FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

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Translational Research

JEAN LUD CADET: A BRIDGE AT NIDA

by Fran Pollner

Jean Lud Cadet is equally at home upstairs and downstairs in the building that houses the NIDA intramural research program at the Johns Hopkins University Bayview campus in Baltimore.

On the fourth floor, Cadet runs the four labs that make up the Molecular Neuropsychiatry Unit, of which he is chief; and on the first floor, he directs NIDA's clinical research program, overseeing the inpatient research unit, the outpatient research program, an adolescent clinic that focuses on smoking cessation, and the 70 currently active clinical protocols—all of which are conducted on-site.

Upstairs, researchers are charting—and figuring out ways to prevent—the neurodegenerative effects of illicit drugs in the brains of mice. Downstairs, they are documenting cognitive and hemodynamic deficits induced by these drugs in the brains of long-term human users—and the persistence of these effects, thus far, despite up to one month's abstinence.

The paths between the first and fourth floors are well traveled, and when Cadet's working in one location, he's never far from the other, either physically or mentally. The hope is that the cellular and molecular mechanisms of toxicity unraveled in the lab will be brought to bear on the prevention and treatment programs in the clinic.

When he arrived at NIDA, in 1992, Cadet had an agenda: to identify the long-term neurological effects of

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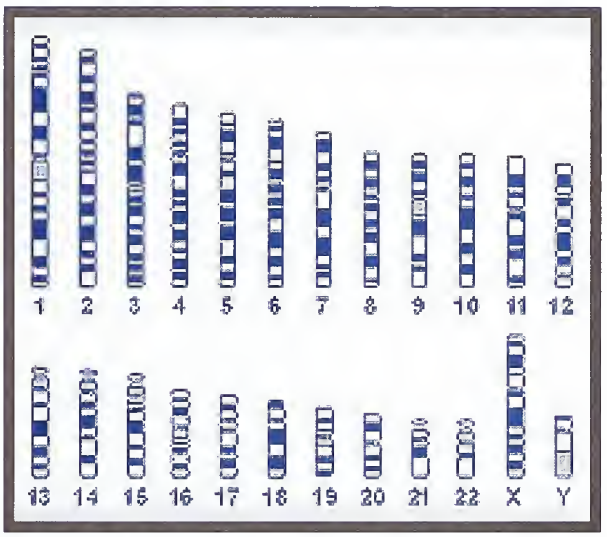
NIH Research Festival

RUNNING WITH THE GENOME: NIH GETS TO WORK WITH THE 'WORKING DRAFT'

by Cynthia Delgado



The "working draft" sequence of the human genome, delivered to the desktops of the biomedical community this summer, may become the most "dog-eared" work-in-progress the world has ever known.

Unlike the first draft of a medical text that requires corrections and updates before it is finally printed, the genome's first draft is out there, and some NIH investigators are using it to make new discoveries—while others are arranging the data to make the material even more meaningful as a resource to the research community.

Simultaneously, the working draft is constantly growing, as sequencing data pours in, nonstop, from centers around the world. The working draft—which was 85–90 percent complete when it was announced in June—should be entirely filled in by year's end. The finished product (see description below) is anticipated in the year 2003, Eric Green said at the NIH Research Festival plenary session on "The Utility of Whole Genome Sequences: Early Glimpses of the Sequence-Based Era."

Calling the human genome a "24-volume encyclopedia set—volumes 1–22, X, and Y," Green, chief of NHGRI's Genome Technology Branch and director of the NIH Intramural Sequencing Center, presented an overview of the fundamentals of the Human Genome Project (HGP).

Rounding out the session, NCBI's Greg Schuler described the computational programs rapidly being developed to tackle the task of assimilating and utilizing the data—and Nick Ryba, chief of the NIDCR Taste and Smell Unit, reported on how strategic use of the HGP's data aided the discovery of a new family of receptors (see "An Acquired Taste," page 6).

The ABCs of Sequencing

Stage 1 of the HGP involved studying and organizing the DNA from each chromosome in a process known as mapping. For physical mapping, each chromosome is broken up into larger or smaller pieces and isolated as DNA

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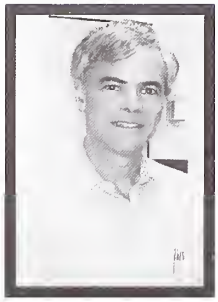
Planning for Change in Biomedical Research



Michael Gottesman

Running the NIH has been described as equivalent to steering an aircraft carrier—you cannot turn on a dime and you have to think way ahead to keep from running aground. Biomedical research is entering an era of enormous change, and we all need to start thinking about how these changes will affect how we will do research in the future. Scientists are by nature conservative—"If it ain't broke, don't fix it!" is a favorite phrase of many bench scientists in describing their experimental approaches. But even the most conservative of us realize that the future will not look like the present. What should the intramural program at NIH be doing to stay one step ahead of new developments in biomedical research?

We will undoubtedly need to deal with the enormous quantities of data currently being loaded into central databases: genome sequences; microarray gene expression analyses as a function of development, disease, tissue type, etc.; complete medical records, including radiological and pathological images; and the entire world's literature at our fingertips. We need networks that allow quick and easy access to this information, software that predigests information or displays it in ways that are meaningful to us, and appropriate computer terminals for all scientists at NIH. The leadership of NIH has been working with Al Graeff, the director of the Center for Information Technology, and with IT staff in the Institutes and Centers to be sure that the most flexible infrastructure exists to support these scientific demands. The Clinical Center has taken the lead in developing a state-of-the-art Clinical Research Information System (CRIS) to replace our outmoded Medical Information System (MIS). This development takes money and talented individuals, and we are making good progress on both fronts.

> What should the intramural program at NIH be doing to stay one step ahead of new developments in biomedical research?

The scale of many of our laboratory activities is also undergoing great change. For example, in the 1940s and 1950s, we were content to purify an enzyme and demonstrate an activity; in the 1960s and 1970s, we wanted to clone and sequence the enzyme; in the 1980s and 1990s, we expected to do all of these and also crystallize it to determine structure, map the gene, and create a genetic model lacking or mutating the enzyme to determine its function. In the new millennium, no one is satisfied with one enzyme—we want to characterize the complete family of such enzymes, its whole evolutionary tree, and perhaps the entire pathway in which the enzyme resides.

In the not too distant future, we will be combining physiological and molecular information to gain insight into how cells actually work, how they integrate into tissues and organs, and how these organs produce organisms that interact with their environments.

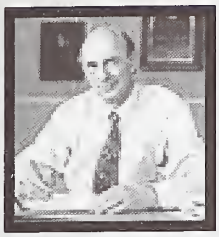
To satisfy these scientific imperatives, we need resources to allow creation of new animal models—housing transgenic mice alone is a major resource commitment—and the requirements for zebrafish and large animal models will be substantial. We are currently planning a new central vivarium on campus that will provide the space and flexibility to support these models and resources for histopathology, genetic manipulation, behavioral analysis, and special surgery.

We will also need resources to support high-resolution structural studies. Currently, the NIH intramural program supports a dedicated X-ray beam line at Brookhaven and one at Argonne for our crystallographers. We have also upgraded our high-resolution electron microscope facilities, which will be housed in Building 50, and we are planning for larger and larger magnets for high-resolution NMR studies of molecular structure. For clinical imaging research, we have a shared in vivo NMR center, and the new animal imaging facility will open in 2001. These facilities will put intramural NIH at the forefront of the technology needed to support our research.

The design of our new laboratory buildings reflects the changing nature of biomedical research. Each of the new buildings on campus has a basic interstitial design, which means that all of the support utilities for the labs are on floors layered between the lab floors. This will make it easy in the future to change and maintain plumbing, electrical, and air supplies to the labs without disrupting the laboratories themselves. Other elements of new lab design include computer networking, electrical supply that meets the high energy needs of current equipment, and more efficient heating and cooling systems. And all of the new buildings bring natural light and more space to our researchers. The NIH Master Planning process has provided a mechanism for rational growth and renovation of our campus, and we are currently considering other ways to meet our burgeoning space needs.

Finally, the vast power that these new research tools give us also brings new responsibilities. Current ethical concerns about clinical research are a direct result of our increasing ability to restructure human genes and human bodies. Our planning for the future must include oversight systems to reassure both ourselves and the public that we are taking the right approaches and continuing to serve humanity. ■

Alter Takes a Lasker



Harvey Alter

This year's Lasker Award for clinical medical research will be shared by Harvey Alter, chief of the infectious diseases section and associate director of research in the CC Department of Transfusion Medicine, and Michael Houghton, of the Chiron Corp. in Emeryville, Calif.

From his co-discovery of the Australia antigen to his uncovering of the existence of a "non-A, non-B hepatitis virus" that was ultimately named the hepatitis C virus, Alter's groundbreaking hepatitis research spans more than 30 years. The Lasker Award cites his pivotal role in ferreting out the cause and drastically reducing the risk of transfusion-associated hepatitis. Houghton was cited for his isolation of the hepatitis C virus.

Notwithstanding the fact that the Lasker Award is popularly known as the American equivalent of the Nobel Prize, Alter received a perhaps even more prestigious and immortalizing honor at the NIH equivalent of the Lasker Award ceremonies—a party to celebrate the event, including a poem on behalf of Alter's viral victims:

Lamentation of the "C's"

When it came to bepatitis
One, undaunted, had to fight us
"Get out of the blood
You no-good crud"
His words did thus befright us

Harvey Alter was his name,
Bashing virus was his game
A researcher unsurpassed
He fought us to the last,
And never lost his aim

Our extinction, number three
Came after "A" and "B"
Our brothers, all so retro
Were the first that Alter let go
Non-A, non-B, we were victim "C"

We tried, in vein, to hide
Unknown, we'd thus reside
So close and yet so far—
Beyond your PCR
But Alter on us spied

His work will surely end us
And to our Maker send us
Before God, we shall ask Her
Why our death brought him the Lasker
When 'twas us
Made him stupendous

— Celia Hooper in consultation with Michael Gottesman
On the Occasion of the Awarding of the Clinical Lasker Award to Harvey Alter, September, 2000

NIAMS Conference on Health Disparities

A conference on "Health Disparities in Arthritis and Musculoskeletal and Skin Diseases" will be held at the Natcher Conference Center **December 15–16, 2000** (Friday from 8:00 am to 7:30 pm, including a reception from 5:30 on, and Saturday from 8 am to noon). Conference co-sponsors include the Office of Research on Minority Health, the Office of Research on Women's Health, the Office of Disease Prevention, and the Office of Behavioral and Social Sciences Research.

