is now a senior investigator in the Liver Diseases Branch, NIDDK.*

My research program focuses on the immunology of viral and autoimmune liver diseases. A major interest is the immunology of hepatitis C virus (HCV) infection. Over the last 10 years, my laboratory has studied components of successful immune responses, as well as mechanisms of immune evasion in HCV infection.

We are using multiple approaches. First, we study immune responses of clinically well-characterized patient cohorts who are prospectively followed in the Liver Diseases Branch.

Second, we use the chimpanzee model, the only animal susceptible to HCV infection, to study virus-host interaction in the early phase of infection and at the site of viral replication—the liver. In this model, we use clonal HCV (HCV-RNA transcribed from HCV cDNA clones) and a unique set of immunologic reagents that we have generated based on the sequence of the infecting HCV and the chimpanzees' MHC haplotype. The model provides the opportunity to rechallenge recovered animals and to test experimental immunotherapies in persistently infected animals.

Finally, we use transgenic mouse models to study basic immunological mechanisms, such as liver-specific autoimmunity, proteasomal processing of viral antigens, and the role of cross-priming in the induction of specific T cells.

Fran Pollner

Barbara Rehermann

Studying a single source outbreak of HCV, we were the first to demonstrate that HCV antibodies may disappear in approximately 40 percent of patients 10 to 20 years after recovery, whereas HCV-specific $CD4^+$ and $CD8^+$ T cells remain readily detectable in the circulation.

In collaboration with Jake Liang, Jay Hoofnagle, and Theo Heller in the Liver Diseases Branch, we subsequently demonstrated HCV-specific T cell responses in the blood of health-care workers shortly after accidental needlestick exposure to HCV-contaminated blood, even when HCV-specific antibodies remained undetectable. HCV-specific T cell responses are also often found in family members of HCV-infected patients and injection drug users who are frequently exposed to the virus but do not show any other evidence of past or present infection.

Collectively, these results suggest that the incidence of recovery from hepatitis C may be underestimated because HCV-specific antibodies may be lost after recovery or never induced, and cellular immune responses are rarely studied.

In collaboration with virologists Stephen Feinstone at the FDA and Charles Rice at Rockefeller University in New York, we then asked the question whether these HCV-specific memory T cells can be protective.

When we rechallenged spontaneously HCV-recovered chimpanzees with homologous and in one case heterologous HCV, we observed an attenuated course of infection with significantly reduced viremia and rapid HCV clearance without elevation of liver enzymes. Intrahepatic and peripheral HCV-specific memory T cell responses, but not antibody responses against HCV envelope proteins, correlated with HCV clearance and needed to be maintained to prevent HCV from becoming active again.

Thus, HCV-specific T cells, although unable to completely destroy the virus, appear to contribute to rapid control and clearance of the challenge inoculum.

These results have prompted us to evaluate strategies to induce novel T cell responses or to modulate and enhance preexisting but apparently ineffective HCV-specific T cell responses in patients who are persistently infected and seem unable to clear the virus spontaneously.

We have, for example, recently used a self-replicating form of recombinant cytopathic pestivirus RNA to express HCV antigens in murine dendritic cells (DCs). In this model, induction of cell death by the cytopathic replication resulted in antigen transfer from vaccine DCs to endogenous DCs in lymphoid organs of vaccinated mice, direct and cross-priming of T cell responses, and protective immunity in a surrogate virus challenge.

These studies are closely related to our current efforts to decipher mechanisms of HCV persistence, such as escape by mutation, adaptation to proteasomal antigen processing, and alteration of dendritic cell and B cell functions. We expect that understanding these mechanisms will enable us to induce protective immune responses via immunotherapy. ■

New Radiation Safety Website

The Radiation Safety Committee (RSC) has created a comprehensive website that houses all the forms and documents needed to submit a clinical protocol to the RSC, apply to become a clinical authorized user, or apply to the Radioactive Drug Research Committee. Also on site are RSC policies, members, and meeting dates—and dosimetry tables. The website was the dream of NCI's Lance Liotta, RSC chair for more than 11 years before handing the role to NIDDK's Ira Levin. For more information, contact Victor Voegtli (who planned and constructed the website) at 301-496-5774 or Lisa Coronado 301-496-2253.

The website—accessible outside as well as within the NIH computer system—is:

<http://www.nih.gov/od/ors/ds/rsb/rsc/>

Reminder to PIs Doing Animal Research

Animal research at NIH involving the use of recombinant DNA or human pathogens cannot proceed without prior approval from the NIH Institutional Biosafety Committee (NIH IBC). Principal investigators are responsible for ensuring that complete and accurate registration documents (form 2960 for recombinant DNA and form HPRD for human pathogens) are submitted to the IBC—together with the relevant animal study proposal (ASP) attached. The NIH IBC meets on the first Wednesday of each month. Review of registration documents proceeds concurrently with Animal Care and Use Committee review of ASPs to expedite the entire review process.

Questions regarding the NIH IBC review process may be referred to Martin Sanders, the executive secretary, at 301-496-2960 or

<mailto:sandersm@mail.nih.gov>

Catalytic Reactions?

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

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

In Future Issues...

- More Bench To Bedside
- Getting Control Of IBD
- IG Inventory

Kids' Catalyst: Rainbow Aglow

A rainbow is a fantastic sight. It's the momentary convergence of light, water vapor, and angles, and can all be explained by math (which you'll encounter soon enough). Actually, the mathematical explanations themselves are beautiful, though not in the way of a rainbow.

Fortunately, you don't need to stare at the sky just waiting for things to fall into place for the perfect rainbow—you can create your own, observe reflection and refraction, and make your own rainbow dance.

For this experiment, you will need:

- A sunny day
- A white piece of paper taped to a piece of cardboard
- A mirror small enough to fit into a shallow dish
- A shallow dish
- Water
- Red, blue, and green food coloring (optional)
- Your favorite set of crayons, colored pencils, or watercolors (not at all optional!)

Fill the shallow dish about three-quarters full of water. Place the mirror in the dish at an angle such that some of the mirror is in the water and some of it is not. (You need the light from the sun to shine through the water and catch the reflection of the submerged mirror.) Take the paper (taped to the cardboard because light would shine right through just a plain piece of paper) and hold it up to the reflection the mirror makes. The reflection of the portion of the mirror *not* in the water will appear as a bright white spot on your piece of paper, but if you move the paper to see the reflection of the mirror that is *inside* the water you get your rainbow!

If you are doing this experiment using a window, tape the paper to a sturdy surface and draw what you see. Just a few changes you can make and observe are:

- How does the intensity of the rainbow's colors change when the angle of the mirror changes?
- How does your rainbow look when you step away?
- Disturb the surface of the water and see your rainbow dance!
- What changes when you add red food coloring to the water? What about blue? Green? (You could, of course, use your watercolors, but depending on the size of your dish, this could use quite a bit of your lovely watercolors. . . stick with the food coloring for quick results.)

Have fun with your rainbow, and if you want to get a teacher on your good side, ask her or him about why the colors are reversed in the second half of a double rainbow. Let me know what happens.

—Jennifer White

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