The deadline for advance registration is **December 1.** Register online at **<http://www.nih.gov/niams/news/hdreg.htm>** or contact Courtesy Associates at (202) 973-8696. For special accommodations, contact Felecia Taylor at 301-594-2463 or e-mail **<taylorf@mail.nih.gov>**. ■

Awesome Foursome

Three of 60 new members elected into the Institute of Medicine in October hail from NIH, and another is the cabinet member who oversees NIH:

- Dennis Charney, chief, Mood and Anxiety Disorder Research Program, NIMH
- Steven Hyman, director, NIMH
- David Lipman, director, National Center for Biotechnology Information, National Library of Medicine
- Donna Shalala, secretary, U.S. Department of Health and Human Services. ■

Required Course

The required course for clinical principal investigators, Clinical Research Training, will be repeated on **December 12, 2000**, 12:00 pm–4:00 pm in Building 10, Lipsett Amphitheater.

The course was designed to address one of the essential standards (Training and Education) recently approved by the NIH for conducting clinical research in the intramural research program. Topics include ethical issues in human subjects research, roles and responsibilities of the investigator and institution, regulatory issues, and clinical investigators and the mass media.

All principal investigators with a protocol approved through the Clinical Center are required to take the course and successfully complete an exam by March 1, 2001.

Registration will be held from **November 1–30**. To register, please visit the course website at **<http://www.cc.nih.gov/ccc/cr/training.html>**.

Duke Masters Degree

Applications for the 2001–2002 NIH-Duke Training Program in Clinical Research are now available in Building 10, Room B1L403.

Designed primarily for clinical fellows and other health professionals training for careers in clinical research, the program offers formal courses in research design, statistical analysis, health economics, research ethics, and research management. Courses are held at the Clinical Center via videoconferencing from Duke University School of Medicine in Durham, N.C., or on-site by adjunct faculty. A Master of Health Sciences in Clinical Research is awarded by Duke to students who complete the required coursework.

Prospective participants should consult with their institute or center regarding the official training nomination procedure. Application deadline is **March 1, 2001**. For more information, visit the program website: **<http://www.cc.nih.gov/ccc/cc_duke/info.html>**.

Jean Lud Cadet
continued from page 1

drug abuse. The literature on that subject, he says, was sparse. It's less sparse today.

Cadet and his colleagues have published extensively on the neurodegenerative effects of amphetamines and MDMA (Ecstasy), drugs of choice among adolescents today because "they're cheap, accessible, and can be made very easily by any good chemist."

In cell culture and with transgenic mice that overexpress superoxide dismutase (SOD)—an enzyme that breaks down superoxide radicals and is abnormal in such conditions as amyotrophic lateral sclerosis—the team has demonstrated that the toxicity associated with methamphetamine and MDMA involves the production of superoxide radicals and can be offset by SOD. The transgenic mice are largely protected against the brain cell death (in the cortex, striatum, and hippocampus) that typically accompanies drug exposure in other mice.

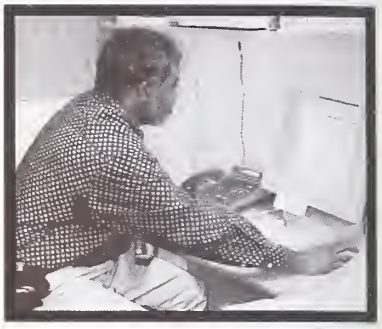
Although SOD is too big a compound to gain easy access to the brain, smaller SOD mimics have shown some promise in experimental stroke models. Notwithstanding that the usefulness of an antioxidant strategy in humans has yet to be proved, Ecstasy makers and users—who apparently read the relevant scientific literature—have been observed at parties to combine the drug with an antioxidant vitamin cocktail.

Biochemical changes in the brain consistent with cell death in humans have been observed in long-term users, Cadet notes, and could account for the cognitive impairment his team has documented in clinical studies designed to determine whether abstinence reverses drug-related cognitive deficits. Thus far, little change has been seen after a month of abstinence in studies involving heavy users of cocaine and alcohol; clinical studies involving amphetamine and Ecstasy users are anticipated next.

Longer-term studies are needed but are problematic, Cadet observes, because it is difficult, if not impossible, either to keep study volunteers confined for longer than a month or to ensure abstinence among a nonconfined population. One of the salient findings in the cognitive studies is that the constellation of deficits varies with the drug of abuse. Although all drugs exert their addictive effects along the dopamine pathway, their cognitive effects are played out in different regions of the brain—a fact that should serve as a guide to tailor treatment programs, Cadet says. "Everyone who comes in for treatment needs to be evaluated neurologically and neuropsychologically so that their therapeutic program can be planned around their particular impairments. Someone with attention deficits, for instance, might need a focusing medication in order to process the information offered in the program."

The fact that cocaine indeed causes cognitive deficits is only now beginning to be appreciated and is still not common knowledge. "It's very new information. Our study (1) is one of the few to document clearly that this is the case," Cadet notes, although, he adds, people who have worked in the field with long-term cocaine abusers have suspected as much for a while now.

In another study undertaken to establish a physical basis for the increased risk of stroke among cocaine users, Cadet and colleagues measured cerebral blood flow using transcranial Doppler (TCD)—a "classical neurological approach." The brain vasculature and increased resistance to blood flow they found in their study population—chronic users in their 30s—resembled that reported for people in their 60s and 70s and for patients with multi-infarct dementia. As in the study of cognitive deficits, no changes were seen in the study cohort after one month of abstinence (2). "I think the blood flow abnormality is also related to the cognition deficits we're seeing," Cadet adds, suggesting that therapies aimed at the one might also benefit the other.



Back to Back: *Jean Lud Cadet wears two seamless hats—all the time—in his dual role as a basic science section chief (molecular neuropsychiatry) and clinical director of the NIDA IRP. His introduction to NIH and with it the realization that he wanted to spend his life in research came when he was a fourth-year medical student at New York's Columbia University College of Physicians and Surgeons and had a three-month rotation at NIMH. He got his M.D. degree in 1979, undertook two residency programs—one in psychiatry and one in neurology—and then returned to NIH in 1984 as an NIMH medical staff fellow and ward chief at St. Elizabeth's Hospital in Washington. He then taught at Columbia before rejoining NIH in 1992—this time at NIDA as chief of the neuropsychiatry and neurotoxicology unit. He became acting chief of the molecular neuropsychiatry section the following year and then chief when he was tenured a year later. He assumed the acting clinical directorship in 1994 and took on that permanent role in 1997.*

Two-thirds of the U-shaped, four-story building that houses the NIDA intramural research program in Baltimore

Using cDNA arrays, Cadet and his team also hope to identify genes that are affected by chronic drug use, the better to get to precise mechanisms of toxicity and devise treatment strategies specific to each of the drugs of abuse. The brain is far too complex, he says, to imagine that one pathway would cover all bases.

References:

(1) K.I. Bolla, F.R. Funderburk, and J.L. Cadet. "Differential effects of cocaine and cocaine + alcohol on neurocognitive performance." *Neurology* **54**:2285–2292 (2000).

(2) R.I. Herning, D.E. King, W.E. Better, and J.L. Cadet. "Neurovascular deficits in cocaine abusers." *Neuropsychopharmacology* **21**:110–118 (1999).

Reed Wickner: Prion Profiler

by Katie Farr

NIDDK's Reed Wickner, one of NIH's two newly elected members of the prestigious National Academy of Sciences, does things a little differently from the rest of the crowd. Wickner's groundbreaking work established that certain elements in yeast are prions—an abnormal form of a protein capable of "infecting" normal molecules of the protein and converting them to the abnormal prion form. Mammalian prions are believed to cause "mad cow" disease and Creutzfeldt-Jakob disease (CJD).

Wickner's route to basic science showed his preference for the road less traveled. As an undergraduate at Cornell, he was drawn to mathematics and earned his bachelor's in that field. But instead of pursuing math further, Wickner decided to follow in his father's footsteps to become a physician. While in medical school, he was more intrigued by the science behind the disease than by the art of diagnosis. This led to yet another career move—becoming a postdoctoral scientist here at NIH. He studied enzyme biochemistry with Herb Tabor, who, Wickner says, "taught me how to do science." Next came training with Jerard Hurwitz at New York's Albert Einstein College of Medicine, where Wickner worked on the purification and characterization of DNA polymerase II.

But it was at NIH where Wickner established his own lab as a principal investigator in yeast genetics. Many factors drew him back. Freedom from writing grants and teaching affords him the luxury of doing experiments himself. "I've been very lucky over the years to have some really excellent postdocs, but I also enjoy doing research myself. And my impression from my friends in universities is they don't really have time."

Pursuing the unusual has paid off for Wickner. His lab studies non-Mendelian genetic elements in budding yeast, which include RNA viruses, a plasmid called 2μDNA, [PSI+], and [URE3]. One of Wickner's key insights came as he was writing a review article on the elements in 1989—a time when he says "the interest in nonchromosomal genetic elements in the yeast world . . . had mostly died out." Wickner realized that two elements, [URE3] and [PSI+], might really be yeast prions. So, he started working on [URE3], building on "beautiful work" by Aigle and Lacroute who discovered it, with elegant experiments of his own.

Fran Pollner

Reed Wickner

In 1994, Wickner proposed three oft-cited genetic criteria for calling something a prion: 1) "Curing" a prion can be reversed—the prion state can spontaneously reappear after the phenotype has vanished; 2) An excess of the normal protein can increase the chance of prion appearance; and 3) The phenotype of an organism with a prion is the same as the phenotype of a mutant in the gene for the protein. As Wickner has shown, [URE3] meets the three genetic criteria for being a prion. [URE3] protein also forms the characteristic aggregates for which prions are famous.

Very recent work from the Wickner lab has found that a protein called Mks1 is required for the transformation of the normal Ure2 protein to the abnormal prion form [URE3]. This is the first report of such a helper protein for prion formation.

Very recent work from the Wickner lab has found that a protein called Mks1 is required for the transformation of the normal Ure2 protein to the abnormal prion form [URE3](see box to right). This is the first report of such a helper protein for prion formation. Identification of an analogous factor in animals could help researchers treat, or perhaps even prevent, prion-induced disease.

Refreshingly enthusiastic about his research, Wickner says the same force that fueled the love of his undergrad major now drives his work. "Mathematics is what I really like—mathematics and physics. Genetics is very logical—it's kind of like the mathematics of biology." At the same time, he says that he has made good use of his medical training. He observed that what he is really studying is an infection of yeast. "I view [the prions] as parasites . . . so that while other people are looking for how this is an advantage to yeast, I'm not always thinking of it in those terms."

Wickner says he would advise early career scientists to do as he did and march to a different drummer. "I'm not sure this advice would be what other people would give, but my advice is . . . don't propose as your work when you become independent a linear continuation of what you've been doing as a postdoc. Propose to do something that is obviously your own." This could mean applying the biochemical or genetic techniques you have learned to a new system, or staying with the same organism, but addressing a new problem. "It's not easy to do," he concedes, but postdocs should try to think beyond their immediate experiments toward the bigger picture. "You need to see something and see its interest and importance that other people don't see." ■

Prize Protégé

NIDDK postdoc Herman Edskes has received the second annual Norman P. Salzman Memorial Award in Virology, an award presented by the Foundation for the NIH for contributions in basic virology while working at NIH or SAIC.

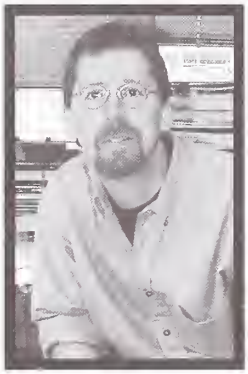
Celia Hooper

Herman Edskes

Edskes received the award for his paper entitled "A protein required for prion generation: [URE3] induction requires the Ras-regulated Mks1 protein"—with special recognition to the winner's mentor, Reed Wickner. ■

Running with the Genome
continued from page 1

clones. These clones are characterized and overlapped on one another by identifying regions in common. The resulting "contigs" constitute a contiguous segment of the starting DNA. "Like a jigsaw puzzle, the larger clones are at first easier to put together into contigs than the smaller clones," said Green.



Fran Pollner

Eric Green

Two DNA cloning systems have been instrumental to the HGP's efforts to map the human genome. In one, the larger pieces of cloned DNA are isolated as yeast artificial chromosomes (YACs); in the other, smaller pieces of cloned DNA are isolated as bacterial artificial chromosomes (BACs). "Each YAC provides multiple pages from one of the hypothetical chromosomal volumes, or, roughly, chapter-size pieces of cloned DNA," Green explained; each BAC clone is approximately page-size. Because of larger size and availability, YACs play a dominant role in constructing the first-generation physical maps of the human genome.

Stage 2 of the HGP, Green continued, involves sequencing the organized DNA—using what is termed a "sequence-ready contig map," or a series of overlapping BACs that map to a certain region of a human chromosome—to construct each human chromosome page by page.

The fundamentals of DNA sequencing—developed in 1977 by Fred Sanger, a British scientist who received his second Nobel Prize in chemistry for work in this field—have not changed, but sequencing efficiency has—dramatically. In one year, Green said, a single person can produce more than one million bases of sequence. "Shotgun sequencing" is the most commonly used method: "BAC clones are selected and large amounts of DNA made (like taking a page and making lots of xerox copies), then randomly fragmented (putting these pages in a paper shredder)." Thousands of these fragments are sequenced and assembled by a computer program. In this way, each fragment of the human genome is essentially sequenced multiple times. Checking for redundancy among these multiple reads ultimately produces a highly accurate "working draft" sequence.

"Sequence finishing" is a term used to describe the hard polishing of the sequence—getting additional sequence reads to improve accuracy and cover gaps— refinements that yield a highly accurate sequence, thereafter known as a "finished" sequence.

Accomplishments of the HGP to date include complete sequencing of a number of microbial genomes, in addition to the first eukaryotic organism, the common brewer's yeast reported in 1997, and the first multicellular genome, the nematode *Caenorhabditis elegans,* in 1998. Earlier this year, a collaboration between Celera Genomics, of Rockville, Md., and the HGP resulted in the completion of the sequence for the fruit fly, *Drosophila melanogaster.*

The G5

The complete working draft of the human genome is expected by year's end, with a projected completion of the finished sequence in the year 2003. The working draft of the mouse genome should be available early next year and

An Acquired Taste

by Nick Ryba, NIDCR

In collaboration with HHMI investigator Charles Zuker and his group at the University of California, San Diego (UCSD), we have used the "working draft" to help uncover a family of taste receptors.

Aversive reactions to bitter tastes protects animals from ingesting toxic compounds. But until human genome sequence information helped identify a new family of receptors we had little idea how many chemically unrelated compounds could all taste bitter.

G-protein coupled receptors (GPCRs) have been implicated in mediating bitter taste, and last year, the ability of humans to taste a specific bitter substance was genetically linked to a region of chromosome 5 (5p15). The NIDCR-UCSD group used tools such as open reading frame-finder coupled with BLASTp and hydrophobicity analysis to identify a new candidate GPCR (T2R-1) in sequence from this interval. But what was really exciting was that tBLASTn searches of draft sequence indicated that T2R-1 was a member of a large family of GPCRs clustered in just a few regions of the genome, all implicated in controlling bitter taste in mammals.

Using molecular biology techniques, we cloned homologous receptor genes from rodents and examined where T2Rs are expressed. As expected, for sensory receptors, T2Rs were found in subsets of taste receptor cells. Then, using a cell-based assay system, we showed that at least some T2Rs responded to bitter-tasting compounds. For example, the highly toxic and bitter molecule cycloheximide selectively activated mouse T2R-5. Intriguingly, the ability of mice to taste low concentrations of cycloheximide has been mapped to a locus at the distal end of chromosome 6, just where the T2R-5 gene is also found. Moreover, nontaster mice have five mutations in T2R-5, and these affect the sensitivity of the receptor in the cellular assay, strongly pointing to a genetic explanation for a behavioral trait.

Why do many unrelated toxic compounds taste bitter? It turns out that taste cells containing one T2R also express most of the other T2R genes. The brain interprets information about patterns of cellular activation rather than which receptor is involved. This means that substances activating different T2Rs are likely to taste similar.

Fran Pollner

Nick Ryba

There is already considerable interest in exploiting this information to modify taste. For example, certain drugs for AIDS, heart disease, and depression taste so bad or so ruin the flavors of food that patients abandon life-saving medications. But the main focus of the NIDCR group will be trying to extend our knowledge of how taste works, ultimately to understand how information is encoded in the tongue, transmitted to the brain, and decoded there to produce the familiar sensations that contribute so much to our everyday enjoyment. ■

For further information about T2Rs see
<http://www.cell.com/cgi/content/full/100/6/693/>
and
<http://www.cell.com/cgi/content/full/100/6/703/>

the finished sequence by 2005, Green said. To meet the deadlines for the human genome sequence, five major sequencing centers, collectively known as "the G5," were responsible for sequencing approximately 85 percent of the human genome. About 12 other centers were responsible for sequencing the rest.

Fran Pollner

Greg Schuler

The G5 are:

- Washington University Genome Sequencing Center, St. Louis
- Whitehead Institute for Biomedical Research/MIT Center for Genome Research, Cambridge, Mass.
- Baylor College of Medicine, Human Genome Sequencing Center, Houston
- U.S Deparment of Energy Joint Genome Institute, Walnut Creek, Calif.
- The Sanger Centre, Hinxton, United Kingdom

The entire human genome of about three billion bases will be able to fit, roughly, on one CD-ROM, Green said. With such rapid accumulation of bulk data, the next phase of the HGP will concentrate on analysis and interpretation and developing the software tools to expedite these efforts. He expects the next few decades to be spent seeking better ways to identify genes and key sequences that determine how, when, and where genes are turned on.

The year 2000, Green said, has been the turning point.

It's a Blast!

"One of the great things about the Genome Project," said Greg Schuler, NCBI staff scientist, "is that you don't have to wait until it's finished to start making use of the data."

Schuler and his NCBI colleagues are getting creative with the sequence data generated by the HGP—data that are regularly downloaded within 24 hours from sequencing centers into the public database, GenBank. Schuler and company are working to make the system user-friendly and optimized for the needs of researchers.

GenBank is equipped with several features that provide pertinent information on the quality of particular working draft sequences, such as redundancy, fragment number, and base quality scores. It also allows users to look at different types of sequence entries—for instance, by chromosomes or large contigs. In many cases, unique qualifiers are used to label data so that known genes and their protein products are distinguished from predicted genes and their protein products. The standard tool for sequence analysis, BLAST (Basic Local Alignment Search Tool), offers multiple searching options: "For example," Schuler said, "suppose you had a query protein and its gene sequence. You could use the software tBLASTn to scan the draft of the genome for any matches in humans or other organisms." Alternatively, he added, one could use the genome to come up with predicted proteins and make a searchable database followed by a BLASTp search and compare results with the query protein. With a predicted protein sequence, one could search for common protein domains to get information about function or look at the percentage of conserved domains.

Schuler emphasizes that the genome sequence provides a uniform frame of reference (or coordinate sytem) for relating the positions of disparate types of genomic features, such as genes, mapped markers, and common sequence variations.

The team has also developed a "locus identifier" and a program called "Refseq," which aims to establish one sequence entry for each naturally occurring DNA, RNA, and protein molecule. ■

GenBank Field Guide, Dec. 14–15

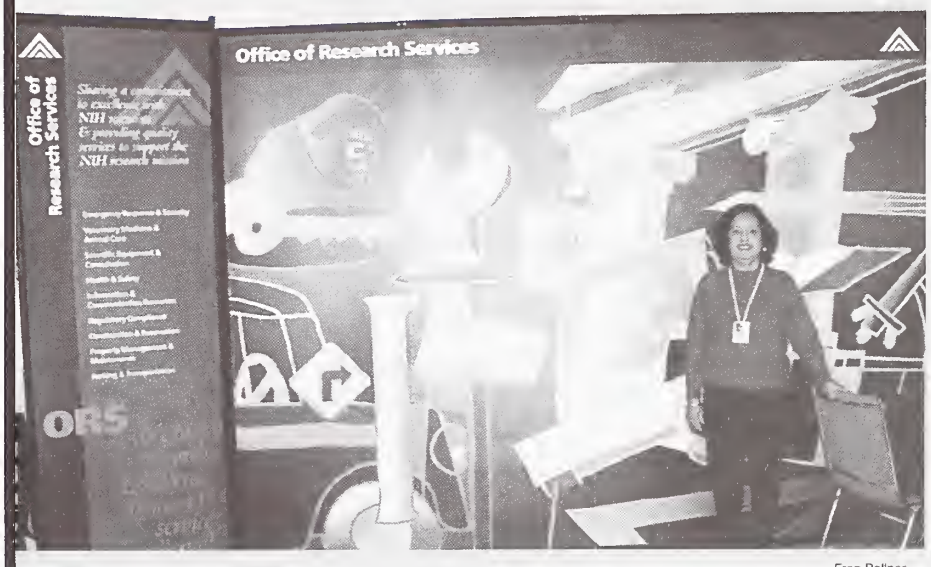
For a free lecture and workshop on GenBank and related NCBI molecular biology databases, register at **<http://www.ncbi.nlm.nih.gov/Class/FieldGuide/nlm.html>**. Questions to Peter Cooper: **<cooper@ncbi.nlm.nih.gov>**.

Getting There

According to Francis Collins, NHGRI director and head of the Human Genome Project, the public working draft version of the human sequence can be found in its most useable forms at the following web sites:

- University of California at Santa Cruz: **<http://genome.ucsc.edu/>**
- National Center for Biotechnology Information: **<http://ww.ncbi.nlm.nih.gov/genome/guide/>** and click "Map Viewer"
- European Bioinformatics Institute: **<http://www.ensembl.org/>**

Service with a Cybersmile



Fran Pollner

Modern Art and Science: *Carmen Kaplan, special projects manager of the NIH Office of Research Services, Office of Quality Management, at her post in the Natcher lobby to provide Research Festival goers with info on the updated, comprehensive, user-friendly ORS web site. The redesign project took six months, she said, and was largely the work of OQM's Pam Dressell. Check it out at* ***<http://www.nih.gov/od/ors>****.*

Eureka! And Beyond: Hard Lessons in Tech Transfer

by Margaret Coulombe

Judging from the experiences of a panel of NIH intramural investigators speaking at the Research Festival in October, tech transfer can be a long journey, a short glide, or an uphill battle after the first heady thrill of discovery.

At the October 12th minisymposium, the Office of Technology Transfer (OTT) presented a panel of scientists whose bright ideas (Eureka!) turned into commercial products and cash for the investigators, the labs, and the federal piggy bank. According to OTT, more than 1,200 licensing agreements have been signed since 1993. A 1998 General Accounting Office (GAO) report on the technology transfer activities of six major U.S. government agencies stated that, since 1996, NIH has generated 95 percent of the total royalties received ($102 million) by the federal government.

Serendipity in Science: The Hepatitis A Vaccine

Robert Purcell, chief of the Hepatitis Viruses Section in NIAID's Laboratory of Infectious Diseases (LID), opened the symposium. His tale, spanning nearly 20 years, began with discovery of the hepatitis A virus (HAV) in 1973 by postdoc Steve Feinstone, now with FDA's CBER. Using immune-electron microscopic techniques developed by LID's Albert Kapikian to visualize transmissible gastroenteritis, Feinstone was able to see HAV structure and went on to develop a diagnostic test for hepatitis A. He also obtained 20 serum samples from another study on post-transfusion hepatitis at NIH and, with his colleagues in the LID and Harvey Alter in the CC Blood Bank, discovered non-A, non-B hepatitis (hepatitis C).

Margaret Coulombe

Robert Purcell

Despite the breakthroughs in visualization and diagnosis, isolation of the virus and production in culture (the first steps toward preparation of a vaccine) proved fruitless. Then, serendipity played a hand. In 1976, Ian Gust, an Australian PI on sabbatical in Purcell's lab, moved the lab closer to success when he brought in stool samples he had collected from a family in Australia that had developed hepatitis A from eating raw mussels.

The strain of HAV recovered from the family's stools, dubbed hepatitis A virus strain HM175, turned out to be critical to the subsequent development of the vaccine because in 1981 Richard Daemer, also now at CBER, isolated the HM175 strain of HAV and was able to grow it in cell culture. Purcell's team was then able, by serial passage in cell culture, to generate a live attenuated virus, which could be tested in nonhuman primates for development of vaccine in humans.

At this point, Purcell and co-workers sought a potential commercial partner to develop a live attenuated hepatitis A vaccine and settled on SmithKline Beecham. In a collaborative effort by Purcell's group, the Walter Reed Army Institute of Research, and SmithKline Beecham, the HM175 strain of HAV was adapted to grow in a cell type suitable for vaccine development (MRC-5 cells). By then, however, SmithKline Beecham was more interested in developing an inactivated vaccine and was working closely with a strain of HAV provided by scientists in Switzerland. Purcell asked SmithKline Beecham if it would compare the HM175 strain with the Swiss strain for suitability as an inactivated vaccine. SKB agreed and found that the HM175 strain was a better inactivated vaccine candidate than the Swiss HAV. They subsequently dropped the Swiss option and pursued an inactivated vaccine with the HM175 strain in collaboration with Purcell's group.

Over the next decade, members of Purcell's lab cloned and sequenced wild-type and attenuated HAV strain HM175 and mapped the location of mutations important for allowing the virus to grow in cell culture and that attenuated virulence.

In all, the researchers in Purcell's lab have applied for more than 60 patents and have secured 21, 10 of which relate to the hepatitis A vaccine; some of these are held jointly with SmithKline Beecham.

In 1991, the HM175 strain of HAV became the first licensed hepatitis A vaccine (licensed first in Switzerland), and it was licensed in 1995 in the United States. It is currently one of two licensed hepatitis A vaccines in the United States (the other is manufactured by Merck Laboratories).

Despite the challenges and potholes on the road to discovery, this line of research, Purcell concluded with a smile, "has been very good to the lab, which," he added, "is now pursuing hepatitis C and E vaccines."

Margaret Coulombe

Frank Robey

The Thioether Linkage

Frank Robey, an NIDCR senior investigator, described the novel chemical process that he and colleagues Wolfgang Lindner and Ray Fields invented and that others have brought to bear in such clinical uses as detecting acute deep vein thrombi and diagnosing and treating non-small-cell lung cancer.

Robey, a chemist whose focus is AIDS vaccine research and immunology, developed an "enabling" technology—one that can be used in many diverse applications, often to speed up product design. In 1986, Robey and colleagues created a method to place a thioether bond at any position in a synthetic peptide—a doorway to new realms in chemistry. Patented in 1991, Robey's invention has found its way into multiple diagnostic and therapeutic products, some of which have been approved by the FDA. He is quick to emphasize, however, that while he provided the novel chemistry underlying emerging patents, the creative use of the linkage and the development of the products drew on the hard work and ingenuity of others.

The leading group to capitalize on Robey's thioether bond technology so far is a New Hampshire–based biotechnology company, Diatide, Inc. Richard Dean and John Lister-James, working at Diatide, have now spun the bond into three products and multiple patents of their own.

Diatide's first product that makes use of Robey's peptide-based thioether bond is called AcuTect®, a diagnostic imaging kit for detecting fresh (acute) blood platelet clots in the deep veins in the legs and pelvic area. AcuTect® was approved on fast track by the FDA and is now in Phase III clinical trials for imaging obstructions in carotid arteries. NeoTect®, a second Diatide product, binds to somatostatin receptors that are overexpressed on several epithelial-derived cancers, permitting, for example, X-ray detection of this cancer in the lung. Neotide®, a third Diatide product, uses Robey's thioether bond as the linker to attach a therapeutic beta-emitting radioisotope, Rhenium-188, to somatostatin, which then binds to and kills malignant tumors overexpressing the somatostatin receptor and kills them. Now in Phase I/II trials, Neotide® has been shown in preclinical animal testing to have an extremely high success rate in

targeting and shrinking or eliminating non-small-cell cancers in lung.

Beyond these three "eldest children," numerous other compounds are now being developed. Robey's method of chemical ligation has become a standard in the field of peptide chemistry and often is used to ligate large peptides together to form even larger proteinlike moieties.

Robey's current research focuses on the utility of such peptide linkages in constructing potential AIDS vaccine components. "Using this technology, we have made peptide polymers, or peptomers, that act as unique immunogens for making antibodies to target peptide conformations in large proteins. Often times, a synthetic peptide will not have any detectable conformation, but we've observed that after it's been polymerized, the peptide then contains constraints that often mimic those found for the peptide in the native protein. We are trying to be extremely creative with peptomer technology," Robey said in an interview with the *Catalyst*.

"Since we do not know the overall conformation of the HIV envelope protein or conformations of its subfragments, we are using the peptomer technology as a shot in the dark to go after certain conserved regions of gp 120. We are finding this approach to be quite successful. We model and then we immunize with these conformationally constrained subfragments."

Many of the conformations in the envelope are highly conserved, Robey notes, and he is in the process of making various components of the HIV envelope that can produce antibodies to "recognize all or most strains of the virus as it mutates." His method, he says, is "geared toward something that is very broadly cross-reactive and cheap to make—something that can cover the poorer populations in Africa and Asia if it ever comes to that level of development."

Cyclodextrins: Victims of Their Own Success?

The path to transforming methodologies and therapeutics is not always strewn with patents, royalties, and glory.

"To start with," advised Josef Pitha, "you need three 'eurekas!'. Not just one—first the discovery, then a patent attorney who will research and write up the proper patent, and, last, a business person who has the capabilities and the intent to get the product to the market."

The former chief of the Section on Macromolecular Chemistry at the NIA Gerontology Research Center, Pitha designed his talk on "Cyclodextrins: Short Road to Discovery, Winding Road to Use!" as an object lesson in the pitfalls of patenting.

Pitha's discovery involved the small carbohydrate compound cyclodextrin, which he was using to try to improve the solubility of another compound. His "eureka" moment came when he realized that cyclodextrin must be chemically modified to make full use of its capsulelike structure. Modified cyclodextrin had the potential to molecularly encapsulate other chemicals, drugs, or even food flavor compounds.

Josef Pitha

Pitha's thoughts went immediately to the desirability of encapsulating steroid hormones. Two things brought steroids to mind: his own experience with testosterone shots and his recollection of a professor of his in Switzerland in the 1930s who'd been given tons of porcine testicular tissue and told to find a hormone that could be administered orally. "Can you imagine such a mess?" Pitha commented.

His research path clear, Pitha soon discovered that cyclodextrin derivatives lent excellent solubility to a variety of steroids; that the encapsulation resulted in full release; and that the process and carrier were safe. He obtained good results with estradiol, progesterone, and testosterone. He was, in fact, his first test subject. He made it possible for the first time to administer unmodified, natural hormones orally to humans. Birth control pills based on natural hormones are an example of how this process could be turned to a revolutionary application.

The potential was not lost upon many watchful eyes. "Others recognized the lucrative outcome of my discovery," he noted. Within 10 years of Pitha's first patent filing in 1983, other individuals had filed 600 related patents, some of which should have been challenged, he muses, but were not. There were also problems arising from licenses granted to small companies that not only did not develop any products but blocked other companies from doing so. Frustrated companies called for a federal investigation; people lost their jobs; and Pitha's patents became "hot potatoes." One patent was involved in an interference case that was not decided for more than 10 years.

Despite the morass of patenting difficulties, Pitha points to the positive outcomes of his journey. As a result of his work, a whole new class of cyclodextrins is available commercially. The principles of his invention are now so widely accepted as to be ubiquitous—though no one knows that he developed them—and, most significantly, many therapeutic applications are on the horizon. "There is," he said, "great satisfaction in that." ■

Who Was that White Knight?

There's an invisible clause attached to exclusive licenses negotiated between the NIH Office of Technology Transfer (OTT) and its industrial partners. It's called the White Knight clause, and it's a voluntary, unwritten but verbally sealed agreement that the involved company will "do good" in relation to the exclusivity of its newly acquired license to what presumably will be a profit maker.

The White Knight program was created five years ago by OTT director Maria Freire in the course of discussions with a small, family-owned business—named White Knight. "It was during the time of the Ebola virus outbreak," Freire recalls, "and during the negotiations, I suggested that they donate their product—gowns coated with a viral barrier—to the Centers for Disease Control for use overseas." Although those particular transactions did not actually come to fruition, the company's name lived on in the concept of the White Knight that crystallized in Freire's mind. It was based on the notion, she says, that "this is NIH and there are other things than financial terms in business deals to be considered."

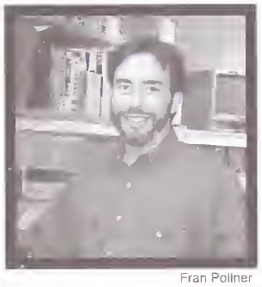
To a very large degree, OTT's business partners have agreed: Approximately 80 percent of the exclusive licensees participate in what Freire considers a "voluntary payback to the community in recognition of the taxpayer's contribution." White Knight offerings have included informational web sites, indigent access to health facilities, vaccines for schools, and drugs for clinical trials.

Among the more recent White Knight deeds was participation by company scientists in the physically demanding as well as exhilarating year 2000 Alaska AIDS ride (see <**http://www.alaskaride.com**>, which raised $4.1 million for AIDS research.

—Margaret Coulombe

Recently Tenured

Jeff Green *received his M.D. in 1981 from McGill University in Montreal and residency training in pediatrics at the Children's Hospital of Philadelphia. He joined the NIH Clinical Center in 1984 as a clinical genetics fellow and subsequently became an NCI biotechnology postdoctoral fellow in the laboratory of the late George Khoury. After an appointment as an investigator in the Laboratory of Molecular Oncology at FCRDC, he joined the Laboratory of Cell Regulation and Carcinogenesis, NCI, in 1997, where he has served as the head of the Transgenic Oncogenesis Group.*



Fran Pollner

Jeff Green

The use of transgenic animals for modeling human diseases has been the primary focus of the work in my laboratory. My early interests involved the phenotypic and molecular characterization of transgenic mice carrying the human T-cell lymphotrophic virus (HTLV-1)-*tax* gene. The *tax* mice were shown to develop perineural tumors with similarities to human neurofibromas, as well as inflammatory lesions in the salivary and lacrimal glands leading to abnormalities similar to those found in human Sjögren's syndrome. Further analyses of these transgenic animals also demonstrated in vivo that the *tax* gene can upregulate important growth regulators, including granulocyte macrophage colony stimulating factor, the interleukin-2 receptor, and nerve growth factor.

With my growing interest in hormone-related malignant disease, I became intent on developing a transgenic model for human prostate cancer. To reach this goal, our lab designed a targeting vector using the C3(1) component of the rat prostate in 5' flanking region. This led to the first transgenic model for prostate cancer that was driven by the expression of large and small T-antigen (Tag) from the SV40 early region. Interestingly, female transgenic mice carrying the same transgene develop mammary cancer that exhibits many important features observed in human breast cancer. Although Tag is not etiologically involved in human prostate or breast cancer, its mechanism of transformation involves the inactivation of two important tumor suppressor genes, Rb and p53. The loss of these tumor suppressors has been implicated in many human cancers, including prostate and breast cancer. Thus, Tag-induced transgenic oncogenesis may involve relevant pathways for human cancer development.

Transgenic prostate and mammary cancer lesions in these mice develop over a very predictable time course. We have taken advantage of this fact to define histopathological and molecular changes that occur at particular stages of tumor formation. The lesions that develop in the prostate appear strikingly similar to human prostate intraepithelial neoplasia and progress to invasive carcinomas. A significant number of these lesions develop *ras* mutations, as occurs in a subset of human prostate cancers. Although most transgenic mammary tumors do not harbor *ras* mutations, amplification of *ki-ras* occurs during tumor progression. We have demonstrated the functional significance of this finding by crossing the C3(1)/Tag mice with *ki-ras* knockout mice. The resulting mice show delayed tumor development. We have also demonstrated that expression of the transgene in the mammary gland is not responsive to estrogen and, as with human breast cancer, expression of estrogen receptor α is lost during tumor progression.

Our work has also demonstrated that there is a biphasic alteration in the apoptotic response in the transformed cells during the development of mammary cancer in the C3(1)/Tag mice: Rates of apoptosis rise during the preinvasive phase, but fall during the transition to invasive carcinomas. Our lab has demonstrated that the *bax* gene appears to be a critical regulator of the early pro-apoptotic response in the mammary tumors—C3(1)/Tag mice lacking bax have an accelerated rate of tumor formation.

Currently, I serve as the principal investigator of the NCI Mouse Models of Mammary Cancer Collective, which is part of the national NCI Mouse Models of Human Cancer Consortium. The NCI Mouse Collective is a community of 25 highly interactive NIH investigators seeking to advance the understanding of breast cancer through animal models.

With support from the Collective, my lab is expanding research using cDNA microarray technologies to define genetic pathways and identify new genes in mammary and prostate tumor development. We are comparing the expression profiles of tumors from several major transgenic mouse models of mammary cancer with those of human breast cancer, as part of the validation process for mouse models of human disease. In addition, we are continuing to use transgenic models to test several therapeutic approaches to mammary and prostate cancer including chemoprevention and antiangiogenesis agents. We are using array technologies to uncover mechanisms of action for these agents.

Our goals in this work and for the future emphasize development of new transgenic models for prostate and mammary cancer and the development of new targeting vectors and strategies to improve heterologous gene expression in vivo.

Vanessa Hirsch *obtained a D.V.M. in 1977 and a Masters of Veterinary Science in pathology in 1981 from the University of Saskatchewan in Saskatoon. She became a diplomate of the American College of Veterinary Pathologists in 1984 and obtained a Doctor of Science degree at the Harvard School of Public Health in Boston in 1988. After four years as a research assistant professor at Georgetown University in Washington, D.C., she joined the Laboratory of Infectious Diseases in 1992 and is now a senior investigator in the Laboratory of Molecular Microbiology, NIAID.*

My research focuses on the pathogenesis of AIDS and the development of a vaccine for HIV-1, using simian immunodeficiency virus (SIV) infection of monkeys as an animal model. SIV induces an immunodeficiency syndrome in macaque monkeys that is remarkably similar to that in HIV-infected humans.

Although HIV-1 infection of humans is fatal, the disease course is highly variable, ranging from asymptomatic survival for more than 15 years to progression to AIDS within two years of infection. The level at which plasma viremia stabilizes after primary infection is a highly significant prognostic indicator of subsequent disease course. This suggests that host immune mechanisms are critical in the control of viremia. Studies in my lab have shown that SIV-infected macaques also exhibit variable disease course and that viral load is a strong predictor of disease progression.

My lab is investigating host and viral factors that contribute to the variable disease course in SIV infection of macaques. We recently demonstrated that the susceptibility of peripheral CD4+ T cells to viral infection in culture is highly predictive of primary viremia in these animals after their inoculation with SIV. The relative proportion of CD4+ T cells, their level of activation, or the level of expression of the major SIV co-receptor, CCR5, does not explain the major differences in susceptibility. This result suggests there are other host cell factors that contribute to the establishment of persistent viral replication and progression to AIDS.

I am also investigating the origins of primate lentiviruses. It is important to remember that SIV infection of macaques, an Asian monkey, is artificial. SIVs originate in primates of African origin, including sooty mangabeys (SIVsm) and African green monkeys (SIVagm). My lab characterized the first SIVsm isolate, SIV strains from three species of African green monkeys, the sole SIV from Sykes' monkeys (SIVsyk), and SIV from L'Hoest monkeys and suntailed monkeys (SIVlhoest and SIVsun). A close genetic relationship between SIV from the latter two monkeys, despite their long-term (over 10,000 years) geographic separation, sup-

ports the hypothesis that the primate lentiviruses co-evolved in African monkeys over the last million years. Interestingly, SIVlhoest and SIVsun are genetically most closely related to SIVmnd from mandrills, despite the fact that mandrills and L'Hoest monkeys are only distantly related. Recently, we characterized SIV from redcapped mangabeys (*Cercocebus torquatus torquatus*) and drill (*Mandillus leucophaeus*) and mandrill monkeys (*Mandillus sphinx*). We have found that many of these SIV isolates induce AIDS in Asian monkeys.

Fran Pollner

Vanessa Hirsch

Despite serologic evidence of widespread SIV infection in African monkeys, AIDS-like disease is observed only in macaques. SIVsm infection of sooty mangabey monkeys is asymptomatic, whereas inoculation of this same virus strain into macaques results in AIDS. My lab demonstrated a similar phenomenon with SIVagm in African green monkeys and macaques. This species-specificity of virulence allows us to examine underlying mechanisms of attenuation in the natural host species and is a focus of my pathogenesis studies.

We recently evaluated plasma viral load and expression of SIV in tissues of naturally and experimentally infected African green monkeys. A wide range in viral load was observed among healthy African green monkeys, ranging from undetectable to concentrations similar to those observed in HIV-infected humans or SIV-infected macaques. Therefore, containment of viremia is an unlikely explanation for nonpathogenicity of SIVagm in its natural host. A major focus of future studies will be virologic and immunologic characterization of experimental SIVagm infection of African green monkeys vs. the susceptible pigtailed macaque host. Determining how host species coexist with their naturally occurring lentiviral infections will aid us in understanding the pathogenesis of HIV infection in humans.

The development of a vaccine for AIDS is the other focus of my research. Although antiretroviral therapy has had a significant effect on the survival of HIV-infected patients, treatment is costly and prone to the emergence of drug-resistant viral mutants. Thus the development of safe, realistic, and effective vaccine strategies is essential. Unfortunately, many of the vaccine approaches tested thus far have resulted in only partial protection from infection in primate models of AIDS.

My lab has been developing a vaccine using live viral vectors to prime a cell-mediated immune response. Using a highly attenuated, modified vaccinia virus Ankara (MVA), we demonstrated that vaccination with MVA expressing SIV genes resulted in significant modulation of viremia and improved survival when animals were challenged with SIV.

In one study of MVA expressing SIV Gag-pol proteins, rhesus macaques received four immunizations with the MVA recombinant virus or nonrecombinant MVA as a control. Gag-specific cytotoxic T lymphocyte (CTL) responses were detected in all experimentally immunized macaques, with levels peaking after the second immunization. After challenge with pathogenic SIV, all macaques became infected; however, viral load was lower in MVA-*gag-pol*-immunized macaques than in the control macaques. The level at which CTL stabilized after resolution of primary viremia correlated inversely with plasma viral load set point. Most importantly, the magnitude of reduction in viremia was predicted by the magnitude of the vaccine-elicited CTL response prior to SIV challenge.

In summary, these studies demonstrate that recombinant MVA-SIV as a sole immunogen generates a robust CTL response in macaques that mediates protection from high levels of viremia after SIV challenge. The effectiveness of recombinant MVA in the macaque suggests that MVA-based vaccines warrant evaluation for preventing AIDS in humans.

Olli Kallioniemi *received his M.D. in 1985 and Ph.D. in 1988 from the University of Tampere in Finland. After residency training in laboratory medicine, he did postdoctoral work at the University of California, San Francisco, and then returned to the University of Tampere, where he became a professor of cancer genetics before joining NHGRI in 1996. He is now a senior investigator in the Cancer Genetics Branch and head of the Translational Genomics Section.*

Galen Perry

Olli Kallioniemi

My interest is in the molecular basis of human breast and prostate cancer and strategies and technologies to translate basic research findings into clinical applications. Our research focuses on the discovery of inherited germ-line alterations, as well as somatic genetic events and gene expression changes involved in tumor progression.

In the area of genetic predisposition, I have collaborated with investigators in Scandinavia on genetic epidemiological studies of breast and prostate cancer. Using genetic linkage analysis of cancer families, we recently identified a putative third major locus, at 13q21-q22, for breast cancer susceptibility. Our laboratory was also involved in the identification of a candidate susceptibility locus for human prostate cancer on the X chromosome (HPC-X).

In 1992, we developed the comparative genomic hybridization (CGH) technique to identify chromosomal regions that are altered in cancer. At NHGRI, we are focusing on the identification of genes that are affected by genomic alterations, particularly high-level DNA amplifications that often take place in genetically unstable cancer cells. In collaboration with other investigators, we have identified several genes whose increased expression as a result of gene amplification may drive cancer progression and the development of therapy resistance. These include androgen receptor gene amplification in prostate cancer, and AIB1 and the ribosomal protein S6 kinase, which are amplified in breast cancer. We are now using a combination of high-resolution DNA chip technologies, such as CGH and cDNA microarray analyses, to rapidly identify amplified and overexpressed genes throughout the genome. Such genes may contribute to the clonal progression of cancer and provide targets for therapy.

In the postgenomic era, translating gene discoveries into clinical applications will be an increasingly important challenge. We recently developed the tissue microarray (TMA) technology to conduct rapid, large-scale analyses of promising candidate genes in hundreds or thousands of clinical tumor specimens. Up to 1,000 tiny "tissue spots" originating from different patients can be arrayed on a single microscope slide. We are applying the TMA slides to study the role of novel genes and proteins in thousands of tissue specimens from different cancer types, associating molecular findings with clinical and treatment outcome information. Such "genome-scale translational research" will be important to identify the most promising diagnostic and therapeutic gene targets from the genomic data now becoming available.

Thomas Kristie *received his Ph.D. from the Committee on Virology at the University of Chicago in 1986 and did postdoctoral work with Phillip Sharp at the Center for Cancer Research, Massachusetts Institute of Technology. He joined the NIAID Laboratory of Viral Diseases in 1993 and is now a senior investigator in the Molecular Genetics Section.*

My laboratory is interested in the molecular biology of herpes simplex virus (HSV), specifically focusing on the biochemical mechanisms of viral gene expression and transcriptional control of the viral lytic-latent cycle.

HSV is a human pathogen affecting a large percentage of the population. After a primary infection, the virus remains latent in the sensory neurons of the individual until complex stimuli such as stress, hormonal

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Fran Pollner

Tom Kristie

alterations, or tissue damage reactivate viral replication. During the lytic cycle, the immediate early (IE) genes of HSV are controlled by a complex viral regulatory enhancer that provides the framework for the assembly of macromolecular complexes. Our focus has been on determining the components, interactions, and functions of the various polypeptides involved.

As a postdoctoral fellow, I worked on identifying and purifying C1 factor, a critical host cell component of the enhancer complex. After arriving at NIH, I began cloning and characterizing this protein. C1 factor is a unique transcription factor produced as a 230-kDa protein and is proteolytically processed into a family of polypeptides. In a series of studies, my laboratory has defined the interactions of the C1 factor with each primary component of the HSV enhancer complex and demonstrated that it is both the coordinator of the enhanceasome assembly and a transcriptional coactivator. We have also isolated a relatively large bank of cellular proteins that interact with various domains of C1. We are now characterizing these to determine the normal functions of the C1 factor in mammalian cells.

One of the most interesting and critical questions in herpesvirus biology is the mechanism for establishment of and reactivation from the latent state. Considering the cell-specificity of latency and the cell stimuli that reactivate the virus, we think cellular factors probably play the most significant role in the lytic-latent switch. It is also likely that the regulation of the IE genes would be a primary target in reactivation. Models for the reactivation of HSV from the latent state propose either that 1) reactivation proceeds through a viral gene expression pattern distinct from the lytic phase or that 2) reactivation is due to coordinated activation of transcription of the five IE genes by cellular transcription factors.

My laboratory has demonstrated that although the C1 protein is localized in the nucleus of most cell types, it is uniquely sequestered in the cytoplasm of sensory neurons. In the mouse model, conditions that reactivate the virus from latency also result in rapid relocation of C1 to the nucleus. This observation and our work on C1 functions led us to propose that the C1 factor is a critical component of the signaling mechanism that initiates viral reactivation.

We are now using biochemical and genetic approaches to find how C1 factor is sequestered as well as the signaling pathway(s) for activation of C1 transport. In addition to determining the role of C1-interacting proteins, we have been developing animal models, including C1 domain-specific knockout mice to aid analysis of the roles of the C1 factor in the regulation of cellular and viral processes.

A second area of interest in the laboratory is the unusual specific proteolytic processing of the C1 factor. The precursor protein is cleaved at a series of 20-amino-acid repeats in the central domain to generate a family of polypeptides. The product polypeptides do not segregate, however, suggesting that proteolysis is a unique mechanism for regulating the activity of the protein. We have determined that the C1 factor itself contains an autocatalytic activity that is responsible for processing of the reiterations. We are now focusing on demonstrating our hypothesis, namely that processing regulates the protein-protein interactions and, therefore, the functional activity of the C1 factor.

Our interest in this area led to the development of a genetic screen for the isolation and characterization of novel site-specific proteases. Site-specific proteolysis plays significant roles in the regulation of many basic normal and disease processes, including:

- The control of cholesterol metabolism by proteolytic regulation of transcription factor SREB
- The cleavage of amyloid precursor protein (APP), which may affect the development of Alzheimer's disease
- The intricate pathway of proteolytic targeting resulting in cell apoptosis

Using a model protease, my laboratory developed a system capable of selectively isolating a rare protease of modest activity from a complex cDNA pool. We are now involved in several collaborative efforts to identify and isolate novel site-specific proteases in a variety of biological systems.

Fran Pollner

Alison McBride

Alison McBride *received a Ph.D. from the Imperial Cancer Research Fund and University of London, U.K., in 1986. She was a postdoctoral fellow and Investigator with Peter Howley in NCI and joined NIAID in 1994. She is now a senior investigator in the Laboratory of Viral Diseases, NIAID.*

I am interested in the strategies that viruses have developed to manipulate key host cell factors at different stages of the virus life cycle. Such studies have helped characterize many fundamental regulatory pathways in eukaryotic cells, such as DNA replication, gene expression, cell cycle control, and signal transduction.

Since joining NIH, I have studied the papillomaviruses. These are small viruses that infect and replicate in the stratified layers of the epithelia and cause benign warts, or papillomas. In some cases these lesions can progress to malignant carcinomas, the most notable of which is cervical cancer. The papillomaviruses also have an interesting biology: The virus infects basal epithelial cells and maintains its genome as an episome within these persistently infected cells. Viral DNA amplification and capsid antigen production occur only in the differentiated layers of a stratified epithelium. The papillomaviruses encode oncogenes that interfere with host cell growth control to enable the virus to replicate in nondividing, differentiated cells.

My research has focused on the molecular mechanisms by which two papillomavirus proteins control the viral life cycle. The viral E1 protein is required to initiate episomal viral DNA replication. The E2 proteins regulate viral transcription, DNA replication, and genome segregation. My colleagues and I have defined the structure, function, and interactions of these proteins.

A few years ago we identified an additional function for the E2 protein. We showed that the E2 protein and viral genomes are bound to mitotic chromosomes in dividing cells. E2 links the genomes to the host chromosomes to ensure that they are not lost as the cells divide, and that they are segregated equally to daughter cells. This finding defines the mechanism by which episomal viruses maintain and segregate their genomes in persistently infected cells. We are currently trying to identify the chromosomal factor to which E2 binds and to determine whether it is a common target of other episomal viruses.

We have also found phosphorylation of E2 regulates its degradation by the proteasome and modulates episomal viral genome copy number. Our current hypothesis is that E2 phosphorylation is cell cycle–specific and regulates genome segregation by determining the amount of E2 bound to mitotic chromosomes. High concentrations of E2 protein can be observed in the differentiated cells of a papilloma that amplify viral DNA, and we are testing whether E2 has yet another role in regulating vegetative viral DNA replication.

In addition to these molecular approaches, we have developed two biological systems with which to study the role of the E1 and E2 proteins. The study of the complete papillomavirus life cycle is difficult because it requires keratinocyte differentiation. We have developed an animal model in which organotypic rafts are generated from bovine or human keratinocytes and are grafted onto immune-compromised mice. When transfected with viral DNA, the grafts develop into papilloma-like lesions that synthesize infectious viral particles. This allows genetic analy-

ses of the viral functions required for the lytic cycle. It also allows us to study DNA segregation and persistence in an animal model.

Certain papillomaviruses are associated with the development of cervical cancer, and inactivation of E1 and E2 gene functions (by viral genome integration) is thought to play a role in malignant progression. Because E1 and E2 are crucial for viral DNA replication, it has been difficult to determine whether it is the absence of these gene products or the integration event per se that is important in carcinogenesis. To study this process, we have developed a system that allows analysis of the effect of mutations in E1 and E2 on biological indicators of malignant progression, in the absence of integration.

We hope that our study of the papillomavirus E1 and E2 proteins will continue to provide important insights into the pathogenesis of papillomavirus infection. This knowledge will be useful in designing strategies to intervene in the viral life cycle and could lead to prevention or treatment of papillomavirus-associated diseases. Our studies will also provide insights into mechanisms of transcriptional regulation and differentiation-dependent regulation of epithelial gene expression. A detailed understanding of the mechanism of papillomavirus DNA replication and segregation could lead to the development of a new generation of persistent extrachromosomal vectors that may have applications for gene therapy and genetic immunization.

Daniel Pine *received his M.D. degree from the University of Chicago-Pritzker School of Medicine and did his postgraduate training at New York's Columbia University before becoming a faculty member in the College of Physicians and Surgeons there. He is now head of the Section on Developmental Psychopathology and Affective Neuroscience, in the Program on Mood and Anxiety Disorders, NIMH.*

My research interests pursue two complementary avenues. First, I am an active investigator in pediatric psychopharmacology. Second, I am testing hypotheses on brain-behavior associations in childhood psychopathology.

My interest in pediatric psychopharmacology developed while I was a member of the Department of Psychiatry at Columbia University. The effectiveness of medications with selective serotonin reuptake inhibiting activity (SSRIs) in adult anxiety disorders led our group to conduct an open trial of SSRIs for childhood anxiety disorders. Results from this study in turn led to our participation in a multisite, randomized, controlled trial of SSRIs in 128 children with a pediatric anxiety disorder. This study established the robust efficacy and safety of SSRIs in children with anxiety disorders.

In light of potential pharmacologic parallels between pediatric and adult anxiety disorders, I have examined the psychobiology of pediatric anxiety. Following work in adult panic disorder, my initial studies found that children with respiratory illnesses, such as asthma associated with dyspnea, faced a higher risk of separation anxiety disorder than did children with other illnesses. My subsequent work, funded by extramural grants from NIMH, demonstrated that children with separation anxiety disorder exhibit the same set of respiratory abnormalities that are classically found in adult panic disorder. These include heightened dyspnea, chaotic breathing, and heightened respiratory response to CO_2 inhalation.

Fran Pollner

Daniel Pine

Because SSRIs ameliorate such breathing abnormalities in panic disorder, I designed a study to test the hypothesis that SSRIs ameliorate these abnormalities in separation anxiety disorder. Through related psychophysiological projects conducted within the context of this study, I am examining the hypothesis, based on animal studies, that antidepressants exert more consistent effects on innate than learned aspects of fear. We are planning studies in the NIMH intramural program to examine the effects of SSRIs on learned and innate fears in children and adolescents.

My prior studies found that only a subset of children with separation anxiety disorder exhibits respiratory characteristics of panic—characteristics that also identify adults with familial forms of panic disorder. Hence, this subgroup of children may manifest a potentially heritable, respiratory-based susceptibility to panic disorder, a hypothesis I have pursued through other NIMH-funded projects.

Supporting this hypothesis, I conducted a longitudinal study showing that most adult panic attacks are preceded by a childhood history of separation anxiety disorder, though most children with separation anxiety disorder do not develop panic. To further test the hypothesis, I developed a portable apparatus for assessing CO_2 sensitivity in children. Our group has used this apparatus to begin comparing respiratory parameters in children of normal parents and parents with three types of disorders: panic, depressive, and anxiety disorders other than panic. In further support of the central hypothesis, the study is based on a sample in which there is a strong familial association between adult panic disorder and childhood separation anxiety disorder.

Beyond studies on anxiety disorders, I have extended to children other adult work on brain-behavior associations. For example, based on the association between adult anxiety and growth hormone deficiencies, I documented a longitudinal association between anxiety in young girls and growth deficits from childhood into adulthood.

Similarly, adult studies document associations among stress-induced anxiety, the hypothalamic-pituitary-adrenal axis (HPA), and hippocampal function. I demonstrated spatial memory deficits and elevated cortisol in children with anxiety disorders. Because spatial deficits, HPA activity, and some forms of anxiety could each relate to hippocampal dysfunction, I developed fMRI methods for assessing hippocampal activity across development using a spatial navigation paradigm. With these methods, I am now testing the hypothesis that enhanced HPA activity in childhood anxiety is associated with both reduced memory-based navigation ability and reduced hippocampal activation during navigation. We also plan to pursue this hypothesis in our intramural lab.

Finally, studies among adults find that abnormalities in impulse control and emotion regulation each show unique associations with distinct brain asymmetry profiles in posterior regions engaged by perceptual tasks. I documented parallel associations with disorders of impulse control and emotional regulation in children, using cognitive and electrophysiological indices of posterior brain asymmetry.

This work in turn led to a series of fMRI studies examining developmental variations in brain regions engaged by emotional perception tasks. In each of these projects, and in proposed projects in the NIMH intramural program, I plan to continue illustrating how findings from adult psychiatry inform research on treatments and risk factors for childhood psychiatric disorders.

Patricia Rosa *obtained her doctorate in 1980 from the Institute of Molecular Biology at the University of Oregon in Eugene. After postdocs at Washington University in St. Louis and the Research Institute of Scripps Clinic in La Jolla, Calif., Rosa joined NIAID's Laboratory of Microbial Structure and Function, Rocky Mountain Laboratories, in Hamilton, Mont. She is now a senior investigator at RML's Laboratory of Human Bacterial Pathogenesis.*

In a broad sense, I am interested in how the phenotype of a cell at any particular time reflects both its genetic structure and the environment in which it is located. This interest probably began with an epigenetics course that I took as an undergraduate and has taken various forms in graduate and postdoctoral studies. Since coming to Rocky Mountain Labs, my research has focused on *Borrelia burgdorferi*, the spirochete that

Recently Tenured

Celia Hooper

Patricia Rosa

causes Lyme disease. Features of this relatively simple bacterium and its infectious cycle present a good system in which to study the adaptive responses of a bacterial pathogen to its vector and host environments. All steps of this infectious cycle can be reproduced in the laboratory, making it accessible to scientific investigation.

Maintenance of *B. burgdorferi* in nature requires efficient transmission between the tick vector and the mammalian host. Like many bacterial pathogens, *B. burgdorferi* must cope with a changing array of environmental conditions to persist, proliferate, and be transmitted between hosts. My lab and others have found good evidence for differential gene expression by borreliae in these disparate settings. Yet, it is unknown how *B. burgdorferi* senses its environment and orchestrates appropriate adaptive responses. What environmental signals define the tick vs. the mammal and induce the appropriate bacterial response? How does *B. burgdorferi* sense these signals and transduce them? Which proteins are made in different places or at different stages of the infectious cycle, and what are their functions? What features of the spirochete or the infection are pertinent to pathogenicity? Our broad objective is to use a molecular genetic approach to answer these questions and elucidate the mechanisms of adaptation and variation in *B. burgdorferi* over the course of the infectious cycle.

Our current knowledge of *B. burgdorferi* at the molecular level represents an interesting paradox; we have the sequence of the entire genome, but we know very little about the functions of most of the encoded proteins. Although we have identified several *B. burgdorferi* genes whose expression or putative function suggest that they are important in the infectious cycle, we do not know the actual biological roles or significance of their protein products.

Ongoing and future studies are designed to test the roles of these genes and their products in the infectious cycle and to identify additional genes that allow spirochetes to adapt, persist, and be transmitted between ticks and mammals. We also want to understand regulation of these genes and their roles in pathogenesis. A major thrust of our work is to analyze the phenotypes of specific gene mutants in the context of the natural infectious cycle.

B. burgdorferi is structurally and genetically quite dissimilar from other bacteria, having a small linear chromosome and a large number of linear and circular plasmids. How these DNA molecules replicate, why the genome is segmented, and the functional significance of this unique structure are not well understood and are another focus of research in my lab. The practical consequence of *B. burgdorferi's* odd genome is that genetic tools and methods developed for more typical bacteria do not work in *B. burgdorferi*, so we have developed basic tools with which to undertake genetic studies in this bacterium.

We have recently succeeded in inactivating genes in pathogenic strains of *B. burgdorferi*. This represents a significant advance because until now, no one had been able to introduce mutations into a wild-type background, impeding analysis of the phenotype of mutant spirochetes in the infectious cycle.

Although the genetic system of *B. burgdorferi* is rudimentary and far from elegant, it still provides a powerful tool with which to explore the unique structure of the borreliae genome and to study the adaptive responses of a bacterial pathogen to its vector and host environments.

Ellen Sidransky *received her M.D. from Tulane University in New Orleans in 1981. She trained in pediatrics at Children's Memorial Hospital–Northwestern University in Chicago, Ill., and in clinical genetics at the NIH Interinstitute Genetics Training Program. She joined the Clinical Neuroscience Branch at NIMH in 1988 and is now a senior investigator leading the Unit on Clinical Genetics.*

My laboratory integrates basic and clinical research in a "bench-to-bedside" approach, focusing on Gaucher disease, the most common of the sphingolipidoses. I use Gaucher disease, which has a broad spectrum of symptoms, as a prototype for other disorders affecting the nervous system. Most of these inherited disorders are characterized by a wide range of presentations, yet the factors contributing to this heterogeneity are often elusive. My clinical, biochemical, and molecular studies of humans and animals are designed to understand this heterogeneity and to improve therapy.

My principal research aim is to understand genotype-phenotype relationships in Gaucher disease and other inherited disorders affecting the nervous system. Our clinical and molecular studies of more than 200 patients have shown that there is significant genotypic heterogeneity among clinically similar patients. Moreover, patients with the same genotype can have different disease manifestations.

LeRoy Sundberg

Ellen Sidransky

Our recent work revealed that the region surrounding the human glucocerebrosidase gene on chromosome 1q21 is particularly gene-rich, with seven genes and two pseudogenes within 75 kb of sequence. We found that in a significant number of patients, mutant alleles arise by recombination or gene conversion occurring between the glucocerebrosidase gene and its nearby pseudogene. We discovered that these recombinations can occur at a variety of sites throughout the gene and by different mechanisms of recombination. In addition to recombination events within and around the glucocerebrosidase locus, the actions of contiguous genes, environmental factors, and modifying genes may contribute to the phenotypes observed. We are actively exploring these possibilities via transcriptional studies of the contiguous genes in the region, transcriptional arrays and mouse models.

Our active clinical service investigates the natural history and spectrum of manifestations in Gaucher disease. We focus on patients with atypical or extreme phenotypes, because they may reflect the involvement of other genes or modifiers. Two fascinating phenotypes I am investigating include Gaucher patients with parkinsonian symptoms and patients with hydrocephalus and cardiovascular involvement. Genotypic analyses reveal that patients in the first group have many different Gaucher mutations, while the latter appear to share a common genotype. In addition, a knockout mouse model of Gaucher disease generated with a null allele led me to recognize an analogous human phenotype—a neonatal lethal form of Gaucher disease. Affected patients die with hydrops fetalis in utero or shortly after birth. Since our original description of this phenotype, dozens of additional cases have been identified.

I also discovered that null allele mice and severely affected human patients have skin ultrastructural abnormalities and altered epidermal barrier function secondary to the deficiency of epidermal glucocerebrosidase. This skin abnormality may serve as a valuable clinical tool, enabling early differentiation of different Gaucher phenotypes.

Another challenge has been to understand the development of neuronopathic Gaucher disease. Because this and other aspects of the pathology of Gaucher disease are not adequately explained by glucocerebroside accumulation, we are also exploring the significance of an alternate substrate, glucosylsphingosine, that we found elevated in brains of patients and mice with neuronopathic Gaucher disease.

In working to improve treatment for Gaucher disease, I participate in a collaborative effort to test chemical modifications of recombinantly produced glucocerebrosidase. Modifications include using molecules such as polyethylene

glycol to prolong circulation of the enzyme. This may permit lower dosage and drug cost, reduce antigenicity, and make it easier and more convenient to administer the enzyme to patients. We are also investigating more efficient production of the enzyme from new transgenic sources, as well as the use of inhibitors of glycolipid synthesis.

Many of the approaches used in our studies of Gaucher disease will also be applied to another group of inherited disorders—congenital disorders of glycosylation (CDG)—in collaboration with Donna Krasnewich of NHGRI. These disorders involve defective assembly of NH_2-linked oligosaccharides. Patients with CDG show diverse symptoms, including cerebellar abnormalities, malformations of facial features, gastrointestinal disease, and profound delays in psychomotor development. CDG provides an opportunity to investigate the elusive correlation between clinical manifestation and the molecular mechanism of the metabolic defect.

The results of our genotype-phenotype studies provide evidence that even well-characterized Mendelian disorders are not necessarily "simple." I believe that investigations into the mechanisms contributing to the heterogeneity encountered in these disorders will ultimately enable us to discover the "magic in the web of it." Moreover, the strategies, experience, and knowledge gained through this work may be helpful in understanding and treating other hereditary diseases, including more "complex" neurologic and psychiatric illnesses.

Lee Weinstein *received his M.D. from New York's Columbia University College of Physicians and Surgeons in 1983 and did a medicine residency at Montefiore Hospital in New York before joining the Metabolic Diseases Branch of NIDDK in 1986. He is now a senior investigator in that branch.*

I am interested in G protein signaling and hormone action. My research at NIDDK has examined the role of G protein genetic defects in hormonal disorders. Our work has focused on the heterotrimeric G protein (Gs) that couples receptors to the enzyme adenylyl cyclase, which catalyzes the generation of intracellular cyclic adenosine monophosphate (cAMP). The Gs α-subunit (Gsα) is ubiquitously expressed and is required for the intracellular cAMP response to hormones and other extracellular signaling molecules.

In my early work at NIH, my colleagues and I showed that mutations that produce a constitutively active Gsα protein are present in a mosaic distribution in patients with the McCune-Albright syndrome, which is characterized by hyperpigmented skin lesions, focal skeletal lesions (fibrous dysplasia), and endocrine hyperfunction. This observation provided the impetus for ongoing studies at NIH on the role of Gs pathways in osteoblast differentiation. We also showed that heterozygous inactivating mutations of the same gene lead to Albright hereditary osteodystrophy (AHO), characterized by obesity, skeletal defects, and, in some cases, mental deficits. Interestingly, maternal transmission of these mutations also leads to multihormone resistance (pseudohypoparathyroidism type Ia, PHPIa) whereas paternal transmission does not (pseudopseudohypoparathyroidism, PPHP).

Fran Pollner

Lee Weinstein

Using a Gsα knockout mouse model, we have shown that Gsα is imprinted in a tissue-specific manner—maternally expressed in some tissues (such as renal proximal tubules, the site of parathyroid hormone action) but biallelically expressed in most other tissues. This provides a likely explanation for the variable clinical presentation in AHO patients (PHPIa vs. PPHP). We also showed that Gsα plays a major role in energy and glucose metabolism. Specifically, maternal vs. paternal transmission of a heterozygous knockout leads to opposite effects on energy metabolism and fat accumulation. However, all heterozygous mice have increased sensitivity to insulin in vivo.

We now appreciate that the Gsα gene (*GNAS1*) has multiple alternative promoters. We have recently identified the fourth one of these that is imprinted, and we believe this promoter region is critical for the tissue-specific imprinting of Gsα. In patients with renal resistance to parathyroid hormone in the absence of AHO (PHPIb), this region has a paternal-specific imprinting pattern in both parental alleles. Therefore, PHPIb is caused by a *GNAS1* imprinting defect that presumably leads to decreased Gsα expression in renal proximal tubules. Analysis of this region provides a useful diagnostic tool for the evaluation of patients who present with parathyroid hormone resistance.

In the future, we hope to determine the mechanisms by which Gsα is imprinted in a tissue-specific manner and by which imprinting of *GNAS1* is established and maintained. We also plan to study the physiological roles of Gsα in greater detail by examining mice with loss of Gsα in specific tissues. We hope these studies will provide important insights into the mechanism of genomic imprinting and the role of Gs signaling in metabolism and hormone action. ■

Opening Day at the Cybercafe

photos by Celia Hooper

A Good Time Was Had By All: *(left) Malissa Murray, technical IRTA in the NIDDK lab of Derek Le Roith, shares a Cybercafe table and a laugh with Joan Schwartz, NINDS section chief and OIR assistant director . . . and . . . (left) Charles Sanders, president of the board of the Foundation for the NIH, unveiled a plaque honoring Harold Varmus (right), Cybercafe enthusiast.*

Former NIH director Harold Varmus, whose advocacy laid the groundwork for the cultivation of graduate programs at NIH, returned in a blaze of good cheer September 18 to participate in the opening ceremony of the Graduate Lounge. Located a few steps below the Building 10 lobby coffee bar, the Cybercafe offers comfortable seating around small tables, corner spots for more private conversations, and, soon, free web access. The furnishings were the gift of Fisher Scientific International, Inc., and its CEO, Paul Montrone, who serves as treasurer of the Foundation for the NIH.

Envisioned as a place for NIH's graduate students and other trainees to mingle, the lounge is open to all; graduate students, however, have priority on reserving space for special events. ■

Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: keeping ahead of research advances, tapping into the human genome, tech transfer, and ways to improve the *Catalyst.*

Send your responses on these topics or comments on other intramural research concerns to us via e-mail: <catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2W23.

In Future Issues...

- Health Disparities
- Angiogenesis
- Research Fest Tidbits

1) What do you think the Intramural Research Program should be doing to stay one step ahead of new developments in biomedical research?

2) Give us your rants and raves regarding your experience tapping the working draft of the human genome. What has worked well? What new tools would make it easier for scientists to use the data?

3) In your experience, what are the potential pitfalls and rewards of patenting and technology transfer at NIH?

4) The *Catalyst* staff and editorial advisory board meet in early December. Do you have any suggestions for us for improving the *Catalyst*—more coverage in certain areas, less in others, a new type of feature?

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

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